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Response in Southeast Asia: Managing diabetes and other endocrine disorders during the COVID-19 crisis

In our medical world and beyond, so much has changed, and still needs to change, since the end of 2019.

It was in December of 2019 when we first heard the news about a cluster of patients with pneumonia in Wuhan, China, caused by a novel coronavirus. We still remember distinctly the news report of a Filipino in Wuhan in lockdown, describing his situation with fear. Since then, the condition has been named COVID-19, and practically all countries in the world have faced this extraordinary challenge and crisis, this pandemic. In our region in Southeast Asia, we feel the extent of this crisis even more deeply in the context of preexisting handicaps in our healthcare systems.

Our borders mostly closed, most communities self-quarantined, and healthcare systems and economies faced challenges like never before in many decades or even since the last century. Governments and their health departments are frantically struggling to combat the pandemic and manage its social and economic repercussions.[1] After months of lockdown, efforts at re-opening the economy are gingerly being implemented as we write, even as anxieties persist over the potential next waves of the virus.

As endocrinologists, we look to addressing chronic conditions as diabetes and other endocrine disorders in these newly difficult times. Epidemiologic data on COVID-19 in the diabetic population is emerging; it is still limited and its timely sharing from various affected countries is imperative.[2]

It is noteworthy that scientific papers in pre-prints (without yet the normal peer review) and pre-proofs (without the usual full-copy editing) become early data sources. We await the development of the vaccine and the clinical trials of medications that will stem the transmission of this virus and eradicate the disease. We await verdicts on effectiveness and safety of treatments, both new and re-purposed drugs, to save patients. We cautiously weigh more evidence even as we hope to use trial treatments effectively and safely for the very sick as a last resort.[3]

We have to adapt faster to the changing times.

The ASEAN Federation of Endocrine Societies (AFES) has been in existence since 1981, with initiatives for collaboration through the years. In a survey about this pandemic, responses by AFES leaders are reported by Dr. Gabriel Jasul Jr., Philippine Society of Endocrinology, Diabetes and Metabolism (PSEDM) Past President. This issue's lead article "**AFES A.S.-O.N.E.**: **A**SEAN **S**urvey **O**f **N**eeds in **E**ndocrinology in the Time of the COVID-19 Pandemic," describes in detail the situations faced by endocrinologists and other practitioners within our region, painting one landscape of ASEAN with distinct features. In many countries, it highlights the tighter limitations in our teaching and training programs in endocrinology, including reduction in opportunities for face-to-face mentoring, given the limited caseload in our specialty as COVID-19 cases are prioritized instead.

This is a critical time, too, where information campaigns are most needed to counter "fake news." We expect specialty organizations to step up, help to streamline content, provide timely position statements, and check on the accuracy and safety of statements already circulating, in order to correct any misinformation or misleading recommendations that tend to spread as fast as the virus, if not faster. In this issue of JAFES, we include position statements from Indonesia and the Philippines.

As face-to-face outpatient consultations have become less feasible, the role of online or remote education in diabetes care to empower the patient has never been greater, utilizing a variety of new platforms. We feature an article on the use of social media for the information needs of persons with diabetes amidst the COVID-19 pandemic, by our group in the Philippines led by Drs. Iris Isip-Tan and Jerico Gutierrez, who previously initiated the use of visual abstracts for JAFES articles and recently expanded into infographics and educational videos for patient education. We include in this issue and in our website some examples and links prepared by the PSEDM.

Physicians are faced with heartbreaking decisions about prioritization of care, given limited hospital beds, breathing devices and ventilators. We need to be guided by clearer ethical guidelines as we take care of patients and attempt to do life-saving research.[4] In this issue, Dr. Marita Reyes elucidates the challenges of research ethics committees in the setting of the pandemic.

With this issue, we are also introducing a new article type, "Endocrine Perspectives," inviting experts to express short commentaries on timely topics. Our first offering is by PSEDM Past President Cecilia Jimeno, on early impressions about new challenges and opportunities in diabetes care during this pandemic. Though it is situated in the Philippine context, we believe the topic is of broader concern.

And so while the whole world is grappling with the COVID-19 public health threat and onslaught, we envision JAFES to be the platform to discuss our regional perspective in Southeast Asia: how COVID-19 is affecting the clinical picture, diagnosis, and subsequent care of our patients with diabetes and other endocrine disorders. We will work on quicker turnaround timelines, and publish online ahead of print. This is our commitment as the voice of endocrinology in Southeast Asia.

We need to move to a new and better normal for everyone in our healthcare systems: improving compensations for nurses and essential services workers, allocating more funds for adequate healthcare capacity including hospital bed and equipment, and cooperating locally, regionally and globally, in order to combat COVID-19 and prepare for the next pandemic. As physicians, we have to genuinely provide nurturing and compassionate care, which is truly our calling, with or without the COVID-19 crisis. We pray that this pandemic also brings out the best in all people.

And before anything else, let us take a moment to honor our fallen heroes, and to say thank you to our health care workers and all those who provide our daily essential needs.

Let us all do our bit, in small ways, and while there is yet so much to be done, with God's graces we will overcome.

Elizabeth Paz-Pacheco
Editor-in-Chief

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FEATURE ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

AFES A.S.-O.N.E.: ASEAN Survey Of Needs in Endocrinology in the Time of the COVID-19 Pandemic

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Abstract

Objectives. The COVID-19 pandemic has made a major impact on hospital services globally, including the care of persons with diabetes and endocrine disorders. The aim of this study is to describe the epidemiology of COVID-19 in the ASEAN Federation of Endocrine Societies (AFES) member countries; to describe challenges, changes and opportunities in caring for patients with endocrine diseases, as well as in fellowship training programs, and endocrine-related research in the AFES countries.

Methodology. The **AFES A**SEAN **S**urvey **O**f **N**eeds in **E**ndocrinology **(AFES A.S.-O.N.E.)** was an open-ended questionnaire that was sent to the presidents and representatives of the AFES member countries by email. Responses from Societies were collated and synthesized to obtain perspectives on the emergent issues in endocrinology in the Southeast Asian region during this pandemic.

Results. The burden of COVID-19 cases varied widely across the AFES member countries, with the least number of cases in Vietnam and Myanmar, and the greatest number of cases in either the most populous countries (Indonesia and the Philippines), or a country with the highest capability for testing (Singapore). The case fatality rate was also the highest for Indonesia and the Philippines at around 6%, and lowest for Vietnam at no fatalities. The percentage with diabetes among patients with COVID-19 ranged from 5% in Indonesia to 20% in Singapore, approximating the reported percentages in China and the United States. The major challenges in managing patients with endocrine diseases involved inaccessibility of health care providers, clinics and hospitals due to the implementation of lockdowns, community quarantines or movement control among the member countries. This led to disruptions in the continuity of care, testing and monitoring, and for some, provision of both preventive care and active management including surgery for thyroid cancer or pituitary and adrenal tumors, and radioactive iodine therapy. Major disruptions in the endocrine fellowship training programs were also noted across the region, so that some countries have had to freeze hiring of new trainees or to revise both program requirements and approaches to training due to the closure of outpatient endocrine clinics. The same observations are seen for endocrine-related researches, as most research papers have focused on the pandemic. Finally, the report ends by describing innovative approaches to fill in the gap in training and in improving patient access to endocrine services by Telemedicine.

Conclusion. The burden of COVID-19 cases and its case fatality rate varies across the AFES member countries but its impact is almost uniform: it has disrupted the provision of care for patients with endocrine diseases, and has also disrupted endocrine fellowship training and endocrine-related research across the region. Telemedicine and innovations in training have been operationalized across the AFES countries in an attempt to cope with the disruptions from COVID-19, but its over-all impact on the practice of endocrinology across the region will only become apparent once we conquer this pandemic.

Key words: survey, Southeast Asia, COVID-19, endocrine care, SARS-CoV-2

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BACKGROUND

The COVID -19 pandemic literally sent shock waves throughout the world. With an extraordinary speed, SARS-CoV-2 virus spread worldwide with reported total number of confirmed cases exceeding 5 million, claiming a total number of more than 330,000 deaths as of May 22, 2020.[1] The huge burden on health care systems globally is unprecedented and varies across regions, countries and economies. Well-recognized fields in medicine, namely, infectious diseases, pulmonary and critical care, and emergency medicine, took the lead in the fight against this pandemic. However, as the pandemic has extended over six months now and appears to continue indefinitely, other specialties have become more involved as important risk factors, like hypertension, diabetes and heart disease, and associated conditions, like stroke, hypercoagulability, cytokine storm and multi-organ failure, were identified in COVID-19.

Endocrinologists took an important role in hospital COVID-19 teams as diabetes mellitus has been noted to be present in a significant number of confirmed cases, ranging from 6 to 21%, and even higher rates of up to 36 to 46% in fatal cases.[2-4] An international panel of experts in the field of diabetes and endocrinology was recently formed to provide guidance and practical recommendations for the management of diabetes during the pandemic. This panel cited that depending on the global region, 20 to 50% of COVID-19 patients had diabetes.[5]

The increased worldwide prevalence of diabetes mellitus, the observed greater risk of COVID-19 severity among people with diabetes and the purported mechanisms underlying the association between diabetes and COVID-19 puts endocrinologists at the center of the critical management of these cases.[6,7] Endocrinologists also have to continue taking care of patients with thyroid diseases, adrenal insufficiency, pituitary disorders, obesity and osteoporosis, among others, as these patients can be similarly infected with the SARS-CoV-2 virus as the general population.

Interestingly, emerging data showed that SARS-CoV-2 cell receptor angiotensin-converting enzyme 2 (ACE2) is expressed in a wide variety of human tissues.[8] It has been reported that ACE2 is expressed in a number of endocrine organs, namely, the pancreas, thyroid, testis, ovary, adrenals, pituitary and adipose tissue, suggesting the possible involvement of the endocrine system in the multi-organ manifestations of COVID-19.[2,9,10] While the evidences on the ACE2 expression in endocrine organs are rather conjectural and derived from early, small studies, especially from other SARS strains, this information can further stimulate the engagement of endocrinologists in COVID-19 management.

Given this background, leading endocrine and diabetes professional organizations have published general recommendations and guidance on the care of patients with diabetes and endocrine diseases during this pandemic. Among these societies were the European Society of Endocrinology,[11] and the Korean Endocrine Society.[2] The applicability of these recommendations in the ASEAN region is questionable, as differences in prevalence and clinical presentation of diabetes and endocrine diseases and disparities in health care exist between the ASEAN countries and the other regions and countries of the world. Generating ASEAN-based recommendations and guidance will thus be a useful undertaking during this pandemic.

As a collaborative project among the member countries of the ASEAN Federation of Endocrine Societies (AFES), we initiated the **AFES A**SEAN **S**urvey **O**f **N**eeds in **E**ndocrinology **(AFES A.S.-O.N.E.)** during the COVID-19 pandemic. The project entailed a brief survey on the emergent issues in endocrinology in the Southeast Asian region during this pandemic (Appendix 1, Survey Form). The objectives of this survey were: first, to obtain basic information on the burden of COVID-19, the burden of diabetes and other endocrine diseases and the challenges in managing them; secondly, to gather data on problems encountered in endocrine fellowship training programs and in endocrine-related research, and thirdly, to determine the utilization of telemedicine and similar initiatives in endocrine care in the AFES member countries during this pandemic.

METHODOLOGY

The **AFES A.S.-O.N.E.** is a 7-item open ended questionnaire that solicited information on the following topics from the AFES member countries: country-specific burden of COVID-19 (population estimates and mortality rates); prevalence of diabetes mellitus (DM) and percentage of cases of COVID-19 cases with DM; challenges in diabetes management and in the care of persons with other endocrine diseases; problems and challenges in implementing endocrine fellowship training programs and in pursuing endocrine-related researches; and initiatives to mitigate the problem of physician access such as telemedicine.

Survey forms were sent through electronic mail to the current leaders of the 7 AFES member societies, namely, the Indonesian Society of Endocrinology (ISE), the Malaysian Endocrine and Metabolic Society (MEMS), the Myanmar Society of Endocrinology and Metabolism (MSEM), the Philippine Society of Endocrinology, Diabetes and Metabolism (PSEDM), the Endocrine and Metabolic Society of Singapore (EMSS), the Endocrine Society of Thailand (EST) and the Vietnam Association of Diabetes and Endocrinology (VADE).

Responses from the leaders of these societies were then collated, tabulated and synthesized to put into perspective the current situation of endocrine care in the region during this pandemic.

RESULTS

Burden of the COVID-19 Pandemic in the AFES Countries

The burden of COVID-19 pandemic in the AFES countries would be best appreciated by looking at the total number of confirmed cases, the number of recovered cases and the number of deaths vis-à-vis the total population estimate in each country. Likewise, case fatality rate (CFR), also called case fatality risk or case fatality ratio, the proportion of people who die from a specified disease among all individuals diagnosed with the disease over a certain period of time, can be used as a measure of disease severity and is used for prognostication predicting disease

course or outcome. Tables 1 and 2 summarized the data on COVID-19 in the AFES countries.

Table 1. Population Estimate in each AFES Member Country

Country	Population Estimate
Indonesia (IN)	273, 217,306
Malaysia (MN)	32,321,966
Myanmar (MY)	54,371,358
Philippines (PH)	109,426,100
Singapore (SG)	5,845,122
Thailand (TH)	69,781,614
Vietnam (VN)	97,241,403

Adapted (as of May 22, 2020)[12]

Table 2. COVID-19 statistics in each AFES member country

Country	Confirmed Cases	Recovered Cases	Deaths	Case Fatality Rate (CFR)
Indonesia	20,796	5,057	1,326	6.37%
Malaysia	7,137	5,859	115	1.61%
Myanmar	199	108	6	3.02%
Philippines	13,597	3,092	857	6.30%
Singapore	30,426	12,995	23	0.08%
Thailand	3,037	2,910	56	1.84%
Vietnam	324	266	0	0%

Adapted (as of May 19, 2020)[13,14]

COVID-19 data from Tables 1 and 2 reflect not only the burden of the pandemic but also the disparities in health care systems, economic structures and political leadership and responsiveness among the AFES countries. The most populous nations, Indonesia and the Philippines, with significant number of confirmed cases (although not the highest), had the most number of fatalities with CFR above 6%. In startling contrast, Singapore, the least populous and with the strongest economy, had the highest number of confirmed cases but one of the lowest CFRs. In between, population-wise, Malaysia and Thailand had positive cases in the thousands but relatively low CFRs under 2%. Myanmar had a very small number of affected cases with a case fatality rate of 3.02%. Vietnam, with a large population size of over 97 million, is definitely the outlier with a low number of affected cases, high recovery rate and zero death despite its proximity to China where SARS-CoV-2 originated. It is widely known that Vietnam declared a travel ban early in January 2020.

Clearly, many factors influenced how the pandemic panned out in each of these countries and in the region in general. Geography, travel patterns, economic systems and political stability will all contribute to the final tally. Factors related to each country's response to the COVID-19 pandemic including public health measures, mass testing and case contact tracing are dependent on the strength of health care systems which in turn are dependent on the economic and political stability in each country. The current status of this pandemic in the region points to much-needed reforms in areas affecting public health and to enhanced regional collaboration.

Burden of Diabetes Mellitus in the AFES Countries

Diabetes mellitus, the most common endocrine disorder and now an identified risk factor for increased severity and complications in COVID-19, naturally deserves attention in assessing the impact of the pandemic on endocrine care in the region. Diabetes prevalence has been considerably high in the region for several decades now. The reported rates summarized in Table 3 are the most current, as reported by the AFES member societies. Asians have a strong ethnic and genetic predisposition for diabetes and have lower thresholds for the environmental risk factors. Compared to their Western counterpart, they develop diabetes at a younger age and at a lower body mass index and waist circumference.[15] The recent prevalence rates ranged from around 5% in Singapore and Vietnam, around 6 to 7% in the Philippines and Thailand, 10 to 11% in Indonesia and Myanmar, and the highest at 17.5% in Malaysia. Certainly, the multi-ethnicity and the sociocultural and religious practices contribute to the increased burden of diabetes in the AFES countries.

It is notable as well that as noted in the data from Indonesia, the Philippines and Vietnam, the prevalence of prediabetes, IFG and/or IGT, is also significantly high. Given this diabetogenic environment, the burden of diabetes is high and magnified by the rapid industrialization in these countries. Preventive strategies are imperative at the primary care level if the goal is to decrease the diabetes burden in the region.

A rough estimation of the proportion of COVID-19 patients with diabetes mellitus showed a low of 5% in Indonesia and a high of 20% in Singapore, revised to roughly 8 to 12% from recent data. In Myanmar, among the 151 confirmed cases, 21 patients, or 13.9%, have diabetes as of 1st May 2020. In Thailand, in a single hospital where 65 COVID-19 positive cases were seen, 15% had diabetes. In Malaysia, out of 106 COVID-19 deaths, 19 cases, or 17.9%, had diabetes. In the Philippines, the ongoing study of the Philippine College of Physicians is expected to generate results in August 2020. A preliminary unpublished report in one

Table 3. Summary of Diabetes Statistics in AFES member countries

Country	Diabetes prevalence (%)	Impaired Fasting Glucose (IFG) prevalence (%)	Impaired Glucose Tolerance (IGT) prevalence (%)	Source or Reference
Indonesia	10.9% (diagnosed 13.8%, undiagnosed 86.2%)	26.3%	30.3%	Basic Health Research 2018, Ministry of Health[16]
Malaysia	17.5% 16.8%			NHMS 2015[17] IDF Atlas 2019[18]
Myanmar	10.8%			Diabetes, Metabolic Syndrome and Obesity[19]
Philippines	6.3% 7.1% 7.9% (based on FBS)	 8.2%		IDF Atlas 2019[18] Age-adjusted % IDF 8th National Nutrition Survey, FNRI 2018[20]
Singapore	5.5%			2019 National Data[21]
Thailand	7.9%			NHES 2018[22]
Vietnam	5.4%		13.7%	National Survey 2012 National Hospital of Endocrinology - Hanoi[23]

Philippine government hospital designated as a COVID-19 center noted that 19% of COVID-19 cases have diabetes. These numbers, while needing validation, approximate the previously reported percentages (6 to 21% that can reach up to 36 to 46%) in China, United States and other countries.[2] An international panel of experts in the field of diabetes and endocrinology cited that depending on the global region, 20 to 50% of COVID-19 patients had diabetes.[5]

Challenges in Diabetes Management in the AFES Countries in the Time of COVID-19 Pandemic

Several areas in diabetes management can be adversely affected during this pandemic depending on the extent of quarantine and other measures imposed to contain the spread of SARS-CoV-2 virus. The availability of medications for the treatment of diabetes, particularly insulins, was not affected in most of the AFES countries. In both Indonesia and the Philippines, the supply of medications did not change in major cities but this may change if the imposed community quarantine will continue and may affect the transport of goods from major cities, especially to far-flung smaller cities. In general, however, there were no reports of shortages in medications so far in the AFES countries.

Access to health care providers, clinics and hospitals can be problematic especially with the imposition of enhanced community quarantine (ECQ) measures, sometimes called "lockdown" or movement control order (MCO), which restricts citizens' movement and travel.

National health coverage in Indonesia allowed routine primary care visits and if necessary, referral for specialty/tertiary care consults. The imposition of "semi-lockdown" however restricted access to these clinics but two-month worth of maintenance medications were prescribed and supplied to patients to prevent interruption of treatment.

In Malaysia, the MCO resulted in reduction of clinic visits and limited access to the clinics. In major hospitals, Malaysian endocrinologists attend to both COVID and non-COVID admitted cases hence, access to diabetes clinics is temporarily affected. A similar situation was reported in Myanmar.

In the Philippines, with the declaration of ECQ in major cities, many endocrinologists have temporarily closed their outpatient clinics. In major hospitals especially those designated as COVID-19 centers, endocrinologists take part in COVID-19 response teams and direct diabetes management in the critical care setting.

In Malaysia and the Philippines, the use of telemedicine and related virtual modes of patient care and contact was noted to be on the upswing. Notably, during the 2-month long "circuit-breaker (CB)" semi-lockdown in Singapore, only essential services/procedures (defined as those which if not provided would result in significant or rapid deterioration of the patient's medical condition and potentially threaten their health and wellbeing) were allowed. Those deemed as non-essential, such as aesthetic medicine, sports medicine services and joint replacement surgery were prohibited. In Vietnam, even during the 15-day lockdown, hospitals and clinics remained open. Because a significant number of endocrinologists are deployed in COVID-19 units in most, if not all, of the 7 countries, quality diabetes care can be delivered to the hospitalized high-risk patients by early detection and management of diabetic emergencies.

Access to adequate and proper dietary sources is affected by the quarantine measures that prevent patients from going to the markets and groceries and from eating out at restaurants. The food choices may have been reduced in the countries where ECQ. MCO or lockdown were imposed. The upside noted in Malaysia was that consumption of healthier foods prepared at home was higher especially with the observation of Ramadan, the holy month of Muslims during which strict fasting from dawn to sunset is practiced.

In the Philippines, the reliance on take-out and delivery service of restaurants and other food outlets has been on the uptrend in the major cities. Mobile applications, like Food Panda and Grab Food, are now widely used for food deliveries since most people opt to follow stay-at-home instructions. Food access is not a major issue in Singapore, Thailand and Vietnam.

Limitations in physical activity were reported in all countries because of the recommended social distancing and home confinement. Patients and physicians have to rely on home-based exercise activities. The impact of this restriction on exercise and other activities is not huge and as noted, patients were advised alternative exercise programs to do at home.

Financial limitations related to the economic lockdown affects the patients' ability to purchase their maintenance medications. In countries with national health coverage and good health insurance plans, i.e., Indonesia, Malaysia, Singapore, Thailand and Vietnam, access to medications is not a problem. In the Philippines where medications are purchased out-of-pocket by the greater majority of the population, reduced income during the ECQ means reduced allocation for purchasing medications. Prioritizing the medical needs then becomes a challenge. In the minority of private, self-paying patients in the other countries, the economic downturn may have similar effects. In Malaysia, it has been noted that because of the expected economic difficulties, the so-called "private" patients may later opt to transfer and seek health care in government hospitals and clinics.

Challenges in the Management of other Endocrine Disorders in the AFES Countries in the Time of COVID-19 Pandemic

Treatment of patients with other endocrine disorders has to continue even if these disorders are often stable and do not appear to be adversely affected by COVID-19. Continuity of care for patients with common thyroid diseases, namely, hypothyroidism, hyperthyroidism and thyroid nodules, was not a problem in Malaysia, Thailand, Singapore and Vietnam. In Indonesia, Myanmar, and the Philippines, close follow-up and monitoring of patients, particularly those with hyperthyroidism, became difficult with the limited access to clinics and laboratories. Thyroid function tests and diagnostic imaging procedures cannot be routinely and regularly performed. Patients controlled on stable doses of thyroid medications, whether anti-thyroid drugs or levothyroxine, are advised to maintain their medications. Virtual consultations were done as

often as necessary, as reported both in Malaysia and the Philippines. In Singapore, it was noted that a few sporadic cases of hypothyroidism and at least one case of thyroid crisis were seen among COVID-19 patients. Incidental findings of thyroid nodules were discovered during CT scan imaging of the thorax in a few COVID-19 patients. Further work-up, including imaging, fine needle aspirations, and elective surgical procedures are temporarily deferred in all 7 countries.

Thyroid cancer management is not a problem in Malaysia, Myanmar, and Singapore amidst the pandemic. In Indonesia and Vietnam, thyroid cancer patients are managed by surgical oncologists. In the Philippines and Thailand, delay in surgical treatment of thyroid cancer patients is expected and dependent on new surgical and anesthesia policies being enforced because of COVID-19.

Adrenal diseases did not present any major challenge in all of the seven countries during this pandemic. The need for stress dosing of steroids in adrenal insufficiency (AI) is well-established and patients with chronic AI have received specific instructions and sufficient supply of steroids. Since regular follow-up is not possible, as noted in Myanmar and the Philippines, patients are advised to continue their current prescribed doses and to seek consultation at the emergency room if emergency arises. In Singapore, AI was suspected in possibly 5 to 10% of hospitalized COVID-19 cases who were evaluated with the short Synacthen test (ACTH stimulation test). These cases had no obvious etiologies of AI and had no previous intake of corticosteroids. The possibility of COVID-19 effects on the hypothalamus-pituitary-adrenal (HPA) axis, through direct viral damage or indirect injury from hyper-immune response, was raised and should thus be considered. This is a reasonable assumption based on the findings of hypocortisolism among SARS survivors[24] and the positive expression of ACE2 in the adrenal glands.[8] A study on AI and HPA axis in COVID-19 patients is planned at the Philippine General Hospital, a designated COVID center in the Philippines.

Management of pituitary disorders was not a problem in Indonesia, Malaysia, Singapore and Vietnam. Myanmar, Thailand and the Philippines raised concerns regarding lack of follow-up and delay in surgical procedures, similarly an issue also seen in diabetes and the other endocrinopathies. Patients were advised to continue currently prescribed doses and to follow-up after the quarantine period. The possible effects of COVID-19 on the pituitary and the other organs, particularly the gonads, were raised by our Singaporean colleague.

Obesity management was not a major concern in the majority of these countries (Indonesia, Myanmar, the Philippines, Singapore and Vietnam). In Malaysia, the lockdown caused disruption in the prescribed diet, exercise and lifestyle modification among obese patients who already attend weight management programs. In Thailand, patients with obesity experience delay in their follow-up appointments. In Singapore, obesity rate is roughly estimated at 15% but it is not a major concern since morbid obesity, particularly body mass index (BMI) in excess of 35 to 40, was not encountered among those stricken with COVID-19. Notably, morbidly obese patients routinely followed up at obesity and bariatric surgery clinics tended to have their regular appointments deferred during the circuit breaker period. In Vietnam, bariatric surgery is not commonly done.

Osteoporosis treatment is not challenging in all the countries during this pandemic. In Myanmar and the Philippines, patients were instructed to continue current prescribed doses and to schedule follow-up after the quarantine period. In Singapore, it was noted that a significant number of the hospitalized COVID-19 patients were over 60 years of age and therefore likely to have osteoporosis. A few cases of hypercalcemia with hypophosphatemia and high intact PTH levels were seen among COVID-19 patients, most likely due to pre-existing parathyroid adenomas. Vitamin D deficiency and secondary hyperparathyroidism were seen in some of the COVID-19 patients as well.

Malnutrition in critical illness was not a commonly seen problem in all the countries. This can be possibly explained by the fact that the critically ill COVID-19 cases were managed in major hospitals which are better equipped. The nutritional management of patients admitted in the smaller hospitals outside the major cities may differ dependent on availability of resources and expertise.

Endocrinology Training Programs in the AFES Countries in the Time of COVID-19 Pandemic

Clinical training in the COVID-19 era presents many unique challenges particularly in areas of clinical skills enhancement when bedside and face-to-face encounters and hands-on experience are limited both in quantity and in quality. The reality of the "new normal" becomes readily apparent when actual patient encounters are minimized particularly in the ambulatory setting. Many outpatient clinics are temporarily closed until measures to ensure safety of patients and physicians alike are in place. Much of endocrine practice is outpatient-based and the resumption of the usually active diabetes, thyroid and endocrine clinics may not happen anytime soon. The inpatient endocrine service can continue as usual, albeit in a setting restricted by delineation of cases into COVID and non-COVID categories and by the fastidious use of full personal protection equipment (PPEs). The imposeds limitations on patient contact and the drop in hospitalized elective/non-urgent cases will affect the number and the variety of cases encountered by clinicians, consultants and trainees alike. With the onset of the pandemic, these conditions had to be adopted almost overnight in nearly all medical centers, many of which are academic/training institutions.

Given such a dramatic change in the learning environment, the status of the endocrinology training programs in the AFES countries needs to be examined in relation to the important responsibility of the AFES and the AFES member societies of training future endocrinologists. The survey results concerning fellowship training are generally consistent among the AFES countries pointing to new and huge challenges in the training programs except for Thailand and Vietnam. Thailand reported that their training program is still on track but through virtual modes of learning. Vietnam noted that during the lockdown period of 2.5 months, teaching was online using Skype and Zoom, without practical bedside learning and without

active case discussion. However, after the lockdown was lifted in Vietnam, the training program has resumed as usual in the pre-COVID mode.

Unfortunately, the 5 other AFES countries have to adapt to the new realities of clinical training. Indonesia did not accept new trainees temporarily and their current trainees have problems with doing research and pursuing exchange studies in other countries. Scientific education will continue to be online/web-based. The ISE now conducts webinars for physicians and distributes lay educational materials on diabetes management during the pandemic.

In Malaysia, the Ministry of Health has put a hold on fellowship training programs where no new fellows-trainees will be hired this year. The current fellows will be put on hold for 6 months, will not rotate to other hospitals and will be part of the general medicine and COVID teams in their current hospital. The duration of training of current fellows is thus extended by 6 months, and completion and assessment will be put on hold from April to October this year. Myanmar, on the other hand, is using Zoom and other web-based applications for teaching seminars and case discussions to address the lack of hands-on training and interactive sessions while practicing social distancing and home stay.

In the Philippines, the PSEDM anticipated a significant drop in the caseload of the current fellows, difficulties in completing research requirements and limitations in teaching conferences and patient advocacy activities. Contingency plans were crafted and these include reduction of fellows' caseload requirement by 50%, modification of nature of research requirement to retrospective, registry-based or meta-analysis, use of online technology for conferences and examinations, the use of social media for patient advocacy and patient education and web-based society conferences.

In Singapore, endocrine fellowship programs will continue in the restructured hospitals but inter-hospital cross-over of trainees is not allowed temporarily to reduce the risk of SARS-CoV-2 transmission among trainees and staff and between hospitals. Inter-institutional training through virtual platforms has been put in place to facilitate productive intellectual exchanges. Overseas endocrine fellowship training have been temporarily put on hold due to travel restrictions in place.

Endocrine Research in the AFES Countries in the Time of COVID-19 Pandemic

Pursuing endocrine-related research can be difficult during this pandemic. All 7 respondents reported the challenges in implementing research activities at this time. Indonesia commented that the present circumstances make it impossible to collect sample, do monitoring and even bring in supplies like reagents for basic research. Malaysia identified several problems related to the safety of research patients from risk of exposure to COVID-19 patients in the hospital and to the COVID-19 status of the research patients since they recruited from the community. For industry-sponsored clinical trials, recruitment of new patients is compromised and patient visits are converted to telephone visits during the MCO period. Investigator-initiated research has been put on hold and unfortunately, this includes the fellows' research projects which are a mandatory part of their training.

Myanmar noted that due to the lockdown, study patients are not able to come for scheduled visits and since only few outpatient clinics are open, new case finding and recruitment of study patients is very minimal. Study patients may have difficulty in getting their supply of study drugs and treatment interruption or incomplete treatment can happen affecting the study results. Contacting the investigator and/or research staff may be difficult during this time in case of adverse drug events or complications.

The Philippines expects that data collection for prospective studies may be difficult because of limited interaction between patients and doctors. Complete evaluation of study patients may also be limited because of abbreviated study visit to limit potential exposure to COVID-19 cases. Alternatively, different study designs, e.g., online surveys, can be considered as research projects especially for the fellows. Thailand also reported that some study patients cannot come for study visits because of travel ban across provinces. A similar situation is noted in Vietnam where enrolling and following up study patients can be difficult because people prefer to stay at home and transportation is also limited.

In Singapore, all non-COVID-19 research have been put on hold during the circuit breaker/partial lockdown period, severely affecting both basic and clinical research projects. The research funding agencies have allowed deferment of progress reports by 6 months. Research key performance indicators (KPIs) and deliverables are affected by this pandemic. Moreover, the government regulates the shipment of laboratory biological samples to overseas laboratories and the delivery of laboratory consumables such as ELISA assay or antibody test kits, thus, affecting the conduct of research until the government gives permission for resumption of these activities (shipments and deliveries).

Telemedicine and Similar Initiatives in Endocrine Care in the Time of COVID-19 Pandemic

One of the most interesting developments in health care during this pandemic is the increased reliance on telemedicine and similar resources to mitigate the limited access to physicians for consultations due to the different lockdown restrictions on people's movement. While the usual telephone-based contact and the more recent telehealth resources have already been available, all the 7 AFES countries have now adjusted to this mode of patient-doctor encounter and are slowly adapting to its use in medical education and clinical training. All 7 countries reported the use of web-based/online resources for telemedicine and other related purposes.

Indonesia appreciated the benefits of implementation of telemedicine with the support from their government but noted that there is currently no regulation on payment of fees for teleconsults. Malaysia reported use of virtual meetings among doctors, Zoom-based discussions for teaching the junior physicians, webinars via Facebook live for the public, and email service for patient consultations. Scheduled virtual consultations by phone or video calls have been initiated and continued with patients to include

review of laboratory results, discussion and prescription and adjustment of medications. Patients who have urgent problems and need to be seen face-to-face are asked to come for scheduled clinic appointments. In Myanmar, patients can contact their endocrinologists via phone, Messenger or Viber messages.

In the Philippines, the PSEDM initiated a Facebook-based patient assistance program that directs the patients to the endocrinologists in their vicinity who are then informed of the consultations. Many of the PSEDM members have engaged their patients through telemedicine applications allowing virtual consultations. Telemedicine has suddenly gained widespread acceptance due to the pandemic and will most likely be a part and parcel of health care moving forward during and after this pandemic. This form of patient encounters appeal to the tech-savvy younger physicians but the traditional patient-doctor contact will be preferred by the more senior physicians who will have to adapt to technology sooner or later.

In Singapore, several telemedicine initiatives have been started to assist mainly in outpatient care and to some extent, in inpatient care as well. We advise caution, however, because the rules of engagement in telemedicine are still being worked out to limit physician exposure to liabilities and other medico-legal issues. In Thailand, the use of telemedicine is for training and webinars for educational purposes. In Vietnam, telemedicine is described as not "high-tech" since most patients still contact their attending physicians through phone calls or messaging. The rare exception is when severe cases are being co-managed by many specialists in different hospitals who are linked through telemedicine.

DISCUSSION

COVID-19's impact has truly been staggering in many areas of daily living but the health care systems received the heaviest blow from this pandemic. The standards and practices are now radically changed in many, if not all, of disciplines in medicine. Endocrinology has not been spared and endocrinologists are now actively engaged in many aspects of COVID-19 medicine, but largely in the field of diabetes care. Recent publications and rapid reviews on diabetes management in COVID-19 patients attest to the significant burden of diabetes in this current pandemic. The proposed mechanisms of increased risk of COVID-19 severity and complications among patients with diabetes are examined in completed researches and in ongoing investigations. Epidemiologic data, practice recommendations and basic science researches are all part of the COVID-19 publication boom, the majority of which tackles diabetes.[2-6, 8-11, 25-30]

The generation of ASEAN-derived data can direct the formulation of practice recommendations relevant to the ASEAN region. The **AFES A.S.-O.N.E.** project is a step towards that direction and entailed a survey on seven areas of concern in endocrine care in AFES countries during the COVID-19 pandemic. From the responses from the current leaders of the 7 AFES member societies, it can be gleaned that the burden of COVID-19 may be aggravated by significant diabetes burden in the region, mirroring the global picture. However, the political and economic structures in these countries clearly influence the disparities in health care systems and the health outcomes during this pandemic. Singapore, with the most robust economy and political stability and lowest population size, had the most number of confirmed cases and yet one of the lowest death rates not only in the region. Vietnam, despite a large population size, had low number of confirmed cases, high recovery rate and zero death, all helped by a stable economy and early and strategic response to COVID-19. Malaysia, Myanmar and Thailand are coping well with the pandemic with low case fatality rates. Indonesia and the Philippines, the most populous nations in the AFES, have the highest death rates.

The other aspects of endocrine care in the AFES countries during the pandemic are similarly affected not only by COVID-19 itself but by the observed disparities in the existing health care systems. Access to endocrinologists and health care facilities is limited in the region during the imposed lockdown but adaptation by patients and physicians averted major health problems through the increased use of telemedicine. Access to medications, adequate dietary sources and physical activity has not been largely affected by the pandemic but if this situation extends indefinitely, it would likely result in shortage of health services and supplies. Management of the endocrine disorders, other than diabetes, is likewise affected by the lack of face-to-face contact and follow-up but virtual consultations are replacing usual patient-physician encounters for now.

Endocrine fellowship training programs in the AFES countries are universally affected by COVID-19 but virtual technology is helpful in addressing the challenges and limitations at this time. Contingency plans are in place to temporarily mitigate the gaps in learning activities and to adjust the minimum requirements in research requirements of the trainees. Endocrine research is adversely affected and non-COVID research is currently limited at this time.

Interest in the involvement of the endocrine organs in COVID-19 pathophysiology is heightened[32-34] and several observations even in the AFES region support this hypothetically. Aggressive calls for rapid communications and publications on diabetes and endocrine disorders in relation to COVID-19 are being made by both international and regional journals.[7, 31-34]

The Journal of the AFES (JAFES) has been promoting endocrine research in the region and its current issue features COVID-19 position statements from Indonesia and the Philippines,[27,28] perspectives[28] and inpatient diabetes management guidelines[29] from the Philippines. Ethical considerations in the conduct of research during the pandemic should also be addressed accordingly.[35]

One of the important findings in this survey was the widespread application of telemedicine and other virtual initiatives in the different areas of endocrinology during this pandemic in the different AFES countries. Patient care, education and research are now arenas of web-based technology circumventing the limitations on actual face-to-face encounters from imposed lockdowns. This adaptation to technology heralds a major reform in health care that happened in response to COVID-19. While virtual technology has been available for quite some

time now, its use was heightened during this pandemic. Caution must be exercised in applying virtual technology to limit the potential risk of exposing clinicians to liabilities and other medico-legal issues.

Implications of the Survey Results

Endocrine practice in the AFES countries even during this pandemic actually share more commonalities despite the disparities in health care systems and the differences in economic and political structures among these countries. Our shared commitment to excellence in patient care, training and education and research is strong among the member societies and should be tapped to decrease the differences between these countries. Collaboration between the AFES member societies can be further enhanced by application of virtual technology. Telemedicine will continue to be an important tool in sharing resources among these AFES societies to improve patient care, to promote scientific exchange between institutions and trainees and to encourage endocrine research during and even after the COVID-19 pandemic.

Limitations of the Survey

This informal survey is limited by the lack of specific outcome measures in the areas of concern, e.g., percentage drop in patient encounters in the endocrine clinics, worsening of laboratory parameters or quality of life measures among patients with diabetes and endocrine disorders, reduction in knowledge base of trainees through formal standardized evaluations or decrease in the number of ongoing researches. Time allowance in completing this survey and inability to validate the responses from the AFES leaders are additional limitations. However, despite these challenges, the survey showed that the AFES countries can come together to complete an important undertaking during this pandemic.

CONCLUSIONS

AFES A.S.-O.N.E. put in perspective the current situation of endocrine care in the AFES member countries in the time of COVID-19 pandemic. The burden of COVID-19 in these countries reflects the disparities in health care, economic and political stability. The huge burden of diabetes in the region is affected by COVID-19 but adaptability and available expertise averted gaps in the care of patients with diabetes. Management of the other endocrine disorders during this pandemic continued despite limited access to endocrine specialists and facilities. Endocrine fellowship training and endocrine research were affected by lockdown-related limitations on physical encounters and interaction. A welcome development during this pandemic is the widespread and wise application of telemedicine and related virtual technology platforms in the different areas of endocrinology during the pandemic. This survey also highlighted the remarkable opportunity for collaboration among the AFES countries during a most challenging time.

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Appendix 1. A Brief Survey on the Emergent Endocrine Issues in Southeast Asia in the Midst of COVID-19 Pandemic

1. What is the latest COVID-19 statistics in your country? (Total number of cases, number of deaths, number of recovered cases). ***Please include date of latest report. Please note as well as the latest population estimate in your country.***

2. Diabetes mellitus is cited as an important co-morbid condition among COVID-19 cases in publications and reports.
   A. What is the prevalence of diabetes mellitus in your country?
   B. What is the estimated number/percentage of COVID-19 patients who also have diabetes mellitus in your country?

3. What are the identified challenges in diabetes management during this pandemic? ***Please check all applicable choices and explain, if necessary.***
   A. Availability of medications, especially insulins
   B. Access to endocrinologists and primary care doctors and to treatment centers/hospitals/clinics
   C. Access to adequate and proper dietary sources
   D. Limitations in physical activity, especially due to social distancing
   E. Limitations in finances for medications, due to economic lockdown
   F. Others

4. Are there identified challenges in the management of other endocrine diseases because of COVID-19? ***YES or NO choices. If the answer is yes, please specify. You may adapt the choices for diabetes management above.***
   A. Thyroid diseases in general (hypothyroidism, hyperthyroidism, benign nodules)
   B. Thyroid cancer
   C. Adrenal diseases, especially adrenal insufficiency
   D. Pituitary diseases
   E. Obesity
   F. Osteoporosis and other bone and mineral disorders
   G. Malnutrition in critical illness
   H. Others

5. Are there identified problems now in continuing endocrine fellowship training programs in your country? ***YES or NO. Please explain and discuss briefly. Please share strategies in place or being planned to address these issues related to training.***

6. Are there identified problems in pursuing endocrine-related research during this pandemic? ***YES or NO. Please explain and discuss briefly.***

7. Are there telemedicine and similar initiatives in place in your country to mitigate the limitation in access to physicians, especially endocrinologists during this pandemic. ***YES or NO. Please discuss briefly and share your experiences.***

Please feel free to add any comments that might have not been covered by the 7 questions in this survey. It will also be most appreciated if you can provide resources and/or links to relevant treatment algorithms, guidelines and consensus statements that are being utilized in your country during this pandemic. Again, thank you very much!

Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

UP Philippine General Hospital Division of Endocrinology, Diabetes & Metabolism Consensus Recommendations for In-Patient Management of Diabetes Mellitus among Persons with COVID-19

Cecilia Jimeno, Ma. Cecille Anonuevo-Cruz, Angelique Bea Uy, Adrian Oscar Bacena, Mark David Francisco, Angelique Love Tiglao-Gica, Racquel Bruno, Diane Grace Corpuz

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Abstract

Diabetes mellitus (DM) is a known risk factor for morbidity and mortality among patients with COVID-19 based on recent studies. While there are many local and international guidelines on inpatient management of diabetes, the complicated pathology of the virus, the use of glucose-elevating drugs such as glucocorticoids, antivirals and even inotropes, and various other unique problems has made the management of in-hospital hyperglycemia among patients with COVID-19 much more difficult than in other infections. The objective of this guidance is to collate and integrate the best available evidence that has been published regarding in-patient management of diabetes among patients with COVID-19. A comprehensive review of literature was done and recommendations have been made through a consensus of expert endocrinologists from the University of the Philippines-Philippine General Hospital (UP-PGH) Division of Endocrinology, Diabetes and Metabolism. These recommendations are evolving as we continue to understand the pathology of the disease and how persons with diabetes are affected by this virus.

Key words: In-patient management, diabetes, COVID-19, SARS-COV-2

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a novel coronavirus that was first recognized in Wuhan, China in December 2019. Since then, it has spread quickly and is now considered a global pandemic. Despite the many researches that have been published, much remains unknown regarding SARS-CoV-2 and its designated disease, COVID-19.

Diabetes mellitus (DM) is a known risk factor for severe illness among patients with COVID-19. In a retrospective cohort study of confirmed COVID-19 patients in China, diabetes was identified as the second most common comorbidity, found in 7.4% of patients.[1] A meta-analysis of 12 studies also from China reported that diabetes was present in 10.3% of more than 2,000 patients with COVID-19,[2] which was similar to their 2013 national prevalence of 10.9%.[3] Diabetes was likewise a prognostic factor for ICU admission, acute respiratory distress syndrome (ARDS) (OR 2.34 [1.35-4.05]), and mortality (OR 2.85 [1.35-6.05].[4-6] Epidemiological studies of countries with high disease burden showed that the risk of dying from COVID-19 is up to 50% higher among persons with diabetes compared to those who do not have diabetes.[7]

While there are many local and international guidelines on inpatient management of diabetes, the complicated pathology of the virus, the use of glucose-elevating drugs such as glucocorticoids, antivirals and even inotropes, and various other unique problems has made the management of in-hospital hyperglycemia among patients with COVID-19 much more difficult than in other infections. Coupled with these are the difficulties in feeding those who have COVID-19 due to the management of respiratory failure that involves putting the patient in a prone position.

The objective of this guidance is to collate and integrate the best available evidence that has been published regarding in-patient management of diabetes among patients with COVID-19. A comprehensive review of literature was done and recommendations have been made through a consensus of expert endocrinologists from the University of the Philippines-Philippine General Hospital (UP-PGH) Division of Endocrinology, Diabetes and Metabolism.

Unique Problems of Diabetes Management among Patients with COVID-19

It is complacent to think that COVID-19 is just another infection that necessarily triggers higher stress conditions and the release of catecholamines and glucocorticoids,

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leading to hyperglycemia and abnormal glucose variability. While it is true that the greater majority of those affected with SARS-COV-2 will have only minor illness and will likely have only mild perturbations of their blood sugar levels, it appears that there are emerging novel aspects of hyperglycemia among those with COVID-19.

One of these unique features is the observation of very high insulin requirements among those with a severe course of the infection, even among those who are not on glucocorticoids. We have observed this even in the cohorts of patients whom we have seen at the PGH, necessitating high doses of insulin given intravenously. According to a recent publication in the Lancet, it appears that the extent of insulin resistance in patients with COVID-19 and diabetes appears to be disproportionate compared with critical illness from other conditions.[8]

There are also reports of a greater incidence of diabetes emergencies among persons with diabetes and COVID-19. It is already established that the virus gains entry to cells through an endocrine pathway, the Angiotensin-Converting-enzyme-2 (ACE2) receptor. Cellular damage can be caused by both acute and chronic hyperglycemia, as the former causes the up-regulation of ACE2 expression facilitating viral entry. Chronic hyperglycemia, on the other hand, causes reduced expression of ACE2 potentially through glycosylation, making the cells vulnerable to the cell-damaging effects of the virus. ACE2 is recognized to have anti-inflammatory and anti-oxidant functions.[9] The pancreatic beta-cells are known to express the ACE2 receptors suggesting (although without yet direct human verification) that the COVID-19 infection can induce new-onset diabetes by beta-cell damage. This could potentially then cause insulin deficiency, explaining the observations of both the UK and Italian investigators of frequent cases of severe diabetic ketoacidosis (DKA) and even atypical ketosis among persons with Type 2 diabetes, at the time of hospital admission.[9-11]

Finally, hypoglycemia (at least one episode of BG <3.9 mmol/L) has been noted in around 10.3% of patients with COVID-19 and diabetes in Wuhan, China.[12] Some of the risk factors for hypoglycemia may include the development of acute renal failure, interruptions in feeding whenever patients are put on prone position as part of the management of respiratory distress, and the use of chloroquine or hydroxychloroquine which are known to cause hypoglycemia as a side effect. This underscores the importance of routinely monitoring the capillary blood glucose of patients started on these drugs.[13] Hypoglycemia has been shown to mobilize pro-inflammatory monocytes and increase platelet reactivity, contributing to a higher cardiovascular mortality in patients with diabetes.[14] These mechanisms may interact with chronic inflammation, increase coagulation activity, further impair immune response and with potential direct pancreatic damage by SARS-CoV-2, may explain the underlying pathophysiological mechanisms contributing to the increased morbidity and mortality of COVID-19 in people with diabetes.[15]

The satisfactory control of diabetes, with avoidance of both hyperglycemia and hypoglycemia is therefore critical in preventing morbidity and mortality among diabetics with COVID-19 infection.

SPECIFIC RECOMMENDATIONS

1. What do we assess at the emergency room?

- Routine point of care testing for blood sugar should be done for all patients with COVID-19 to rapidly identify new cases of diabetes and to assess blood sugar control; any random CBG >140 mg/dl (>7.8 mmol/L) should routinely be monitored within the next 24 hours.
- Urine or serum ketone determination, in all patients with known diabetes or those with admission glucose over 220 mg/dl (12 mmol/L), as COVID-19 infection causes ketosis or ketoacidosis, which may increase the length of hospital stay and mortality.[16,17]
- Identify obese patients because the interaction of diabetes and obesity increases the risk for severity of COVID-19.[18]
- Triage: Identify those with diabetic emergencies who need ICU admission

1.1 Recognition of Acute Hyperglycemic Emergencies: DKA or HHS should be considered among those with known or suspected diabetes presenting with:
- Nausea and vomiting, abdominal pain
- Signs and symptoms of dehydration, hypotension or shock
- Acid-smelling (alcohol) breath
- "Acidotic" breathing (tachypneic but with clear breath sounds)
- Altered consciousness or coma
- High blood sugar [CBG or RBS ≥250 mg/dL (13.9 mmol/L)]
- A history of Type 1 DM or being on insulin
- Precipitant risk factors such as severe infection

1.2 General Plan of Management:
See Appendix A for Management of Adult Patients with DKA or HHS.

2. What baseline laboratory tests should be done?

Baseline laboratory tests to determine glycemic control such as HbA1c (if without anemia or with acceptable hemoglobin levels), fasting blood sugar or random blood sugar should be obtained. Point-of-care testing by obtaining the capillary blood glucose level should be done upon admission. Other diagnostic examinations to determine the presence of DM-related complications should be requested such as creatinine with estimated glomerular filtration rate, urinalysis with urine albumin, glucose and ketones and 12-lead ECG.

Some studies show development of ketosis and severe insulin resistance among patients with COVID-19 and diabetes, thus laboratory tests such as serum sodium, potassium, blood urea nitrogen, chloride and arterial blood gas are important and should be done, along with blood or urine ketones. Additionally, serum albumin, phosphorus and magnesium can be taken for complete nutritional assessment, as well as calcium to assess risk for arrhythmias. Coagulation profile may be warranted,

since apart from COVID-19-related inflammatory processes, insulin resistance and Type 2 diabetes mellitus are associated with endothelial dysfunction, and enhanced platelet aggregation and activation. These abnormalities contribute to the development of a hypercoagulable prothrombotic state.[6]

3. What should be the frequency of blood sugar monitoring?

There is no reason to believe that the established guidelines and standard of care for the treatment of infections among patients with diabetes may not be extended to those who are diagnosed with COVID-19. In particular, the 2020 ADA Standards of Diabetes Care[19] recommends the following schemes for monitoring of blood glucose:

a. In hospitalized patients with diabetes who are eating, glucose monitoring should be performed before meals and at bedtime;
b. In those not eating, glucose monitoring is advised every 4–6 hours.
c. More frequent blood glucose testing ranging from every 30 min to every 2 hours is the required standard for safe use of intravenous insulin.

Special consideration must be taken for patients who have blood glucose values that are 250-300 mg/dL (>15 mmol/); for those who are critically-ill in the intensive care unit, there may be a need to start an insulin drip using a standard protocol which would require hourly monitoring. Diabetes emergencies also need to be ruled out for these severely elevated values for which more dynamic drip protocols are needed (Section 5).

Once blood sugar is controlled and glycemic targets achieved, CBG monitoring may be adjusted accordingly.

Additionally, the Philippine Society of Endocrinology, Diabetes, and Metabolism (PSEDM), in their Position Statement published March 2020[20] recommends the following:

a. Patients who have stable vital signs may be allowed to take their own blood glucose test while being visually monitored by a nurse or physician.
b. When possible, the use of continuous glucose monitoring (CGM) is encouraged to help mitigate the exposure of healthcare workers to COVID-19 cases, provided regular calibration with the standard blood glucose testing is undertaken.

4. What are the expected glycemic targets? [20-22]

The general treatment goals for patients with diabetes are to address or prevent acute glycemic decompensation, prevent or delay the development of microvascular and macrovascular disease complications, avoid adverse events like hypoglycemia, decrease mortality, and provide a smooth transition to outpatient care.

The general target blood glucose levels for hospitalized patients is around 140 to 180 mg/dl (7.8 to 10 mmol/l). Blood glucose levels >180 mg/dl (10 mmol/l) may require an increase in insulin dose.

5. When should we refer to an endocrinologist?

5.1 When caring for hospitalized patients with diabetes and COVID-19 (suspected, probable or confirmed), we recommend ROUTINE referral to endocrinology service or a specialized diabetes or glucose management team whenever possible.[19,20] This is especially true for moderate and severe cases of COVID-19 where the hyperglycemia is more likely.

5.2 Particularly, the following patients should be referred to the Endocrinology Service as soon as possible:

- Any person with Type 1 diabetes
- Known diabetes with poor blood sugar control [HbA1c ≥9% or BG values 200 mg/dl (11.1 mmol/l) and above]
- Newly-diagnosed diabetes
- Elderly with diabetes
- Known patient with diabetes on insulin therapy
- Pregnant women with diabetes (overt, gestational or pre-gestational diabetes)
- Known or suspected hyperglycemic or hypoglycemic emergencies.
- Known patients with diabetes with multiple comorbidities such as chronic kidney disease, heart failure or previous acute coronary syndrome, stroke, peripheral arterial disease/prior amputation.

6. Management of Hyperglycemia and Associated Metabolic Conditions [23,24]

Hydration and nutrition therapy are integral components of patient care, both for critical and noncritical COVID-19 patients.

6.1 Fluids / Hydration (for those allowed oral intake with no prescribed limitations):

- Approximately 3 liters of fluid intake per day
- Optimal fluids: clear liquids with calories and protein, oral rehydration solutions or low glucose sports drinks
- Fluid limitation and caution on hydration is advised for those with Acute Respiratory Distress Syndrome (ARDS)/ Severe Acute Respiratory Infection (SARI)/ Heart Failure/ Acute Kidney Injury or Chronic Kidney Disease.

6.2 Medical Nutrition Therapy: Equal caloric distribution per meal throughout the day is recommended with the following guidance:

- Total Caloric Requirement: Generally computed as 25-30 kcal/kg per day with specific recommendations for the critically and those at risk of refeeding syndrome (Appendix B)
- Protein: ≥1 gram/kg per day

- The nutritional needs of patients should be optimized through a multi-disciplinary team of clinical nutritionists, dieticians and specialized physicians.

See Appendix B1 and B2 for Guidance on Nutrition Therapy for Adults with confirmed or suspected SARS-COV-2 Infection (PhilSPEN and ESPEN Guidelines)

6.3 Should oral antidiabetic agents be continued during admission? [8,25]

6.3.1 Most anti-diabetic agents may need to be discontinued during admission in favor of insulin, unless the blood sugar control is good and the COVID-19 infection is mild. This is especially true for metformin, SGLT-2 inhibitors and sulfonylureas/glinides, and probably the only exception might be DPP4-inhibitors. Take note that hydroxychloroquine (HCQ) is known to cause hypoglycemia among those on oral hypoglycemic agents or insulin, and in fact is licensed as an anti-diabetic agent in India.

6.3.1.1 Metformin may cause lactic acidosis in patients who are dehydrated. Those with severe COVID are also prone to acute kidney injury, increasing the risk for metformin-associated lactic acidosis (MALA).

6.3.1.2 Sulfonylureas such as glibenclamide, gliclazide, glimepiride and glipizide should generally be discontinued for most patients during hospitalization, because of the risk for hypoglycemia, especially when combined with insulin and hydroxychloroquine.

6.3.1.3 Sodium-glucose-co-transporter 2 (SGLT-2) inhibitors, e.g., canagliflozin, dapagliflozin and empagliflozin, may cause dehydration and predispose to acute kidney injury, and may also precipitate diabetic keto-acidosis during the hospitalization.

6.3.1.4 Glucagon-like peptide-1 receptor agonists (GLP-1 RA) including exenatide (and exenatide extended release), liraglutide, lixisenatide and semaglutide should be used with caution and are generally discontinued in the seriously ill. These agents increase risk of nausea and vomiting, which may induce dehydration.

6.3.1.5 Dipeptidyl peptidase-4 inhibitors (DPP-4i) include alogliptin, linagliptin, saxagliptin, sitagliptin and teneligliptin. There is some concern about these drugs because the DPP-4 enzyme has been identified in cell studies as a receptor for the human coronavirus-Erasmus Medical Center (hCoV-EMC), the virus that causes Middle East respiratory syndrome (MERS).[26] It is still unknown whether these mechanisms apply to COVID-19 and whether treatment with DPP4-inhibitors could potentially influence the course of the infection. However, if these mechanisms are translatable to SARS-CoV-2, then the use of these agents could potentially reduce DPP-4 concentrations and thus, present as opportunities for its treatment.[27] These drugs are also generally safe and well tolerated, and can be continued even during the hospitalization.

7. How should insulin be administered? [28]

7.1 Administration of insulin using prolonged "Sliding Scale" alone is NOT recommended as it is reactive to a pre-existing hyperglycemia and if improperly timed may lead to hypoglycemia. These oscillations are termed "glycemic variability." Both hyper- and hypoglycemia have been known to be pro-inflammatory and thus, may aggravate the already overactive inflammatory response in COVID-19. Coupled with this is the fact that large glycemic variability is *per se* predictive of high ICU mortality.[29]

7.2 Generally, the ideal regimen should be a basal-bolus regimen, with a long acting basal insulin analogue given once a day or NPH insulin given once to twice a day, plus rapid-acting or regular insulin given pre-meals.

In starting insulin, calculate the today daily dose as follows:

- Elderly (aged 70 years and above) and/or glomerular filtration rates less than 60 ml/min: 0.2 to 0.3 U/kg of body weight per day
- Adults with blood glucose concentration 7.8-11.1 mmol/L. (140-200 mg/dL): 0.4 U/kg of body weight per day
- Adults with blood glucose concentration 11.2-22.2 (201-400 mg/dL): 0.5 U/kg of body weight per day

Distribute the total calculated dose as approximately 50% basal insulin and 50% bolus insulin divided into three pre-meal doses. Adjust insulin dose(s) according to the result of bedside blood glucose measurements.

7.3 Generally, for patients who are on insulin as their previous management, basal insulin (NPH insulin 2x/day or Basal insulin analogues: Glargine U100, Detemir) should be continued and adjusted accordingly, adding on prandial insulin coverage depending on how the patient will be fed.

7.4 For severe cases of COVID-19. An expert opinion from European authors has stated that there is a, "…. liberal indication for early intravenous insulin therapy in severe courses

(ARDS, hyperinflammation) for exact titration, avoiding variable subcutaneous resorption, and commonly seen very high insulin consumption"[8] (Section 7.1).

8. Other Medications

8.1 Statins: There is also some concern for the use of statins, as its use has been associated with the up-regulation of the ACE2 receptor levels, and in fact this is the mechanism that has been used to explain the pleiotropic anti-inflammatory effect of this drug. Again, this upregulation may facilitate the entry of the virus. However, most of the experts across the world have recommended that statins should be continued among patients with diabetes and COVID-19 not only because of its long term benefit for cardiovascular disease reduction in established diabetes, but also because mechanistically its discontinuation may tip the balance towards a cytokine storm by causing rebound increases in the levels of IL-6 and IL-1.[8]

8.2 Anti-hypertensives: The fact that the SARS-COV2 uses the ACE-2 receptor as the entry point inside the cells has created some concern over the use of ACE-inhibitors and Angiotensin Receptor Blockers (ARBs). However, there appears to be no definite evidence that the use of these drugs worsens the outcome for those who use it. This is the position of most expert groups including the European Society of Cardiology and the Heart Failure Society of America, American College of Cardiology, American Heart Association, and even the local Philippine Society of Hypertension. These organizations strongly recommend continuation of treatment with ACE inhibitors and angiotensin 2 receptor blockers unless there are contraindications such as shock or acute kidney injury.[30,31]

8.3 Anti-platelets: Low dose aspirin or clopidogrel is typically given to persons with diabetes who are at high risk of major adverse cardiovascular events.[32,33] It is therefore reasonable that among those who are taking these drugs as maintenance medications, they should be continued during the hospitalization unless there are specific contraindications to their use especially among those with severe COVID-19 infections.

9. Special Circumstances

9.1 Identifying the critically ill patient (who is not diagnosed to be in Hyperglycemic Emergency) who may require an insulin drip protocol

The following are the indications for those who may require an Insulin Drip:

- CBG ≥180 mg/dl on 2 consecutive CBG, and
- On (prolonged) NPO or on Total Parenteral Nutrition (TPN), or
- Severe cases of COVID-19 (SARI) or critically ill with shock and on inotropes not diagnosed as DKA and HHS

The Yale insulin infusion protocol was modified because of the revision of the blood glucose targets to a higher range of 140-180 mg/dl among critically ill patients. These changes were made due to findings of previous RCTs with blood glucose levels of 80 -100 mg/dl showed increased mortality rate and increased risk of hypoglycemia. The modified Yale protocol was validated among patients admitted to ICU units in UP-PGH and has been in use since 2009. It is considered to be effective with shorter median time to normoglycemia (70-180 mg/dl) (4 vs 12 hours) and greater mean percentage of total measurements blood glucose level within normoglycemic range (BG 70-180 mg/dl) (73.84%±17.68% vs 51.74%±25.03%, $p<0.0001$) as compared to historical control group. It is also considered to be safe with rare episodes of hypoglycemia and with no episodes of severe hypoglycemia.[34,35]

See Appendix C for the PGH Modified Yale Insulin infusion protocol.

9.2 Glucocorticoid Use in COVID-19

Glucocorticoids (GCs) have a potent anti-inflammatory effect and antifibrotic properties, thus, their use was explored for moderate to severe COVID-19 infections. However, there are no published randomized controlled trials to support its use due to lack of effectiveness and possible harm by delaying viral clearance and risk of concomitant infections. A conditional recommendation of use may be made for patients with concomitant asthma exacerbation or COPD or sepsis/septic shock refractory to vasopressors and fluids due to the possibility of critical illness-related corticosteroid insufficiency (CIRCI).[13,36-38]

9.2.1 The development of insulin resistance manifests mainly with postprandial hyperglycemia, and varies depending on the type of steroid used. The use of methylprednisolone has been proposed for severe COVID-19 infection.[32] It is classified as an intermediate-acting GCs, with a peak of action 4-6 h following administration. Its effect on glucose levels is mainly during the afternoon and night without much effect on fasting glucose when administered in a single dose but glucocorticoids cause persistent hyperglycemia when administered in divided doses.

9.2.2 Management of hyperglycemia among those being given glucocorticoids[39]

9.2.2.1 Capillary glucose monitoring should commence from the start of steroid treatment. Hyperglycemia develops within 1-2 days of initiation of steroid therapy.

- In nondiabetic patients who maintain glucose levels <140 mg/dL without insulin requirements for 24-48 h, glycemic monitoring can be discontinued.
- In patients with glucose levels >140 mg/dL with persistent insulin requirements, a basal/bolus subcutaneous insulin scheme may be started (Section 6.5).

9.2.2.2 Among those who require insulin, steroid-induced hyperglycemia will typically have a much higher prandial insulin requirement compared those who are not on steroids.

9.2.2.3 In patients with severe and/or persistent hyperglycemia despite a subcutaneous regimen, insulin by infusion pump should be started (Appendix C).

CONCLUSIONS

These recommendations are meant to be guides in managing patients with diabetes and COVID-19 infection. They are not meant to replace sound judgment and individualized therapy according to the specific patient circumstances. These guidelines are also a work in progress and feedback from other experts, scientists and clinicians are appreciated so that this manuscript can continue to be revised and improved.

Finally, these recommendations are evolving as we continue to understand the pathology of the disease and how persons with diabetes are affected by this virus.

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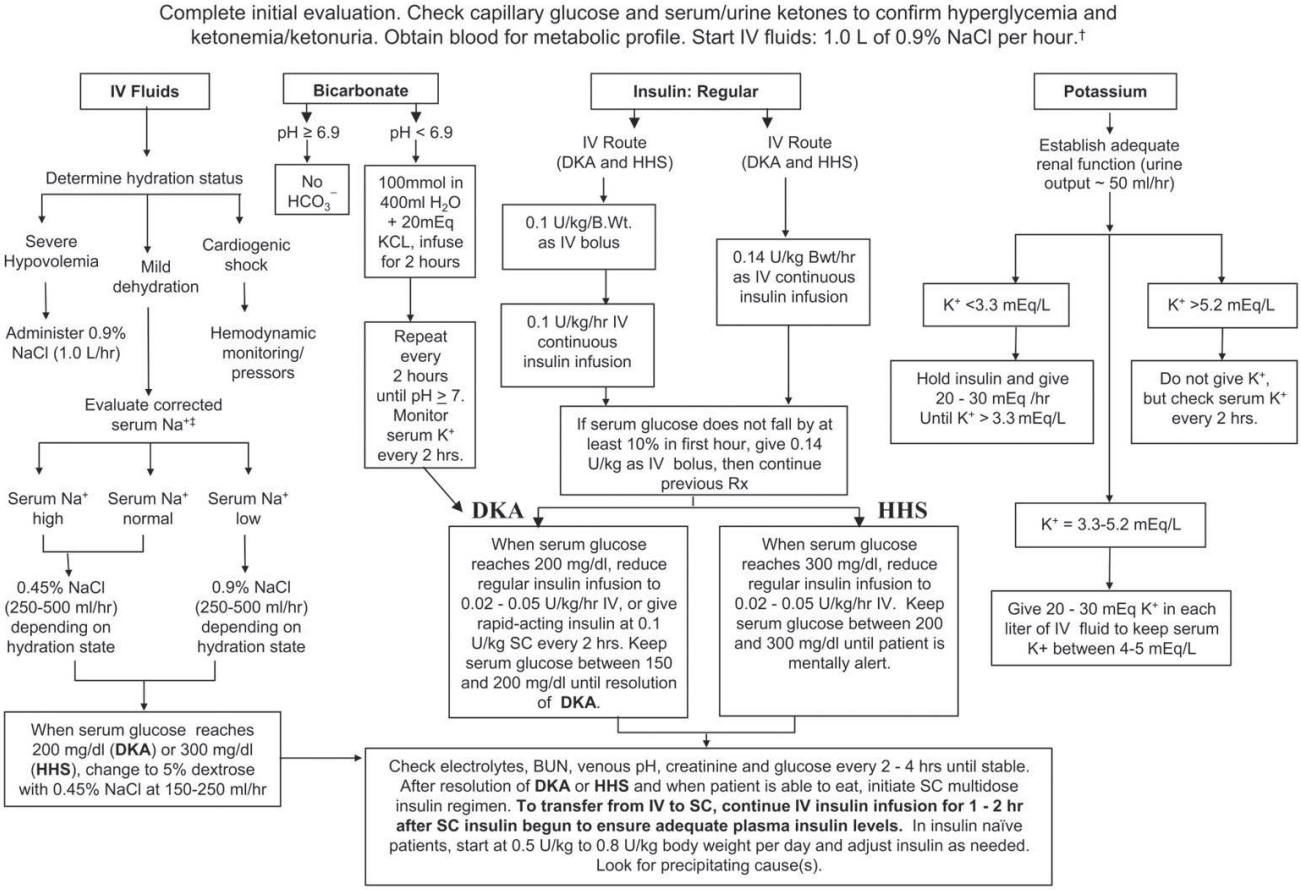
APPENDICES

Appendix A. Protocol for Management of Adult Patients with Diabetic Ketoacidosis or Hyperglycemic Hyperosmolar State[40]



Protocol for management of adult patients with DKA or HHS. DKA diagnostic criteria: blood glucose 250 mg/dl, arterial pH 7.3, bicarbonate 15 mEq/l, and moderate ketonuria or ketonemia. HHS diagnostic criteria: serum glucose >600 mg/dl, arterial pH >7.3, serum bicarbonate >15 mEq/l, and minimal ketonuria and ketonemia. †15–20 ml/kg/h; ‡serum Na should be corrected for hyperglycemia (for each 100 mg/dl glucose 100 mg/dl, add 1.6 mEq to sodium value for corrected serum value). (Adapted from ref. 13.) Bwt, body weight; IV, intravenous; SC, subcutaneous.

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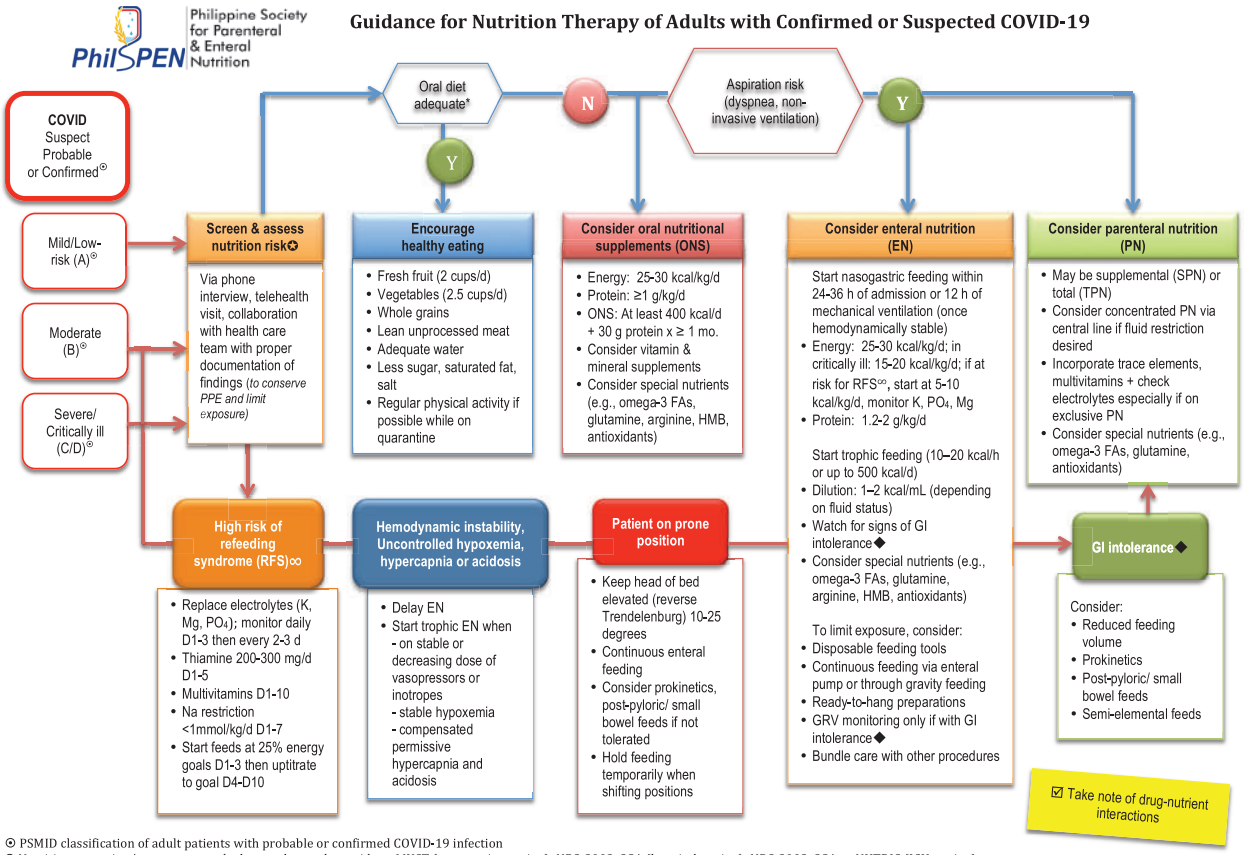
Appendix B.1. Philippine Society for Parenteral and Enteral Nutrition Guidance for Nutrition Therapy[24]



⊙ PSMID classification of adult patients with probable or confirmed COVID-19 infection
✪ Nutrition screening/assessment tools that can be used as guides – MUST (community setting); NRS-2002, SGA (hospital setting); NRS-2002, SGA or NUTRIC (ICU setting)
* Adequate - >/=75% of total energy requirement
∞ Risk factors for refeeding syndrome (RFS): BMI <18.5 kg/m², unintentional weight loss >10% past 3-6 mos., little or no nutritional intake for >5 days, history of bariatric surgery, short bowel syndrome, alcohol abuse or drugs (incl. insulin, chemotherapy, antacids or diuretics), low baseline levels of potassium, phosphate or magnesium; other patients at high risk – tumor patients, frail elderly with chronic debilitating disease
◆GI intolerance - abdominal pain, nausea, diarrhea, abdominal distention, dilated bowel loops with air/fluid levels, pneumatosis intestinalis, increasing NG outputs

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Appendix B.2. European Society of Parenteral and Enteral Nutrition Practical Guidance for Nutritional Management of Individuals with SARS-CoV-2 Infection (Adapted)[23]

1. Check for Malnutrition
Patients who are at risk for worst outcomes and higher mortality following infection with SARS-COV-2, namely older adults and polymorbid individuals, should be checked using the MUST* Criteria or for hospitalized patients, the NRS-2002** criteria.

INDIVIDUALS AT RISK OR INFECTED WITH SARS-COV-2

2. Optimization of Nutritional Status
Subjects with malnutrition should undergo diet counseling from experienced professionals.

3. Supplementation with Vitamins and Minerals
Subjects with malnutrition should ensure supplementation with vitamin A, vitamin D and other micronutrients.

4. Regular Physical Activity
Patients in quarantine should continue regular physical activity while taking precautions.

5. Oral Nutrition Supplements (ONS)
ONS should be used whenever possible to meet patient's needs, when dietary counseling and food fortification are not sufficient to increase dietary intake and reach nutrition goals.

6. Enteral Nutrition (EN)
In patients, whose nutritional requirements cannot be met orally, EN should be administered. Parenteral nutrition (PN) should be considered when EN is not indicated or insufficient.

ICU PATIENTS INFECTED WITH SARS-COV-2

7. Medical Nutrition in Non-Intubated ICU Patients
If the energy target is not reached with an oral diet, ONS should be considered first and then EN treatment. If there are limitations for the enteral route it could be advised to prescribe peripheral PN in the population not reaching energy-protein target by oral or enteral nutrition.

8. Medical Nutrition in Intubated ICU Patients I
EN should be started through a nasogastric tube; post-pyloric feeding should be performed in patients with gastric intolerance after prokinetic treatment or in patients at high-risk of aspiration.

9. Medical Nutrition in Intubated ICU Patients II
In ICU patients who do not tolerate full dose EN during the first week in the ICU, initiating parenteral nutrition (PN) should be weighed on a case-to-case basis.

10. Nutrition in ICU Patients With Dysphagia
Texture-adapted food can be considered after extubation. If swallowing is proven unsafe, EN should be administered.

Nutritional management in individuals at risk for severe COVID-19, in subjects suffering from COVID-19, and in COVID-19 ICU patients requiring ventilation. For details, see text.

* MUST Criteria: is a five-step screening tool to identify adults who are malnourished, at risk of malnutrition (undernutrition), or obese. It can be downloaded for free at this website: www.bapen.org.uk

** NRS-2002 is a method endorsed by the ESPEN, to detect the presence of undernutrition and the risk of developing undernutrition in the hospital setting. It contains the nutritional components of MUST, and in addition, a grading of severity of disease as a reflection of increased nutritional requirement.

Appendix C. PGH Modified Yale Protocol for Insulin Infusion[35]

1. INSULIN INFUSION: Mix 1 unit Human Regular Insulin per 1 cc 0.9% NaCl. Administer in infusion pump (in increments of 1 unit/h).
2. PRIMING: Flush 50 cc of infusion through all IV tubings before infusion begins (to saturate the insulin binding sites in the tubing).
3. THRESHOLD: Start IV insulin if BG is **>180 mg/dl.**
4. TARGET BLOOD GLUCOSE LEVELS: **140-180 mg/dL**
5. BOLUS & INITIAL INSULIN INFUSION RATE: If initial BG >180mg/dl but <300 mg/dl, divide by 100, then round to the nearest 1 unit for initial drip rate, (don't give IV bolus insulin). If initial BG is ≥300 mg/dl, divide by 100 for bolus and initial drip rate.

BLOOD GLUCOSE MONITORING

1. Check blood glucose hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary blood glucose (i.e., fingersticks) may be inaccurate and obtaining blood sample from an indwelling vascular catheter may be preferable.
2. Then check blood glucose q 2 hours; once stable x 12-24 hrs. Blood glucose checks can then be spaced to q 4 hrs. IF:
   a. no significant change in clinical condition AND
   b. no significant change in nutritional intake
3. If any of the following occur, consider the temporary resumption of hourly blood glucose monitoring, until blood glucose is again stable (2-3 consecutive BG values within target range):
   a. any change in insulin infusion rate (i.e., blood glucose out of target range)
   b. significant changes in clinical condition
   c. initiation or cessation of pressor or steroid therapy
   d. initiation or cessation of renal replacement therapy (dialysis, CVVH, etc.)
   e. initiation, cessation, or rate change of nutritional support (TPN, PPN, tube feedings, etc.) initiation, cessation, or rate change of nutritionals (TTPN, PPN, tube feedings, etc.)

CHANGING THE INSULIN INFUSION RATE

If BG <50 mg/dL:
D/C INSULIN INFUSION:
Give 1 amp (25 g) D50 IV; recheck blood glucose q 15 minutes.

- When blood glucose ≥ 100 mg/dL, wait 1 hour, recheck BG. If still ≥ 100 mg/dL, restart infusion at 50% of most recent rate.

If BG 50-69 mg/dL:
D/C INSULIN INFUSION:
If symptomatic (or unable to assess), give 1 amp (25 g) D50 IV; recheck blood glucose q 15 mins.
If asymptomatic, give ½ amp (12.5 g) D50 IV; recheck BG q 30 mins.

- When BG ≥ 100 mg/dl, wait 1 hour, recheck BG. If still ≥ 100 mg/dl, restart infusion at 75% of most recent rate (round off to the nearest 1 unit)

If BG 70-99 mg/dL:
D/C INSULIN INFUSION FOR 30 mins:
If repeat CBG ≥ 100 mg/dl, restart insulin infusion at 75% of most recent rate (round off to the nearest 1 unit).
If repeat CBG is still <100 mg/dl, re-chek CBG after 1 hour., resume insulin infusion only at 75% of most recent rate once repeat CBG is ≥ 100 mg/dl (round off to the nearest 1 unit).

If BG ≥100, go to Step 2

BG 100 - 139 mg/dl	BG 140 - 179 mg/dl	BG 180 - 249 mg/dl	BG ≥ 250 mg/dl

STEP 2: Determine the RATE OF CHANGE from prior BG level - identifies a CELL in the table. Then move right for the INSTRUCTIONS:

(Note: If the last BG was measured 2-4 hrs. before the current BG, calculate the hourly rate of change.)

BG 100 - 139 mg/dl	BG 140 - 179 mg/dl	BG 180 - 249 mg/dl	BG ≥ 250 mg/dl	Instructions
		BG ↑ by: >40 mg/dl/hr	BG ↑	↑ Infusion by "2Δ"
	BG ↑ by: >20 mg/dl/hr	BG ↑ by: 10 - 40 mg/dl/hr OR BG unchanged	BG unchanged OR BG ↓ by: 1 - 40 mg/dl/hr	↑ Infusion by "Δ"
BG ↑	BG ↑ by: 10 - 40 mg/dl/hr OR BG unchanged OR BG ↓ by: 1 -20 mg/dl/hr	BG ↓ by: 1 - 40 mg/dl/hr	BG ↓ by: 41-80 mg/dl/hr	No infusion change
BG unchanged OR BG ↓ by: 1 -20 mg/dl/hr	BG ↓ by: 21 - 40 mg/dl/hr	BG ↓ by: 41 - 80 mg/dl/hr	BG ↓ by: 81 - 120 mg/dl/hr	↓ Infusion by "Δ"
BG ↓ by: > 20 mg/dl/hr * see below	BG ↓ by: > 40 mg/dl/hr	BG ↓ by: > 80 mg/dl/hr	BG ↓ by: > 120 mg/dl/hr	Hold x 30 mins., then ↓ Infusion by "2Δ"

* **D/C INSULIN INFUSION**, check CBG after 30 mins, when BG is ≥100 mg/dl, restart infusion at 75% of most recent rate.

CHANGES IN INFUSION RATE ("Δ ") are determined by the current rate[35]

Current Rate (units/hr)	Δ = rate change (units/hr)	2Δ = 2x rate change (units/hr)
<3	0.5	1
3 - 6	1	2
6.5 – 9.5	1.5	3
10 - 14.5	2	4
15 - 19.5	3	6
20 - 24.5	4	8
≥25	≥5	10 (consult MD)

Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

In-patient Care for People with COVID-19 and Diabetes in Myanmar

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Key words: recommendations, in-patient, Myanmar

INTRODUCTION

These recommendations are synthesized from international references coupled with expert advice from endocrinologists and doctors caring for patients with COVID-19, to help guide physicians in Myanmar in managing persons with diabetes who are admitted.

UPON ADMISSION

Blood glucose should be checked in all patients admitted to the hospital. Additionally, blood ketone testing should be done in all patients with diabetes especially those with an initial blood glucose greater than 12 mmol/L (Table 1).[1] COVID-19 disease precipitates atypical presentations of diabetic emergencies such as mixed diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS)], and thus, we need to be alert for these conditions. Laboratory criteria for hyperglycemic emergencies are presented in Table 2. Hyperglycemia may also be caused by new onset diabetes, sepsis, missed treatments for diabetes and systemic steroids.[1]

Table 1. Ketone levels and appropriate steps

Blood ketones	Interpretation/recommendation
<0.6 mmol/L	Safe
1.5 to 2.9 mmol/L	Increased risk for DKA[a]
≥3 mmol/L	Check venous blood gas pH and bicarbonate

[a]DKA, diabetic ketoacidosis
Adapted[1]

Table 2. Criteria for diagnosis of hyperglycemic emergencies

Parameter	DKA[a]	HHS[b]
Blood glucose	>11 mmol/L[c]	≥30 mmol/L
Ketones	Blood ≥3 mmol/L, Urine ≥+2	–
pH	<7.3	>7.3
Serum bicarbonate	<15 mEq/L	–
Serum osmolality	–	>320 mOsm/kg

[a]DKA, diabetic ketoacidosis
[b]HHS, hyperglycemic hyperosmolar state
[c]can be <11 mmol/L if on sodium glucose cotransporter 2 (SGLT2) inhibitor treatment, pregnant and/or has severe COVID-19 infection
[d]calculated as (2 x Na) + glucose + urea
Adapted[1]

BLOOD GLUCOSE TARGETS

The target glucose range for majority patients with diabetes whether critically ill or not, is 7.8 to 10.0 mmol/L (140 to 180 mg/dL),[2,3] keeping in mind that individualization of goals should still be done in consideration of the severity of the infection and the age of patients (Table 3).

Table 3. Individualized glycemic recommendations

Patient Profile	Fasting blood glucose	2-hour postprandial or random blood glucose
Mild presentation of COVID-19	4.4 -6.1 mmol/L	6.1 - 7.8 mmol/L
Severe or critically ill COVID-19	7.8 - 10.0 mmol/L	7.8 - 13.9 mmol/L
Older with mild COVID-19 or use of glucocorticoids	6.1 - 7.8 mmol/L	7.8 - 10.0 mmol/L

Adapted[4]

FREQUENCY OF GLUCOSE MONITORING

Among patients who are able to eat regularly, glucose monitoring should be performed before each meal, and more frequently e.g., every 4-6 hours among those who are not eating. In resource limited settings, blood glucose (BG) monitoring two times a day is satisfactory.

INSULIN ADVICE

In all diabetes patients, previous insulin use should always be inquired. Among persons with known type 1 diabetes, basal insulin should always be continued, as DKA may result with insulin discontinuation.

Subcutaneous or intravenous insulin should be initiated for those with persistent blood sugar elevation at levels ≥10.0 mmol/L (≥180 mg/dL).[3] Those who are very ill or unable to eat may benefit from intravenous insulin infusion. An alternative subcutaneous (SC) insulin regimen may be used in mild to moderate DKA, or in the absence of an infusion pump for intravenous insulin.[1]

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In the intensive care unit (ICU), continuous intravenous insulin infusion is the best method of delivery, with blood glucose monitoring every 2 hours. A basal + correction regime is an alternative. Significant insulin resistance has been seen in people with type 2 diabetes in ICU settings, and intravenous insulin protocols may need amending, as there have been reports of patients requiring up to 20 units/hour.

Outside of the ICU, SC short or rapid-acting insulin may be given before meals if the patient is able to eat, or every 6 h if no meals are given or if the patient is receiving continuous enteral/parenteral nutrition.[5] Basal insulin or a basal plus correction regimen is preferred. If the patient is eating, insulin injections are scheduled before meals. For those who have poor oral intake, a safer procedure might be to administer the rapid-acting insulin immediately after eating. A recommended strategy for insulin initiation is given in Table 4.

Table 4. Calculation of the total daily insulin dose

Age, year	eGFR[a], mL/min/1.73 m^2	BG[b] on admission, mg/dL	Total daily dose of insulin, unit/kg/day
>70	<60		0.2 to 0.3
<70	>60	140–200	0.4
<70	>60	201–400	0.5

[a] eGFR, estimated glomerular filtration rate; [b] BG, blood glucose
Adapted[6]

The calculated total daily dose is distributed as 50% basal insulin and 50% correctional insulin. Basal insulin is given once (detemir/ glargine) or twice (NPH/ detemir) daily, being injected at the same time each day.

Correction with rapid-acting insulin analog or regular insulin

Subsequently, insulin doses are adjusted according to the results of bedside BG measurements (Table 5). If a patient is able and expected to eat all or most of his/her meals, correction doses are given before each meal and at bedtime following the usual column. If a patient is not able to eat, the correction doses are given every 6 hours following the insulin-sensitive column.

Table 5. Recommended correction doses of insulin

Blood glucose, mg/dL	Additional correction dose		
	Insulin-sensitive	Usual	Insulin-resistant
141-180	2	4	6
181-220	4	6	8
221-260	6	8	10
261-300	8	10	12
301-350	10	12	14
351-400	12	14	16
>400	14	16	18

Adapted[6]

If the fasting and premeal plasma glucose are persistently above 140 mg/dL in the absence of hypoglycemia, it is recommended to increase the selected insulin scale from insulin-sensitive to usual, or from usual to insulin-resistant.

If a patient develops hypoglycemia (defined as BG <70 mg/dL), regular or rapid-acting insulin should be decreased and the patient category classified from insulin-resistant to usual, or from usual to insulin-sensitive.

FLUID MANAGEMENT

The recommended fluid replacement for hyperglycemic emergencies may be individualized in patients with evidence of pulmonary edema or myocarditis. The recommended amount of required intravenous fluids may be reduced to half to avoid exacerbating adult respiratory distress syndrome. Involvement of the critical care team is also recommended. In situations where ketosis is observed to persist despite appropriate treatment, the use of 10 to 20% glucose may be considered.[1]

OTHER ANTI-DIABETIC AGENTS

Sulphonylureas are known as a drug class to increase the risk of hypoglycemia and are thus, generally avoided in hospitalized patients with severe medical illness.[1]

The use of dipeptidyl peptidase-4 (DPP-4) inhibitors in individuals with COVID-19 and concomitant clinically significant volume depletion or sepsis may necessitate dosage adjustment due to a reduction in renal function.[7]

SGLT2 inhibitors and metformin should be discontinued in all admitted patients.[1]

Although glucagon-like peptide-1 receptor agonists (GLP-1RA) safely lower blood glucose in short term studies of ventilated patients with critical illness, there is insufficient experience in critically ill subjects to make therapeutic recommendations for use of these agents in the context of coronavirus infection.[7]

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

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FEATURE ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Research in the Time of COVID-19: Challenges of Research Ethics Committees

Marita Reyes

National Ethics Committee

Abstract

Compliance with ethics guidelines for research are even more critical in the time of emergency public health situations such as a pandemic. Underpinned by the principles laid out in the 1979 Belmont report, conduct of research at any time should focus on respect for persons, beneficence and justice. Certain Standard Operating Procedures (SOPs) in research ethics committees may be revised to provide a quicker turn-around and timely review. Key elements in effective review of studies include rigorousness, responsiveness and timeliness. It is crucial to recognize that ethics review committees share responsibility with researchers and its institutions, funding agencies and regulatory agencies for upholding ethical principles in research at all times.

Key words: research ethics, ethical standards, global health emergencies,ethics review, health research

INTRODUCTION

Ethics guidelines for research in many countries including the Philippines are underpinned by the principles presented in the 1979 Belmont Report[1] which are respect for persons, beneficence and justice. These principles basically describe the duties of researchers toward their study participants whose human rights, dignity and welfare have to be protected, who should benefit for being involved in the study or, at least, not be harmed, and who should be fairly treated.

Emanuel et al.,[2] also recommended a set of requirements for evaluating clinical research studies that have since then been adopted for studies involving human participants even for non-clinical research. These requirements are:

1. Value-contribution to scientific knowledge and relevance to community problems;
2. Scientific soundness-rigorous methodology;
3. Fair subject selection-inclusion criteria based on scientific objectives and potential for distribution of burdens and benefits;
4. Favorable risk-benefit ratio-potential benefits for individuals and knowledge gains outweigh risks;
5. Independent review-review and approval by committees with unaffiliated individuals;
6. Informed Consent-participants provide voluntary consent after being adequately informed about the study; and
7. Respect for enrolled subjects-protection of the privacy rights, dignity and well-being of participants.

Thus, research ethics committees evaluate research proposals by determining the extent of compliance of the study to these criteria before the grant of an ethical clearance.

To ensure consistency, transparency and quality in the evaluation of study proposals and in monitoring these during implementation, research ethics committees have been required by the Philippine Health Research Ethics Board (PHREB) to put in place standard operating procedures (SOPs). These SOPs include provisions on selection of members, conduct of meetings (frequency and quorum policies), protocol and Informed consent assessment procedures, and forms. Regular meetings are usually scheduled once a month and the shortest review time from receipt of complete dossiers to notification of ethics committee assessment (or approval) is four (4) weeks.[3]

Since 2005, the Philippines has established a national system for research ethics review that includes accreditation policies and procedures. Only Level 3 accredited research ethics committees are authorized to review clinical trials of investigative new drugs for registration at the Philippine Food and Drug Administration. Level 2 committees review mostly academic-initiated research while Level 1 committees are newly established committees that are closely monitored. As of February 2020, the Philippines has 102 accredited research committees, 46 of which are in level 3 including the Single Joint Review Ethics Board under the auspices of the Department of Health, that reviews multi-site clinical trials in coordination with the ethics committees of involved trial sites.

The challenge to ethics review committees in the time of COVID-19 is how to review research during this

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public health emergency situation when research results are needed as soon as possible because the generated knowledge could be essential to the immediate response of the health system, e.g., diagnosis; management; prevention of illness, disability and death; and to support recovery.

This paper will attempt to answer the following important questions that are related to doing research in the time of the pandemic. Are standard ethics requirements for review and conduct of research different in public health emergencies? How is this justified? Could SOPs be revised to suit the demands for rapid review? How can review turn-around time be shortened? In an environment of panic, fear, and uncertainty, how does one invite a patient to join a study that does not ensure immediate benefit to him or her? In a country of low resource, how does one ensure that the research intervention is not presumed as the treatment ("therapeutic misconception") by the patient being recruited into a clinical trial? Should the ethics review committee consider the compassionate use of an unregistered drug or the off-label use of one that is registered, as akin to research and, thereby, subject these to an ethics review like a drug trial? In summary, should the application of ethical principles be less restrictive to allow more leeway for emergent scientific pursuits and, could established standard operating procedures be modified for rapid review?

Conveniently, relevant information regarding the above questions can be found from several references:

1. WHO Ethical Standards for Research during Public Health Emergencies: Distilling Existing Guidance to Support COVID-19 R&D[4]
2. Nuffield Report on Global Health Emergencies: Ethical Issues[5]
3. the Report of Saxena et al., on Ethical Preparedness: facilitating ethics review during outbreaks, Recommendations from an Expert Panel[6]
4. PHREB Resolution on conduct of ethics review during COVID-19.[7]

APPLICATION OF THE PRINCIPLES OF RESEARCH ETHICS IN EMERGENCY PUBLIC HEALTH SITUATIONS

All of the references are united in emphasizing that during public health emergencies, the ethical principles and values embodied in international research guidelines must be upheld. Specifically, Reference #1 stated that, "In all cases, including emergencies, our obligation is to uphold internationally accepted ethical standards. However, these universal ethical standards may be adapted to particular circumstances and contexts"[4] The nature and extent of adaptation is where more clarity in application is needed. It is in this regard that Reference #2 provided a moral compass that consists of three important values with brief contextual explanations which are paraphrased for brevity as follows:

1. **Equal respect**. This is defined as treating others as moral equals, including respecting their dignity, humanity and human rights; an openness and willingness to engage in dialogue and deliberation, on terms of equality and equal recognition; and may also be expressed as mutual respect, emphasizing the two-way nature of relationship. Additionally, this also means being sensitive to cultural plurality and diversity.

2. **Helping reduce suffering**. These values is expressed as acting in accordance with fundamental duties, founded on solidarity and humanity, to help those in need, or suffering from disease; and thus, conducting research that can contribute to improving the effectiveness of the emergency response, both at the time and for the future. This is the whole point of doing research. It has implications on publishing both negative and positive results, and those that work well and those that do not. It is also important to recognize competing demands because of other social goals like addressing poverty, malnutrition, gender issues, antimicrobial resistance, and loss of biodiversity. It is also important to realize that if people's basic needs (food, shelter, security and basic health needs) are not met, recruitment for the research is hardly respectful nor fair.

3. **Fairness**. This includes both duties of non-discrimination in the treatment of others, and of the equitable distribution of benefits and burdens. This also includes fairness in the prioritization of research and consideration of whose interests are being served by that research, fairness in the design of research, including inclusion criteria; fairness in the recruitment and treatment of research participants; fair treatment of front-line researchers and of other local collaborators; and fair distribution of the benefits of the research.

Thus, going back to the questions we posed earlier: in an environment of panic, fear, stress, distrust and frustration – how does one invite a patient to join a study that does not ensure immediate benefit to him? The guidance lies in establishing mutual respect, an openness to a dialogue regarding the objectives of the research and how their participation could generate knowledge that may help solve present and future problems. This, without forgetting that basic needs of the potential participants should have been met.

The same approach is important in ensuring that in a country of low resource, one can ensure that the research intervention (which is experimental) is not presumed as the intended treatment by the patient being recruited into a clinical trial. This therapeutic misconception can be overcome by a careful and respectful explanation of the nature of the study and the uncertainty of treatment benefit, and by giving the prospective subject the space to articulate his/her own fears, frustrations and expectations. In the recently launched multi-country WHO Solidarity Clinical Trials in connection with COVID where several drugs are being tested for efficacy and safety, it will be good to ascertain whether the COVID-19 patients can have a choice of which trial to be a participant and/or if they have a choice of whether to be in the experimental or control group. I would advise the ethics review committee to allow this while enjoining the researchers that such choices in the data and making provisions as a subset in the analysis.

The compassionate use of an unregistered drug or the off-label use of one that is registered is dealt with in provision

#37 on "Unproven Interventions in Clinical Practice," of the 2013 Declaration of Helsinki.[8] It states that, **"***In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, reestablishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available***."** This means that compassionate use of unregistered drug or the off-label use of one is considered as part of clinical practice rather than research. However, it requires expert advice, informed consent, and a diligent recording of clinical data, and should subsequently proceed into a clinical trial if possible.

COULD SOPs BE REVISED TO SUIT THE DEMANDS FOR RAPID REVIEW? HOW CAN REVIEW TURN-AROUND TIME BE SHORTENED?

In insisting that independent ethical review provides an important safeguard for research participants, and that the *standard* of review should not be compromised in any way by the emergency context, Reference #2 explains that the *processes* used to achieve that scrutiny, on the other hand, can and should be adapted as necessary to the context, including scope for expediting urgent applications, with flexible means of communication and deliberation.

Processes for ethics review of researches during public health emergencies were further elaborated as the subject of deliberation in a two-day workshop convened in March 2018 by the World Health Organization Global Health Ethics Team and the African coalition for Epidemic Research, Response and Training, with representatives of National Ethics Committees.[3] The recommendations are reported in Reference #3. The recommendations revolved around the need for preparedness of ethics review systems during public health emergencies. They advised that a formal national standard operating procedure for emergency response ethical review be put in place. A procedure that can be unique during emergencies is the conduct of a pre-review of generic protocols. However, there was no clear agreement on terminology and expectations. Establishment of mechanisms for multi-country emergency ethical consultation, and of procedures for communication between national ethics committees and other oversight bodies and public health authorities were deemed beneficial. They were considered to be so important that they should be promoted. Furthermore, ethics committees are encouraged to initiate the idea of data sharing and sample sharing among researchers, and to develop a plan that outlines the benefit to the population from which data and samples are to be drawn.

When the Philippine Health Research Ethics Board released its 2017 National Ethical Guidelines for Health and Health-related Research Health, it included a special set of guidelines for research involving populations in disaster situations. The guidelines were intended for doing "research among populations that have experienced extreme stress due to natural calamities, armed conflict, or other forms of violence."[3] The group of authors and contributors did not have in mind a situation like the COVID-19 pandemic. Thus, in response to the current public health crisis, PHREB issued a resolution (Reference #4) giving interim authority to all RECs to suspend the application of pertinent provisions of their SOPs to the extent necessary to enable them to conduct online meetings to review research protocols and for other purposes, provided that:

1. Only RECs with level 3 accreditation may review and approve clinical trial protocols;
2. Deviation from the RECs' SOPs is limited primarily to the REC Members' online presence instead of physical presence and to related provisions such as the acceptance of electronic rather than hardcopy documents;
3. Deviations and proceedings will be properly recorded in the minutes of meetings;
4. RECs give due consideration to the risks to privacy and confidentiality arising from the conduct of online meetings and the electronic transmission of documents;
5. RECs will promptly report to PHREB when such meetings are conducted and what challenges are encountered;
6. RECs consider immediate amendments to their SOPs to address the issues that are now being encountered because of the national health emergency and in anticipation of similar future contingencies.

AN EXAMPLE OF A RESEARCH ETHICS COMMITTEE FUNCTIONING IN THE TIME OF COVID-19

Zhang et al.,[9] described the operations of an ethics review committee in China from February 2 to March 7, 2020. The authors noted that the committee met 4 times in 35 days compared to the once a month conference prior to the pandemic. The committee used video conferencing to review batches of project applications which were formally reviewed by the committee secretary and forwarded to members of the committee for review prior to the meeting. Quorum during meetings was maintained, decisions were based on clear reasons and suggestions for revisions were given after full discussion. The mean time was 2.13 days from application submissions until initial review decision was made, and for applications that required modifications, the mean time was 1.81 days for resubmission to be reviewed again. Six were approved while four were disapproved. Out of the 41 studies, 31 required modification. Findings for those that needed modifications included lack of statistical basis for sample-size calculation, defective inclusion and exclusion criteria, defective efficacy and safety indicators, and insufficient risk minimization criteria. Other observations included unclear description of benefits for future patients and society, insufficient team members in key roles, necessary research equipment not available, insufficient background evidence and unsatisfactory operating procedures. Some of the more important reasons for requiring modification of the informed consent forms included incomplete description of research risks, unreasonable compensation for participant, misrepresentative language to induce participation, unclear description of participation steps, non-objective description of benefits, and insufficient explanation for alternative treatment.

Two of the studies that were disapproved had the reason that the laboratory biosafety level was inadequate.

From this report from China, one can deduce the rigorous application of research ethics principles by the committee based on the findings that required modifications. But most impressive is the very short mean time between application and release of initial review decisions. This was achieved by more frequent meetings done by videoconferencing while maintaining quorum and review by members of research documents prior to the meeting. Recommendations for revisions and justifications for disapprovals were also made after full discussions.

SUMMARY AND CONCLUSIONS

The Nuffield Report on Global Health Emergencies (Reference #2) states that the key elements in effective review of studies are **rigorousness, responsiveness and timeliness**. Rigorousness is the consistent upholding of ethical principles which are contextualized in the public health emergency through the values of equal respect, helping reduce suffering and fairness. Responsiveness does not only include timeliness, but is a characteristic of ethics committees that shows openness to adoption of innovative research designs, and to having consultations with researchers and affected communities. Timeliness can be achieved by revision of standard operating procedures in the review process that may include increased frequency of meetings, use of technology like teleconferencing, electronic submission of study documents and prior review by members.

It must also be recognized that ethics review committees are not the only ones responsible for upholding ethical principles in research. The other responsible members of the research ethics ecosystem are the researchers, funders/sponsors, regulatory agencies, research institutions and the affected communities. The ethics review committees and these stakeholders need to work together to continue to uphold ethical principles in research even during the COVID-19 pandemic.

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FEATURE ARTICLE

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Use of Facebook to Serve Information Needs of Persons with Diabetes in the Philippines amid the COVID-19 Pandemic

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Abstract

Objectives. The use of Facebook (FB) to share and gather information on diabetes is commonplace but no data is available on its use among Filipinos during the COVID-19 pandemic. We sought to determine the engagement from instructional slide decks on diabetes and its management shown on two Philippine-based FB pages under the Enhanced Community Quarantine (ECQ).

Methodology. We used Insights data from the slide decks and slide shows shown on the Philippine Society of Endocrinology, Diabetes and Metabolism's (PSEDM) public FB page and the *Endocrine Witch*'s FB page. The slide set contained a mix of mostly images and text on COVID-19 and Diabetes, dietary advice, medications and self-care in the setting of the ECQ where access to insulin, ambulatory clinics and healthy food is limited. Data was summarized in terms of post clicks, reactions, shares and comments. Total engagement rate was computed.

Results. We noted a high engagement rate (4-15%) in both public FB pages with higher engagement rates in slides shown in the Filipino language for most topics. The slides that gathered more shares and reactions were primarily those containing general information on COVID-19 and diabetes, nutrition including the safety of canned goods, as well as sick day rules.

Conclusion. In the setting of the ECQ, the use of image and text-based slide-decks on the PSEDM and *Endocrine Witch* FB pages to communicate health information yielded high engagement.

Key words: social media, health information, FB, diabetes mellitus, COVID-19

INTRODUCTION

Seventy-six million Filipinos are active social media users. Facebook is the most commonly utilized social media platform, used by 92% of all Filipinos with social media access from April 2019-April 2020.[1]

Even before the COVID-19 pandemic, Filipinos with diabetes have been using FB public support groups such as the Diabetes Health Community Support Group and the Philippine Diabetes Support Group having 8,339 and 16,564 members respectively (as of May 11, 2020). Smaller closed FB groups which are institution- or area-based like the Diabetes group of Koronadal (328 members), Knowledge and Care of Diabetes Center from Olongapo City (246 members), and Diabetes Education by Lucena Diabetes and Health Care Center (571 members), were also already formed. While a formal investigation has not been done on the topics shared by members within these Filipino groups, studies involving diabetes FB groups in other countries showed that posts on the latest diabetes research and providing education alongside sharing of personal experiences were the most common contents.[2] De la Torre-Diez found 527 diabetes groups with a total of 564,023 users on FB and Twitter in 2011. The top three most common purposes of these diabetes groups were to find a cure for the disease, to support patients and their relatives and to provide information about diabetes.[3]

While FB can be a vast source of information including misinformation (Figure 1), it is still considered a popular and useful platform where questions from persons with diabetes and/or their relatives can be answered by public health institutions, healthcare professionals or other stakeholders.[4] This is because the numbers of persons with diabetes continue to increase while physicians taking care of them may not always be available face-to-face because of locality or limited clinic hours among other reasons. The Philippines has a physician to patient ratio of 1:33,000 and only has 320 board-certified endocrinologists. These endocrinologists are also clustered in urban areas. Dr. Iris Thiele Isip-Tan, a Filipino endocrinologist, started her FB page *Endocrine Witch* in 2012. This page now has 153,507 followers (as of May 11, 2020); however, not more physicians are taking up her lead to go on social media to help combat online health misinformation.

Perhaps a better approach would be for organizations advocating for diabetes care to engage with Filipinos with diabetes online. In 2010, the Philippine Society

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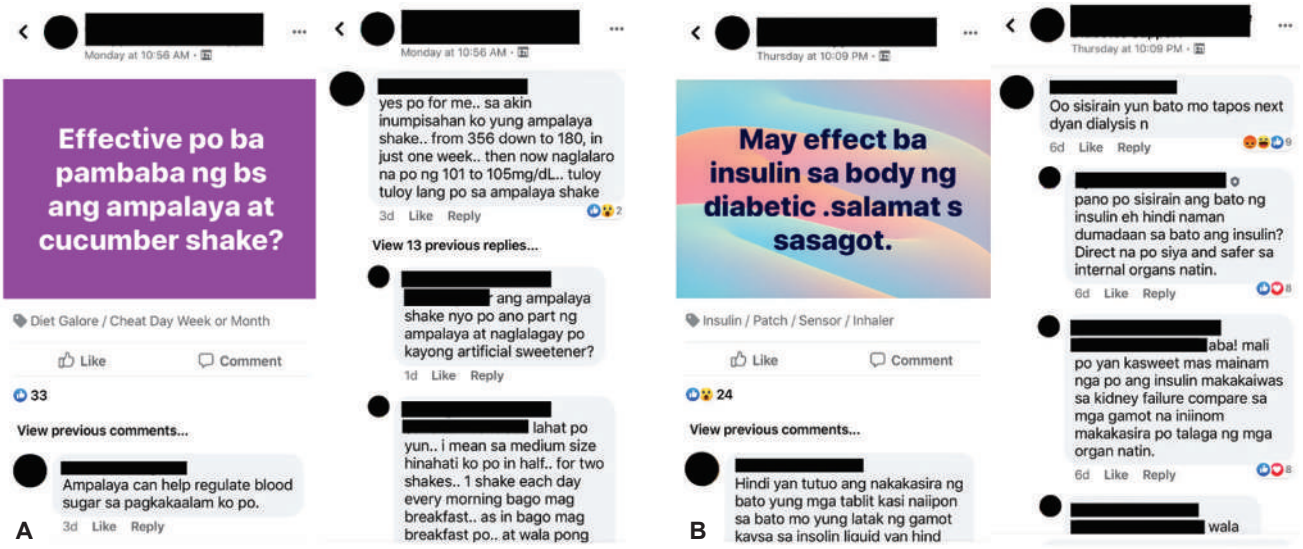

Figure 1. Misleading information about insulin and non-medicinal food to lower blood sugar. Translation: **(A)** Post: Are blended bitter gourd and cucumber effective for lowering blood sugar? First comment: "Bitter gourd helps in regulating blood sugar as to my knowledge." Second comment: "Yes. I started taking blended bitter gourd and my blood sugar went down from 365 to 180 in one week." **(B)** Post: Does insulin have an effect to the body. First comment: "That's not true. Tablets are the ones that cause kidney damage because their residues accumulate in the kidney, unlike insulin which is liquid." Second comment: "Yes. It will damage your kidney that will eventually lead to the need for dialysis." Third comment: "How can it damage your kidneys? It doesn't pass through the kidneys. It acts directly." Fourth comment: "That is wrong it is better than tablets because you can avoid kidney failure. Tablets damage the kidneys."

of Endocrinology, Diabetes and Metabolism (PSEDM) established the Hormone Hotspots page as a way to share lay articles in the society's newsletter with 1,230 followers. It has maintained an FB page since January 16, 2020, and has 3,096 followers.

The first case of COVID-19 infection in the Philippines was confirmed on January 30, 2020. Subsequently, the Philippine government implemented enhanced community quarantine for the island of Luzon on March 16, 2020. This social distancing measure has affected continuity of care for people with diabetes as outpatient clinic services were temporarily suspended. Continuity of care and support for persons with diabetes is critical as they are more likely to get the severe form COVID-19 infection. Initial clinical data on COVID-19 studies show a high prevalence of diabetes among COVID-19 mortalities.[5] It is crucial that blood glucose is maintained within treatment goals as this might help reduce the risk and severity of infection.[6] As clinics are closed and health care needs for persons with diabetes continue, social media platforms like FB must be utilized to meet the need for guidance in self management of disease, such as dose adjustment on insulin, sick-day rules, proper diet, and to supply knowledge on how COVID-19 infection could affect persons with diabetes.

The COVID-19 pandemic is anticipated to have a sequelae of effects on public health. Tseng described these health footprints as the consequence and collateral damages brought about by the pandemic. As the healthcare system suffers from the direct effects of COVID-19 and resources are restricted on non-urgent clinical conditions, care for chronic illnesses like diabetes is negatively affected. This collateral damage of COVID-19 pandemic should be anticipated. Early preparation and employment of strategies to address the third wave effect of the pandemic is important.[7] This paper explores how FB can be used to serve information needs of persons with diabetes amid the COVID-19 pandemic.

METHODOLOGY

During the community quarantine, frequent queries were posted at the *Endocrine Witch* FB group and at the Philippine Diabetes Support Group, regarding insulin substitution, lessening frequency of insulin injections and switching to generic brands for oral medications as Filipinos. At the same time, the Philippine Society of Endocrinology, Diabetes and Metabolism (PSEDM) through its Diabetes Advocacy Council realized the need to educate persons with diabetes about the relationship of COVID-19 infection and diabetes as the number of cases start to rise. The society initially posted a slide deck as photos in a FB album, in Filipino and in English language to educate persons with diabetes about COVID-19 infection and how it could potentially affect them. With the overwhelming number of queries and concerns raised about diabetes on FB, the author coordinated with the PSEDM Diabetes Advocacy council to address these concerns through more slide decks. Thirty-six members of PSEDM from all over the Philippines were recruited by the Diabetes Advocacy council and grouped into three teams. Each team was assigned topics related to diabetes care in the time of pandemic (Appendix A). Relevant topics were made based on the most common questions persons with diabetes posted on the *Endocrine Witch* and The Philippine Diabetes Support Group since March 16, 2020. On March 22, 2020, members of each group were assigned to be (1) content creators, (2) translators for two language formats [English and Filipino], and (3) graphics designers. The content of the slide decks were reviewed by a designated council to verify content before posting on social media (Figure 2). Coordination

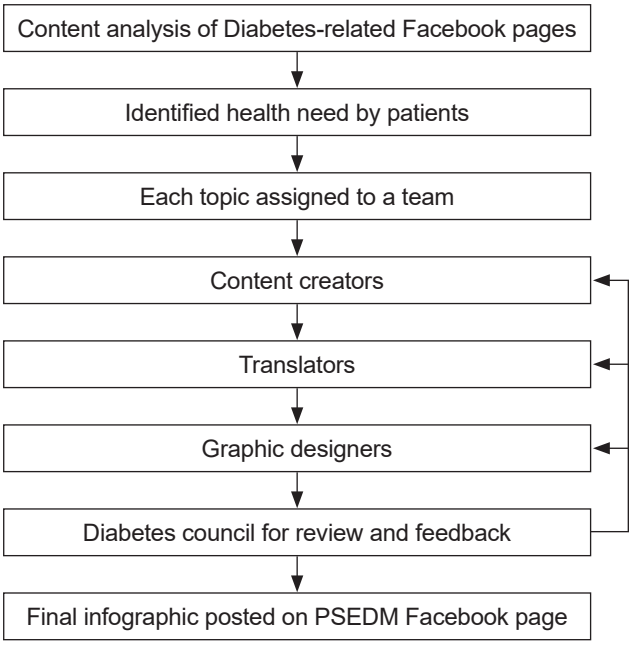

Figure 2. PSEDM workflow.

among team members was through Viber and/or Slack. The slide decks were designed following a specific format such as font, font size, image size, and image and figure colors, in order to convey a uniform branding for PSEDM.

The slide deck format with photos measuring 1,600 x 630 pixels was used for this initiative. This is the standard size in FB that allows users to see the entire photo without having to click it. A series of photos was used instead of a long infographic, to deliver information in manageable chunks. The timing of posting varied between 9:00 AM and 11:00 PM. Except for one slide deck, the English and Filipino versions were posted on the same day.

On the other hand, Dr. Isip-Tan used the FB slideshow option to show the slide deck of photos for five seconds each in a video format on her FB page. Reminders to use the pause button were made to allow enough time for users to read and understand the content. As the slideshow option is limited only to ten photos, some of the slide deck sets were shown in two parts. Only the Filipino version of the topics were shared on her page. Although only 7 of the slide decks were shown as a slideshow, the engagement statistics from the page may still reveal insights regarding the video format and having more page followers and thus was included.

Figure 3 shows some of the examples posted on the official FB page of PSEDM (https://www.FB.com/filipinoendocrinologists/). Each slide deck was posted on the official FB account of PSEDM as an album of photos. One topic, in both language formats, was posted every week. The process is shared here as an example of a medical society-led team approach in mounting a health information campaign on FB.

RESULTS

Appendix A shows statistics of engagement, available via the Insights panel of the FB page for the PSEDM and the *Endocrine Witch* FB pages respectively. These statistics were gathered on May 16, 2020, 23 days after the last slide deck was posted. Though older posts may have possibly accumulated more engagement, this may not unduly affect the results. Bhattacharya et al., in a social media engagement analysis of US Federal health agencies on FB found that 80% of a post's last activity was on the day of posting. [8]

In the hierarchy of engagement with FB posts, reactions (thumbs up, heart, sad face etc.) are considered the lowest form of engagement since it employs a simple and quick response. Sharing, on the other hand, is considered a medium form of engagement since the user is able to identify with the post's content, prompting the user to share it in his or her own FB account. Commenting is considered as the highest form of engagement because this action involves a process wherein a user reflects on a topic, formulates a text, and states it publicly on FB.[9]

Noticeably the more common forms of engagements in all of the PSEDM's slide decks (regardless of language used) and the *Endocrine Witch*'s slideshows are reactions and shares. There were only 120 comments in all the slide decks, both in English and Filipino formats in the PSEDM FB page. These included tagging other FB users to read the infographic, thanking the person who shared the post, and lastly other comments such as (consult 1, sharing personal problem 1, direct message to the person who shared the post 1). While there were more comments on the *Endocrine Witch* slideshows, the themes of the comments were similar.

For both English and Filipino versions of PSEDM's slide deck, the themes with the highest engagement rates were those giving general information on diabetes and its management: types, proper use of and storage of insulin (English), and diabetes and COVID-19 (Filipino). Themes about diabetes self-management such as general sick day rules (English) or medication-adjustment in the event of diarrhea (Filipino) followed, with engagement rates as high as 9 and 13 percent respectively. Diabetes self-management slides on hyperglycemia and hypoglycemia (English) were the next most visited, while this did not hold true for its Filipino counterpart. Instead, more users clicked on the slide decks on the safety of canned goods for persons with diabetes as well as the proper diabetic diet during the pandemic. We also observed that across all topics, there was a greater engagement rate in the slide decks presented in Filipino (7 out of 12).

A similar pattern in themes is observed from the *Endocrine Witch*'s page with the highest engagement rates coming from topics about diabetes and COVID-19, diarrhea and oral medication adjustment, brand switching in case stocks of medications run out, as well as hypoglycemia self-management. No stats are available for diet management as the slide deck on the topic was not included in the page.

DISCUSSION

The interruption of regular ambulatory clinics because of the COVID-19 pandemic has presented a challenge in the care continuum of persons with diabetes. This study showed that the use of FB as a platform to educate about COVID-19 and to provide helpful instruction on

Figure 3. Examples of infographics posted on the Philippine Society of Endocrinology, Diabetes, and Metabolism FB page **(A)** in Filipino and **(B)** in English. *(Adapted from https://www.facebook.com/filipinoendocrinologists).*

diabetes self-management is doable and yields high user engagement.

The predominant themes on diabetes management, and diet seen in this project mirror findings of studies done even pre-pandemic where social media users would visit more posts on management, diabetes technology and nutrition than any other diabetes-related topic[9,10] or were more likely to engage in posts on FB groups/communities about different diabetes management strategies shared by patients.[11] Although no paper on FB use and diabetes care during the era of COVID-19 has been published so far to our knowledge, the high engagement rate seen particularly for PSEDM's slide decks on diabetes self-management (i.e., insulin uptitration, diarrhea and sick-day management, adjustment of insulin during exercise) may be a reflection of the current interest and/or information needs of Filipino social media users whether for themselves or for their relatives and friends during this pandemic. Social media users tend to patronize posts that are relevant to them. It may be to reinforce what was already taught to them by their physician, or may actually be the very first medium of instruction for them on a topic, which was not tackled during prior clinic visits.

PSEDM's Diabetes Advocacy council made use of photos/infographics to convey information towards its potential consumers. In general, health information can be uploaded on FB in many different formats i.e., text only, images, videos, or links. There are conflicting results as to which

format is more effective and engaging in providing health information. In a participative study done on the social media followers of the Norwegian Diabetes Association, the preferred format of health information varied according to age. Text format was preferred by adults and images were preferred by younger individuals.[4] However, another study showed that images in the post were the strongest predictor of likes, shares, or comments. Images have been described to be effective in modifying behavior through communication responses. Information relayed via images are processed faster, retained, and retrieved from memory by eliciting strong emotional reactions.[12] Information in graphic format is also believed to enhance understanding and ability to make decisions.[13]

Meanwhile, another study showed that videos attracted the greatest amount of user engagement as opposed to links and text-only formats even if the topic is of great relevance.[14] We surmise that the use of photos and slide-shows (videos) in the PSEDM and the *Endocrine Witch*'s page not only provided a medium that was easily understandable but was something that was also preferred by most Filipino FB users and thus helped in achieving the high engagement. Perhaps a survey or focused group discussion on patient preferences must be done to identify the most effective format for communicating health information and one that will maximize user engagement.

An average engagement rate on a FB post is 3.22%.[15] All posts in the PSEDM and the *Endocrine Witch* FB accounts had an above average engagement rate. We also noted a higher engagement rate in the slide decks presented in the Filipino language versus English. Intuitively, persons with diabetes or persons taking care of them would likely choose a language which they can easily comprehend in order to maximize the learning from a post and likewise communicate it effectively to others. Still, there may be other elements accounting for the high engagement seen.

Evidence-based guidelines in commissioning health infographics for use with the public health suggest the following principles of design: familiarization with the audience and the key message that must be shared, restriction of the number of colors used in the design, alignment of elements of the design consistently, prioritization of parts focal points in the infographic, emphasis on heading, wise use of imagery, careful selection and use of charts or graphs.[16] A study done by McKown that developed an infographic and made a formative assessment on it by conducting a survey on diabetes educators showed that the health educators believe that infographics are accurate, easy to understand for diabetes educators, and agreed that these infographics would be understable by consumers as well. Open ended questions in the survey revealed recommendations such as utilizing colors for infographics to make it visually appealing, adding contact information for further information, utilizing a bigger font size, and using gender neutral images.[17]

Another study on young individuals tried to evaluate key characteristics of nutrition infographics that will make them more memorable and compelling revealed that action-oriented titles were related to better message recall than the use of color or humor. This result suggests that a carefully created title is an important key element to the effectiveness of infographics together with short texts all throughout the infographic.[18] These findings emphasize important features of infographics that will make them effective and should be considered in designing infographics for public health consumption.

As this was a society-led initiative, the slide decks used a uniform font, font size, image size, and image and figure colors. This is worth noting as a study by Park et al., of health organizations' FB pages showed that most organizations were not using branding techniques. Branding may be crucial in that the public may easily recognize and trust the information being presented more if it is known to be by a reputable medical society.[19]

Another social media platform that is used to share pictures is Pinterest. Users can interact with a post called a pin, by liking, commenting, or saving a pin to a user's collection of photos. A study performed a content analysis of 238 diet-related infographics and pictures that promote healthy eating posted on Pinterest. Results revealed that most infographics did not contain health behavior theory constructs but those that contained them had a higher user interaction in the form of repins, likes and comments. Characteristics of infographics that contain health behavior theory constructs include use of text, a photograph of a real person or a cartoon, or images of food. However, less than half of infographics included in the analysis had images of real people. The study suggested that using more realistic images in infographics may be more likely to promote behavioral change like promoting good eating habits.[20] Another content analysis study on 214 images and infographics posted on Pinterest for COPD self-management revealed the use of photographs of real people was associated with higher user engagement. Photographs of real people presenting with COPD self-management information had more likes and infographics were repinned or saved more. The results of these studies can serve as a guideline in making an effective image for social media use and should be considered in every infographic or image design.[21]

Lastly, we noted a low number of comments in both pages as opposed to reactions and shares. This finding is similar with the results of a study done by Rus and Cameron. They theorized that the images either fail to stimulate comments or potentially inhibit commenting from users. This relationship remains to be elucidated but there is a possibility that images stimulate concrete-experiential processing of messages, which stimulates reactions such as liking and sharing but inhibits the abstract, linguistic processes employed in writing comments.[22-23]

Limitations

The images made by PSEDM and the slideshow posted on the *Endocrine Witch* FB page were based on the most common concerns posted on popular diabetes support FB pages based in the Philippines. However, the parameter with which success of disseminating information could be measured was not predefined. Being a project that was not originally intended for research but for advocacy purposes only, no such definitions of success in spreading health information with the use of infographics were made other than the counts of engagements. Given the potential of the use of images and infographics in disseminating

information, it is crucial to establish the evidence on its efficacy in relaying information and determine the characteristics or elements of an infographic that make them more effective.

CONCLUSION

The power of social media together with the effectiveness of images in conveying information should be harnessed to promote public health. Patient health information needs must be identified and key characteristics of an effective image or infographic must be used wisely in order to stimulate the reader's attention, relay information effectively, and enhance retention and hopefully, effect a call to action.

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The authors certified fulfillment of ICMJE authorship criteria.

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Appendix A.

Table 1. FB-derived engagement statistics for photo albums on PSEDM FB page

Title	Language/Date/Time posted	Post clicks	Reaction*	Comments	Shares	Reach	Engagement Rate (%)**
Diabetes in the Time of COVID-19 (Risks, mortality, general information)	English 03/24/2020 1:05 PM	3	0	0	1	76	4
	Filipino 03/21/2020 11:51 AM	9,562	1,291	29	446	57,271	15
What are The Types of Insulin? (Background knowledge on different kinds of insulin,duration of action, onset, etc)	English 03/29/2020 10:58 PM	146	14	0	1	948	12
	Filipino 03/29/2020 11:07 PM	59	27	1	6	1,273	5
Oral Medications of Persons with Diabetes (Information about oral medications and brand substitution)	English 04/07/2020 9:41 AM	111	34	0	11	1,905	6
	Filipino 04/07/2020 9:48 AM	69	22	4	1	744	11
Diarrhea in COVID-19 (Diarrhea and medication adjustment)	English 03/27/2020 9:32 PM	37	41	2	9	841	7
	Filipino 03/27/2020 9:36 PM	5,643	717	39	307	42,172	13
How to monitor your blood sugar? (Knowledge on blood sugar monitoring)	English 04/01/2020 10:32 PM	118	46	0	17	2,130	6
	Filipino 04/01/2020 10:45 PM	83	39	0	16	1,305	8
Hyperglygemia or High Blood Sugar–What to Do? (Hyperglycemia and insulin adjustment)	English 04/03/2020 9:41 PM	108	36	2	8	1,071	8
	Filipino 04/03/2020 9:45 PM	55	36	1	5	1,148	6
Hypoglycemia or Low Blood Sugar–What to Do? Hypoglycemia, symptoms, first aid treatment, and insulin adjustment	English 04/04/2020 8:18 PM	151	37	7	57	917	8
	Filipino 04/04/2020 8:21 PM	77	57	1	5	1,552	9
Diabetes During an Illness (Sick-day rules)	English 04/19/2020 11:53 AM	234	17	3	16	2,335	9
	Filipino 04/19/2020 11:57 AM	107	6	11	13	2,855	4
Matching Insulin with Food Intake (Insulin matching with food)	English 04/15/2020 8:59 PM	127	1	0	5	1,064	9
	Filipino 04/19/2020 11:57 AM	107	17	3	16	1,450	7
Adjusting Insulin Dose for Exercise (Exercise and precautions for persons using insulin)	English 04/23/2020 11:02 AM	134	2	1	5	1,364	8
	Filipino 04/23/2020 11:05 AM	161	48	2	29	2,036	8
Is It Safe to Eat Canned Goods? (Safety of canned goods due to limited access to quality food)	English 04/08/2020 10:16 PM	71	45	1	6	2,088	8
	Filipino 04/08/2020 10:20 PM	200	141	18	25	910	12
What Should My Diet Be? (Proper diet during a pandemic)	English 04/09/2020 11:09 PM	89	19	0	8	1,499	6
	Filipino 04/09/2020 11:12 PM	148	200	6	35	2,566	9

* Reactions are the total number of likes, hearts, haha, wow, sad, and angry
** FB engagement rate = total engaged users divided by total reach then x 100
total engaged users = number of people who engaged with the post by commenting on it, reacting, sharing or clicking on it.

Table 2. FB-derived engagement statistics for slideshows on *Endocrine Witch* FB page *(Adapted from https://www.facebook.com/EndocrineWitch)*

Title *	Date/Time posted	Post clicks	Reactions	Comments	Shares	Reach	Engagement Rate (%)
Diabetes in the Time of COVID-19	03/21/2020 11:19 AM	6,100**	981	188	738	59,133	10
What are The Types of Insulin?	03/30/2020 8:00 AM	1,100**	292	25	125	16,352	6
Diarrhea in COVID-19	03/31/2020 9:25 AM	2,700**	472	44	251	25,307	10
How to monitor your blood sugar?	04/02/2020 8:05 PM	868	223	33	95	14,361	6
Part 1. Insulin Adjustment	04/04/2020 9:47 AM	749	194	18	85	14,582	5
Part 2. Insulin Adjustment [premixed or combination insulin]	04/04/2020 10:09 AM	429	147	9	48	10,639	5
Part 1. Oral Medications of Persons with Diabetes	04/07/2020 12:44 PM	689	205	4	43	10,639	7
Part 2.Oral Medications of Persons with Diabetes	04/07/2020 12:50 PM	1,800**	370	26	176	20,550	8
Part 1 Hypoglycemia or Low Blood Sugar–What to Do?	04/08/2020 6:30 PM	578	114	9	50	7,306	7
Part 2. Insulin Adjustment for Hypoglycemia	04/08/2020 6:40 PM	649	157	27	57	13,635	5

* Titles are written in English in the table but the actual posts on FB are in Filipino.
** Estimates (actual raw number not given) as it appears in FB Insights panel.

Journal of the ASEAN Federation of Endocrine Societies

REVIEW ARTICLE

Diabetes and COVID-19: A Review

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Abstract

Coronavirus Disease 2019 (COVID-19) is an emerging disease and since its first identification in Wuhan, China, in December 2019, there has been a rapid increase in cases and deaths across the world. COVID-19 has been shown to have an immense impact in infected persons with diabetes, worsening their outcome, especially in elderly, smokers, obese, those having CVD, CKD, poor glycemic control and long duration of diabetes. In this review we summarize the current understanding of `the impact of COVID-19 on diabetes and discusses the pathophysiological mechanisms and management of diabetes and its complication in this scenario.

Key words: Corona Virus, COVID-19, diabetes mellitus

BACKGROUND

Globally, COVID-19 has impacted several millions of lives and is steadily increasing in number. The coronavirus has derived its name because of resemblance of its shape to a crown or solar corona when imaged using an electron microscope. So far three deadly human respiratory coronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus (MERS-CoV) and coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) which causes COVID-19 (Coronavirus Disease-2019), have been detected.

Human coronavirus (HCoVs) have long been considered inconsequential pathogens, causing the "common cold" in otherwise healthy people. However, in the 21st century, 2 highly pathogenic HCoVs - severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have emerged from animal reservoirs to cause global epidemics with alarming morbidity and mortality.

In December 2019, yet another pathogenic HCoV, 2019 novel coronavirus (2019-nCoV), was recognised in Wuhan, China, and has spread currently to almost more than 130 countries resulting in a pandemic and caused serious illness and death.[1]

Across the world, COVID-19 has become most critical public health emergency and as per recent reports 15% of the cases are severe cases.[2] The incubation period varies from 2 to 14 days (average 5.2 days) and the symptomatic phase varies between 6 to 41 days (average 14 days).

Diabetes has been reported as one of the most common comorbidities and is correlated with higher mortality and is significantly worsened with increasing age and longer duration of uncontrolled diabetes. Depending on the report, pre-existing co-morbid conditions of COVID-19 patients range between 25% to 50%.[3] The Case Fatality Rate (CFR) has varied significantly between countries and age-groups. Patients with diabetes have 7.3% CFR as compared to 2.3% in the general population. Subjects with diabetes and SARS-CoV-2 infection exhibit enhanced disease severity due to compromised innate immune response. Multiple organ failure is the final cause of death because of acute respiratory distress syndrome and septic shock among patients with COVID-19.

This article summarizes the current understanding of the impact of COVID-19 on diabetes and discusses the pathophysiological mechanisms and management of diabetes and its complication in this respect.

COVID-19 AND OTHER CORONAVIRUS DISEASES: SIMILARITIES AND DISSIMILARITIES

Like any other flu, COVID-19 is characterised by a wide spectrum of symptoms including fever, sneezing, coughing, myalgia and respiratory problems like respiratory distress due to viral pneumonia and in some cases, ultimately

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Table 1. Comparison of Characteristics of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Coronavirus Disease 2019 (COVID-19)*

Characteristics	Severe Acute Respiratory Syndrome	Middle East Respiratory Syndrome	Coronavirus Disease-2019
First patients reported	Guangdong, China, November 2002	Zarga, Jordan, April 2012 and Jeddah, Saudi Arabia, June 2012	Wuhan, China, December 2019
Virus	SARS-CoV	MERS-CoV	SARS-CoV-2
Type of coronavirus	betacoronavirus	betacoronavirus	betacoronavirus
Host cell receptor	Angiotensin converting enzyme 2	Dipeptidyl peptidase 4	structural analysis suggests Angiotensin converting enzyme 2 receptor
Incubation period			
Mean (95% CI: days)	4.6 (3.8-5.8)	5.2 (1.9-14.7)	5.2 days (95% confidence interval [CI], 4.1 to 7.0); 95th percentile of the distribution was 12.5 days
Range (days)	2-14	2-13	2-14
Time from illness onset until hospitalization	2-8 days	0-16 days	12.5 days (mean)(95% CI, 10.3 to 14.8) - onset before January 1 9.1 days (mean); 95% CI, 8.6 to 9.7 January 1-11
Patient characteristics			
Adults	93%	98%	Nearly all reported patients are adults
Haematological abnormalities			
Leukopenia	25-35%	14%	9-25%
Lymphopenia	65-85%	32%	35-70%
Thrombocytopenia	40-45%	36%	5-12%
Mortality			
Mortality Rate	9.6%	34.4%	2.3%

*Modified from Rasmussen et al.,[11] Wan Y et al.,[12] Li Q. et al.,[13] Lu R et al.,[14] Shen KL et al.[15]

respiratory failure. But unlike the common flu, the number of hospitalizations due to severe respiratory distress are much higher and can lead to death.[4-9] What is most disturbing is that a large number (81%) of infected people are without symptoms (yet remain infectious) or have only mild symptoms.[10]

SARS and COVID-19 have many similarities from the virus homology to the origin and transmission routes, but there are several clinical differences which have emerged. Many more patients with COVID-19 compared to SARS have mild symptoms that contribute to spread because these patients are often missed and not isolated. Also, COVID-19 has higher transmissibility than SARS (Table 1).

PATHOPHYSIOLOGY OF COVID-19

COVID-19 is classified under the orthocoronavirinae subfamily with the subgenus sarbecovirus and also represents the seventh member of the coronavirus family and is sufficiently different from SARS-CoV.[16] COVID-19 is also classified by the World Health Organisation (WHO) as a βCoV of group 2B.[17] One study shows ten genome sequences exhibited 99.98% sequence identity which has been obtained from a total of nine patients infected with COVID-19.[14]

A few articles already confirm that SARS-CoV-2 requires the angiotensin-converting enzyme 2 (ACE2), just like SARS-C, as a receptor to enter host cells.[18] The pathogenesis of infection is determined by the binding of the virus with host cell receptors.

Spike (S), envelope (E), membrane (M) and nucleocapsid (N) genes are the four structural genes which encode SARS-CoV-2 membrane structural proteins.[19,20] In SARS-CoV-2 *orf1ab* is the largest gene which encodes the pp1ab protein and 15 nsps. When the SARS-CoV-2 binds with the host receptor, it leads to a structural change in S protein which, through the endosomal pathway, facilitates viral envelope fusion with the cell membrane (Figure 1). The RNA of SARS-CoV-2 is then released into the host cell and is finally translated into relevant viral proteins. Subsequently, in the endoplasmic reticulum (ER) the genome mRNA and viral proteins are assembled into virions and then transported via vesicles and released out of the cell (Figure 1).

In the respiratory system, angiotensin II degrades to angiotensin 1–7 by ACE2. When ACE2 is inhibited and as a consequence ACE1 activity is increased, there is a substantial increase in aldosterone secretion because that intact angiotensin II acts via the angiotensin 1 receptor (AT1R) or AT2R to exert pro-inflammatory responses.[21] Thus, during infection with COVID-19, blood pressure increases due to the stimulated aldosterone secretion and potentially causes hypokalemia which leads to an increased risk of respiratory distress syndrome. Severe COVID-19 patients have an imbalance in angiotensin system with an increase in the activation of AT1R and AT2R which further worsens in T2DM, hypertension and insulin-resistant states.

In patients with COVID-19 infection significantly high blood levels of chemokines and cytokines were noted which included IL7, IL8, IL9, IL10, IL1-β, IL1RA, IFNγ, IP10, basic FGF2, GCSF, GMCSF, PDGFB, TNFα, MCP1, MIP1α, MIP1β and VEGFA. High levels of pro-inflammatory cytokines including IL2, IL7, IL10, MCP1, MIP1α, GCSF, IP10 and TNFα that are thought to promote disease severity were observed in some of the severe cases that were admitted to the intensive care unit.[22]

CLINICAL PRESENTATION AND DIAGNOSIS OF COVID-19

The symptoms of COVID-19 appear after an incubation period of approximately 5.2 days.[23] The period from the onset of COVID-19 symptoms to death ranges from 6 to 41 days with a median of 14 days.[24] It is shorter among patients who are more than 70 years of age.[25]

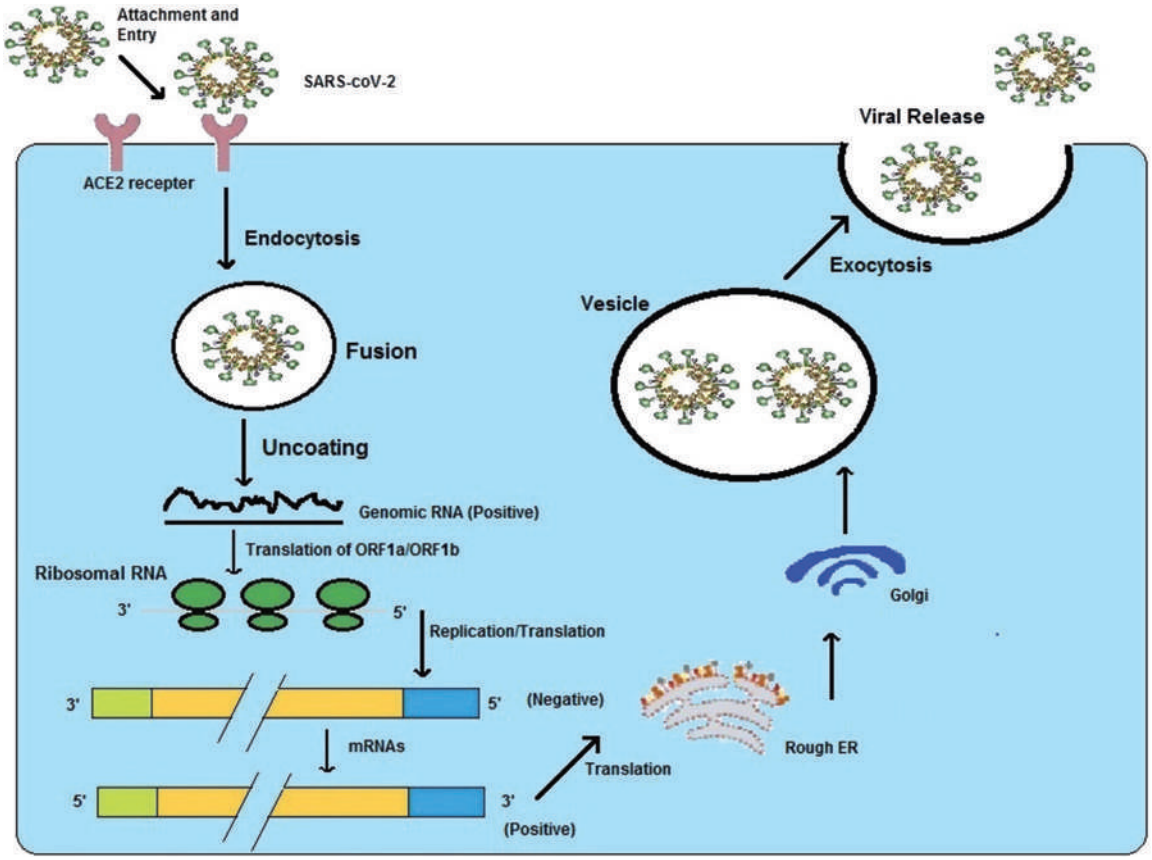


Figure 1. The life cycle of SARS-CoV-2 in host cells.

The clinical diagnosis of COVID-19 is mainly based on clinical manifestations, epidemiological history and some auxiliary examinations, such as nucleic acid detection (RT-PCR) from nasal and preferably nasopharyngeal swab, immune identification technology (Point-of-care Testing) (POCT) of IgM/ IgG, enzyme-linked immunosorbent assay (ELISA), chest CT scan and blood biochemistry. The clinical symptoms and signs include cough, fever, dyspnea, while other symptoms include sputum production, haemoptysis, tightness of chest, dysgeusia, diarrhoea, abdominal pain, anosmia, headache, dizziness, myalgia, encephalopathy, stroke, seizures, arrhythmias and heart failure. The blood biochemistry profile includes lymphopenia, thrombocytopenia, leucopenia; increased Hs-CRP, IL-6, ferritin, D-Dimer and prothrombin time.[26-28] A chest CT scan generally reveals ground-glass opacities.[29] Both systemic and localized immune response causing increased inflammatory flare, leads to multiple peripheral ground-glass opacities in subpleural regions of both lungs.[30]

It is important to note that in COVID-19 and earlier betacoronavirus features such as dyspnoea, dry cough, fever and bilateral ground-glass opacities share similar features in the symptoms and chest CT scans. However, some unique clinical features present with COVID-19 which include the targeting of the lower airway as evident by relatively low incidence of upper respiratory tract symptoms like sore throat, sneezing and rhinorrhoea.[31,32] Increasing dyspnea with hypoxemia with infiltrates in the upper lobe of the lung is also observed on chest radiographs.[33] Gastrointestinal symptoms like GI distress and diarrhoea can also develop in patients infected with COVID-19.[34-36]

Fever, pulmonary complications (including ARDS), cytopenias and hyperferritinemia are cardinal features of sHLH (secondary Hyperphagocytic Lymphoreticulosis-Hyperinflammatory) syndrome which is triggered by viral infection and sepsis.[37]

IMPACT OF COVID-19 ON DIABETES

Elderly people are at a higher risk of COVID-19 infection due to their decreased immunity and body reserves, as well as multiple associated co-morbidities like diabetes, hypertension, chronic kidney disease and chronic obstructive pulmonary disease. Moreover, the course of the disease tends to be more severe in elderly, possibly due to aging, resulting in higher mortality (CFR-15% above 80 and 8% in 70 to 79-year-old patients).[38] The CFR in persons with diabetes is 7.3% whereas it is around 6% in hypertensives and chronic pulmonary disease patients increasing to 10.5% in patients with CVD.[39]

In COVID-19 infected patients, diabetes is the one of the major risk factors specially when it is uncontrolled with significant blood glucose variability. Wu et al., in a study among 52 intensive care subjects, found that diabetes was a comorbidity in 22% of 32 non-survivors.[2] In one study of 173 patients, 16.2% patients were with diabetes and severe symptoms of the disease. Zhang et al., found 12% of 140 hospitalized patients with COVID-19 have diabetes.[6,7] A recent study also reveals a twofold increase in the incidence of patients in intensive care having diabetes, when compared to intensive care and non-intensive care patients with COVID-19.[40] This study also confirmed that

the mortality rate almost increased up to three folds in subjects with diabetes compared with the general mortality of COVID-19 in China.

Several aspects of immune response to viral infection are affected by uncontrolled diabetes and can lead to the high chance of bacterial secondary infection in the lungs.[41,42] Obesity in type 2 Diabetes (T2DM) is also a risk factor for severe infection.[43,44]

In addition, there is a direct link of coronavirus infection in T2DM patients. In the pancreas when SARS-CoV-2 binds with the ACE 2 receptor, it damages islets and reduces insulin release.[40] Yang et al., found that more than 50% of patients became diabetic during hospitalization for the SARS-CoV infection and only 5% of patients remained diabetic after 3 years of recovery. T2DM patients might be particularly vulnerable to the insult from a coronavirus infection due to increased expression of ACE2 in the pancreas, as demonstrated in mice.[41]

Subjects with diabetes and infected with SARS-CoV-2 might trigger stress and have increased secretion of hyperglycemic hormones, such as catecholamines and glucocorticoids which results in elevated glucose levels in blood, abnormal glucose variability and diabetic complications.[47,48] People with diabetes do face an increased risk of diabetic ketoacidosis (DKA) and or hypoglycemia.[44] DKA is commonly experienced by patients with type 1 diabetes.

Among hospitalised patients with COVID-19 infection the reported rates of chronic kidney disease appear to be low (1-3%) but this can increase if the patients have uncontrolled diabetes and hypertension as comorbidities. Sepsis is one of the dangerous systemic responses in persons who catch the new coronavirus. Check the patient's fluid and electrolyte levels and treat the sepsis. Uncontrolled diabetes with DKA cause electrolytes imbalance which can make sepsis harder to control. Highly elevated levels of inflammatory cytokines, termed as a cytokine storm, has been implicated in the multi-organ failure in patients with diabetes and infected with COVID-19.[50]

IMPACT OF DIABETES ON COVID-19

In diabetes subjects, the immune system is in a compromised state due to metabolic inflammation and the body's ability to tackle the infection is reduced. As a consequence, recovery is prolonged by affecting the healing process.

An animal model demonstrated that due to immune dysregulation, MERS-CoV infection was enhanced in T2DM comorbid condition.[46] In this study, it was observed that human DPP4 expressed in mice resulted in susceptibility to MERS-CoV and showed altered cytokine profile following infection with increased expression of IL-17α.

These data support the hypothesis that a more aggravated and prolonged lung pathology which occurs in patients with type 2 diabetes who were symptomatic with COVID-19, is mainly due to dysregulated immune response in this comorbid condition.[47]

Impaired immune-response mainly induced by abdominal obesity results in abnormal secretion of adipokines and cytokines like TNF-alfa and interferon. Obese patients with uncontrolled diabetes also have an increased asthma risk and as well as reduced oxygen saturation of blood which leads to mechanical respiratory problems.[48-49] In individuals with uncontrolled diabetes, in response to lipopolysaccharide stimulation, secrete less interleukin-1 (IL-1) and IL-6 from their mononuclear cells and monocytes, and the reduced production is a consequence of an intrinsic defect in the cells.[51,52] There are several other studies which confirms that individuals with uncontrolled diabetes are more susceptible to respiratory infection than compared to individuals without diabetes.[52-54]

Hypertension is an important comorbidity of diabetes, which is linked to COVID-19.[55-56] With an estimated prevalence of 15%,[6] a recent Chinese article confirms that in 1099 patients, hypertension was the most frequent coexisting condition apart from diabetes and undoubtedly this comorbidity was much lower than other viral infections.[57,58] Coronavirus generally binds to target cells through angiotensin-converting enzyme 2 (ACE2) and these receptors are present at epithelial cells in the intestine, blood vessels and lungs.[59,60] In a study done in comparably small population, it was found that patients with COVID-19 have elevated levels of plasma angiotensin II[47] which were in turn correlated to degree of lung injury and total viral load.[61] It has also been observed that the expression of ACE2 is increased in patients treated with ACE and angiotensin II receptor blockers.[62] Therefore, it has been suggested that in patients with hypertension and diabetes, ACE2 expression may be increased, which could increase the risk of severe disease and fatality and facilitate infection with COVID-19.

Furthermore, corona virus pneumonia causes abnormal hemoglobin metabolism in humans. Patients with uncontrolled diabetes have higher glycated hemoglobin or deoxyhemoglobin. One very recent study done by Wenzhong Liu et al.,[63] has confirmed that heme on the beta chain of hemoglobin of host cell is attacked by orf1ab, ORF3a, and ORF10 of coronavirus and thus, patients with uncontrolled diabetes with high glycated haemoglobin are at higher risk of COVID-19 infection.

TREATMENT OF TYPE 2 DIABETES WITH COVID-19

Maintaining good glycemic control with frequent monitoring of blood glucose levels is the most important and key factor to reduce the probability of not only being infected with COVID-19 but also the severity of the infection. As social distancing is one the major steps as per government mandate, it is currently difficult to exercise in gyms or in crowded places like parks, public gardens, play grounds, etc. Patients with diabetes must carry-on with their recommended physical activity in their respective homes. They should consume colorful fruits and vegetables, soy (antiviral effect-nicotianamine, anti-inflammatory effect-IRW), yogurt (promoting favorable gut microbiota) and stopping tobacco. It is important to have adequate sleep and reduce stress (ie., doing yoga).

Patients who are already on antibiotics and drugs like glucocorticoids need to be monitored with frequent blood glucose tests, and do proper dose adjustment accordingly. Patients who are moderately or severely infected with

COVID-19 should immediately discontinue metformin and SGLT2i (Sodium glucose transporter 2 inhibitor).[64] SGLT2i promotes renal ACE2 activity which has already proved in human studies. For patients with impaired kidney function linagliptin or other dipeptidyl peptidase 4 (DPP-4) inhibitors can be considered, as DPP4is do not alter ACE2 activity in diabetic mice and it might exert an overall anti-inflammatory role in human body.[64]

If patient's calorie intake is low, a high dose of sulphonylureas may induce severe hypoglycemia, so the doses of sulphonylureas have to be monitored carefully. Pioglitazone and liraglutide as shown in animal studies may be involved in upregulation of ACE2 in insulin sensitive tissues and pulmonary tissue, therefore use of this drug may theoretically be a concern during COVID-19 infection, however there is no data on human pulmonary ACE2 expression.[64]

Insulin is the preferred choice and should be initiated as early as possible to uncontrolled T2DM.[64] Rapid acting bolus insulin can be considered instead of basal insulin to reduce the chance of hypoglycemia.[65] In case of hospitalisation due to severe illness, the patient must be put on continuous insulin infusion and intravenous fluids as per standard protocols. No change in drugs is required in patients with diabetes who have not contracted SARS-CoV-2 infection. Animal studies done in diabetic mice have already established that insulin reduces renal ADAM-17 (a disintegrin and metalloproteinase-17 enzyme that cleaves and inactivates ACE2) expression thus further reducing urinary ACE2 shedding and increasing intrarenal ACE2 expression. There is still no human data regarding human use of insulin during COVID-19 pandemic.

Hydroxychloroquine (HCQ) deserves special mention. This drug (400 mg OD) has been approved in 2014 from the Drug Controller General of India (DCGI) as an adjunct to diet, exercise and two drugs (metformin plus sulphonylureas) to improve glycemic control in type 2 diabetes and it has shown promising results in COVID-19. Novel mechanism of blood glucose lowering action with HCQ is observed as it offers post receptor inhibition of insulin degradation and reduces inflammatory loads.[64] Several studies has already confirmed HbA1c reduction of 0.87-3.3% along with significant reduction in fasting and post prandial blood glucose with HCQ in uncontrolled T2DM subjects.[65-67]

The 2018 Research Society for the Study of Diabetes in India (RSSDI) guidelines also have placed hydroxychloroquine as third line of drug indicated for the management of T2DM.[68]A recent study shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.[69]

Figure 2 depicts the probable mechanism by which hydroxychloroquine prevents COVID-19. An in-vitro study done by Yao et al., recommended hydroxychloroquine 400 mg BID at day 1 and 200 mg BID day-2 to day-5 for patients who are infected with COVID-19.[71]

The Indian Council of Medical Research (ICMR) has advised hydroxychloroquine prophylaxis in health care workers involved in the care of suspected or confirmed COVID 19 infected patients and contacts of confirmed cases.[72] Furthermore, HCQ is also one of the medications being evaluated as a treatment in these patients. Since it is likely that there could be many patients on this medication detailed drug interactions and precautions are also included in Table 2.

The dual benefit in terms of glycemic control as well as protection from COVID-19 makes HCQ a preferred add-on drug in uncontrolled persons with diabetes.

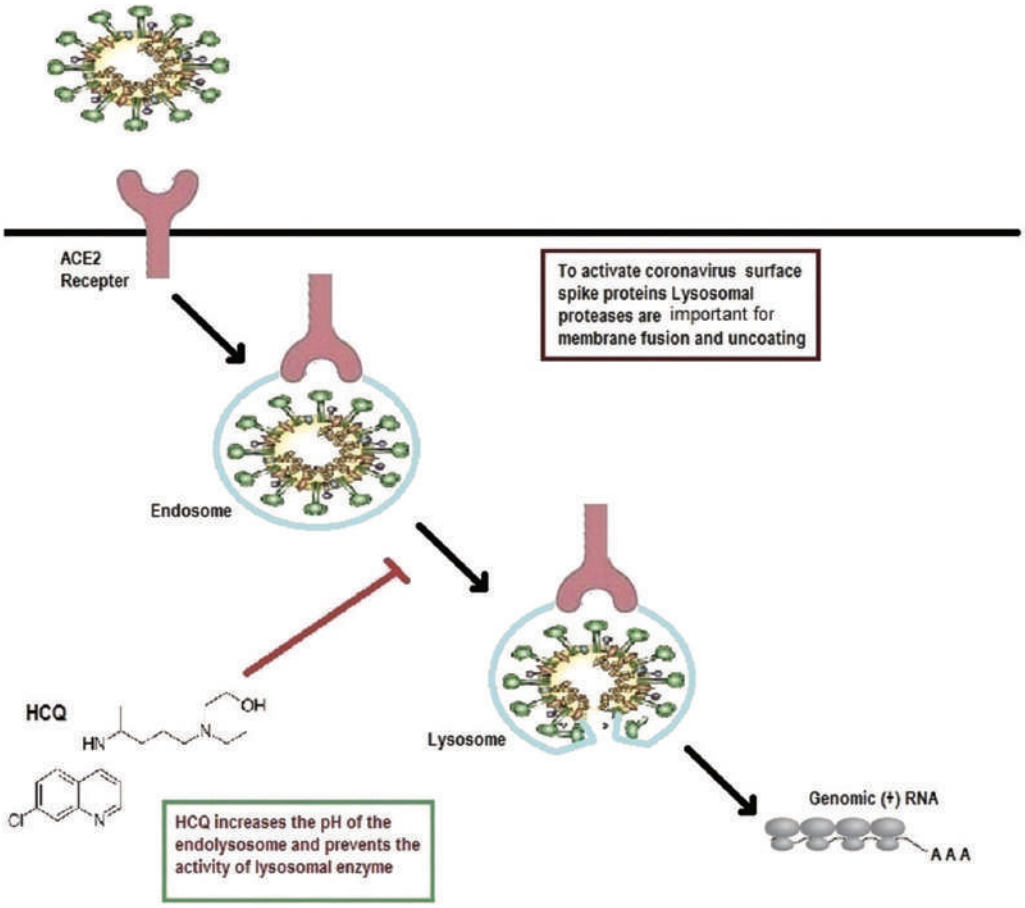
The American College of Cardiology and American Heart Association have recommended withholding the drug in patients with prolonged QT interval (like azithromycin).[73]

The European Medicines Agency (EMA) has approved trials with the following drugs: remdesivir, lopinavir/Ritonavir,

Table 2. Medications which have been used in various small clinical trials but are still not validated by any RCT's.*

Drugs	Types	Mechanism of Action	Past Evidence
Chloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevent viral entry, transport and post-entry events.	Inhibits infection of cells by SARS-CoV-2 in vitro, approved for malaria treatment and prophylaxis.
Hydroxychloroquine	4-aminoquinoline	Not clearly known, changes the pH of endosomes and believed to prevent viral entry, transport and post-entry events.	Inhibits infection of cells by SARS-CoV-2 in vitro, approved for malaria treatment and prophylaxis and autoimmune disease (e.g. rheumatic diseases). Approved for treatment of T2DM in India.
Azithromycin	Macrolide Antibacterial	Immunomodulatory mechanisms may include reducing chemotaxis of neutrophils (PMNs) to the lungs by inhibiting cytokines (i.e., IL-8), inhibition of mucus hypersecretion, decreased production of reactive oxygen species, accelerating neutrophil apoptosis, and blocking the activation of nuclear transcription factors.	Used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
Remdesivir	Adenosine nucleotide analogues	Inhibits viral application	Effective against SARS and MERS. Several large clinical trials are underway.
Ribavirin	Nucleoside analogue	Inhibits viral replication	Mixed result against MERS
Ribavirin plus Interferon	Nucleoside analogue	Inhibits viral replication	Mixed result against MERS
Tocilizumab	Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody	inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors.	Preliminary data suggest tocilizumab may have clinical benefit as adjunctive therapy.
Lopinavir/Ritonavir	Protease inhibitors	Blocks viral cell entry	Effective against SARS-CoV-1 both in vitro and human studies, approved for HIV-1 treatment. Preclinical data suggested potential benefit; however, more recent data has failed to confirm.

*Smith T et al.[80]



1. Hydroxychloroquine acts on host target respiratory cells by increasing the endosomal pH required for the virus-host target cell fusion.[70]
2. Hydroxychloroquine was found to interfere with the glycosylation of cellular receptor of the virus.[57]
3. Hydroxychloroquine acts as inophonic agent for Zinc ions which adhere to the RNA dependent RNA polymerase enzyme of the virus and stops COVID-19 polymerization intracellularly.[70]
4. TNF alpha and IL6 production might be inhibited by HCQ and subsequently blocks the cascade of COVID-19 infection.[57]
5. Chloroquine could prevent gene expression (orf1ab, orf3a, and orf10) to attack the heme to form the porphyrin, and inhibit the binding of orf8 and surface glycoproteins to porphyrins to a certain extent.[57]

Figure 2. The mechanisms of action of hydroxychloroquine (HCQ) against COVID-19.

IL-beta1a, HCQ and immunoglobulin. The dosage of these drugs in the multi center/country DisCoVeRy trial in hospitalized patients is as follows: Remdesivir-100 mg/d IV for 10 days; Lopinavir-400mg/Ritonavir-100 mg orally every 12 hours for 14 days with or without IL-beta1a- 44 ug SC on D1, D3, D6; HCQ-400 mg (Ryles tube-600 mg) BD on D1 and 400 mg/d for 9 days.[74]

The other therapeutics under investigation include tocilizumab (IL-6 antagonist) in severe cases, ivermectin (inhibits viral replication affecting viral proteins), camostat (serine protease inhibitor acting on TMPRSS2 and restricting viral entry in host cell) and convalescent plasma.[74]

TREATMENT OF TYPE 1 DIABETES WITH COVID-19

In patients with type 1 diabetes treated with basal bolus or insulin pump therapy, the insulin doses should be titrated using frequent glucose and ketone monitoring to avoid hypoglycaemia in patients with reduced food intake, and adding correctional boluses of rapid-acting insulin to avoid severe hyperglycaemia and ketoacidosis. In case of illness, patients should not stop insulin but follow sick days rule and contact their health care provider. In case of hospitalisation due to severe illness, the patient must be put on IV insulin and fluids as per the standard protocol.[75] Acetaminophen can impact CGM sensor. [76]

TREATMENT OF COVID-19 WITH DIABETES

The only approved preventive measures today for COVID-19 are social distancing and quarantine. General measures to prevent COVID-19 include thorough and proper hand washing with soap and water and/or alcohol-based hand rubs, practice of proper respiratory hygiene, minimising contact with affected individuals and avoiding nonessential travel to affected areas.

Until now, treatment is available only for affected cases who are severely symptomatic. To treat or control novel coronaviruses, no specific effective drugs and vaccines are available.[77] However, in the latest clinical treatments, several old drugs have been found to inhibit some viral pathology, for example, chloroquine/hydroxychloroquine phosphate has a definite effect on the novel coronavirus pneumonia.[78,79]

As coronavirus pneumonia might be closely related to abnormal hemoglobin metabolism in humans, scientists suggest the therapeutic effect of chloroquine/HCQ phosphate on this infection [57]

Plasma Therapy

One small study from China showed convalescent plasma therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases.[81]

Vaccines

For reducing disease severity, viral shedding and transmission, effective SARS-CoV-2 vaccines are essential to helps prevent and minimize coronavirus outbreaks. For animals with SARS-CoV and MERS-CoV several vaccination strategies have been applied including a live-attenuated virus, inactivated virus, viral vectors, subunit vaccines, recombinant DNA, and proteins vaccines.[82] SARS-CoV-2 vaccines are in various stages of development. But it requires months and years to develop vaccines for human use.[83]

Special Precautions

There are also several suggested measures for patients with diabetes and COVID-19 infection. These include notifying the appropriate health authorities when there is a clinical suspicion for COVID-19, isolating for 14 days or until symptoms resolve, and maintaining hydration and symptomatic treatment. Patients with type 1 diabetes should measure blood glucose and urinary ketones frequently in case of fever with hyperglycemia. Antihyperglycemic treatment should be adjusted to avoid hypoglycemia and volume depletion and patients should follow sick days guidelines. In severe cases when patients are hospitalized, it is recommended to frequently monitor blood glucose and discontinue oral agents, especially metformin and sodium-glucose cotransporter-2 inhibitors, as insulin is the preferred treatment modality in this scenario.

Few preclinical works have pointed out that ACE2 expression increases by RAAs inhibitors which put a question regarding their safety in patients with COVID-19. The beneficial effect of RAAS inhibitors on heart failure, myocardial infraction and associated cardiovascular complications is well established [84] and the abrupt withdrawal of these drugs may result in clinical instability and current evidence is not strong enough to recommend discontinuing these medications.[85]

A recent article mentioned a few cases where the use of non-steroidal anti-inflammatory drugs causes severe adverse events in COVID-19 infected patients who had no other comorbid conditions.[86]

CONCLUSIONS

Infection with COVID-19 is associated with significant morbidity especially in patients with comorbid conditions like diabetes, hypertension, chronic kidney disease, etc. On the other hand, uncontrolled diabetes subjects have increased chance of being infected with COVID-19 and have significant morbidity and mortality. Thus, although COVID-19 is primarily not a metabolic disease, good glycaemic control is the key to reduce the probability of infection with COVID-19 and reduce the chance of acute metabolic decompensation in patients who are already infected and symptomatic. However, a specific and mechanistic approach which reduces the local inflammatory response and blocks viral entry into cells and prevent and ameliorate the acute effects of this virus is warranted.

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Position Statement on How to Manage Patients with Diabetes and COVID-19

Epidemiology, clinical features, and mortality of COVID-19

In 31 December 2019, 27 cases of pneumonia of unknown aetiology were identified in Wuhan City, Hubei Province in China; and in 7 January 2020, The Chinese Centre for Disease Control and Prevention (CCDC) subsequently named the cause of this disease as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Thereafter, the World Health Organization (WHO) declared this outbreak as a Public Health Emergency of International Concern in 30 January 2020; and then in 11 February 2020 this disease was named Coronavirus Disease 2019 or COVID-19 by WHO.[1,2]

The most frequent clinical features of COVID-19 are fever, cough, and shortness of breath; although recently some unusual symptoms such as loss of smell and taste are reported. The incubation period of the disease is between 2-14 days.[1] Based on a review and meta-analysis by do Nascimento et al., of a total of 61 studies including 59,254 patients, it found that the most common disease-related symptoms were: fever (82%), cough (61%), muscle aches and/or fatigue (36%); dyspnea (26%), headache (12%), sore throat (10%), and gastrointestinal symptoms (9%).[3] Another systematic review and meta-analysis on data from Wuhan also showed very similar result that fever, cough, fatigue, and dyspnea were the most frequent clinical symptoms. It was found that the most prevalent co-morbidities were hypertension (17%), diabetes (8%), cardiovascular diseases (5%) and respiratory system disease (2%).[4]

Summary of a report of 72,314 cases from the CCDC revealed that spectrum of disease was mild 81% (36,160 cases), severe 14% (6,168 cases) and critical 5% (2,087 cases). The case-fatality rate (CFR) of the disease was 2.3% (1,023 of 44,672 confirmed cases), 14.8% in patients aged >80 years (208 of 1,408) , 8.0% in patients aged 70-79 years (312 of 3,918), and 49.0% in critical cases (1,023 of 2,087). The CFR was elevated among those with pre-existing comorbid conditions, i.e.: 10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer. Among diabetics, CFR is actually 3 times higher compared to general population.[5] Based on the latest global situation reported by WHO (April 20, 2020), there are 2,314,621 person with confirmed COVID-19 and 157,847 death (6.8%).[2] In Indonesia, the latest report from *Gugus Tugas Percepatan Penanganan COVID-19* (April 20, 2020) showed the number of people confirmed with COVID-19 were 6,760 with 590 death (8.7%) cases related to COVID-19.[6]

Diabetes and immune dysfunction

Patients with diabetes in general are categorized as immunocompromised hosts, which means there is dysfunction of immunity related to capability against infection. Therefore, infectious diseases are more frequent and more serious in patients with diabetes compared to those without diabetes. The course of the infection is also more complicated in diabetes patients. One of the possible causes of this increased prevalence of infections is defects in immunity. In patients with diabetes there are alterations in proliferation of T cells and macrophages and impairment in NK cells and B cells function, which represents abnormal innate and adaptive immunity.[7,8]

Other causes of reduced capacity against infection also involves other complications related diabetes such as depression of antioxidant system, micro- and macro-angiopathies, neuropathy, decrease in the antibacterial activity of urine, gastrointestinal and urinary dysmotility, and greater number of medical interventions.[9]

General and specific precautions for patients with diabetes during a pandemic

It is reasonable to assume that people with diabetes are at increased risk of developing infection including COVID-19. Coexisting heart disease, kidney disease, advanced age and frailty are likely to increase the severity of disease. The following measures are suggested for prevention of this disease in patients with diabetes as proposed by Gupta et al.:[10]

A. Specific measures in patients with diabetes:

1. Maintain good glycaemic control, as it might help in reducing the risk and severity of infection. More frequent self monitoring of blood glucose levels is required. Good glycemic control may lessen chances of superimposed bacterial pneumonia as well.

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2. Patients with diabetes and co-existing heart disease or kidney disease need special care and attempts should be made to stabilise their cardiac/renal status.
3. Attention to nutrition and adequate protein intake is important. Any deficiencies of minerals and vitamins need to be corrected.
4. Exercise has been shown to improve immunity, though it might be prudent to be careful and avoid crowded places like gymnasia or swimming pools.
5. It is important to update influenza and pneumonia vaccinations. The latter may decrease chances of secondary bacterial pneumonia after respiratory viral infection, however, data in present viral epidemic is not available.

B. General preventive measures:

1. Thorough handwashing with soap and water should be encouraged since it kills the virus. Use of alcohol-based hand rubs is also useful.
2. Practice proper respiratory hygiene by covering of mouth and nose with bent elbow or tissue when coughing or sneezing. Touching of mouth, nose and eyes should be avoided.
3. Contact with an affected person needs to be minimised. Use face masks as advised if you have contact with someone with respiratory symptoms.
4. Avoid non-essential travel to major affected areas in order to restrict the spread of infection.

Diabetes management in patients with COVID-19

Patients with diabetes and COVID-19 may have more fluctuations in blood glucose levels due to conditions such as: irregular diet, reduced exercise or physical exercise, gastrointestinal symptoms; stress conditions like infection which increases glucocorticoid secretion; use of glucocorticoids in treatment can lead to a sharp rise in glucose; interruption or non-standard OAD treatment in isolation wards; fear, anxiety and tension; and COVID-19 itself can cause the human body to produce a large number of inflammatory cytokines and lead to extreme stress in some severe and critical patients.

People with diabetes are not more likely to get COVID-19 than the general population. The problem this group faces is primarily worse outcome, not a greater chance of contracting the virus. In China, where most cases have occurred so far, patients with diabetes had much higher rates of serious complications and death than those without diabetes. When sick with a viral infection, diabetes patients have an increased risk of diabetic ketoacidosis (DKA), commonly experienced by people with type 1 diabetes. Diabetic ketoacidosis can be a challenge for physician in managing fluid intake and electrolyte levels especially in sepsis and septic shock, which are serious complications found in COVID-19 patients.[11] A study by Guo et al., supported the notion that diabetes should be considered as a risk factor for a rapid progression and bad prognosis of COVID-19. They concluded that patient with diabetes should be given more attention especially in patients with rapid deterioration.[12]

The UK National Health Service (NHS) has proposed a clinical guide for the management of people with diabetes during the coronavirus pandemic.[13] There are the following categories of diabetes patients to consider:

1. Obligatory admissions and inpatients**:** Continue to require admission and medical management, eg., diabetic ketoacidosis (DKA). We must expedite treatment to avoid delay and expedite discharge to minimise length of stay.
2. Secondary care services: Outpatient attendances should be kept to the safe minimum. Consider using virtual clinics and remote consultations.
3. Primary care delivered diabetes services: Implications for routine diabetes care should be considered in the context of broader long-term condition management and prioritisation, taking into account individual risk factors and clinical needs.

Glucose control is key in the management of diabetes with COVID-19 because it impacts Infection control. Since COVID-19 patients with diabetes have higher mortality and also a higher proportion of critically ill adults, good glycemic control during hospitalization is particularly important in the comprehensive treatment of COVID-19. In diabetes patients, each patient should have individualized blood glucose target goals and treatment strategies.

Since there are currently no specific guidelines on plasma glucose targets in patients with diabetes and COVID-19, previous existing guideline can be implemented for them. For outpatients or inpatients in general ward, plasma glucose target in fasting or pre-prandial state is 80-130 mg/dL and 1-2 hour(s) post-prandial is <180 mg/dL. Whereas patients with critical illness who are treated with continuous intravenous insulin drip in Intensive Care Units, the plasma glucose target is between 140-180 mg/dL.[14,15]

Based on their experiences in China, Ma and Ran have proposed the target of blood glucose for patients with diabetes and COVID-19 based on the severity of COVID-19 (Table 1).[16] For patients with mild symptoms, a strict glycemic control target (fasting plasma glucose [FPG] 4.4-6.1 mmol/L [80-100 mg/dL], 2-hour postprandial plasma glucose (2 h PG) 6.1-7.8 mmol/L [100-140 mg/dL]) are recommended; a target for the glycemic control of common type patients (FPG 6.1-7.8 mmol/L [100-140 mg/dL], 2 h PG 7.8-10.0 mmol/L [140-180 mg/dL]) and subcutaneous insulin deliver therapy are recommended; a target non fasting blood glucose range of 10.0 mmol/L (180 mg/dL) or less for severe-type COVID-19 patients, a relatively less stringent blood glucose control target (FPG 7.8-10.0 mmol/L [140-180 mg/dL], 2 h PG 7.8-13.9 mmol/L [140-250 mg/dL) for critically ill patients and intravenous insulin infusion therapy are recommended. Due to the rapid changes in the condition of some patients, the risk of DKA or hyperglycemic hyperosmolar status (HHS) may

occur during the treatment. Blood glucose monitoring, dynamic evaluation and timely adjustment of strategies should be strengthened to ensure patient safety and promote early recovery of patients.

In mild cases, both oral anti-diabetic (OAD) and insulin treatment can be maintained and it is not necessary to adjust original regimen. In moderate cases, the original treatment can be maintained if patient's mental condition, appetite and glucose control are within normal range. Patients who are previously on OAD with obvious COVID-19 symptoms that cannot eat regularly may be treated with insulin instead. Patients with premix insulin regimen may be switched to basal-bolus regimen or insulin pump to manage glucose more flexibly. In severe or critical cases, intravenous insulin should be the first-line therapy. In these cases, metformin may raise lactic acid levels, while the SGLT2 inhibitors cause volume contraction, fat metabolism, and acidosis. Glucagon-like peptide receptor–1 analogues should also be stopped since they can cause nausea and vomiting, and pioglitazone is also not recommended because it can cause fluid overload. Once the patient has recovered and stabilized even during hospitalization, the treatment can be switched back to the previous regimen and noninsulin therapy can be reintroduced.[17]

Table 1. Targets for the blood glucose management in COVID-19 patients with diabetes according to the severity of the COVID-19[16]

Severity of the COVID-19	Diabetic condition	Indicator	Glucose control recommendation
Mild-type	Younger patients or patients with a short duration of disease, long life expectancy, no complications, and no significant CVD, without significant hypoglycaemia.	FPG 2 h PG	4.4-6.1 mmol/L (80-100 mg/dL) 6.1-7.8 mmol/L (100-140 mg/dL)
Common type	Older patients or patients with a history of Severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions and long-standing diabetes	FPG 2 h PG	6.1-7.8 mmol/L (100-140 mg/dL) 7.8-10.0 mmol/L (140-180 mg/dL)
Severe type		FPG 2 h PG Non-fasting	6.1-7.8 mmol/L (100-140 mg/dL) 7.8-10.0 mmol/L (140-180 mg/dL) 7.8-10.0 mmol/L (140-180 mg/dL)
Critical type		FPG 2 h PG Non-fasting	7.8-10.0 mmol/L (140-180 mg/dL) 7.8-13.9 mmol/L (140-250 mg/dL) 7.8-11.1 mmol/L (140-200 mg/dL)

FPG = fasting plasma glucose, 2hPG = 2 hours postprandial plasma glucose.

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The Philippine Society of Endocrinology, Diabetes and Metabolism

Position Statement on COVID-19 Infection and Diabetes

Coronavirus disease 2019 (COVID-19) has affected millions of lives worldwide, posing unprecedented challenges to global public health. It has infected people of different backgrounds, and from all industries, including healthcare workers. In China, an estimated 3000 health care workers have been infected and at least 22 have died.[1] This illness has disrupted the flow of outpatient and inpatient processes, a difficult challenge for both patients and doctors.

During this time, all physicians are mobilized to make sure that the stability of healthcare continues to be provided despite the crisis. Endocrinologists have joined the frontline forces as direct health providers and/or responders to tele-consults. However, during such a crisis, it is imperative that guidelines and/or recommendations are shared to all medical practitioners and to patients as well to ensure timely provision of care.

The PSEDM would like to provide recommendations for the clinical care of endocrine diseases during this COVID-19 crisis.

DIABETES MELLITUS AND COVID-19

Diabetes has been identified as one of the risk factors for increased severity of COVID-19. Persons with diabetes of older age (>60 y/o), with uncontrolled blood sugar, and the presence of complications of diabetes is associated with poor outcome of COVID-19. Based on the data from China,[2] the case fatality rate of people with diabetes who were diagnosed with COVID-19 was 7.3%. In Italy, diabetes accounts for 36% of COVID-19 related deaths.[3] Reports from the Philippine Department of Health (DOH) show that diabetes and hypertension are the most common co-morbidities among the mortalities of COVID-19 infected Filipino patients.[4]

Recommendations for persons with diabetes in preventing COVID-19[5]

1) Wash your hands often. Avoid touching your face.
2) Diabetic patients should stay home and practice social distancing. Limit your exposure to potential carriers of the virus.
3) Continue to take your regular oral medications or injectable medications.
4) Maintain a healthy and balanced diabetic diet. This should be complemented with proper exercise.
5) Monitor your blood sugars regularly using capillary blood glucose. Check for hypoglycemia if you do not feel well.

Get in touch with your doctor for your next follow up.

Handwashing is a recommendation to the general population and must become a regular habit. This applies specifically to persons with diabetes in how they handle their medications, both oral and injectable. Proper handwashing is easy yet essential to avert the transmission of infection.

Our country is under an enhanced community quarantine which means the public is strongly advised to stay at home. Diabetics should go out only when it is extremely necessary, We recommend that social distancing of at least 1 meter be strictly followed. These measures will reduce the exposure of persons with diabetes to infections like COVID-19.

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Staying at home means that outpatient follow ups with the healthcare providers are impeded. We recommend that for any health-related concerns, patients with type 1 diabetes should get in touch with their endocrinologists, while type 2 diabetics should be in communication with their endocrinologists, or internal medicine specialists, or general practitioners for continuity of care. We discourage clinic encounters with the physicians as persons with diabetes should avoid crowded areas (such as waiting rooms). We uphold the move of the Philippine Food and Drug Administration to recognize the use of electronic prescriptions to ease patient procurement of medications. We recommend that patients stock enough medications and supplies for blood glucose monitoring for the entire duration of the quarantine.

Uncontrolled blood sugar predisposes a diabetic to contract severe infections. To avoid such occurrence, strict glycemic control should be maintained at all times. We recommend that persons with diabetes follow proper dietary intake and that they exercise at home, as adherence to these practices are known to improve glycemic control, thus, curbing the risk for infection.

Recommendations for Diabetic patients with COVID-19 infection

1) Seek immediate medical attention if you are manifesting respiratory signs and symptoms consistent with COVID-19 infection. Proper assessments and recommendations should be followed.
2) Continue to take your regular oral medications or injectable medications.
3) Continue to monitor your blood sugars regularly using capillary blood glucose. Check for hypoglycemia if you do not feel well.
4) If your condition gets worse please seek immediate emergency room consultation.

All persons with diabetes, whether type 1 or type 2, may experience fluctuations or worsening of glycemic control. Implementation of "sick day rules" is therefore mandatory to overcome potential diabetes decompensation. Close monitoring of blood glucose is recommended, with a frequency of at least 2-3x a day, to properly observe and account the behavior of the patient's blood glucose during the illness.

If a person with diabetes experiences possible symptoms of COVID-19 such as fever, cough, shortness of breath, joint or body pains (myalgia), and/or diarrhea, they should immediately communicate with their health care provider, and seek advice regarding measures to avert possible deterioration of glycemic control. In case of moderate to severe symptoms, or severe hypoglycemia or hyperglycemia with changes in sensorium, it is necessary to seek immediate emergency consultation.

Recommendation for healthcare providers

1) Physicians should provide a means to communicate with patients with diabetes for continuity of care. (Remote consultation)
2) In the outpatient setting: Insulin titration, episodes of hypoglycemia and hyperglycemia should be discussed.
3) Among admitted patients:
    a. All physicians must wear proper personal protective (PPE) equipment in seeing suspected and confirmed COVID 19 patients.
    b. Allow patients that have stable vital signs to take their own blood glucose test while being visually monitored by a nurse or physician.
    c. Allow patients that have stable vital signs to take their oral medications or insulin injections while being visually monitored by a nurse or physician.
    d. When possible, use continuous glucose monitoring (CGM) to help mitigate the exposure of healthcare workers to COVID-19 cases. When using a CGM, we recommend its regular calibration with standard blood glucose testing.

We recommend that hospitals and satellite clinics develop a system optimizing emails, video and phone calls as means of consultation to provide continuity of care and to ensure that patients will be able to seek advice from their physicians. We recommend that physicians provide a means for their patients to communicate with them regarding issues of insulin titration, hypoglycemia and hyperglycemia. This is particularly true in patients with uncontrolled diabetes and those with gestational diabetes.

In the hospital setting, we recommend that all physicians wear the proper PPE in seeing PUIs (Suspect) and COVID positive (Confirmed) patients. To reduce exposure of healthcare workers to COVID-19, we recommend that PUIs and COVID+ patients who have stable vital signs and oxygenation be allowed to monitor their blood glucose and to take their oral anti-diabetic agents on their own, and if they are on insulin, be allowed to inject themselves, provided that they are visually monitored by the nurse or by their attending physician.

We recommend the use of continuous glucose monitoring, whenever possible, to closely monitor the patient's blood glucose as this may reduce the healthcare worker's exposure to the disease. It must be noted, however, that this may have to be compared to finger prick glucose testing for proper calibration and validation.

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ENDOCRINE PERSPECTIVES

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Challenges and Opportunities for Diabetes Care in the Philippines in the Time of the COVID-19 Pandemic

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Patients with diabetes constitute a vulnerable population in the surge of the COVID-19 pandemic. COVID-19 is a viral illness caused by the virus SARS-CoV2 which originated in China, presenting with a range of clinical manifestations from fever, cough, myalgia, resembling a systemic viral illness which can progress to acute respiratory failure, and multiple organ dysfunction. In the Philippines, the burden of both diseases is high. The prevalence of diabetes, a chronic, metabolic disorder characterized by hyperglycemia, is about 7.1% in adults between 20-79 years old in 2019.[1] The country has been afflicted by a COVID-19 outbreak and as of this writing, there are already more than 6000 cases of COVID-19 infection, and more than 400 individuals have died of the disease in the Philippines. This led the government to declare an enhanced community quarantine (ECQ), which entails restricted operation and movement of people and goods, except for essential services, throughout the island of Luzon-the largest island in the Philippines, which comprises of about 57 million people, last March 16, 2020. This ECQ has been extended twice, and will remain enforced until May 15, 2020 at the earliest,[2] in order to control the outbreak while boosting testing capacity and the ability of healthcare facilities to respond to COVID-19 cases.

Those with diabetes can be both a direct and a collateral victim of this pandemic. Poor blood sugar control may lead to an immunocompromised state, leading to an increased risk of contracting and developing the complications of COVID-19. As a chronic disease, diabetes entails multimodal management integrating medical nutritional therapy, exercise, pharmacologic therapy, close monitoring and follow-up. Quarantine measures and restrictions in mobility have made diabetes care more challenging. The other way that persons with diabetes become collateral damage is because of the focus now on treating persons who have the COVID infection. The Philippine government has designated 19 COVID-referral hospitals in the National Capital Region, and 75 facilities throughout the Philippines. These referral hospitals were preferentially equipped by the government with manpower, personnel protective equipment, medications and other needs to be able to manage persons infected with COVID who are referred to their hubs from the community or other hospitals. However, most of the other hospitals still mostly admit only patients with COVID. This has led to a significant number of patients who would have been previously admitted to be turned away from hospitalization to prevent them from becoming infected, and instead given medications for home management. This is true for various disease conditions, including persons with diabetes.

COVID-19 INFECTION IN AN INHERENTLY HIGH-RISK POPULATION

Several theories have been proposed to explain the increased susceptibility of patients with diabetes to acquiring COVID-19 infection and developing fatal sequelae of the disease. Molecular studies have shown that in people with diabetes, the expression of the angiotensin-converting enzyme 2 (ACE-2) is augmented. SARS-CoV2, the virus responsible for the illness COVID-19 binds to its target cells through ACE-2. It is hypothesized that an increased expression of ACE-2 leads to a higher risk of COVID-19 infection with severe manifestations.[3] Another theory raised is impairment in the immune response of patients with diabetes in the form of dysfunction in the lymphocyte proliferative response, complement activation, monocyte, macrophage, and neutrophil actions.[4] Endothelial dysfunction also plays a role in the poor outcomes of T2DM patients with COVID-19 infection.

In a study of 1527 patients in China, 9.7% of the cohort had diabetes. It was found that the risk of developing severe clinical manifestations necessitating admission to an intensive care unit was twice higher in patients with diabetes and hypertension compared to other patients.[5] In China, the mortality rate of patients with diabetes and with COVID-19 was as much as 7.3%, which was significantly higher than those of patients without any co-morbidities, which was at 0.9%.[6] Indeed, the pandemic poses new demands on diabetes care in a developing country such as the Philippines.

CHALLENGES REGARDING NUTRITION

Diet is a central aspect of diabetes management. The COVID-19 pandemic gave rise to barriers to the attainment of adequate and optimal nutrition for patients. A diabetic diet consisting of a balanced diet made up of carbohydrates from fruits, vegetables, whole grains, legumes, and low-fat dairy products, and protein[7] is difficult to obtain in the time of COVID-19 because lockdown measures restricting mobility and tightly regulated periods to buy food result in limited food choices. Some localities in the Philippines have been placed under extreme enhanced community

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quarantine and hard lockdown in order to control outbreaks, which has made it difficult for people to buy fresh food. Under a quarantine set-up, most people resort to buying food that do not spoil easily such as canned goods and processed food so that supplies would last until the next market day. Canned goods and processed food usually contain a lot of additives, with a high amount of sodium and fat. Such food choices are detrimental for patients with cardiovascular and renal complications of diabetes.

Another co-morbidity that is usually associated with diabetes is obesity, and the burden of this disease is also significant in the Philippines at about 4.7%.[8] High prevalence clusters of obese individuals are usually found in urban areas,[9] because of the higher intake of processed, calorie-dense foods, and lower level of physical activity compared to their rural counterparts, who are usually engaged in farming or fishing as livelihood. Patients with diabetes and obesity have diminished food options during the lockdown, making them unable to comply with their nutritional prescriptions. In the Philippines, the officials of the smallest government unit, the *barangay*, usually distribute foodstuffs, which is uniform for everyone, making it difficult to adhere to the diabetic diet.

Malnutrition is a significant health problem in the Philippines, even prior to the surge of COVID-19 cases. In a cross-sectional study done locally, moderate and severe undernutrition was found to be as much as 20.5%.[10] Restrictions in trade have caused significant reductions in the supply of nutritious food, thereby worsening malnutrition across populations. The enhanced community quarantine also had dire economic consequences. Because of the lack of employment during this period, a lot of citizens do not have the financial resources to purchase even the most basic needs such as food. Government assistance strove to mitigate the economic ramifications of the pandemic through the provision of food and other basic necessities but issues on access and sustainability of such assistance still need to be addressed.

CHALLENGES WITH PHARMACOLOGIC MANAGEMENT

Majority of patients with diabetes are on multiple drugs for glycemic control and cardiovascular protection. The COVID-19 pandemic gave rise to barriers to access to pharmacologic therapy on multiple levels. Lockdown measures, not only in the Philippines, but in many parts of the word, led to interruptions in the manufacturing and delivery of drugs, causing a lot of medications to be out-of-stock. For instance, China and India, both of which are major sources of imported drugs, are severely hit by the pandemic, thus creating major roadblocks in the supply chain. Another barrier to access is the inability of patients to refill their prescriptions in the setting of an enhanced community quarantine. In order to address this hurdle, the Food and Drug Administration (FDA) issued a circular (No. 2020-007) last March 17, 2020, honoring electronic prescriptions made by physicians.[11] This is a positive move in terms of improving access to medications; however, several gaps remain such as indigent patients being unable to obtain prescriptions due to lack of access to the Internet. It is still unclear whether or not old prescriptions will be considered valid in pharmacies during this time of the pandemic. Lack of mobility also affects access to medications and this drawback is more pronounced in rural areas where there are only a limited number of pharmacies that are operational during the lockdown and they are usually few and far apart. Many patients are unable to travel to these drug stores because of the ban on public transportation during the lockdown.

The most prevalent barrier to access is the high cost of medications, especially for indigent individuals who have difficulty purchasing their own medications even before this pandemic. A significant number of patients with diabetes are daily wage earners, and the loss of income during the enhanced community quarantine makes them unable to secure their medications. Access programs from the Department of Health for both insulins and oral anti-hyperglycemic agents are halted during COVID-19. Even households from the middle-income class have also lost their livelihood during the enhanced community quarantine and patients from this socio-economic class do not receive full government assistance financially and are seldom enrolled in these access programs prior to the pandemic. The pandemic indeed magnified inequities in care. With this, another threat unfolds after the COVID-19 pandemic-with poor control of diabetes and other co-morbidities during this crisis, there will be a large number of patients seeking care for diabetes-related complications thereafter.

GAPS IN FOLLOW-UP AND MONITORING

Diabetes is an intricate chronic disease that entails regular follow-up and monitoring. Assessing the status of patients with diabetes in the time of COVID-19 has been challenging both in the hospital and outpatient setting. The need for consultation and monitoring ought to be balanced with the urgency to reduce the exposure to infection of both patients and healthcare workers. Patients who have issues with health literacy, problems with mobility, and lack of access to resources such as mobile phones and the internet are at high risk of succumbing to diabetes-related morbidity and mortality in the time of COVID-19.

OPPORTUNITIES FOR INNOVATIVE DIABETES CARE DURING THE COVID-19 PANDEMIC

Recognizing that patients with diabetes represent a highly susceptible population, cooperation between healthcare workers, institutions, and patients gave rise to innovative solutions to respond to the challenges brought about by the COVID-19 pandemic. These strategies emphasize patient empowerment especially in the aspects of self-monitoring of blood glucose, adherence to lifestyle modification, hygiene and pharmacologic management, and monitoring for treatment-related adverse events like hypoglycemia. Tools like instructional videos, digital pamphlets, and infographics are increasingly being used today to enhance the health literacy of patients and caregivers. More efficient systems such as continuous glucose monitoring systems that enable real-time assessment of glucose control with minimal risk of transmission have been put in place.

Telemedicine, which pertains to the delivery of healthcare services by medical professionals in a setting where in physical distance is a limiting factor through information and communication technologies,[12] is now widely used in the country. This platform facilitates physician-patient interaction, allowing for the analysis of subjective complaints, blood glucose levels, and the provision of treatment and lifestyle advice. Through telemedicine, physicians are able to advise patients more thoroughly

on how to cope in terms of their nutrition, lifestyle and medications during the lockdown period. For instance, patients receive advice on better food choices such as fresh vegetables and home-cooked meals to consume, rather than calorie-dense, processed foods that are high in sodium and fat. Lack of exercise is also an issue discussed with patients with diabetes and strategies to address this such as home exercises (dance, stretching, yoga) that can be performed in a limited space are raised. Medication adjustments and sick day guidelines are also discussed.[12] Previous experiences suggest that telemedicine can be an effective tool for diabetes care. In a Cochrane review involving 2,768 patients from 21 randomized controlled trials, it was found that the HbA1c of patients on the telemedicine arm decreased by 0.31% (p <0.001).[13] Telemedicine also forged closer networking among physicians in the Philippines and also abroad, enabling physicians from different working environments, with varying levels of experience with treating diabetes and COVID-19, to share helpful insights with each other.

Another key strategy in improving diabetes care in the time of COVID-19 is close coordination among healthcare providers, local government agencies, and other organizations giving aid in order to deliver services that are compatible with the needs of patients with diabetes. Nutritionists at the local government level can be tapped to provide diabetic diet for patients.[14] Diabetes-specific formulas can also be distributed to patients with diabetes for either supplemental nutrition or meal replacement to improve glucose control. Fresh produce, instead of mostly canned goods, can be provided by local government units as well, to promote more healthy food choices among its citizens. It is paramount for barangay health care workers to identify patients with diabetes in the community because these patients should keep a vigilant eye on their symptoms and there should be a lower threshold for COVID-19 testing and hospitalization of patients with diabetes.

FUTURE CHALLENGES AHEAD

Patients with diabetes are especially vulnerable to the harsh consequences of the COVID-19 pandemic. Holistic diabetes care involves protecting these patients as healthcare systems transition to the "new normal." Once healthcare facilities reopen for diabetes follow-up, anticipatory care involves assessing patients for end-organ damage, checking vaccination status such as for influenza and pneumococcal vaccinations, and also evaluating for anxiety and depression levels of these patients in order to facilitate appropriate psychiatric referrals and assistance if necessary. Adhering to precautions against COVID-19 infection such as regular handwashing, cough hygiene, and social distancing,[10] must be inculcated to patients even after lockdown measures are lifted. Clinics must also be restructured to incorporate safety equipment and facilities to avoid the spread of infection. As we usher in a "new normal" for persons with diabetes, greater collaboration between the diabetes specialists- endocrinologists- and doctors in the community is encouraged so that not only preventive care is continued at the grassroots, but screening for diabetes and its complications continue with timely referral to specialists. The anticipated future then, after this crisis, is one of strong partnerships between doctors, patients, and institutions which are pivotal in improving the quality of diabetes care amidst formidable challenges in this global pandemic.

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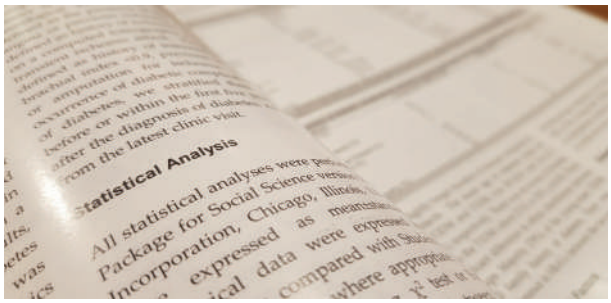

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ORIGINAL ARTICLE

Congenital Hypothyroidism in Children – A Cross-Sectional Study in a Tertiary Centre in Malaysia*

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Abstract

Introduction. The causes of congenital hypothyroidism (CHT) are thyroid dysgenesis (TD), dyshormonogenesis (TDH) or transient hypothyroidism (TH).

Methodology. This is a cross-sectional study looking at data over a period of 16 years (2000-2016). Confirmed cases had thyroid scan at the age of 3-years-old and repeated TFT (after 6 weeks off medications). Relevant data was collected retrospectively.

Results. Forty (60% female) children with CHT were included in the study. Thirty (75%) children presented with high cord TSH. Nine (23%) presented after 2 weeks of life. Majority were diagnosed with TDH (42.5%) with TD and TH of 40% and 17.5% respectively. Median cord TSH of children with TD was significantly higher compared to TDH and TH (p=0.028 and p=0.001 respectively). L-thyroxine doses were not significantly different between TD, TDH and TH at diagnosis or at 3 years.

Conclusions. TDH is highly prevalent in our population. TD may present after 2 weeks of life. One in five children treated for CHT had TH. Differentiating TD, TDH and TH before initiating treatment remains a challenge in Malaysia. This study provides clinicians practical information needed to understand the possible aetiologies from a patient's clinical presentation, biochemical markers and treatment regime. Reassessing TH cases may be warranted to prevent unnecessary treatment.

Key words: congenital hypothyroid, thyroid dysgenesis, thyroid dyshormonogenesis, transient hypothyroid, thyroxine, cord blood TSH

INTRODUCTION

Thyroid hormone is vital for the normal functioning of various organs in the body, including neural growth and transmission. This is especially important as studies have shown that there is a close association of thyroid hormone with foetal brain development.[1] Congenital hypothyroidism (CHT) is the term used when the production of the thyroid hormones are inadequate or deficient in newborn babies. It is an important diagnosis to be made early to prevent mental retardation in children. Cord blood or early serum TSH screening has been widely used to detect CHT.[2-3]

Permanent or true congenital hypothyroidism is divided into thyroid dysgenesis (agenesis or ectopics) (TD) or thyroid dyshormonogenesis (TDH). Children with permanent congenital hypothyroidism require lifelong thyroxine replacement. There is an increasing recognition of transient hypothyroidism or subclinical hypothyroidism, which can be due to maternal thyroid disease, prematurity or iodine deficiency. These children are usually on temporary thyroxine replacement.

The prevalence of congenital hypothyroidism worldwide is around 1 in 4000 livebirths in USA, Canada and Western Europe.[4] In our neighbouring country, Singapore,[5] the prevalence was reported as 1 in 3000 live births. Local studies in Malaysia have reported the prevalence of CHT as between 1600 to 3500 per 100,000 live births.[6,7] The prevalence of CHT in University Malaya Medical Centre (UMMC) was reported as 1 in 1515 term babies, slightly higher than previously reported Malaysian data.[7]

Data obtained from Leicester Royal Infirmary in UK,[8] reported that congenital hypothyroidism is more prevalent in Asians compared to non-Asians, with the affected population of children mostly had thyroid dysgenesis (1 in 4000). Another study from the University of Montreal, Canada,[9] found that for thyroid dysgenesis,

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females were more affected compared to males. In Yazd, Central Iran,[10] a larger population (54.5%) of children with transient hypothyroidism was reported compared to permanent hypothyroidism. However, the study population was small with only 22 children. In Malaysia, there is inadequate data to suggest distribution, however, a short report in 2009 showed thyroid dyshormonogenesis was much more prevalent than thyroid dysgenesis.[7,11]

Initial presentation of children with CHT can be variable, with most being asymptomatic if detected early. Other symptoms include sleepiness, poor feeding, cold extremities, prolonged neonatal jaundice, lethargy, hypotonia, macroglossia, umbilical hernia, coarse facies and dry skin. Delayed bone maturation is shown through delayed closure of posterior fontanelle, large anterior fontanelle and wide sagittal suture. CHT if not treated will cause significant reduction in irreversible, permanent nervous system damage and a consequent developmental delay. Previous studies have shown that the first 4 to 6 weeks of life is a phase crucial for postnatal brain development and a delay in treatment for one week can cause a significant reduction of IQ (approximately 10 points) in children with CHT.[12] This is why early detection and early treatment is so important. Meanwhile a study conducted by Albert BB et al., in New Zealand[13] has shown that children with CHT even when treated early had delayed normalisation of the T4 values that may affect the child's motor balance. This suggests the importance of early and aggressive treatment in this group of patients.

The Malaysian National CHT screening programme was initiated in October 1998. TSH levels are taken from cord blood due to logistics purposes.[14] Babies with cord blood TSH more than 40 mIU/L is highly suspicious for CHT. Cord blood TSH between 20-40 mIU/L will also be recalled for a repeat test. Serum fT4 and TSH between day 3 and 5 would be done for confirmation. Abnormal TFT performed between day 3 and 5 are treated according to AAP 2006 guidelines.[15] Those born prior to 2006 were treated according to AAP guidelines 1993.[16] Babies with normal cord blood TSH but later found to have abnormal TFT levels (TSH >10 mIU/L with a relatively lower fT4 levels <15 pmol/L) were treated.

In developed countries, thyroid scans are done shortly after positive initial screening. However, in Malaysia, due to the limited availability of thyroid scans, babies suspected to have CHT were not subjected to thyroid scan at initiation of treatment, compared to some other centres in the world. Instead the scan is done at age 3 years. Babies who were started on treatment would have their levels monitored monthly for the first 6 months, then every 2 to 3 months until 2 years old and subsequently every 3 to 4 months until the age of 3 years. At that point, treatment would be stopped for 4-6 weeks before the children were sent for thyroid scan. TFT would also be taken just prior to the thyroid scan. Thyroid dysgenesis (TD) is diagnosed if the child has both abnormal thyroid scan and TFT at 3 years old. Children with abnormal TFT but have normal thyroid scan are considered to have thyroid dyshormonogenesis (TDH). Transient hypothyroidism (TH) children will have normal scan and normal TFT. Only those with TD or TDH will eventually need thyroxine for life.

This study aims to guide clinicians in developing countries with limited resources to understand the aetiologies and possible outcome based on patients' clinical presentation. This includes timing of presentation, biochemical markers and treatment regimes.

METHODOLOGY

A cross-sectional study was conducted looking at data over 16 years from 2000-2016. This is to determine the prevalence, demographic profile, clinical and biochemical parameters of all CHT patients on follow-up at UMMC Paediatric Endocrinology clinic. UMMC is a tertiary referral centre in the urban population of Kuala Lumpur. Our study population were term babies born between year 2000 to year 2013 without any congenital anomaly or suspected syndrome. We identified CHT cases based on 3 sub-group diagnosis namely thyroid dysgenesis, dyshormonogenesis and transient hypothyroidism. These cases must have complete confirmatory diagnostic tests (re-testing TFT and thyroid scan) which was performed at 3 years old. We then collected data retrospectively from each case for analysis. All subjects were anonymised and potential identifiers removed. Relevant data was tabulated and analysed using SPSS software 22.0. This study was approved by the hospital ethics committee MREC No 2018913-6676.

Early presentation is defined as a patient presenting with either high cord blood TSH at screening or with symptoms before 2 weeks of life and late if presented after 2 weeks of life.

STATISTICS

Period prevalence was calculated based on the centre's livebirth registry and confirmed CHT cases. Kruskal-Wallis test was performed to compare the three types of CHT and post hoc analysis was done to explore the differences. Fishers exact test for gender and ethnicity was also performed to reflect association between the groups.

RESULTS

Total number of livebirth from 2000-2013 was 72,652 in this centre. A total of 223 cases were suspected to have CHT. Only 40 cases met the inclusion criteria and were included in the analysis. These cases were confirmed to have congenital hypothyroidism (CHT). The calculated period prevalence in this study group is 0.055%. The most common type of CHT seen is thyroid dyshormonogenesis (n=17,42.5%), followed by thyroid dysgenesis (n=16,40%) and transient hypothyroidism (n=7,17.5%). Despite being the least common, about 1 out of 5 children with CHT had transient hypothyroidism and were treated with thyroxine for at least 3 years.

Demographics

We have found that CHT in our population has a female preponderance (60% p=0.019) (Table 1). This is especially true with thyroid dysgenesis (81.3% female) and transient hypothyroidism sub-groups (71.4% female) (Table 1). Apart from gender, ethnicity difference was equally significant across 3 major ethnicity group in Malaysia (p=0.027). Chinese ethnicity was the majority in this population (47.5%). However, comparing sub-groups, 50%

Table 1. The distribution by gender in different types of congenital hypothyroidism

Types of CHT	Male	Female	Total
TD	3 (18.8%)	13 (81.3%)	16
TDH	11 (64.7%)	6 (35.3%)	17
TH	2 (28.6%)	5 (71.4%)	7
Total	16	24	40

p=0.019 *Fisher's Exact test

of the children who had thyroid dysgenesis were Malays, 70.6% of children with thyroid dyshormonogenesis were Chinese and 42.9% of those with transient hypothyroidism were Indians (Table 2).

Table 2. The distribution by ethnicity in different types of congenital hypothyroidism

Types of CHT	Malay	Chinese	Indian	Total
TD	8 (50%)	5 (31.3%)	3 (18.7%)	16
TDH	5 (29.4%)	12 (70.6%)	0 (0%)	17
TH	2 (28.6%)	2 (28.6%)	3 (42.9%)	7
Total	15	19	6	40

p=0.027 *Fisher's Exact test

Timing of presentation

Among all the children with CHT (n=40), 31 (77.5%) of them presented early with high cord blood TSH or abnormal TSH above 10 mIU/L within first 2 weeks of life. The remaining 9 (22.5%) presented at or more than 2 weeks of life. Only 1 in 8 children with thyroid dysgenesis and thyroid dyshormonogenesis presented late. Majority of children (57%) with transient hypothyroidism presented late (Table 3).

Table 3. Timing of presentation

CHT Type	Within first 2 weeks of life (Early Presentation)	More than 2 weeks of life (Late Presentation)	Total number of cases
TD	14 (87.5%)	2 (12.5%)	16
TDH	14 (82.4%)	3 (17.6%)	17
TH	3 (42.8%)	4 (57.2%)	7
Total	31 (77.5%)	9 (22.5%)	40

Clinical presentation

Clinically, children who presented early (n=31) were asymptomatic regardless of the type of CHT. Two cases of thyroid dysgenesis presented late. One had a missing record of cord blood TSH, however despite reminder, parents did not turn up for a repeat test and returned to their rural hometown for confinement. The second case had normal cord blood TSH. Both presented at much later stages with profound hypothyroidism (umbilical hernia, skin mottling, feeding difficulty and absent of femoral epiphyses). All late presenters from thyroid dyshormonogenesis group presented with mild symptoms of prolonged jaundice. It was more common for cases with transient hypothyroidism to present later with delayed TSH rise. Most were asymptomatic. One was incidentally found to have abnormal T4 levels during extensive workout for hypotonia and poor weight gain. She was treated with thyroxine when her T4 was persistently low (<15 pmol/L) despite normal TSH (6.33 mIU/L) (Table 3.1).

Biochemical levels

Median cord blood TSH level was observed to be higher in children with thyroid dysgenesis and dyshormonogenesis as compared to those with transient hypothyroidism. There was significant difference between the cord blood TSH level when compared to all sub-groups (*p*=0.01) (Table 4).

Post hoc analysis confirms statistically significant difference between levels in thyroid dysgenesis and thyroid dyshormonogenesis (*p*=0.028) and when compared between thyroid dysgenesis and transient hypothyroidism (*p*=0.001) (Table 4.1).

Dosing and treatment

At initiation of treatment, the mean starting dose of L-Thyroxine for thyroid dysgenesis, thyroid dyshormonogenesis and transient hypothyroidism were 11.83±3.88, 8.84±3.83 and 6.34±1.97 mcg/kg/day respectively. Although it appears to be different, Kruskal-Wallis test showed no significant difference between the three groups (*p*=0.614).

Similarly at 3 years old, there were no statistical difference between the doses taken by the children comparing all groups (*p*=0.056). The mean L-thyroxine dose were 3.18±0.69, 2.56±0.79 and 1.91±0.82 mcg/kg/day for thyroid dysgenesis, thyroid dyshormonogenesis and transient hypothyroidism respectively (Table 5).

DISCUSSION

The maturation process of the brain in a child requires thyroid hormone.[17] The significant role that thyroid hormone plays in brain development is undeniable, at which the deficiency of it would then cause cretinism. Fortunately, this form of mental retardation can be avoided[18] if hypothyroidism is detected and treated early. Thus, neonatal screening is crucial because early detection and treatment of congenital hypothyroidism can prevent mental retardation. In addition, early detection

Table 3.1. Case demographics of late presenters

Cases	Age presented to UMMC	Gender	Clinical presentation	Cord TSH (miu/L)	Diagnosis
1	4 weeks	Girl	Macroglossia, umbilical hernia, hypotonia, constipation	Missed, No follow- up	TD
2	5 months	Girl	Macroglossia, umbilical hernia, hypotonia, constipation, goitre, absent of tibia epiphysis on bone radiography	8.0	TD
3	3 – 4 weeks	Girl	Prolonged jaundice	12.0	TDH
4	3 – 4 weeks	Girl	Prolonged jaundice	6.0	TDH
5	3 – 4 weeks	Boy	Prolonged jaundice	4.0	TDH
6	>2 weeks (6 weeks old)	Boy	Delayed TSH rise	7.0	TH
7	2 weeks of life	Girl	Delayed TSH rise	7.0	TH
8	>2 weeks (9 months old)	Girl	Hypotonia, poor weight gain, low T4, normal TSH	21.0	TH
9	>2 weeks (3 weeks old)	Boy	Delayed TSH rise	5.0	TH

Table 4. Median cord TSH values of different subgroups of CHT

CHT Type	TD (n=16)	TH (n=7)	TDH (n=17)	*p*-value
Median Cord TSH (miu/L)	109.80	21.30	28.64	0.01*
Maximum level (miu/L)	595.00	28.00	167.00	
Minimum level (miu/L)	8.00	5.00	4.00	

**p*-value calculated using Kruskal-Wallis test

Table 4.1. Post Hoc analysis

Comparison	*p*-value
Transient (TH) – Dyshormonogenesis (TDH)	0.337
Transient (TH) – Dysenesis (TD)	0.001*
Dyshormonogenesis (TDH) – Dysgenesis (TD)	0.028*

**p*-value calculated using Kruskal-Wallis test

Table 5. Mean dosage (initial dose and last dose) of L-Thyroxine/day in children with thyroid dysgenesis (TD), thyroid dyshormonogenesis (TDH) and transient hypothyroidism (TH)

Types of CHT	Starting thyroxine		Last dose thyroxine at 3-years-old	
	Early	Late	On treatment	Not on treatment
TD n=16(40%)	15 (94%)	1 (6%)	16 (100%)	0
Mean dose (mcg/kg/day)	11.8 ± 3.88		3.18 ± 0.69	
TDH n=17(42.5%)	11 (64%)	6 (36%)	17 (100%)	0
Mean dose (mcg/kg/day)	8.84 ± 3.83		2.56 ± 0.79	
TH n=7(17.5%)	2 (28%)	5 (72%)	6 (86%)	1 (14%)
Mean dose (mcg/kg/day)	6.38 ± 1.97		1.91 ± 0.82	
	**p=0.614		**p=0.056	

also ensures better developmental outcomes through early thyroid hormone replacement in children with congenital hypothyroidism.

University Malaya Medical Centre (UMMC) has been practicing neonatal screening for congenital hypothyroidism using cord blood TSH since the late 1980's. Further confirmation by serum TFT would be then carried out on day 3 to 5 of life, at which treatment is instituted if the diagnosis was made. At the age of 3 years, all children treated for CHT were subjected to thyroid scan to confirm the cause of CHT. From diagnosis to 3 years old, these children were monitored closely and dosage adjustment was done according to laboratory tests, the TSH and fT4 levels.

We report significant proportion in relation to gender. More females were found to have CHT (thyroid dysgenesis and transient hypothyroidism) in our population. However, for thyroid dyshormonogenesis, boys predominate. Although not widely reported, this trend was also seen in few research studies published on the demographics of population of children with congenital hypothyroidism, where female to male ratio is 2:1.[4, 15, 19]

In previous studies, Asians are shown to have much higher incidence of thyroid dyshormonogenesis.[20] Screening in the North West health region of England also showed a significantly higher incidence of congenital hypothyroidism in Asian families--1/918 compared with 1/3391 in non-Asians.[21] A study from the UK[22] also showed predominance in Asian families to have CHT and females are more affected than males. In our study, the majority (42.5%) of our children with CHT had thyroid dyshormonogenesis. This is followed by thyroid dysgenesis (40%) and the remaining 17.5% transient hypothyroidism. We have demonstrated the ethnicity predisposition for CHT. This result also supports a paper published on New Zealand Asian births which had higher rates of dyshormonogenesis compared to New Zealand Europeans[23] and consolidates our previous report where we found that the majority of our patients with congenital hypothyroidism are thyroid dyshormonogenesis.[11]

Malaysia has a total population of 32.6 million, the majority are Malays (69%, followed by Chinese (22.8%) and Indians (6.9%).[24] We found that distribution of CHT in our centre affects more Chinese (47.5%), followed by Malays (37.5%) and the Indians (15%). The Chinese population were found to be more predisposed to have thyroid dyshormonogenesis (70.6%), while the Malays (50%) had thyroid dysgenesis and Indian population tend to have transient hypothyroidism. This report supports another study by Lee et al., who reported 4 Malaysian-Chinese children with thyroid mutation genes (c.2268dup) related to thyroid dyshormonogenesis.[25] Lee et al. also describes similar findings in 2 siblings with CHT who presented with goitre during late teenage years.[26] Studies from California also showed increase prevalence of CHT in certain Chinese and Asian Indian ethnic groups.[27]

One would anticipate a child with thyroid dysgenesis would not be able to produce thyroxine hence the high levels of cord TSH. We report 2 cases (12.5%) who presented late with profound symptoms. One child had no record of cord TSH. This was a missed case (inadequate cord blood sampling). Unfortunately, due to logistics issue, parents did not return child for a repeat sample at D3-5 despite reminder. This child presented with profound symptoms at 4 weeks old. The other child had a normal cord TSH which was unexpected. She presented much later with profound symptoms. Hypopituitarism was excluded. This 'normal' cord TSH could have been a diluted sample or contaminated with maternal blood.

In thyroid dyshormonogenesis, the gland is normally formed but its function is abnormal, resulting in inadequate T4 and T3 levels, inducing an increase in TSH levels. Depending on the severity, cord TSH may not be as high and abnormal as thyroid dysgenesis. Some may have either normal or borderline raised levels and these children may present later with milder symptoms. In this study, we report 3 cases (17%) who presented with prolonged jaundice and had normal cord TSH with delayed TSH rise.

Majority of the children with transient hypothyroidism had delayed rise in TSH levels and their cord TSH are well within the normal range. These babies were recalled every 1-2 weeks to monitor their TSH levels. If the TSH remains abnormal according to AAP 2006 guidelines, we started them on low dose thyroxine replacement to prevent further rise in TSH levels. Three out of four late presenters were asymptomatic. The child who presented with hypotonia

and poor weight gain was extensively investigated and was found to have persistently abnormal T4 levels between the age of 8-9 months. The cause of hypothyroidism was not identified.

There are a few possibilities to the causes of transient hypothyroidism.[28] Iodine deficiency is a condition to consider. Malaysian population is at high risk of iodine deficiency. Nazaimoon et al., has shown that up to 49% of children between 8-10 years old are iodine deficient.[29] Another report from Sabah showed that iodine deficiency among pregnant and breastfeeding mothers in Malaysia is high.[30] This is surprising as Sabah is known to have sufficient supply of seafood sources throughout different levels of society.

In Kuala Lumpur, although the hospital is situated in an urban location, the mean monthly household income is approximately RM 5000 (equivalent to USD 1200),[31] fish and seafood can be expensive and unaffordable to many. More local studies and data are needed to measure iodine levels in babies and their mothers especially the ones presenting later or with subclinical hypothyroidism. Other reasons included maternal thyroid disease or postnatal exposure to iodine (in our cases none had these) or maternal TRabs (We did not investigate this further).

When comparing cord blood TSH levels between the 3 sub-groups, we found that the median cord TSH in children with thyroid dysgenesis is expectedly higher than the children with thyroid dyshormonogenesis and transient hypothyroidism. However, between thyroid dyshormonogenesis and transient hypothyroidism, there is no significant difference in the median cord TSH level. This data suggests that as clinicians, although one can easily suspect a case with thyroid dysgenesis, one should not assume or predict the diagnosis without proper diagnostic testing. In our centre and in Malaysia generally, the diagnostic test can only be done at the age of 2-3 years old after stopping thyroxine for 4-6 weeks.

At diagnosis, children with thyroid dysgenesis and dyshormonogenesis were relatively given higher doses as compared to children with transient hypothyroidism. We used the recommended guidelines of 10-15 mcg/kg at diagnosis and adjustment was made according to biochemical levels.[15,32] Children with transient hypothyroidism were given a lower dose, which was found to be adequate enough to suppress their mildly elevated TSH. However, there was no statistical difference in the median thyroxine doses for the different 3 sub-groups. This suggests that clinicians are following general guidelines of treating CHT regardless of cord blood TSH levels. Further analysis on the titration of dosages and timing for TSH to normalise may give more insight to clinician to suspect the severe cases of CHT. Mathai et al., from New Zealand reported the variability and pattern, however the aetiologies were different from our population.[33]

By the time these children were 3 years old, children with dysgenesis and dyshormonogenesis remained on slightly higher dose as compared to those with transient hypothyroidism. However, our data was not significant enough to suggest that children on lower doses would likely be transient. Titrating doses according to TSH trends were performed regularly. None had a trial of stopping thyroxine despite using lower doses due to fear of potential neurocognitive impairment.

The next question is whether stopping treatment earlier for children whom we suspect have transient hypothyroidism can be safely done. From this report, we do know that they usually present later, are mostly asymptomatic, and required relatively lower doses. JCEM 2014 guidelines suggests re-evaluation after stopping thyroxine preferably after 3 years of life, however earlier retesting may be possible in cases suspected with transient hypothyroidism. Bloods should be repeated after 2 weeks of stopping and monitored regularly.[34]

We would suggest clinicians, especially general paediatricians in Malaysia, to consider titrating further and stop thyroxine earlier (before 3 years old) in children suspected with transient hypothyroidism. This should be done under proper monitoring and guidance of an experienced paediatric endocrinologist.

CONCLUSION

The most common type of CHT seen were thyroid dyshormonogenesis followed by thyroid dysgenesis and transient hypothyroidism. Children with thyroid dysgenesis may present after 2 weeks of life. One in 5 children who were treated for CHT had transient hypothyroidism. Given that the prevalence of transient hypothyroidism is common, clinicians may consider withholding or tapering off thyroxine earlier than 3 years old with careful assessment and diligent monitoring.

This study provides clinicians with practical information to understand the possible aetiologies of CHT from a patient's clinical presentation, biochemical markers and treatment regime. Although genetic mutations for thyroid dysgenesis and dyshormonogenesis are available in some centres worldwide, funding and opportunity may not be sufficient for most centres in Malaysia to proceed with genetic diagnosis.

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ORIGINAL ARTICLE

Glycemic Patterns and Factors Associated with Post-Hemodialysis Hyperglycemia among End-Stage Renal Disease Patients undergoing Maintenance Hemodialysis*

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Abstract

Introduction. Chronic and post-prandial hyperglycemia are independent risk factors for diabetic complications. Glycemic patterns among hemodialysis end-stage-renal-disease (ESRD) differ as glucose metabolism changes with declining kidney function with more pronounced glycemic fluctuations. The objectives of this study are to determine glycemic patterns on hemodialysis days, the magnitude of post-hemodialysis rebound hyperglycemia (PHH) and their associated factors.

Methodology. 148 patients on hemodialysis were analysed, 91 patients had end-stage-diabetic-renal disease (DM-ESRD), and 57 patients had end-stage-non-diabetic renal disease (NDM-ESRD). Glycemic patterns and PHH data were obtained from 11-point and 7-point self-monitoring blood glucose (SMBG) profiles on hemodialysis and non-hemodialysis days. PHH and its associated factors were analysed with logistic regression.

Results. Mean blood glucose on hemodialysis days was 9.33 [SD 2.7] mmol/L in DM-ESRD patients compared to 6.07 [SD 0.85] mmol/L in those with NDM-ESRD ($p<0.001$). PHH occurred in 70% of patients and was more pronounced in DM-ESRD compared to NDM-ESRD patients (72.5% vs 27.5%; OR 4.5). Asymptomatic hypoglycemia was observed in 18% of patients. DM-ESRD, older age, previous IHD, obesity, high HbA1c, elevated highly-sensitive CRP and low albumin were associated with PHH.

Conclusion. DM-ESRD patients experienced significant PHH in our cohort. Other associated factors include older age, previous IHD, obesity, high HbA1c, elevated hs-CRP and low albumin.

Key words: renal dialysis, glycemic variability, diabetes complications, hyperglycemia, risk factors, Asians

INTRODUCTION

Over two million people worldwide currently on renal replacement therapy have Type 2 Diabetes Mellitus (T2DM), the leading cause of end-stage-renal-disease (ESRD).[1,2] In Malaysia T2DM accounted for 61% of new dialysis patients.[3]

Glycemic patterns among diabetic patients with ESRD (DM-ESRD) whether or not on hemodialysis differ from those of diabetic patients without ESRD as glucose metabolism changes with decline in kidney function. Glycemic fluctuations are more pronounced among DM-ESRD as they may experience hemodialysis induced hypoglycemia and hyperglycemia.[4,5] Furthermore, hemodialysis per se is an independent risk factor for glycemic fluctuations as glucose is freely filtered and insulin is absorbed during hemodialysis.[6]

Fluctuations in glucose metabolism have proven to be detrimental in DM-ESRD as they leads to poor survival mainly owing to cardiovascular complications.[7] This was demonstrated by a six-year cohort study among DM-ESRD patients that showed a U-shape association between glycemic control (HbA1c <6% and >8%) and a decrease in overall survival.[8] This U-shape association might indicate that chronic hyperglycemia is not the only indicator for morbidity and mortality, but also hypoglycemia and glucose fluctuations.[7,8] Furthermore, many studies have shown glycemic variability (GV) as an independent risk factor for both morbidity and mortality among diabetic populations.[9]

Therefore, this study focused on glycemic patterns on hemodialysis days and non-hemodialysis days among ESRD patients. We also looked at post-hemodialysis rebound hyperglycemia (PHH), and its associated factors, as identifying these factors is hoped to optimize the management of this high-risk group.

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METHODOLOGY

Study design and sample population

One hundred and fifty ESRD patients on maintenance hemodialysis (93 DM-ESRD patients and 57 NDM-ESRD patients), were recruited in this cross-sectional study. Sample size was calculated by multiple logistic regression using G Power software.[10] Based on a study by Jin Y.P, 2015 we estimate the occurrence of post haemodialysis hyperglycemia among the DM-ESRD patients to be threefold that of NDM-ESRD patients.[11] We considered a model with one binary covariate X with event rate under Ho, $p_1 = 0.13$ and the event rate under X = 1, $p_2 = 0.40$, giving the odds ratio of ~ 4.5. We further assumed $R^2 = 0.1$, and an imbalanced design ratio of 2:1 between the 2 groups. The estimating sample size necessary to achieve a two-sided test with alpha of 0.05 and power of at least 80% was 102. Considering a 30% non-response rate, the final sample size was 146 rounded to 150.

Inclusion criteria were: adults age more than 18 with or without diabetes, patients on maintenance hemodialysis for at least three months. NDM-ESRD patients were included to observe the effect of hemodialysis on non-diabetic patients. Exclusion criteria were: Type 1 diabetes mellitus patients, presence of acute inflammatory state, hemoglobinopathy, history of blood transfusion or hospitalization for the last three months, and diagnosis of malignancy.

Socio-demographics, co-morbidities and laboratory data

Socio-demographic characteristics, clinical data, co-morbidities and medication lists were obtained using a standardized questionnaire. At recruitment, baseline blood investigations were taken: glycated hemoglobin –A1c (HbA1c), lipid profile, renal profile, albumin, hemoglobin, inflammatory markers, iron studies and bone parameters.

Glucose monitoring on hemodialysis and non-hemodialysis days

Glucose values in our study were obtained from capillary glucose measurements using capillary glucometers (Bayer contour plus®). Patients were taught to self-measure the capillary glucose and were assisted during the hemodialysis sessions. Patients were advised to record the glucose values and medications taken and were also educated to recognize hypoglycemic signs and symptoms. On hemodialysis days, a 11-point capillary self-monitoring glucose (SMBG) profile was obtained with hourly capillary glucose taken during the hemodialysis sessions. On non-hemodialysis days, 7 points SMBG were taken by the patients. Patients were not required to fast during hemodialysis but were asked to report and food consumed that was out of their ordinary diet.

Statistical analysis

Analyses were performed using R studio version 1.0.153 using the STATS package for statistical analysis. In descriptive statistics, categorical data results were described as count and percentage while continuous data in mean and standard deviation (SD). Overall glycemic profile, specifically looking, as post hemodialysis glucose value was measured in terms of means glucose ± SD. The data was checked for normality visually by histogram and statistically using the Shapiro Wilk test. For bivariate analysis, a chi squared test was used for comparing categorical data. An independent t-test was used to compare means between the groups as the data was normally distributed. The assumption of equal variance was met using Levene's test. The level of significance was set at 0.05. In order to determine the association between PHH with clinical and laboratory variables, simple logistic regression was done to derive the crude odd ratio. Subsequently, the variables which were significant at $p < 0.15$ were included in the final multivariate logistic regression analysis. All the crude and adjusted odds ratios were presented with 95% confidence intervals. For missing data, the Listwise deletion method was used.

RESULTS

Socio-demographics, co-morbidities and laboratory data analysis

From the total of 150 patients recruited, 148 patients data were included in the final analysis due to missing data from two patients. Table 1 demonstrates the baseline sociodemographics and co-morbidities of our cohort. Ninety-one (61.5%) patients had diabetes with a mean age of 57.6 years and mean duration of diabetes of 16.4 years. Mean duration of hemodialysis in DM-ESRD and NDM-ESRD patients were 3.8 and 4.5 years, respectively. Body mass index (BMI) in the majority of patients was Obese Class 1. The difference in socio-demographics and co-morbidities among both groups were not statistically significant apart from DM-ESRD patients having higher BMI and higher prevalence of smoking among NDM-ESRD patients. Ischemic heart disease (IHD) was present in one-fourth of the patients. Blood pressure control was poor with only 16 (10.7%) of DM-ESRD and 47 (31.3%) of NDM-ESRD patients achieving pre and post hemodialysis target blood pressure of less or equal to 130/80 mmHg.

In terms of medications, 50 (54.9%) of diabetic patients were on insulin therapy, 18 (19.7%) on oral hypoglycemic agents (OHA), and 23 (25.2%) were not on regular medications. The majority of patients, i.e., 56 (82.3%) patients, would not take their medications on hemodialysis days. Patients on OHA alone would not take their OHA on hemodialysis days, while patient on basal-bolus insulin, would omit the insulin dose before their hemodialysis session.

Table 2 compares the baseline blood parameters between DM-ESRD and NDM-ESRD patients. Both groups had a non-significant difference in terms of blood parameters apart from HbA1c, phosphate and albumin. Mean HbA1c among DM-ESRD patients was 7.4% with 37% having HbA1c less than 6.5% and 30% falling between 6.5% to 8%. Analysing the highly sensitive C-reactive protein (hs-CRP) as a surrogate marker for cardiac disease showed both groups having high hS-CRP levels with means of 8.91mg/L and 7.03 mg/L among DM-ESRD and NDM-ESRD patients respectively. Albumin levels were significantly lower among DM-ESRD patients, while phosphate levels were higher among NDM-ESRD patients.

In our DM-ESRD cohort, 13 (14.3%) took their OHA/insulin on hemodialysis days with 3 (3.3%) of patients reporting hypoglycemic symptoms during hemodialysis sessions. Almost all (94.7%) patients ate during hemodialysis.

Table 1. Baseline socio-demographic and clinical characteristics of patients

Characteristics	DM-ESRD n (%)	NDM-ESRD n (%)	Test statistic*	p value
Sex			0.165	0.685
Male	51 (56.0)	30 (52.6)		
Female	40 (44.0)	27 (47.4)		
Race			1.078	0.583
Malay	79 (86.8)	52 (91.2)		
Chinese	1 (1.1)	1 (1.8)		
Indian	11 (12.8)	4 (7.0)		
BMI			10.729	**0.030*** **
Underweight (<18.5)	1 (1.1)	4 (7.0)		
Normal (18.5 – 22.9)	11 (12.8)	15 (26.3)		
Overweight (23.0 – 24.9)	15 (16.5)	7 (12.3)		
Obese Class 1 (25.0 – 29.9)	41 (45.1)	16 (28.1)		
Obese Class 2 (>30.0)	23 (25.3)	15 (26.3)		
BP Target Pre HD			1.383	0.240
Pre-HD BP (≤130/80)	12 (13.2)	4 (7.0)		
Pre-HD BP (>130/80	79 (86.8)	53 (93.0)		
BP Target Pre HD			3.426	0.064
Post HD BP (≤130/80)	34 (37.4)	13 (22.8)		
Post HD BP (>130/80)	57 (62.6)	44 (77.2)		
Smoking			7.074	**0.008*** **
Yes	4 (4.4)	10 (17.5)		
No	87 (95.6)	47 (82.5)		
Hypertension			2.311	0.128
Yes	90 (98.9)	54 (94.7)		
No	1 (1.1)	3 (5.3)		
IHD			1.038	0.308
Yes	26 (28.6)	12 (21.1)		
No	65 (71.4)	45 (78.9)		
Gout			1.415	0.234
Yes	6 (6.6)	7 (12.3)		
No	85 (93.4)	50 (87.7)		
Stroke			0.307	0.580
Yes	5 (5.5)	2 (3.5)		
No	86 (94.5)	55 (96.5)		
Hyperlipidaemia			2.857	0.091
Yes	56 (61.5)	27 (47.4)		
No	35 (38.5)	30 (52.6)		
	Mean (SD)	**Mean (SD)**	**Test statistic****	**P value**
Age (years)	57.6 (11.1)	49.0 (11.2)	-4.590	**<0.001*** **
Duration of HD (years)	3.8 (3.1)	4.5 (3.3)	1.310	0.198
BMI (kg/m^2)	27.1 (4.4)	26.2 (6.6)	-0.862	0.391

Table 1 shows the baseline sociodemographic and clinical characteristics of patients (n=148), values expressed as mean ± standard deviation. DM-ESRD, diabetic-end stage renal disease; NDM-ESRD, non diabetic end-stage-renal-disease; HD, hemodialysis; BP, blood pressure; BMI, body mass index. *Chi square test **Independent t-test ***P value<0.05

Table 2. Mean (SD) blood parameters comparing DM-ESRD and NDM-ESRD

Characteristics	DM-ESRD Mean (SD)	NDM-ESRD Mean (SD)	T statistic	P value
Hemoglobin (g/dL)	10.47 (1.7)	10.38 (1.7)	-0.339	0.735
HbA1c (%)	**7.40 (1.6)**	5.41 (0.5)	-10.845	**<0.001***
Total cholesterol (mmol/L)	4.8 (1.3)	5.0 (1.2)	1.003	0.318
LDL (mmol/L)	2.97 (1.16)	3.10 (1.18)	0.664	0.508
TG (mmol/L)	2.30 (1.7)	2.04 (1.4)	-1.030	0.304
HDL (mmol/L)	0.97 (0.22)	1.08 (0.29)	2.560	0.012
HSCRP (mg/L)	8.91 (10.2)	7.03 (7.1)	-1.310	0.192
Ferritin (ug/L)	554.1 (402)	665.2 (435)	1.497	0.137
Transferrin saturation (%)	23.96 (11.2)	24.82 (8.8)	0.526	0.600
Calcium (mmol/L)	2.16 (0.22)	2.19 (0.24)	0.883	0.379
Phosphate (mmol/L)	1.85 (0.54)	2.18 (0.73)	**2.893**	**0.005***
iPTH (pmol/L)	73.6 (58.3)	103.7 (105.1)	1.889	0.063
ALP (U/L)	176.32 (173.3)	143.37 (112.2)	-1.413	0.159
Albumin (mmol/L)	**38.3 (4.2)**	40.1 (2.7)	3.190	**0.002***

Table 2 shows the baseline blood parameters of patients (n=148), values expressed as mean ± standard deviation. HbA1c, glyclated hemoglobin A1c; LDL, low density lipoprotein; TG, triglycerides; HDL, high density lipoprotein; HSCRP, highly sensitive C-reactive protein; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase. * p < 0.05.

Figure 1 illustrates mean blood glucose on hemodialysis days, which were significantly different (p<0.01) between DM-ESRD and NDM-ESRD patients. The mean (±SD) blood glucose was 9.33±2.7 mmol/L in DM-ESRD and 6.07±0.85 mmol/L in NDM-ESRD. The mean fasting blood glucose was 7.9 mmol/L and 5.1 mmol/L in DM-ESRD and NDM-ESRD patients, respectively.

During the intra-dialytic period, the mean blood glucose was 8.1 mmol/L and 5.9 mmol/L in DM-ESRD and NDM-ESRD groups, respectively. Among DM-ESRD, 61 (67.0%) of patients had readings within the suggested limits (4.4–8.5 mmol/L). Thirty (32.9%) patients recorded blood glucose more than 8.5 mmol/L. Among NDM-ESRD patients, the majority recorded values within the

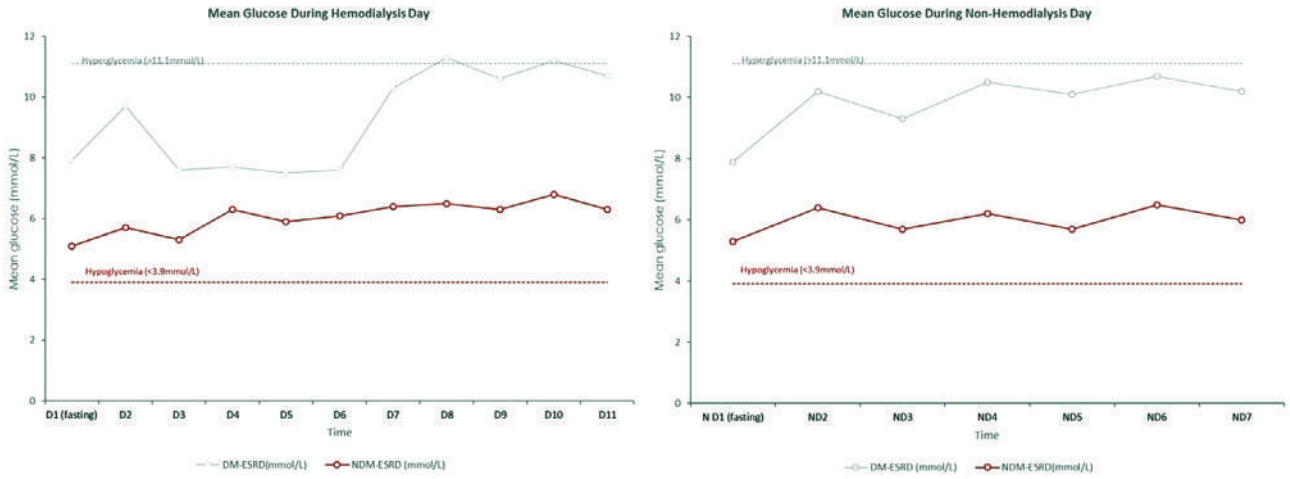

Figure 1. Glycemic patterns among DM-ESRD vs. NDM-ESRD during hemodialysis days and non-hemodialysis days.

Legend: DM-ESRD shows more marked glucose fluctuations during hemodialysis days with prominent post-hemodialysis hyperglycemia coupled with persistent hyperglycemia until the end of the day. Glycemic fluctuations were not prominent during non-hemodialysis days in both DM-ESRD and NDM-ESRD. Timing hemodialysis day: D1 = Fasting, D2 = Prior hemodialysis, D3 = 1st hour hemodialysis, D4 = 2nd hour hemodialysis, D5 = 3rd hour hemodialysis, D6 = 4th hour hemodialysis, D7 = 2 hours post hemodialysis, before meal, D8 = 2hrs post meal, D9 = before dinner, D10 = 2 hours post dinner, D11= before sleep. Timing non-hemodialysis: ND1 = Fasting – before breakfast, ND2 = 2 hours post breakfast, ND3 = before lunch, ND4 = 2 hours post lunch, ND5 = before dinner, ND6 = 2 hours post dinner, ND7 = before sleep.

suggested intradialytic glucose limits. Eighteen (12%) patients i.e. 7 (7.6%) with DM-ESRD and 11 (19.3%) with NDM-ESRD, experienced intradialytic asymptomatic hypoglycemia. This phenomenon which was seen predominantly among NDM-ESRD patients occurred mainly during the first hour of hemodialysis with mean pre-hemodialysis blood glucose of 4.3 mmol/L among NDM-ESRD patients.

Post-hemodialysis trends showed a mean pre-prandial reading among DM-ESRD patients of 10.4 mmol/L and a mean post-prandial reading of 11.1 mmol/L. Among DM-ESRD patients, 70 (77%) had blood glucose of more and equal to 7.0 mmol pre-prandially, while 65 (72%) had blood glucose more than 8.0 mmol/L post-prandially. Figure 1 shows that the DM-ESRD group had persistently high glucose level post-hemodialysis until the end of the day, which was not seen in the NDM-ESRD group.

Post-hemodialysis hyperglycemia (PHH)

PHH (defined as blood glucose ≥ 11.1 mmol/L 2-hours after first meal) post hemodialysis was prominent among DM-ESRD patients, as almost 75 (82.4%) of them experienced more than 80% increase of blood sugar, compared to NDM-ESRD patients during the end of hemodialysis, odds ratio 4.5 (CI: 2.2 – 9.6) (Figure 2). However, among NDM-ESRD patients, almost half of the patients, i.e. 25 (43.8%) experienced a reduction in blood sugar post hemodialysis as compared to only 14 (15.4%) of DM-ESRD patients.

Glycemic pattern on non-hemodialysis days

On non-hemodialysis days (Figure 1), there were significant differences between blood sugar profiles among DM-ESRD and NDM-ESRD patients, where the mean (SD) blood glucose was 9.85 ± 3.1 mmol/L and 6.0 ±0.88 mmol/L, respectively. In DM-ESRD patients, post-prandial hyperglycemia more or equal to 8.5 mmol/L were observed in 61 (67.0%) patients with 28 (30.8%) experiencing blood sugar more or equal to 11.1 mmol/L (mean preprandial 9.1 ± 3.1 mmol/L and post-prandial 10.4 ± 3.3 mmol/L).

Correlation between mean blood glucose and HbA1c

In our population, there was a strong correlation between mean blood glucose and HbA1c among all patients with R^2 = 0.73. However, among DM-ESRD patients, the correlation was moderate with R^2 = 0.59.

Factors associated with PHH

Table 3 demonstrates a simple logistic regression analysis of clinical characteristics and blood parameters associated with PHH. In this study, DM-ESRD, obesity, previous IHD, older age, high HbA1c, elevated hs-CRP and low albumin were associated with the risk of PHH. Table 4 shows the final multivariate logistic regression model, the model is fit with R^2 of 0.258. Increasing age of the patient are significant with adjusted odds ratio of 1.04, while DM-ESRD had adjusted odds ratio of almost three times higher than NDM-ESRD.

DISCUSSION

Cardiovascular disease is the leading cause of morbidity and mortality in ESRD particularly in diabetic patients, where the excessive cardiovascular risk may be attributed to underlying co-morbidities and population-based factors; however, these do not account for all the observed risk.[4] Studies have shown that besides the average HbA1c (a marker for chronic hyperglycemia), short-term glycemic variation (GV) is also an independent risk factors for diabetic complications.[12–14] GV, which describes glycemic fluctuations or oscillations around a mean value, is an independent risk factor for diabetes-associated morbidity and mortality.[15] Post-prandial hyperglycemia; among the main contributors to GV, similar to PHH, was shown to play a significant role in the pathophysiology of diabetic complications in terms of inducing oxidative stress and the inflammatory process.[16,17] Hence, it is crucial to evaluate the glycemic pattern in hemodialysis patients, especially emphasizing PHH, as it is one of the main contributors to glycemic fluctuations.

Table 3. Factors associated with post haemodialysis hyperglycaemia (PHH) using simple logistic regression

	PHH		Test statistic	P Value	Crude Odds ratio (95% CI)
	Increase	Decrease			
Diabetes			3.989	**<0.01**	
Yes	74 (72.5)	17 (37.0)			4.5 (2.2, 9.6)
No	28 (27.5)	29 (63.0)			Reference
Gender			0.650	0.515	
Female	48 (47.1)	19 (41.3)			1.26 (0.63, 2.58)
Male	54 (52.9)	27 (58.7)			Reference
Smoking			-0.991	0.322	
Yes	8 (7.8)	6 (13.0)			0.56 (0.19, 1.82)
No	94 (92.2)	40 (87.0)			Reference
BMI (kg/m²)			22.7	**<0.01**	
Normal (18.5 – 22.9)	16 (15.7)	10 (21.7)			Reference
Underweight (<18.5)	2 (2.0)	3 (6.5)	0.877	0.380	2.40 (0.34, 20.77)
Overweight (23.0 – 24.9)	14 (13.7)	8 (17.4)	0.951	0.342	2.63 (0.36, 23.37)
Obese 1 (25.0 – 29.9)	41 (40.2)	16 (34.8)	1.404	0.160	3.84 (0.59, 31.31)
Obese 2 (>30.0)	29 (28.4)	9 (19.6)	1.592	0.111	4.83 (0.70, 41.37)
IHD			1.53	**0.125**	
Yes	30 (29.4)	8 (17.4)			1.98 (0.86, 5.01)
No	72 (70.6)	38 (82.6)			Reference
Gout			-0.600	0.549	
Yes	8 (7.8)	5 (10.9)			0.70 (0.22, 2.43)
No	94 (92.2)	41 (89.1)			Reference
Hyperlipidaemia			0.999	0.318	
Yes	60 (58.8)	23 (50.0)			1.43 (0.71, 2.89)
No	42 (41.2)	23 (50.0)			Reference
Stroke			0.147	0.883	
Yes	5 (4.9)	2 (4.3)			1.13 (0.23, 8.13)
No	97 (95.1)	44 (95.7)			Reference
Hypertension			0.0808	0.419	
Yes	100 (98.0)	44 (95.7)			2.27 (0.27, 19.43)
No	2 (2.0)	2 (4.3)			Reference
	Mean (SD)				
Age (years)	56.6 (12.0)	49.2 (10.2)	3.383	**<0.01**	1.06 (1.03, 1.10)
Duration HD (years)	3.9 (3.1)	4.5 (3.4)	-0.983	0.326	0.95 (0.86, 1.06)
BMI (kg/m²)	27.3 (5.1)	25.6 (5.8)	1.756	**0.079**	1.06 (0.99, 1.14)
HbA1c (%)	6.9 (1.6)	6.1 (1.5)	2.613	**<0.01**	1.44 (1.12, 1.94)
HSCRP (mg/L)	8.4 (8.3)	6.4 (6.1)	1.42	**0.155**	1.04 (0.99, 1.10)
Ferritin (µg/L)	622.2 (413.1)	560.2 (421.7)	0.807	0.412	1.00 (0.99,1.00)
Albumin (mmol/L)	38.5 (4.0)	39.9 (3.0)	-2.109	**0.035**	0.89 (0.80, 9.88)
Clearance (%)	69.5 (9.0)	69.0 (9.4)	0.260	0.795	1.01 (0.97, 1.05)
LDL (mmol/L)	3.0 (1.2)	3.0 (1.0)	0.115	0.908	1.02 (0.75, 1.39)
HDL (mmol/L)	0.99 (0.2)	1.0 (0.3)	-1.174	0.240	0.44 (0.11, 1.74)
HB (g/dL)	10.44 (1.7)	10.40 (1.7)	0.168	0.866	1.02 (0.83, 1.25)
TG (mmol/L)	2.3 (1.8)	1.9 (1.1)	1.334	0.182	1.20 (0.94, 1.61)
Transferrin saturation	24.0 (10.2)	25.2 (10.9)	-0.611	0.541	0.99 (0.96, 1.02)
Calcium (mmol/L)	2.17 (0.21)	2.16 (0.24)	0.336	0.737	1.31 (0.26, 6.34)
Phosphate (mmol/L)	1.9 (0.6)	2.1 (0.7)	-1.408	0.160	0.68 (0.39,1.16)
ALP (U/L)	148.6 (108.0)	175.0 (154.4)	-1.169	0.242	0.99 (0.99, 1.00)
iPTH (pmol/L)	78.1 (67.6)	100.5 (102.4)	-1.465	0.162	0.99 (0.99,1.00)

Table 3 shows simple logistic regression analysis of sociodemographic, clinical co-morbidities and blood parameters among patients in cohort (n=148) with post hemodialysis hyperglycemia (PHH). Diabetes, Body Mass Index (BMI) category, Ischemic Heart Disease (IHD), age, glycated hemoglobin (HbA1c), highly sensitive C-reactive protein (hs-CRP) and albumin were significant at P<0.15 to be included in multiple logistic regression.

Table 4. Multiple logistic regression analysis for factors associated with post hemodialysis hyperglycemia (PHH) (N=148)

Variable	β	SE	Wald	Adjusted OR (95% CI)	P-Value
Diabetes	**1.08**	**0.56**	**1.951**	**2.96 (1.01, 9.09)**	**0.050***
Age (years)	**0.041**	**0.019**	**2.157**	**1.04 (1.00, 1.08)**	**0.031***
IHD	0.584	0.515	1.134	1.80 (0.68, 5.22)	0.257
HBA1c (%)	0.004	0.176	0.026	1.00 (0.72, 1.44)	0.980
Albumin (mmol/L)	-0.093	0.065	-1.429	0.91 (0.80, 1.03)	0.153
HSCRP (mg/L)	0.0152	0.031	0.497	1.02 (0.96, 1.08)	0.620
BMI (kg/m²)					
Normal (Reference)	-	-	-	Reference	
Underweight	0.588	1.05	0.558	1.80 (0.22, 16.89)	0.577
Overweight	0.023	1.10	0.021	1.02 (0.12, 10.28)	0.983
Obese	0.643	1.02	0.628	1.90 (0.25, 16.94)	0.530
Obese Class 1	1.12	1.06	1.051	3.06 (0.38, 29.24)	0.293

Table 4 shows multiple logistic regression analysis of significant factors associated with post hemodialysis hyperglycemia among ESRD patients during hemodialysis (HD) day. OR, odd ratio; HbA1c, glyclated hemoglobin; HSCRP, highly sensitive C-reactive protein; Ischemic Heart Disease (IHD) and BMI class. R^2= 0.258 (Nagelkerke) *P<0.05.

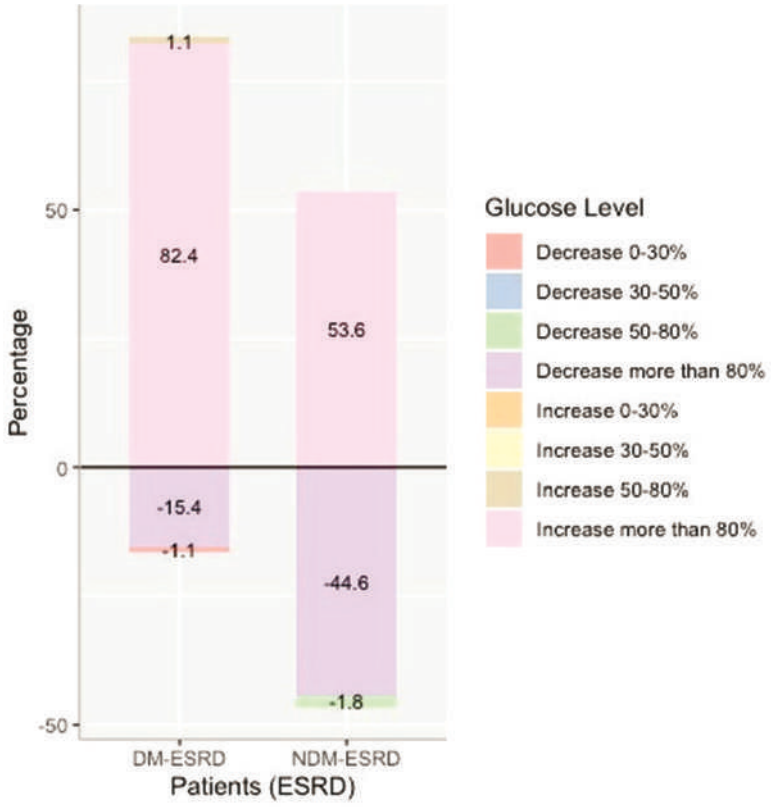

Figure 2. Capillary glucose changes post hemodialysis sessions.

Legend: Figure 2 showing the capillary glucose changes occurs post hemodialysis session between DM-ESRD and NDM-ESRD. In DM-ESRD, 75 (82.4%) experienced more than 80% increased of blood sugar value, compared to NDM-ESRD during the end of hemodialysis with odds ratio of 4.5 (CI: 2.2 – 9.6).

In our study, DM-ESRD patients had more significant glycemic fluctuations compared to those with NDM-ESRD. During hemodialysis days, we observed that PHH was fourfold higher in DM-ESRD compared to NDM-ESRD patients. An 80% rise in blood glucose post-hemodialysis occurred in 82% of diabetic patients. This hyperglycaemia was subsequently persistent throughout the day. On the other hand, this persistent hyperglycemia post hemodialysis was not seen among NDM-ESRD patients. This shows that hemodialysis predisposes DM-ESRD patients to constant hyperglycemia. Other patients exhibited lowered blood glucose levels in the first hour of hemodialysis, which subsequently became constant over the four hours of hemodialysis. This asymptomatic intradialytic hypoglycemia was observed in 18 (12.6%) patients, and more markedly seen in NDM-ESRD patients i.e., 11 (19.3%) patients. In the DM-ESRD patients, only 7 (7.8%) of out of the 91 patients developed intradialytic hypoglycemia; and the majority occurred in the first hour of hemodialysis with a mean blood glucose pre-hemodialysis of 5.4 mmol/L. Most of these patients were on insulin treatment. Although patients with NDM-ESRD had no significant glycemic fluctuations during hemodialysis, almost half experienced a reduction in blood sugar levels post-hemodialysis. Development of intra-dialytic hypoglycemia and reduction of blood sugar among ESRD patients even non-diabetic was an important observation, as currently there are no guidelines on management of insulin or OHA on hemodialysis days, which is left to the nephrologist's discretion.[7] However, we demonstrated that the number of patients developing intra-dialytic hypoglycemia was small compared to those developing PHH, which is similar to previous studies.[18–20] Furthermore, among our population, all patients were encouraged to eat during hemodialysis to prevent episodes of hypoglycemia.

Our observations were similar to other studies on hemodialysis patients. Abe et al. showed that plasma glucose decreased with hemodialysis and hyperglycemic spikes were observed post hemodialysis which were attributed to decreased insulin due to hemodialysis clearance and/or the release of counter-regulatory hormones.[6] Similar intradialytic glucose reduction and PHH were observed by Gai et al., which demonstrates PHH occurs 150 minutes post-hemodialysis.[20] Kazempour-Ardenilli et al., showed glycemic readings were lower on hemodialysis days as compared to non-hemodialyis days.[18] Both Mirani et al., and Jin et al., showed that GV was more pronounced on hemodialysis days, however, mean blood glucose was lower on hemodialysis days compared to non-hemodialysis days.[11,19]

This observation of intra-dialytic hypoglycemia coupled with significant PHH should prompt the nephrologist to adjust glycemic management of DM-ESRD patients. Possible administration of additional insulin or less hypoglycemic agents e.g., dipeptidyl-peptidase 4 inhibitors or glucagon-like-peptide analogs post-hemodialysis or on hemodialysis days will eventually help reduce glycemic fluctuations.[6,21–23] Development of intradialytic-hypoglycemia should be taken seriously because, as shown in our study and previous studies, a majority of these

events were asymptomatic (role of autonomic neuropathy in long-standing diabetes).[5,24] Events of intradialytic hypoglycemia were mostly asymptomatic in our study and previous studies, suggesting underlying autonomic neuropathy from long-standing diabetes. These might suggest the possibility of other undetected hypoglycemic events which may further aggravate glycemic fluctuations. Therefore, the role of additional intra-dialytic glucose monitoring should be further studied.

In our study, we report that PHH, as reported by SMBG, is more significant in patients with DM-ESRD, older age, obesity and previous IHD. Other associated blood parameters include high HbA1c, elevated hs-CRP and lower albumin. The association between HbA1c levels and glycemic fluctuations and mean blood glucose had been heavily investigated previously with conflicting results. Conversely, studies have shown that HbA1c has a weak correlation with glycemic fluctuations but has a significant relationship with chronic hyperglycemia and mean blood glucose.[25–28] Interestingly, recent studies among Asian populations showed similar findings to our study where HbA1c correlates with glycemic variability indices.[29,30] Notably, most of these studies exclude ESRD patients where HbA1c is a less reliable surrogate for glycemic control as it may falsely increase or decrease due to factors related to ESRD, e.g. anemia and uremia.[7,31] Anemia present in 42% of our population may have confounded our findings of 68% of patients with HbA1c less than 8%, with mean of 7.4% (reasonable control). The correlation between mean blood glucose and HbA1c in our population was moderate with R^2 of 0.59, similar to other studies on DM-ESRD where the R^2 is not more than 0.50 compared to NDM-ESRD with R^2 more than 0.80.[27,32] Nonetheless, HbA1c level more than 8.5% in DM-ESRD patients was related to increased mortality and should not deter clinicians from controlling the glucose level.[31]

PHH is also associated with older age in which there is pancreatic beta cell dysfunction with limited capability to generate coupled with insulin resistance.[33,34] Studies have shown that beta-cell dysfunction plays a significant role in explaining dysglycemia, where insufficient insulin secretion for accurate glycemic regulation may lead to glucose-related metabolic disorders, resulting in increase glucose fluctuations and sustained hyperglycemia.[35,36] Other studies also showed similar findings where glucose fluctuations are more marked in the older age population.[29,30]

Previous IHD, high hs-CRP along with low albumin and relative obesity can be explained by the malnutrition-inflammatory complex syndrome (MCIS), which a term coined to describe the chronic inflammatory state in hemodialysis patients, which is usually accompanied by malnutrition or protein-energy wasting (PEW).[5] Oxidative stress and high inflammatory levels are associated with endothelial dysfunction and subsequently, micro and macro-angiopathy in diabetic patients, particularly resulting in cardiovascular complications.[37]

We specifically looked at the inflammatory biomarker hs-CRP to add prognostic information on cardiovascular risk in our population. A previous study evaluated the role of hs-CRP and showed that there was a linear relationship with vascular risk; a value of less than 1mg/L (lower risk), 1 to 3 mg/L (moderate risk) and more than 3mg/L (higher risk).[38] In hemodialysis patients, although elevated hs-CRP at a single time point is an important predictor of cardiovascular events, the values are not static and may reflect the chronic inflammatory process due to hemodialysis, intercurrent clinical events, decreased residual renal functions and PEW.[39–41] A study done in hemodialysis patients showed that serum CRP levels increased annually during the follow up period.[42] In our study, the mean hs-CRP in DM-ESRD and NDM-ESRD patients were 8.91 mg/L and 7.03 mg/L respectively, with only 41 (27.7%) of patients with level less 3 mg/L. This suggests that hemodialysis patients, regardless of their diabetic status, were in a constant state of inflammation, which predisposes them to a higher risk of a cardiovascular event. PEW, on the other hand, represented by low albumin, is common among patients undergoing maintenance hemodialysis and is by far the strongest risk factor for adverse outcomes and death.[43]

A 10-year cohort study which evaluated serum albumin, C-reactive protein, and carotid atherosclerosis as predictors of 10-year mortality in hemodialysis patients showed that serum albumin concentration was superior as a predictor of mortality.[44] However, in our cohort, the difference between 38 mmol/L among patients experiencing PHH compared to 40 mmol/L maybe hard to appreciate in clinical setting. Nonetheless, by addressing the issue of malnutrition and chronic inflammation among hemodialysis patients, we may improve the occurrence of glycemic fluctuations and subsequently improve outcomes in these patients.

The first limitation of this study was its cross-sectional design and one-off blood sugar monitoring during hemodialysis and non-hemodialysis days. This design may not accurately represent the overall picture of the patients, as many factors can influence single snapshot monitoring. Another limitation was the usage of SMBG instead of continuous glucose monitoring system (CGMS) in assessing PHH. CGMS is preferable as SMBG can miss specific peaks and nadirs in glucose values.[45,46] However, it is challenging to perform CGM in daily practice, given discomfort, cost, and the need for calibration compared to the SMBG. The practical aspect of SMBG in terms of easy availability, monitoring and interpretation, and lower cost makes it the preferred method in our population. We did not limit or measure dietary intake of patients during the study period, which makes it an additional confounding factor in the glycemic profile of the patients. Some previous studies restricted dietary intake or asked the patient to fast during hemodialysis to reduce confounding. However, doing so is not reflective of the normal day-to-day glucose fluctuations of patients, and allowing normal dietary intake reflects real-life data and consequently will allow meaningful alterations in management.

CONCLUSION

DM-ESRD patients experienced more significant fluctuations of glucose level, in particular, PHH on hemodialysis day compared to those with NDM-ESRD. Other associated factors for PHH include older age group, previous IHD, obese patient, high HbA1c, and hs-CRP coupled with low albumin. Malnutrition-inflammatory-complex syndrome, together with protein-energy wasting

commonly seen among chronic hemodialysis patients, should be cornerstones in managing this group of patients as improving this phenomenon may improve glucose control and subsequently improve diabetes-related complications and mortality. Regular glucose monitoring via SMBG may provide valuable insights for treating physicians among this high-risk group.

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ORIGINAL ARTICLE

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Clinical Characterization of Post-parathyroidectomy Patients with Primary Hyperparathyroidism and the Concordance of Preoperative Localization Imaging with Histopathology at a Tertiary Hospital in Manila, Philippines

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Abstract

Background. Philippine studies on primary hyperparathyroidism (PHPT) and preoperative localization are scarce, making improvements on detection and recognition particularly difficult.

Objective. Describe the clinical profile of post-parathyroidectomy PHPT patients at The Medical City (TMC) and assess localization rates and concordance of neck ultrasound (UTZ) and 99mTc-sestamibi scan (MIBI) with surgical histopathologic findings.

Methodology. Retrospective chart review of PHPT Filipino patients who underwent parathyroidectomy at The Medical City from January 2004 to August 2018. Clinical profile and presentations were described and compared with international data. Imaging results were compared with surgical histopathology findings and the level of agreement was determined.

Results. Thirty-five patients were analyzed with female predominance (63%) and an average age of 53 years. Our population had more overt manifestations including skeletal abnormalities (51%), renal calculi (49%) and musculoskeletal symptoms (43%) prior to surgery compared to western countries, where symptoms were noted in less than 20%. MIBI had higher rates of detection than UTZ (80% versus 58%) but had similar localization rates (96.4% versus 94%). When performed together, given a positive result from either test, a much higher yield (93.8%) was observed. The level of agreement between MIBI and surgery was 72.5% (κ=0.54) while UTZ and surgery was 54.1% (κ=0.38).

Conclusion. Our Filipino subjects had predominantly overt symptomatic hyperparathyroidism upon diagnosis prior to surgery as opposed to more asymptomatic surgical patients in western countries. Combining UTZ and MIBI is a more successful preoperative localization approach in our setting than performing either imaging alone, especially in patients with nodular goiter.

Key words: primary hyperparathyroidism, parathyroidectomy, parathyroid localization

INTRODUCTION

Primary hyperparathyroidism is a disorder characterized by excessive secretion of parathyroid hormone (PTH) due to one or more hyperactive parathyroid glands, most commonly caused by a parathyroid adenoma. In recent years, the usual presentation in the United States, Canada and Germany is asymptomatic PHPT diagnosed through biochemical tests which are routinely done in these countries.[1] With the dawn of automated serum calcium measurements in the 1970s, the incidence of hyperparathyroidism increased significantly without relying on the presentation of severe sequelae of the disease, such as osteitis fibrosa cystica or nephrolithiasis, for diagnosis.[2-4] Because of this regular screening process, the disease is detected early in its course and the opportunity for early intervention, if needed, is presented before the onset of overt symptoms and complications. Consequently, approximately 20% of patients exhibit overt symptoms and complications at diagnosis and considered for surgery.[5] Locally, there is a paucity of studies on patient characteristics and the present state of this disease in our population, limiting discovery of areas for improvement in recognition and diagnosis.

Currently, surgery remains the only curative therapy, with bilateral neck exploration as the gold standard surgical approach yielding a 95% cure rate.[6,7] Precise preoperative localization has made it possible to implement more focused and minimally invasive surgeries with high success rates. Minimally invasive parathyroidectomy was found to be cost-effective, and with shorter operative duration and more rapid recovery. It could also achieve a cure rate as high as 98.6% with less surgical complications, such as postoperative hypocalcemia and recurrent laryngeal nerve injury.[8-10] In our institution, the most commonly used

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preoperative imaging studies are neck ultrasonography and 99mTc-sestamibi scan. The accuracy of these modalities in locating abnormal parathyroid glands varies among international studies. Generally, in the western countries, neck UTZ is reported to have a sensitivity of 45 to 88% and a specificity of 94 to 98%. For MIBI, the reported sensitivity is 54 to 70% and specificity 95 to 100%.[11-13] Nevertheless, it should be noted that preoperative localization is primarily done not to influence the decision to operate but to aid in planning the surgical approach by suggesting either the location of a single lesion or increase suspicion for multiglandular disease.[14] Abnormal parathyroid glands may still be found in diagnosed patients regardless of imaging result, so that a negative imaging study does not preclude parathyroid surgery. A negative result may suggest multiglandular disease or an ectopic parathyroid tumor, which may then indicate the need for more extensive surgical exploration to locate the pathologic gland. A review of a prospective database in a tertiary care center in the United States showed that of those who underwent neck exploration for PHPT, 40% of the patients with negative results in both UTZ and MIBI had multiglandular disease. The findings provided additional value and importance to preoperative localization studies in surgical planning.[15]

Published literature on parathyroid diseases in the Philippines generally discuss atypical case presentations or management outcomes. The biggest cohort study of Filipino patients described clinical profiles of hemodialysis patients with diabetic kidney disease and secondary hyperparathyroidism.[16] There is a scarcity of local data assessing the efficiency of imaging modalities in localizing pathologic parathyroid glands. Potential improvement in preoperative planning and techniques remains a challenge. Consequently, this study aims to describe the clinical profiles of Filipino patients with primary hyperparathyroidism who underwent parathyroidectomy and to assess the concordance of commonly utilized preoperative localization imaging (UTZ and MIBI) with surgical histopathologic findings.

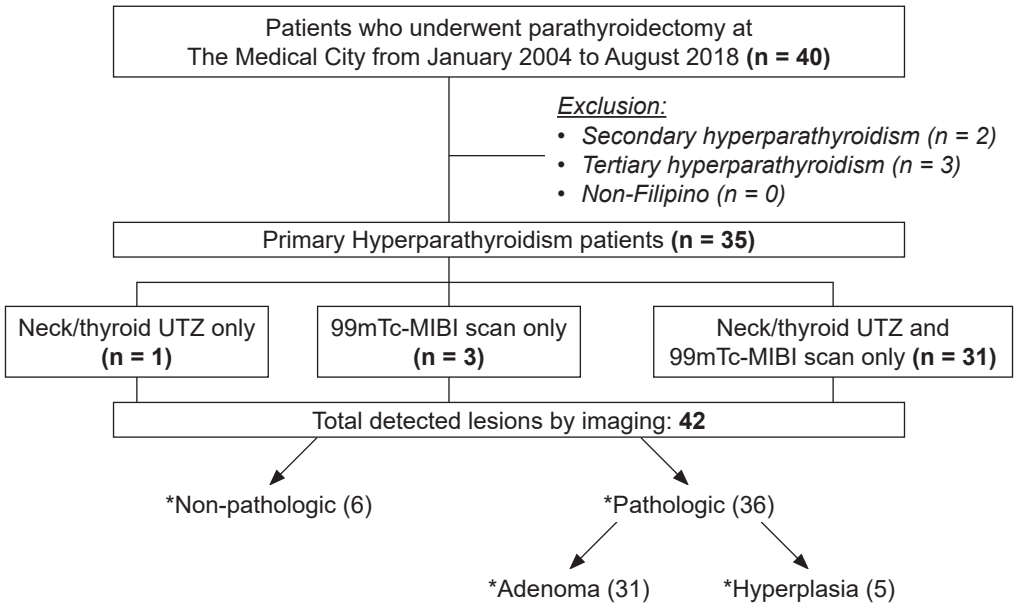
METHODOLOGY

A cross-sectional study was conducted among patients with PHPT who underwent parathyroidectomy at The Medical City from January 2004 to August 2018. The study protocol was approved by the hospital Institutional Review Board. The search terms "hyperparathyroidism," "parathyroidectomy" and "parathyroid surgery" were used at the Medical Records database and yielded a total of 40 hyperparathyroid patients post-parathyroidectomy. The records of all 40 patients were retrieved and reviewed for this study. The subjects were classified based on their clinical history and biochemical test results using the following definitions:

1. primary hyperparathyroidism: above normal intact PTH (iPTH) accompanied by elevated levels of ionized calcium in the absence of end-stage renal disease,
2. secondary hyperparathyroidism: above normal iPTH accompanied by low levels of ionized calcium, and
3. tertiary hyperparathyroidism: above normal iPTH accompanied by elevated levels of ionized calcium in a patient with long-standing end-stage renal disease prior to the diagnosis of hyperparathyroidism.

Filipino patients clinically diagnosed and biochemically confirmed to have PHPT on the basis of elevated ionized calcium and iPTH levels, with neck or thyroid ultrasonography and/or parathyroid scintigraphy as preoperative localization imaging, and with available postoperative histopathology result were eligible for inclusion in the study. Thirty-five subjects were included in the analysis (Figure 1).

Demographic and clinical data were gathered from medical and attending physician records. These included age, gender, symptoms, comorbidities, family history of parathyroid and thyroid disease, risk factors for hyperparathyroidism (lithium intake, thiazide intake, neck radiation exposure), estimated duration of signs and symptoms prior to surgery, time interval from diagnosis



* Surgical histopathology report of each lesion detected through imaging.

Figure 1. Flow diagram of study patients and imaging findings.

to surgery, indications for surgery and type of surgery done. Biochemical test results included preoperative ionized calcium, iPTH, serum phosphorus, serum creatinine and eGFR (CKD-EPI equation) and vitamin D.

Asymptomatic PHPT was defined as a diagnosis made by routine laboratory testing without any overt clinical signs or symptoms of the disease. Indications for surgery for these patients were based on the 2014 Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism.[17] All official imaging results were retrieved from the Radiology and Nuclear Medicine Departments of TMC. The Siemens Acuson S2000™ was used for ultrasonography from 2008 until 2018. Seven patients had their UTZ done before 2008 using an older version of the current machine, but with the same frequency and with no significant difference in resolution. TMC radiologists have been using high frequency linear transducers with color Doppler interrogation since 2004, with no change in technique. The results, however, were interpreted by 16 different radiologists through the years. The MIBI scans, on the other hand, were performed with ^{99m}Tc using the single photon emission computed tomography (SPECT) dual-phase technique. A planar technetium 99m-pertechnetate/technetium 99m-MIBI subtraction scintigraphy and tomographic images were acquired after intravenous injection of technetium 99m-MIBI. The MIBI scan reports were read by 12 different nuclear medicine consultants within the years included in this study. With the exception of 3 images that were done outside our institution, all studies were confirmed and signed by a single senior consultant from our Nuclear Medicine Department. These were then compared with the surgical and histopathologic findings acquired from the operative records and the Pathology Department which served as the gold standard. Since distinguishing between the upper and lower gland locations may be difficult due to anatomic variability, imaging results were compared against tumor laterality alone. The imaging characteristics that were gathered included the number and location by laterality of the parathyroid lesion detected. The histopathologic characteristics taken were the number, location, size and histologic type (adenoma, hyperplasia, carcinoma or non-pathologic) of the parathyroid gland.

A positive preoperative imaging test, either by neck UTZ or MIBI scan, is defined as having detected the presence of a parathyroid lesion. Localization was considered correct when the imaging correctly identified the side of the neck in which the histopathologically confirmed abnormal gland was surgically found. The preoperative imaging is said to be concordant if it showed the lesion at the same side of the neck as with the surgical findings, and discordant if the lesion on the imaging is at the opposite side of the neck seen intraoperatively. The degree of agreement between surgical findings and imaging results was analyzed.

Descriptive statistics were used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. We determined the Kappa statistic to calculate the degree of concordance of the neck UTZ and MIBI localization with the histopathologic localization. The formula for kappa coefficient, κ, is:

$$\frac{P_o - P_e}{1 - P_e}$$

where P_o is the actual observed agreement and P_e is the expected agreement. The expected agreement is the proportion of localizations expected to agree due to chance. Missing variables were neither replaced nor imputed. Stata 15.0 was used for data analysis.

RESULTS

A total of 35 patients with primary hyperparathyroidism who underwent parathyroidectomy were included in the analysis (Table 1). The mean age was 53 years with a female predominance (63%). Surgery for PHPT was more frequent in the age groups of 51 to 70 years among females and 41 to 50 years among males. The most common specific manifestations were osteoporosis/osteopenia (51%) and nephrolithiasis (49%). Muscle or joint pains (43%), constitutional (34%) and various gastrointestinal symptoms (31%) were found to be the more common nonspecific presentations. Twenty percent had behavioral changes, with depression and irritability or emotional lability being most commonly observed. Other infrequent nonspecific symptoms included an anterior neck mass, changes in posture and height, and neurologic symptoms such as headache and dizziness. There were 27 (77%) patients

Table 1. Clinical characteristics of patients with primary hyperparathyroidism who underwent parathyroidectomy

Characteristic	Total n=35
Mean age, year (SD[a])	53 ± 13.48
Female gender (%)	22 (62.86)
Presentation (%)	
Asymptomatic	3 (8.57)
Specific signs and symptoms	
Osteoporosis or osteopenia	18 (51.43)
Nephrolithiasis and nephrocalcinosis	17 (48.57)
Bone fracture	4 (11.43)
Nonspecific signs and symptoms	
Constitutional symptoms	
Easy fatigability, lethargy or weakness	12 (34.29)
Weight loss	6 (17.14)
Gastrointestinal symptoms	11 (31.43)
Nausea or vomiting	2 (5.71)
Abdominal pain	6 (17.14)
Constipation	3 (8.57)
Anorexia	1 (2.86)
Pancreatitis	1 (2.86)
Peptic ulcer or gastroesophageal reflux disease	4 (11.43)
Muscle or joint pains	15 (42.86)
Psychiatric or behavioral changes	7 (20)
Palpitations or chest pain	6 (17.14)
Others	10 (28.57)
Medical history	
Hypertension	22 (62.86)
Thyroid disease	27 (77.14)
Diabetes	14 (40)
Chronic kidney disease	12 (34.29)
Stage 1	1 (8.33)
Stage 2	2 (16.67)
Stage 3	8 (66.67)
Stage 4	1 (8.33)
Heart or coronary artery disese	4 (11.43)
Lithium intake	1 (2.86)
Neck radiation exposure	0
Thiazide use	2 (5.71)
Others	10 (28.57)
Family history	
Thyroid disease	9 (25.71)
Parathyroid disease	1 (2.86)

[a] SD, standard deviation

Table 2. Preoperative laboratory profiles

	All subjects (n = 35)	CKD[c] subgroup (n = 12)	Reference range
Ionized calcium, mg/dL	6.12 (5.45-8.44)	6.56 (5.48-8.44)	4.6-5.32
iPTH[a], pg/mL	202.6 (69.89-849.4)	261.05 (118-849.4)	15-65
Phosphorus, mg/dL	2.63 (1.95-3.5)	2.59 (2.24-2.91)	2.29-4.71
Vitamin D, ng/mL	25.8 (12.1-42.22)	26.56 (12.99-42.22)	>30
Serum creatinine, mg/dL	1.06 (0.48-2.4)	1.49 (1.17-2.4)	0.55-1.02
eGFR[b], mL/min/1.73 m^2	66 (21-120)	44 (21-64.5)	>120

Median laboratory values. Ranges given in parentheses.
[a] iPTH, intact parathyroid hormone
[b] eGFR, estimated glomerular filtration rate, by CKD-EPI equation
[c] CKD, chronic kidney disease

who had multinodular goiters, 3 of whom had papillary thyroid cancer. Nine patients (26%) had reported thyroid disease in the family, while only one had a family history of parathyroid disease.

Preoperatively, the median ionized calcium was elevated (6.12 mg/dL), while median phosphorus was normal (2.63 mg/dL). iPTH levels varied widely from 69.89 to 849.4 pg/mL (reference value 15-65 pg/mL), as observed in the typical biochemical picture of primary hyperparathyroidism (Table 2). None of these patients had longstanding end-stage renal disease. Analyzed separately, the patients with chronic kidney disease had elevated iPTH (median 261.05 pg/mL), elevated serum ionized calcium (median 6.56 mg/dL) and normal phosphorus (median 2.59 mg/dL), consistent with primary hyperparathyroidism. The lone patient with stage 4 CKD had an earlier episode of acute kidney injury due to renal stones months before her parathyroidectomy, and was unable to regain her previous renal function. Approximately 67% of the CKD patients had chronic hypercalcemia, and the ensuing azotemia was attributed to obstructive uropathy caused by PHPT. The median vitamin D in this subset of patients with CKD was slightly below normal (26.56 ng/mL), with only one patient having a level below 20 ng/mL.

Table 3. Operative and histopathologic profiles

Characteristic	Mean or frequency
Estimated duration of signs and symptoms prior to surgery, year (range)	2 (0.04-13)
Estimated time from diagnosis to surgery, month (range)	4 (0.25-72)
Frequency of surgical indications (%)	
Osteoporosis/osteopenia	18 (51.43)
Nephrolithiasis	17 (48.57)
Muscle or joint pains	15 (42.86)
Age <50 years	14 (40)
Easy fatigability/lethargy	12 (34.29)
Gastrointestinal symptoms	11 (31.43)
eGFR[a] <60 mL/min/1.73 m^2	9 (25.71)
Fracture	4 (11.43)
Suggestive of cancer	1 (2.86)
Surgery performed (%)	
Parathyroidectomy only	15 (42.86)
Total thyroidectomy + parathyroidectomy	9 (25.71)
Thyroid lobectomy + parathyroidectomy	8 (22.86)
Subtotal thyroidectomy + parathyroidectomy	3 (8.57)
Largest size of parathyroid lesion per subject (n=33) (%)	
≤1 cm	7 (21.21)
1.1 to 2.0 cm	15 (45.45)
2.1 to 3.0 cm	8 (24.24)
>3 cm	3 (9.09)
Actual largest size of parathyroid lesion, cm (SD[b])	1.83 (0.92)
Type of suspected parathyroid lesions detected through imaging (n=42) (%)	
Non-pathologic	6 (14.29)
Pathologic	36 (85.7)
Adenoma	31 (86.1)
Hyperplasia	5 (13.9)

[a] eGFR, estimated glomerular filtration rate, by CKD-EPI equation
[b] SD, standard deviation

The estimated mean duration of signs and symptoms prior to surgery was 2 years, with a wide range from a few weeks to as long as 13 years. The approximate time interval between diagnosis and parathyroid surgery was 4 months (Table 3). The predominant indications for surgery in this population reflected the most frequent clinical manifestations of osteoporosis and nephrolithiasis. Other indications are seen in Table 3. With the exception of one, all patients had multiple indications for surgery at presentation. Eighteen (51%) subjects had at least 3 indications, while 6 (17%) had 5 or more. There were only 3 (9%) asymptomatic patients in this population. These patients presented with incidental findings of hypercalcemia (more than 1 mg/dL above the normal limit) and decreased eGFR (<60 ml/min/1.73 m^2), serving as their indications for surgery.

Neck UTZ and MIBI was not done in all patients: 32 (91.4%) had UTZ and 34 (97.1%) had MIBI. Of the 35 patients, 31 (88.6%) had both imaging done leaving only one patient with UTZ alone and 3 patients with MIBI only. Collectively, there was a total of 42 suspected lesions detected by imaging from the 35 subjects. A summary of imaging findings for each of the 42 suspected lesions is seen in Tables 4 and 5. Single-gland disease was the predominant finding. There

Table 4. Individual preoperative imaging results of each specimen (n=35)

	Non-pathological (n=6)	Adenoma (n=31)	Hyperplasia (n=5)	Total lesions (n=42)
UTZ[a] (%)				
Positive	0	18 (58.06)	0	18 (42.86)
Negative	3 (50)	12 (38.71)	4 (80)	19 (45.24)
No imaging	3 (50)	1 (3.23)	1 (20)	5 (11.9)
MIBI[b] (%)				
Positive	6 (100)	25 (80.65)	5 (100)	36 (85.71)
Negative	0	4 (12.9)	0	4 (9.52)
No imaging	0	2 (6.45)	0	2 (4.76)

[a] UTZ, neck ultrasound
[b] MIBI, 99mTc-sestamibi scan

Table 5. Combined preoperative imaging results of each specimen (n=31)

	Non-pathological (n=6)	Adenoma (n=31)	Hyperplasia (n=5)	Total lesions (n=42)
Positive on both (%)	0	15 (53.57)	0	15 (42.86)
Positive UTZ[a] and Negative MIBI[b] (%)	0	2 (7.14)	0	2 (5.71)
Negative UTZ[a] and Positive MIBI[b] (%)	3 (100)	9 (32.14)	4 (100)	16 (45.71)
Negative on both (%)	0	2 (7.14)	0	2 (5.71)

[a] UTZ, neck ultrasound
[b] MIBI, 99mTc-sestamibi scan

were 3 (8.6%) diagnosed to have multiple gland disease after surgery, in whom 2 pathologic parathyroid lesions were confirmed. Through histopathologic examination, the number of true pathologic lesions was 36 out of the 42 detected through imaging. These were composed of 31 adenomas (86.1%) and 5 hyperplastic glands (13.9%); the remaining 6 suspected lesions through imaging turned out to be non-pathologic. Although MIBI notably detected 6 false positives, it was able to detect all of the hyperplastic glands which UTZ failed to recognize. In addition to this, UTZ had 3 times more false negative results for adenomas compared to MIBI (38.7% versus 12.9%). When both imaging procedures were done as seen in 31 of the subjects, there were 2 adenomas found during surgery that were not seen on both UTZ and MIBI. There was no apparent common characteristic that could explain the negative imaging result. The sizes of the missed adenomas were more than 1 cm (1.3 and 2.6 cm), with associated PTH levels close to 3 times higher than normal (185.5 and 218.4 pg/mL). Although both were found in patients with multinodular goiters, there were 20 other adenomas found in patients with nodular goiters that were detected by either or both UTZ and MIBI. Imaging results of the 31 subjects were seen in agreement in 17/35 (48.6%) of lesions (positive in 15, negative in 2) and in disagreement in 18/35 (51.4%) of lesions (UTZ-positive/MIBI-negative in 2, UTZ-negative/MIBI-positive in 16) including the 3 false positives in MIBI.

A total of 32 confirmed pathological glands was seen among the 31 patients who had both imaging tests performed (Figure 2). MIBI detected a proportionally bigger percentage of the pathologic lesions compared to UTZ (87.5% versus 53%). The average lesion size identified on UTZ (1.95 cm) was comparable to the size detected in MIBI (1.75 cm). The average PTH levels were 321.44 pg/mL and 292.27 pg/mL for UTZ-positive and MIBI-positive lesions, respectively. Although PTH levels for UTZ-positive lesions were higher, PTH may not truly distinguish the 2 groups in this study since the highest (849.4 pg/mL) and lowest (below 100 pg/mL) were detected by both modalities. In terms of localization, whether individual or combined, they had a small range of difference in rate from 93 to 97% (Figure 2). Comparing with surgical findings, the concordance of UTZ with histopathology in locating lesions was fair (kappa=0.375), while that of MIBI was moderate (kappa=0.535) (Table 6).

Table 6. Concordance in localization between imaging and surgical histopathology findings

	Agreement (%)	Expected agreement (%)	kappa[c]
UTZ[a]	54.05	26.52	0.375
MIBI[b]	72.50	40.88	0.535

[a] UTZ, neck ultrasound
[b] MIBI, 99mTc-sestamibi scan
[c] kappa statistic interpretation according to Landis and Koch: ≤0, none; 0-0.20, poor; 0.20-0.40, fair; 0.40-0.60, moderate; 0.60-0.80, substantial; 0.8-1, almost perfect; 1, perfect

DISCUSSION

In the study population, there were more women who underwent parathyroidectomy for PHPT, with a ratio of 2:1, compared to 3 to 4:1 in published data.[1,18] Disease manifestation in males in this study population appeared to be more common at a younger age—at or before the fifth decade of life—in contrast to females who presented with the illness beyond their fifth decade. The most common presentations were bone-related pathology (63%) and kidney stones (48.6%), also seen in published data on Asian populations. In contrast, studies in North America and Europe report primary hyperparathyroidism detected by routine biochemical screening, when complications of overt skeletal and renal abnormalities have not yet occurred.[19] As a result, the indications for surgery are predominantly asymptomatic PHPT with abnormal biochemical profiles. In these developed countries, overt renal stone disease was noted in less than 20%, while skeletal abnormalities were much less common at 2%.[19,20] Gastrointestinal manifestations such as peptic ulcer disease, on the other hand, appear to be similar to the general population at 10%.[21] In Asian countries, where screening methods are not as regularly done as in the West, clinically apparent disease sequelae are more frequent, as patients tend to seek consult once symptoms are already overt and bothersome.[12,22,23] In a study of PHPT patients in India, skeletal manifestations (75.5%) were reported as the most common presentation similar to our population, followed by renal calculi (40.5%) and proximal muscle weakness (45.5%). The mean duration of symptoms was 2.8 years.[21] Similarly, in Saudi Arabia, skeletal manifestations (45.7%) and renal stones (15.2%) were also common, with an average duration of symptoms of 39 months or 3.2 years.[22] Comparable findings in Thailand showed skeletal symptoms in 66.7%, renal impairment in 15.6% and mixed symptoms in 86.7%.[23] In the Philippines, a retrospective review of 20 post-parathyroidectomy patients with hungry bone syndrome showed renal calculi (45%) as the top preoperative presentation, followed by osteoporosis (30%), parallel to our data.[24]

The mean duration of signs and symptoms prior to surgery was approximately 2 years (ranging from 2 weeks to 13 years), similar to other Asian countries. About 40% of the subjects underwent surgery within one year of suspected signs and symptoms of the disease, while 31% remained symptomatic for one to 5 years before undergoing surgery (Table 3). This is likely due to delayed consultations for mild and tolerable symptoms and underestimation of the disease by patients, as exemplified by irregular follow-up consultations until more severe and debilitating complications are present. Nonetheless, once the diagnosis has been made, half of the patients were able to undergo parathyroidectomy within 6 months (Table 3). Unfortunately, due to the subjective nature of nonspecific symptoms—body weakness, depression and abdominal pain—together

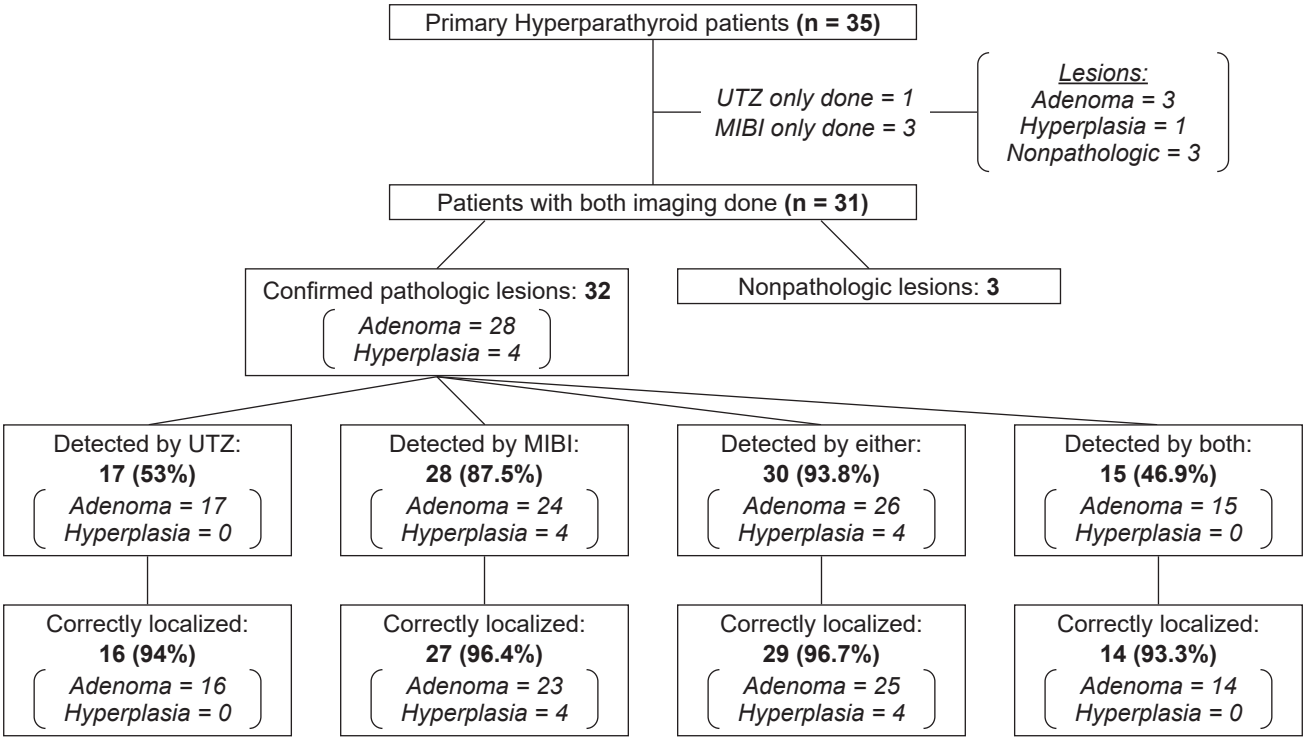


Figure 2. Preoperative imaging detection and localization rates of confirmed pathologic lesions in patients with both UTZ and MIBI.

with the lack of routine biochemical tests including calcium levels, the distinction between asymptomatic and symptomatic primary hyperparathyroidism is not always clear. Therefore, estimation of duration of symptoms relied heavily on persistent and significantly bothersome symptoms reported by the patients.

There was an observed discrepancy between UTZ and MIBI, wherein only 58% of adenomas were detected by UTZ as opposed to 80% by MIBI scan (Table 4). The low detection rate of UTZ in this study is speculated to be due to several factors, including thyroid nodularity, operator differences in reading abilities and existing incomplete ultrasound protocols. In this study, 26/35 (77%) of the subjects had multinodular goiters: in those who had both imaging studies, UTZ was able to detect 58% of lesions while MIBI detected 85%. Similarly, Erbil et al noted a decrease in sensitivity in parathyroid lesion detection from 100% to 79% using UTZ in the presence of thyroid nodules.[25] Additionally, in our institution, there are more operators and readers of parathyroid ultrasonography than parathyroid scintigraphy, which would inevitably result in greater inter-observer variability. Moreover, neck and thyroid UTZ protocols do not routinely search for parathyroid glands, so that these are not always described unless requested by the physician or suggested by the clinical impression. As a result, there are different levels of experience in recognizing parathyroid glands among readers which could greatly affect imaging results. Future studies may consider having a single sonographer and routine inclusion of the parathyroids in thyroid or neck UTZ protocols.

Despite this low detection rate, UTZ remains as one of the most commonly requested imaging tools, as it provides useful information regarding the thyroid gland and its relation to the parathyroids. Evaluating the thyroid for concomitant disease is imperative prior to a primary operation for hyperparathyroidism in order to minimize reoperations. The clinical importance of thyroid nodules lies with the need to exclude thyroid cancer, which occurs in 7 to 15% depending on demographics and presence of risk factors.[26] The Philippine Thyroid Diseases Study in 2012 found that the prevalence of nodular goiter was 4.1%.[27] Several comparison studies have shown that Filipinos are 2 to 3 times more likely to develop thyroid cancer and are significantly more likely to develop cancer recurrence (25%) compared to American and Canadian populations (9.5%).[28-30] It is then essential to include thyroid evaluation in planning for parathyroid surgery especially among Filipinos.

Although UTZ and MIBI together had low positive correspondence at 46.9% (Figure 2), the use of both and consideration of at least one positive imaging for preoperative localization appears to overcome the inherent limitations of each modality alone and increases detection rate to 93.8%. MIBI aids in interpreting UTZ results, especially in cases of ectopic parathyroid glands, small adenomas, and concomitant thyroid nodules, while UTZ provides detailed anatomic information not seen in nuclear imaging. Analysis of concordance showed higher agreement of MIBI scans (72.5%) with surgical location compared to UTZ (54.1%) (Table 6). However, even at a moderate level of agreement beyond chance (κ=0.535) with MIBI, the percentage of reliable data reaches only 35 to 63%—still inadequate for clinical application. In health research, an acceptable inter-rater reliability is at least 80%, since this translates to only 20% of the data as faulty or erroneous.[31] The accuracy of MIBI may be dependent on several factors, including the quality of the equipment, technique used, frequency of scans being done

in an institution and the ability of the reader. The effects of these factors should be investigated and considered in formulating ways to improve MIBI scan precision.

The findings of this study are limited by its retrospective design and small sample size. Variable qualities of history taking and documentation by different interviewers allowed unsystematic, non-uniform and occasionally incomplete sets of data. Missing data per patient, especially laboratory values and maintenance medications, restricts adequate characterization of this population. It would have been ideal to have information on the dose and duration of vitamin D supplementation or other medications such as thiazide diuretics and cinacalcet if there were any given. Additionally, determination of the 24-hour urine calcium levels of these patients would have been able to objectively identify cases of familial hypocalciuric hypercalcemia.

CONCLUSION

This cohort of Filipino patients at The Medical City demonstrated similar characteristics and manifestations with our neighboring Asian countries. Surgical indication was predominantly due to overtly symptomatic disease as opposed to more asymptomatic surgical patients in western countries. Although UTZ showed very low detection rates, there is still merit in doing both UTZ and MIBI scan for preoperative localization. These are done to increase detection, to assess the thyroid gland by UTZ, and to localize pathologic parathyroid lesions better with the MIBI scan in patients with nodular goiter.

Future studies should investigate the impact of regular calcium screening for hyperparathyroidism to clinical outcomes in the general Philippine population, including whether overt symptoms and end-organ complications may be reduced prior to surgical intervention as seen in western countries. Together with this, prospective investigations on preoperative planning and more comprehensive and uniform clinical examination should be made to adequately confirm our findings and discover modifiable factors that could influence localization imaging reliability.

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ORIGINAL ARTICLE

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Correlation Study Between Erythrocyte Acetylcholinesterase Activity, Serum Malondialdehyde and Insulin Sensitivity in Agricultural Workers and Non-agricultural Workers in Nat-Kan Village, Magway Township

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Abstract

Objective. This study determined the correlation between erythrocyte acetylcholinesterase (AChE) activity, serum malondialdehyde (MDA) and insulin sensitivity in agricultural workers and non-agricultural workers.

Methodology. The cross-sectional comparative study was undertaken in 45 agricultural and 45 non-agricultural workers from Nat-Kan Village, Magway Township. Erythrocyte acetylcholinesterase activity and serum malondialdehyde were measured by spectrophotometric method. Insulin sensitivity was calculated by homeostasis model assessment (HOMA-IR).

Results. Mean erythrocyte AChE activity was significantly lower in agricultural (3553.99 IU/L) compared with non-agricultural workers (4432.68 IU/L) (p<0.001). A significant high level of mean serum MDA was observed in agricultural workers (0.74 versus 0.28 µmol/L, p<0.001). Median HOMA-IR value was significantly higher in agricultural (2.74) than that of non-agricultural workers (2.28) (p<0.05). The risk of insulin resistance was 2.8 times greater in agricultural workers than non-agricultural workers (OR 2.8, 95% CI, 1.18 to 6.72). Erythrocyte AChE activity had weak negative correlation with serum MDA level (r=-0.357, p<0.001) and HOMA-IR (ρ= -0.305, p<0.05). There was a significant but weak positive correlation between serum MDA level and HOMA-IR (ρ=0.355, p<0.001).

Conclusion. Organophosphate pesticide exposure lowered erythrocyte AChE activity and increased oxidative stress. Oxidative stress is partly attributed to the development of insulin resistance.

Key words: erythrocyte acetylcholinesterase activity, serum malondialdehyde level, HOMA-IR, agricultural workers

INTRODUCTION

With agriculture as the main industry in Myanmar, many workers have become reliant on toxic pesticides to increase farm productivity. Agricultural workers are inevitably exposed to pesticides during preparation and application of the pesticide spray solution. As a consequence, agricultural workers face a greater risk of exposure to pesticides than non-agricultural workers.

Organophosphate (OP) pesticides are liquid at room temperature and can be absorbed through intact skin and through the gut after ingestion of contaminated food. They also penetrate the skin, respiratory tract epithelium and cornea, as they easily vaporize.[1] As inhibitors of the enzyme acetylcholinesterase (AChE), OP pesticides allow accumulation of acetylcholine (ACh) and continuous stimulation of ACh receptors at the neuromuscular junction. This is the suggested mechanism of toxicity of OP pesticides.[2]

Chronic exposure to OP pesticides affect different organs and body systems such as the skeletal muscles, gastrointestinal tract, urinary bladder, secretory glands, central nervous system and respiratory system. These are manifested as weakness, glandular secretion, fasciculation, acute pancreatitis, convulsion and respiratory failure.[3] Hyperglycemia has often been reported to be one of the most common manifestations of chronic OP pesticide toxicity in experimental animal models as well as in cases of human exposure.[4-8]

The cholinergic action of OP pesticides in inhibiting AChE and increasing ACh activity induces hyperesthesia, intermittent spasm, muscular tremors, sustained seizures and muscle fasciculation. These involuntary energy-demanding activities trigger the release of glucose by glycogenolysis and gluconeogenesis. There is an ensuing increase in glucose-6-phosphatase enzymes leading to hyperglycemia. These also stimulate glycolysis in the liver and muscle, and the subsequent release of adenosine triphosphate (ATP) to meet the body's energy requirements. Thus, OP pesticides may influence the pathways involved in enzymatic glucose homeostasis.[6,9,10] In addition to hyperglycemia, inhibition of AChE by OP pesticides can induce significant increases in hepatic lipid peroxidation,

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as indicated by the biomarker malondialdehyde.[10-12] This is the proposed mechanism underlying the causal relation between oxidative stress and insulin resistance.[13,14] However, only one study reported the association between serum concentration of malathion and elevated HOMA-IR among 98 farmers without diabetes.[14]

While research activities on the toxic effects of OP pesticides in developed countries have increased public awareness, we have limited studies of our own. The data may be used to institute programs to promote awareness of the health problems of pesticide usage in our country. Thus, this study aims to investigate erythrocyte AChE activity and insulin sensitivity in agricultural and non-agricultural workers in Nat-Kan Village, Magway Township. This study will determine the effects and mechanisms involved in OP pesticide toxicity on glucose homeostasis. The findings will be used to help farmers become aware of the potential dangers of pesticide handling and use in daily farming activities, and to prevent accidental poisoning.

METHODOLOGY

This cross-sectional comparative study was undertaken in villagers 18 to 45 years of age living in Nat-Kan Village. History taking and physical examination were carried out according to the *pro forma*. After explaining the procedure for data collection, written informed consent was obtained. Weight measurement was done by using a calibrated bathroom scale. Standing height was measured with the use of a measuring tape. After body mass index (BMI) calculation, subjects with BMI between 18.5 to 24.9 kg/m^2 were included.

The sample size was calculated by the following formula:

$$n_1 = \left[\frac{Z_1 - \frac{\alpha}{2}\sqrt{pq\left(1+\frac{1}{r}\right)} + Z_1 - \beta\sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]_2$$

$r=n_2/n_1$, $q_1=1-p_1$, $q_2=1-p_2$

$\overline{p}=p_1+p_2r/1+r$, $\overline{q}=1-\overline{p}$

P_1=Proportion in group 1=27.4% (derived from Panda et al[32])

P_2=Proportion in group 2=57.6%

Z_1-$\alpha/2$=reliability coefficient=1.96 (95% Confidence Interval)

Δ=0.05

Z_1-β=0.84 (80% power of the test)

$n_1=n_2$=39

Drop out=10%

Required $n_1=n_2$=39+4=43

Therefore, required sample size for each group (exposed and non-exposed group) was 43.

Forty-five agricultural workers who have been using OP pesticides (Acephate and Chlorpyrifos) in the processes of formulating, mixing, loading and spraying for a period of at least one year were recruited in this study. However, different types of pesticides have also been used in orchards to control various insect pests. The agricultural workers recruited in the present study were also exposed to other types of pesticides such as Imidacloprid, Cypermethrin, Acetamiprid and Azoxystrobin (Table 1). Another control group of 45 subjects whose work did not involve pesticide application (sellers, carpenters and bricklayers) and lived in an area at least 100 meters away from processes of pesticide use were selected as control subjects. Control subjects were matched to study group by age, sex and BMI. This study was approved by the Ethics and Research Committee of the University of Medicine, Magway.

Table 1. Active compounds in pesticides commonly used in Magway Region

Brand Name	Item	Active compound
Min Ma Haw	Cupro Star 85	Copper oxychloride 85%
	No Two Super	Acetamiprid 15% + Lambda-cyhalothrin 10%
Aw Ba	Revive 25 SC	Azoxystrobin 25% w/v
	Phosdrin 40EC	Chlorpyrifos 40%
	Carbofuran 3G	Carbofuran 3%
	AZPHATE 75SP	Acephate 75%
	Better 25 WP	Acetamiprid 20% + Lambda-cyhalothrin 5%
	Demon 1.8 EC	Abamectin 1.8%
	Unity 32.5 SC	Difenoconazole 12.5% + Azoxystrobin 20%
	Cyclone 505 EC	Chlorpyrifos 45.9% + Cypermethrin 4.59%
	THUNDER 250 EC	Cypermethrin 25%
	DOZER 20 WP	Imidacloprid 20%
	DOZER 70 WP	Imidacloprid 70%
	ALARM 15 WP	Emamectin benzoate 5 % + Lambda-cyhalothrin 10%
Min Mida	70 WDG	Imidacloprid 70%
Syntech	Carbine 3 G	Carbofuran 3%
Shwe Chin Thae	COBRA 40 EC	Chlorpyrifos 40%

All 90 subjects were assessed for their eligibility to the study by inclusion and exclusion criteria. Subjects with a history of heavy smoking, heavy alcohol drinking, hypertension, heart disease, diabetes mellitus, chronic renal disease, signs and symptoms of heavy metal poisoning (e.g. diarrhea, nausea, vomiting, abdominal pain and shortness of breath) and intake of antioxidant drugs (e.g. zinc tablets) were excluded from the study. Heavy smoking was defined as consumption of at least 20 cigarettes daily, and heavy alcohol drinking as more than 30 mL per day.

Visits were made from June to August during pesticide spraying season. The investigator visited agricultural workers every two weeks for three times: the first visit was performed for observation of pesticide application processes, the second for observation of continuation of the process, and the third for preparation of data collection. During visits, safe handling procedures for pesticide storage and application were explained to agricultural workers. Signs and symptoms of acute or severe pesticide poisoning, such as fever, dizziness, confusion, restlessness, muscle twitching, staggering gait, slurred speech, fits and unconsciousness, were also noted. Moreover, first aid and immediate assistance were provided to any person found to have mild or severe pesticide poisoning. Subjects with severe poisoning were excluded from the study.

Data collection was also done during pesticide spraying season. On the day of blood extraction, all subjects were instructed to be present at the office of the local administrator at 0600H after fasting for 10 hours (from

2000H to 0600H). Upon arrival, a 7 mL blood sample taken by venipuncture was collected from each subject in 3 separate blood collecting tubes: 1 mL in a tube containing sodium fluoride 10 mg for determination of blood sugar, 3 mL in a plain tube for serum separation, and 3 mL in an ethylenediaminetetraacetic acid (EDTA) tube for packed cell separation. All blood samples were transported to the Common Research Laboratory, University of Medicine, Magway using an effective cold chain system.

Upon arrival, the blood sample in the plain tube was allowed to clot for 30 minutes at room temperature. Once clotted, centrifugation at 3000 rpm for 15 minutes was done. Serum was collected in two separate sample tubes and stored at -4°C until blood sample analysis: one for determination of serum MDA and another for serum insulin. The sample in the EDTA tube was centrifuged at 1000 rpm for 15 minutes. The supernatant plasma and buffy coat were removed. Packed cells were washed three times with isotonic saline. These were then stored at 2ºC before analysis. AChE activity was determined within 3 days. Blood glucose level was determined on the same day of blood collection. Those with fasting plasma glucose (FPG) more than 100 mg/dL were excluded from the study. Erythrocyte AChE activity and serum MDA were measured by spectrophotometric method.

Ellman's spectrophotometrical method for cholinesterase activity determines the rate of production of thiocholine as acetylthiocholine is hydrolyzed. The enzyme activity is measured by following the increase in yellow color produced from thiocholine when it reacts with dithiobisnitrobenzoate ion. This method has the sensitivity to determine human erythrocyte AChE activity. The Ellman assay for AChE is well known in the detection of OP pesticide exposure. We utilized Ellman's spectrophotometrical method to investigate the erythrocyte AChE activity in our study.[15]

Fasting plasma glucose was measured by glucose oxidase method. Fasting serum insulin was determined by enzyme-linked immunosorbent assay (ELISA). Insulin sensitivity was calculated by HOMA-IR as shown in the equation:[16]

$$\text{HOMA-IR} = \frac{\text{insulin (}\mu\text{IU/mL) x glucose (mmol/L)}}{22.5}$$

Data entry and analysis were done by SPSS Statistics version 16.0. Normally distributed variables were expressed in mean (SD). Comparison of the data between study group and control group was done by unpaired Student's t test. Skewed data were expressed as median (interquartile range, IQR) and they were computed by non-parametric tests using the Mann-Whitney U test. Correlation studies were done by Pearson's correlation. Another non-parametric test, Spearman's rank, was used when the data did not follow a normal distribution. Chi-squared test was used to determine the risk of insulin resistance in agricultural workers. Differences were considered significant when $p<0.05$.

RESULTS

A total of 100 subjects, composed of 50 agricultural workers exposed to OP pesticides and 50 non-agricultural workers, were initially recruited to participate in this study. Of these, three agricultural workers and two control subjects were dropped due to incomplete data. Another two agricultural workers with hypoglycemia were excluded from this study. Three control subjects who were unable to follow instructions were also excluded. The final group included 45 agricultural and 45 non-agricultural workers. The general characteristics of the study participants are shown in Table 2. There were no significant differences in age, sex distribution and BMI.

Table 2. General characteristics of study participants

Parameter	Agricultural workers (n=45)	Non-agricultural workers (n=45)
Mean age, year (SD)	28.67 (4.12)	27.53 (4.00)
Sex (Male:Female)	1:1	1:1
Mean body weight, kg (SD)	62.56 (4.12)	59.47 (3.33)
Mean height, m (SD)	1.65 (0.57)	1.61 (0.47)
Mean body mass index, kg/m^2 (SD)	22.91 (1.13)	22.92 (1.35)

The comparison of erythrocyte AChE and MDA parameters are shown in Figures 1 and 2. Mean erythrocyte AChE activity of agricultural workers (3,553.99 ± 855.6 IU/L) was significantly lower compared to the non-agricultural workers (4,432.68 ± 1,287.86 IU/L) ($p<0.001$). However, mean serum MDA was significantly higher in agricultural workers (0.74 ± 0.05 μmol/L) compared with

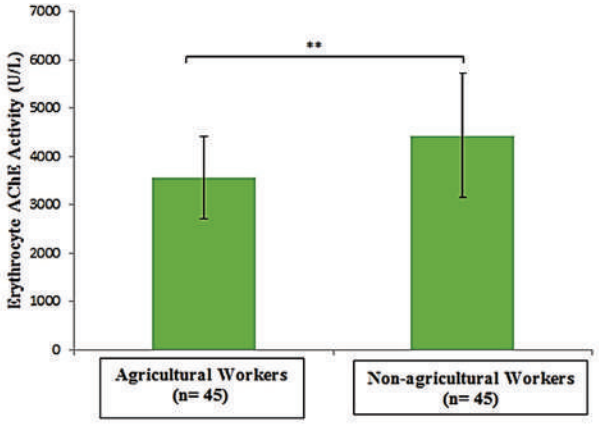

Figure 1. Comparison of erythrocyte acetylcholinesterase (AChE) activity in agricultural and non-agricultural workers. **, significant difference ($p<0.001$).

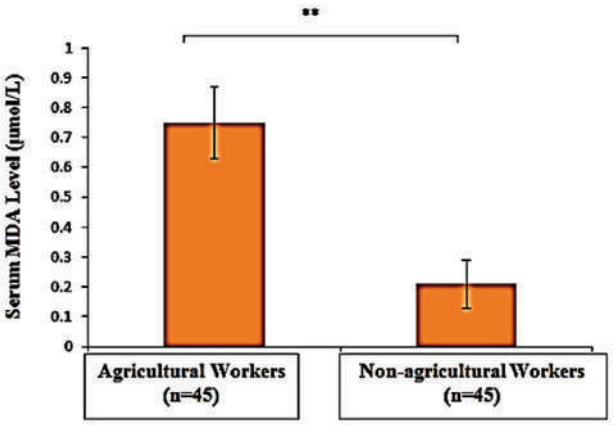

Figure 2. Comparison of serum malondialdehyde (MDA) levels in agricultural and non-agricultural workers. **, significant difference ($p<0.001$).

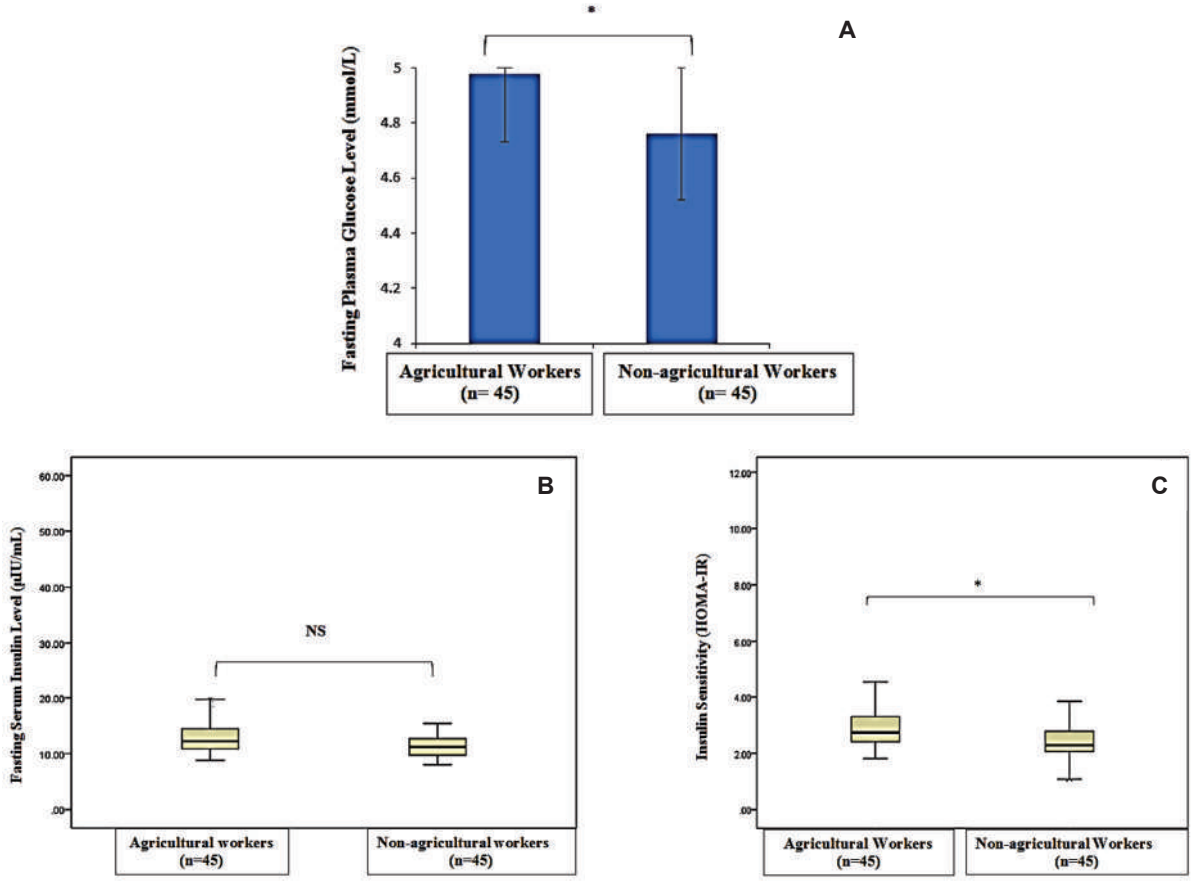

Figure 3. Comparison of fasting plasma glucose **(A)**, fasting serum insulin **(B)** and insulin sensitivity by homeostasis model assessment (HOMA -IR) **(C)** in agricultural (n=45) and non-agricultural workers (n=45). *, significant difference (p<0.05).

non-agricultural workers (0.28 ± 0.06 µmol/L) (p<0.001). Agricultural workers had a higher mean FPG, whereas serum insulin levels were not significantly different between study groups (Figure 3A and B). A higher HOMA-IR value in agricultural workers [median IQR, 2.74 (2.37-3.3)] compared to non-agricultural workers [median IQR, 2.28 (2.03-2.78)] indicated that insulin sensitivity was significantly reduced in agricultural workers (p<0.05) (Figure 3C). Erythrocyte AChE activity was weakly and negatively correlated with serum MDA level (r=-0.357, p<0.001) as well as HOMA-IR (ϱ=-0.305, p<0.05) (Figures 4 and 5). A significant weak positive correlation between serum MDA level and HOMA-IR was also demonstrated (ϱ=0.355, p<0.001).

DISCUSSION

Nowadays, the living population is continually exposed to numerous environmental contaminants such as industrial waste, polluted air and pesticides. In Myanmar, where agriculture is the main industry, pesticides are used countrywide for pest control and crop protection. Pesticides are among the leading causes of environmental pollution, with harmful effects on human health. Organophosphate pesticides are a diverse group of chemicals that have been commonly used since 1975. The chemicals mostly used in these compounds are acephate, diazinon, dimethoate, parathion, phosmet, malathion, fenthion, dichlorvos, chlorpyrifos, ethion and azamethiphos. In Myanmar, many pesticides are commercially distributed under the names like *Min-Ma-Haw*, *Aw-Ba*, *Shwe-Chin-Thae*, *Shwe-Nagar* and *Ar-Mo*. These are composed of organophosphate compounds and other pesticides such as copper oxychloride, imidacloprid and carbendazim. Table 1 lists the pesticides that are utilized in Magway Region, Myanmar. Among them, *Aw-Ba* was the brand most commonly used in the region at the time of sample collection. Other brand alternatives were also reported to be in use. The agricultural workers who participated in the present study were also exposed OP and other pesticides such as imidacloprid, cypermethrin, acetamiprid and azoxystrobin. These other pesticides are considered to have low acute and chronic toxicity to humans.[17] All agricultural workers who participated in study had been working as pesticide spraying service professionals for many years, with a mean duration of OP pesticide exposure of 4 ± 1.5 years. The mean frequency of pesticide spraying process by pesticide applicators was 58.2 ± 1.4 per year.

Many animal and human studies have reported the association of OP pesticide toxicity with hyperglycemia, suggesting an underlying influence on liver enzymes involved in glucose homeostasis pathways.[5,6,18,19] Moreover, some studies postulated that pancreatic toxicity and oxidative stress induced by OP pesticides may impair glucose homeostasis.[6,9,10] There is increasing interest on the effect of environmental pesticide exposure on glucose homeostasis. The present study investigated insulin resistance in agricultural workers exposed to these pesticides.

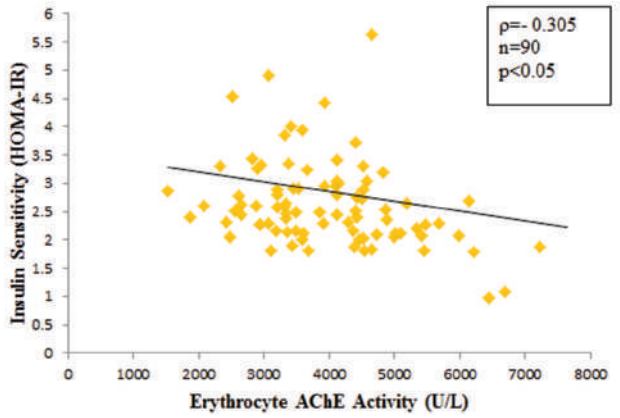

Figure 4. Correlation between erythrocyte acetylcholinesterase (AChE) activity and serum malondialdehyde (MDA) level in agricultural and non-agricultural workers. r, Pearson's correlation coefficient; *n*, total number of subjects.

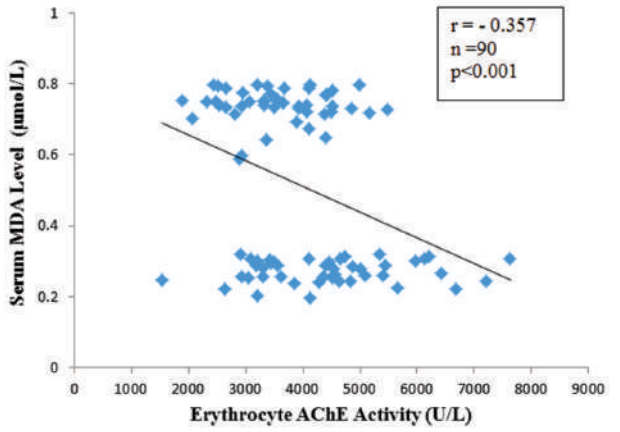

Figure 5. Correlation between erythrocyte acetylcholinesterase (AChE) activity and insulin sensitivity by homeostasis model assessment (HOMA-IR) in agricultural and non-agricultural workers. ρ, Spearman's correlation coefficient; *n*, total number of subjects.

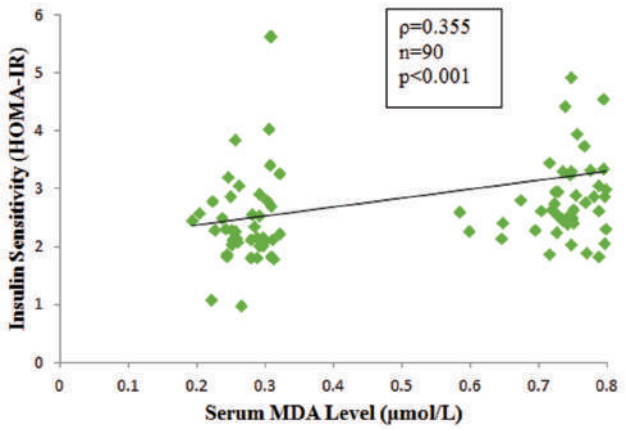

Figure 6. Correlation between serum malondialdehyde (MDA) level and insulin sensitivity by homeostasis model assessment (HOMA-IR) in agricultural and non-agricultural workers. ρ, Spearman's correlation coefficient; *n*, total number of subjects.

Measurement of erythrocyte AChE activity has been recognized as a human biological marker of OP pesticide exposure. Inhibition of acetylcholinesterase activity in erythrocyte membranes has been reported as a useful indicator of chronic exposure to OP.[3,20,21] Upon entering the body, OP pesticides avidly form covalent bonds with oxygen in serine, located at the active site of AChE. These transform into irreversible phosphorylated inactive AChE.[21,22] While erythrocyte AChE activity is also reduced in aging RBC, chronic renal failure and heavy metal exposure, these conditions were part of the exclusion criteria in the present study based on history taking and physical examination.[24,25] Based on a study on Kenyan agricultural workers, cutoffs for AChE activity were defined as low (≤3.95 IU/mL, high inhibition), medium (3.95 to ≥5.95 IU/mL, mild inhibition) and normal (>5.95 IU/mL, no inhibition).[20] The mean value of erythrocyte AChE activity of agricultural workers in the present study was 3,553.99 ± 855.6 IU/L (range 1,867 to 5,470 IU/L), significantly lower compared to the results of other studies.[3,20,21] Thirty out of 45 agricultural workers in the present study had high inhibition of erythrocyte AChE activity, while the. remaining had mild inhibition Erythrocyte AChE activity of agricultural workers was significantly lower compared to non-agricultural workers in the present study (p<0.001). This was in agreement with the findings of previous studies.[3,18,20] The low level of erythrocyte AChE activity in agricultural compared to non-agricultural workers showed that there was an inhibitory effect on erythrocyte AChE activity by OP pesticides.[22,23]

In the present study, the mean erythrocyte AChE activity in non-agricultural workers were 4,432.68 ± 1,287.86 IU/L (range, 3,129 IU/L to 7,632 IU/L). Accordingly, normal erythrocyte AChE activity (more than 5.95 IU/mL) was seen only in seven control subjects in the present study. Most of control subjects (n=38) in the present study had mild inhibition of erythrocyte AChE activity due to indirect exposure to OP pesticides. The findings also suggested that non-agricultural control subjects who lived at least 100 meters away from pesticide application process were not spared from OP pesticide exposure. Farms that use pesticides were located around the villages where they were residing. Non-agricultural workers may be exposed to OP pesticides indirectly by means of inhalation and ingestion of contaminated food and water. One limitation of our study was that investigation of the status of anemia and heavy metal contamination of food and water, which possess an inhibitory effect on AChE activity, were not performed.

The present study also investigated the serum MDA level to detect oxidative stress.The mean serum MDA was significantly higher in agricultural (0.74 ± 0.05 µmol/L) compared to non-agricultural workers (0.28 ± 0.06 µmol/L) (p<0.001). This finding was similar to other studies.[10,11,12] Lipids are susceptible to oxidation, and lipid peroxidation products are potential biomarkers for oxidative stress status.[10,11,12] MDA is the most relevant and widely used in determining free radical reactions.[26,27] Accordingly, the significantly higher levels of serum MDA in agricultural workers was interpreted as reliable evidence of oxidative stress. The present study used thiobarbituric acid reactive substances to measure lipid peroxidation.[28] However, determination of MDA with

thiobarbituric acid is considered nonspecific, as it is only considered as an indirect measure of reactive oxygen species (ROS), and it can react with peroxidation products of non-lipid origin. It may lead to substantial controversy in the quantification of serum MDA level.

Organophosphate pesticides inhibit the AChE enzyme and consequently increase the activity of the nicotinic type of ACh receptor, resulting in uncoordinated nerve and muscle stimulation. This manifests as sustained seizures and muscle fasciculation.[28] Thus, oxygen and glucose demand as well as ATP requirements are greatly increased in the muscle. Thereafter, the glycolytic pathway is activated to meet the increase in energy requirement. Nicotinamide adenine dinucleotide + H or NADH, a side product of the pathway, is oxidized by using atmospheric oxygen, leading to increased production of free radicals in the form of ROS. These ROS alter the cellular macromolecules of lipids, proteins and deoxyribonucleic acid. Lipids are the most susceptible to oxidative stress, causing release of MDA by the oxidation of the lipid layer of the cellular membrane.[30,31]

The present study also showed a significant but weak negative correlation between serum MDA level and AChE activity (r=-0.357, n=90, p<0.001). This finding was similar to a previous study, where serum MDA level was found to be significantly increased with the severity of OP pesticide poisoning, suggestive of increased oxidative stress.[32] It may be inferred that higher serum MDA levels of agricultural workers in the present study might be partly due to exposure to OP pesticides through the mechanism of oxidative stress.

Fasting plasma glucose level was significantly higher in agricultural (4.98 ± 0.40 mmol/L) compared to non-agricultural workers (4.76 ± 0.32 mmol/L) (p<0.05) in our study, despite falling within normal range (3.5 to 6.1 mmol/L). Previous animal studies reported the hyperglycemic effect of malathion, acephate and dimethorate compounds of OP pesticides after intraperitoneal injection in rats.[4,5] It has also been shown that acephate and malathion OP pesticide compounds enhance the breakdown of hepatic glycogen contents, with acephate causing an increase in hepatic glucose-6-phosphate activity.[4,6] Additionally, the development of hyperglycemia in OP pesticides-exposed rats was found to be due to stimulation of hepatic gluconeogenesis and glycogenolysis.

With advanced modern farming technique, pesticides quickly became widely used by farm workers. Consequently, an increasing awareness of the association between hyperglycemia and organophosphate pesticides in humans was borne out of many studies.[18,33,34] A longitudinal study done observed the increased risk of diabetes in pesticide applicators who had used OP compounds.[7] Another study noted that 28 out of 102 patients with a history of OP pesticide poisoning had random blood sugar levels >140 mg/dL.[32] Similarly, a study of acute OP pesticide poisoning cases reported hyperglycemia in 21%.[19] Because these previous studies examined patients with OP pesticide poisoning and our study examined agricultural workers who were exposed to OP in pesticide application process, the results cannot be compared. It can be assumed that normal FPG levels of agricultural workers in the present study were attributable to low doses of pesticide exposure. However, because of the stimulation of the enzymatic glucose homeostasis and subsequent release of glucose to meet involuntary energy demanding activities by OP exposure, significant increases in fasting plasma glucose level in agricultural workers in the present study may be due to direct exposure, or a certain amount of exposure through pollution compared to non-agricultural workers.[6,9]

The gold standard method for measuring insulin sensitivity is the euglycemic hyperinsulinemic clamp (EHC) method developed by DeFronzo et al.[35] The homeostasis model assessment is recommended for large scale studies because of its simplicity and validity, with an excellent correlation with insulin sensitivity measured using EHC.[16] HOMA requires the measurement of plasma insulin level in the basal level (i.e. less than 2.1 mIU/L) and the plasma glucose level at or below 3.5 mmol/L. For normal subjects, a one unit increase in plasma glucose level from 3.5 mmol/L (i.e. 4.5 mmol/L) increases plasma insulin secretion by 5 mIU/L from its basal value. Therefore, for a given level of blood glucose, prevailing insulin level reflects insulin resistance. HOMA uses fasting plasma glucose and fasting insulin concentrations related by the feedback of glucose on pancreatic beta cells to increase insulin secretion. Insulin resistance (HOMA-IR) may then be mathematically computed using a derived equation.

In the present study, HOMA-IR value was significantly higher in agricultural than in non-agricultural workers [median IQR, 2.74 (2.37-3.3) versus 2.28 (2.03-2.78), p<0.05]. This finding of decreased insulin sensitivity in agricultural workers was in line with another study in farmers who were exposed to malathion pesticides.[14] A HOMA-IR value of more than 2.6 was regarded as insulin resistance.[36] Accordingly, insulin resistance was observed in 13 (28.8%) control subjects as well as 24 (53.3%) agricultural workers in this study. The risk of insulin resistance was 2.8 times increased in agricultural workers compared to controls [odds ratio (OR), 2.8; 95% confidence interval (CI), 1.18-6.72). This study shows that agricultural workers who were exposed to OP pesticides have a greater risk for insulin resistance.

A previous longitudinal study revealed that incident diabetes was 51%, 63%, and 94% in applicators who had used the organochlorine insecticides aldrin, chlordane, and heptachlor, respectively.[7] In the present study, pesticide applicators mostly used chlopyrifos and acephate. However, a recent study reported that the occurrence of diabetes mellitus in Thai farmers was associated with all types of pesticide (OR, 1.35; 95% CI, 1.04-1.76), especially with organophosphates (OR, 2.22; 95% CI, 1.17-4.19).[8]

The present study also showed that HOMA-IR had a positive correlation with oxidative stress, as measured by MDA (ρ=0.355, p<0.001), and a negative correlation with erythrocyte AChE activity (ρ=-0.305, p<0.05) in all study groups. There are many relevant underlying mechanisms that the oxidative pathway is linked to erythrocyte AChE activity and insulin sensitivity (HOMA-IR).

Accordingly, oxidative stress may lead to the development of insulin resistance, based on the proposed the mechanisms on their correlation.[13,37] In the presence of oxidative stress,

ROS is produced in increased amounts by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX4), a powerful oxidizing enzyme. As a consequence, there is a shift in the phosphatidylinositol-3-kinase (PI3K) insulin signaling pathway to phosphorylate RacGTPase as an alternative to phosphotidylinositol biphosphate (PIP2). Subsequently phosphorylated RacGTPase amplifies the activity of NOX4 resulting in increased ROS, which in turn activate casein kinase-2 (CK2) and continue to activate the retromer. It causes the trans-Golgi network downstream. Glucose transporter type 4 (GLUT4) is transported to lysosomes for degradation instead of the plasma membrane. Thus, intravascular glucose levels remain elevated and insulin resistance ensues.[5,38]

Another possible mechanism is endoplasmic reticulum (ER) dysfunction. The endoplasmic reticulum is important for cellular functions, such as intracellular calcium storage.[39,40] Cellular stress conditions increase endoplasmic reticulum demand, a condition called ER stress. Unfolding protein response (UPR) and sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump activity are activated in the organelle itself, a condition also called ER homeostasis.[40] When ER homeostasis is impaired, as in prolonged exposure to oxidative stress, SERCA activities are reduced, decreasing endoplasmic reticulum calcium concentration and subsequently increasing intracellular calcium concentration, contributing to insulin resistance.[39]

CONCLUSION

We found that agricultural workers had significantly lower erythrocyte AChE activity than non-agricultural workers. Insulin sensitivity was decreased in agricultural workers based on the observed increase in HOMA-IR scores. Serum MDA level was significantly higher in agricultural compared to non-agricultural workers.

We also found a significant negative correlation between erythrocyte AChE activity and serum MDA level as well as HOMA-IR score. A positive correlation was also observed between serum MDA and HOMA-IR score. Insulin sensitivity was decreased significantly with increased oxidative stress and increased inhibition of erythrocyte AChE activity, the latter indicative of the severity of OP pesticide exposure. OP pesticides inhibit the erythrocyte AChE activity and consequently increase the activity of nicotinic type ACh receptor, leading to oxidative stress. These findings support the hypothesis that OP pesticide exposure increases oxidative stress and contribute to the development of insulin resistance.

Limitations of the study

The present study does not explore other conditions which may also affect AChE activity, such as anemia and heavy metal contamination of food and water. Determination of MDA by thiobarbituric acid reactive substances test is nonspecific and may affect adequate quantification of serum MDA level. As a preliminary study, ours is the first to assess erythrocyte AChE activity in agricultural workers exposed to organophosphate pesticides, and its association with oxidative stress and insulin sensitivity in agricultural workers in our country. As a cross-sectional study, it cannot clearly establish causality between exposures and outcomes. The study is not powered for a multivariate analysis where the interaction of various environmental and subject -related factors can be analyzed to look at the effects on the outcome of insulin sensitivity.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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ORIGINAL ARTICLE

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Development of a Patient Decision Aid for the Treatment of Osteoporosis Among Filipino Postmenopausal Women

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Abstract

Background. Guidelines for osteoporosis have provided recommendations on when to offer pharmacologic management for postmenopausal women, but do not specify which "best" medication to start. The choice of therapy depends on the efficacy, safety/tolerability of the drug and the patient's profile and preferences. Patient decision aids (PtDA) are tools designed to facilitate shared decision-making (SDM) between the patient and health care provider for conditions where there are several available options, and the "best" choice is unclear. We aimed to develop a culturally acceptable patient decision aid on the treatment of osteoporosis among Filipino postmenopausal women at risk of osteoporotic fractures.

Methodology. A qualitative approach and an iterative process was employed in this study following the guidance of the International Patient Decision Aid Standards (IPDAS). Phase 1 (Needs Assessment) involved interviews with 8 physicians who are involved in the care of women with osteoporosis and focus group discussions with 19 postmenopausal women with osteoporosis who have received treatment. Phase 2 (PtDA Development) involved a systematic review of evidence and development of an initial prototype through several iterations with an expert panel. The final prototype was pilot tested in actual clinical encounters (Phase 3).

Results. The final PtDA consists of 6 laminated flashcards, which illustrate the different considerations that are important to patients when selecting an anti-osteoporosis treatment (efficacy, method, frequency of administration, side effects and cost), and a fracture worksheet to illustrate individualized effects of the treatments on the patient's fracture risk. These are accompanied by a clinician guide on how to use the PtDA during consultations, which includes information on non-pharmacologic management of osteoporosis. The PtDA was acceptable to physicians and patients.

Conclusion. With the integration of decisional needs assessment, clinical expertise, user preference and iterative revision testing, we were able to develop a culturally adapted PtDA on the treatment of osteoporosis among Filipino postmenopausal woman at risk of osteoporotic fractures for use during clinical encounters.

Key words: patient decision aid, shared decision-making, osteoporosis, treatment

INTRODUCTION

Osteoporosis remains a growing health problem in a population that is aging. With the growing population, the number of Filipinos at high risk of osteoporosis is projected to reach 4 million by 2020 and 10.2 million by 2050.[1] As such, the burden of osteoporosis-related fractures cannot be underrated since it leads to diminished quality of life, disability and death. These fracture risks, along with its associated morbidity and mortality, can be reduced with early identification and treatment of patients at risk of osteoporosis.

Pharmacologic therapy in the prevention of postmenopausal osteoporosis fracture consists of antiresorptive agents (bisphosphonates, estrogens, selective estrogen-receptor modulators, denosumab) and an anabolic agent (teriparatide).[2] Despite the availability of these effective medications, there remains a treatment gap in the management of osteoporosis. Cited reasons were failure of the physicians to prescribe medications; if prescribed, patients were not taking it at all.[3]

Guidelines recommend when to offer pharmacologic management, but it has not clearly stated which "best" medication to start.[4] The available treatments have similar efficacy, but have different routes of administration, dosing regimens, prices and clinical safety profiles.[2] Patients who are advised to initiate therapy in osteoporosis are placed in a preference-sensitive situation because more than one treatment option exists. The decision as to which medication to choose is a complex one, and is

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usually based on what the patient values the most.[5] In a six-month, prospective, randomized, open label study comparing once monthly ibandronate 150 mg versus weekly alendronate 70 mg, 66.1% preferred once a month treatment with ibandronate due to ease of following the treatment regimen.[6] Issues on the cost of treatment and side effects also affect treatment outcomes, as these are the common reasons for discontinuation of treatment.[7] Due to the variations in preferences of patients, physicians should incorporate them in the decision-making process in order to ensure successful treatment of this long term condition, since poor adherence could be a result of unmet preferences.[8]

Shared decision-making, wherein the physicians "understand patient goals and priorities, incorporate clinical and patient priorities, and address obstacles to care" may help patients arrive at a decision that is consistent with their preference.[9] In order to engage patients towards SDM, it is important that evidence be translated into a simple, easy-to-understand format containing important points needed to come up with a decision that is in line with their values.[10] Patient decision aids are evidence-based tools that support SDM. They are intended to: 1) increase the patient's knowledge and understanding of the disease and its associated risks using plain language that is easy to comprehend by the general population, 2) provide structured guidance in making decisions consistent with the patient's values, and 3) improve the quality of the decision-making process. Their use has enhanced patient-doctor communication and has reduced the proportion of people who remained undecided post-intervention.[11]

Currently, there are existing PtDAs on the initiation of treatment of osteoporosis. These aids have been found to increase in transfer of knowledge, decrease decisional conflict and improve patient involvement in the decision-making process. However, its impact on treatment adherence in the long run remains to be determined.[12–14]

To date, there is no existing PtDA tailored for Filipino postmenopausal patients with osteoporosis who have opted to initiate treatment. The development of a PtDA that is simple to use and easy to understand could potentially improve SDM in the treatment of osteoporosis. The primary objective of the study was to develop a culturally adapted PtDA to help Filipino postmenopausal women who have decided to initiate osteoporosis treatment choose which treatment to start. Moreover, the study aims to describe the decision support needs of physicians and postmenopausal women regarding the treatment of osteoporosis, and to present in detail the systematic manner on how the patient decision aid was developed.

METHODOLOGY

Study setting and population

A qualitative design using an iterative approach was employed from July 2018 to June 2019 at the outpatient department of a tertiary government hospital in Manila, Philippines that mostly caters to patients from low income families.

The methodology was guided by the International Patient Decision Aid Standards (IPDAS) providing developers with quality standards regarding PtDA content and development process.[15] The study involved 3 phases: Phase 1, needs assessment; Phase 2, development of the PtDA; and Phase 3, pilot testing of the PtDA in an actual clinical encounter (Figure 1).

The protocol was approved by the University of the Philippines Manila Research Ethics Board (UPM REB 2018-117-01) prior to the initiation of the study.

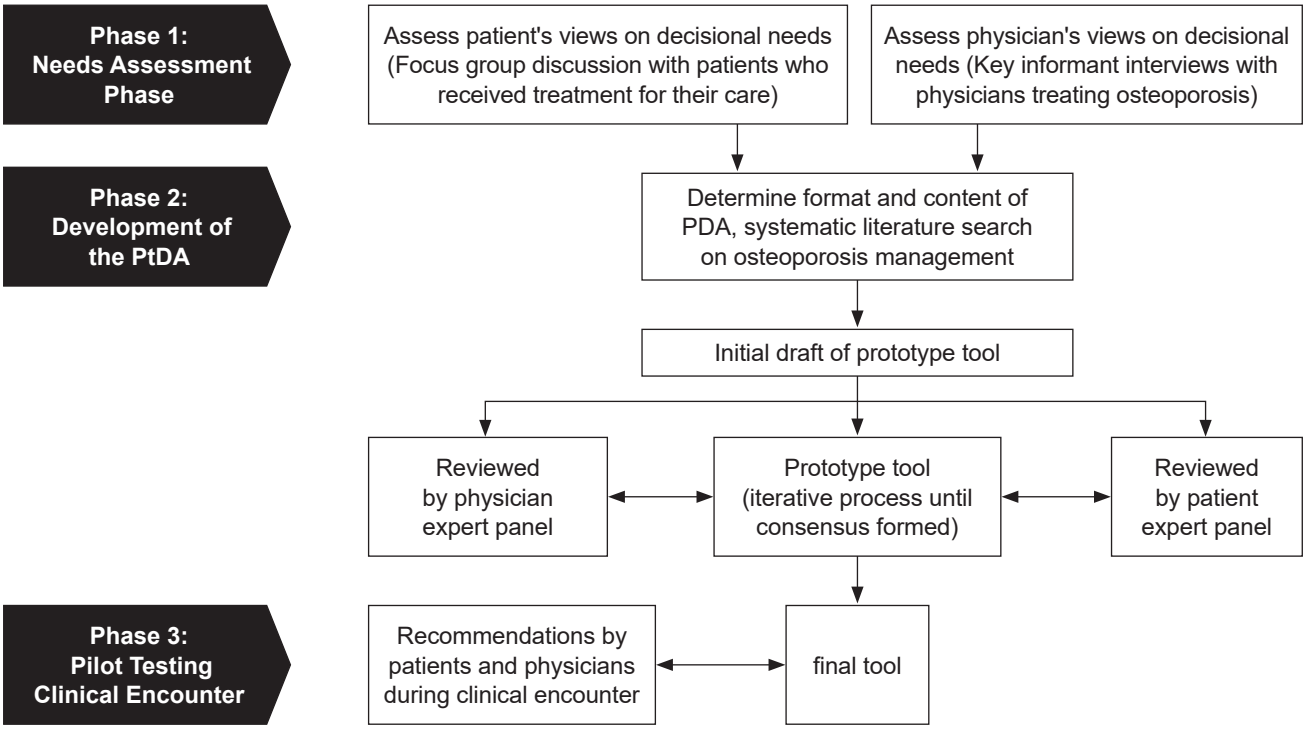

Figure 1. Flow diagram of the steps in the development of the patient decision aid.

Phase 1: Needs Assessment

A needs assessment was performed to elicit views of physicians and patients on the challenges and resources that helped them with making decisions in the treatment of osteoporosis.

A. Key informant interviews with physicians

Key informant interviews with 8 physicians from different services involved in the care of osteoporosis (endocrinology, rheumatology, orthopedics, family medicine and internal medicine) were conducted by the primary investigator using a semi-structured questionnaire. Interviewees were selected through convenience sampling and an informed consent was obtained prior to the interview. The interviews covered the perceived challenges postmenopausal women face in making decisions on osteoporosis treatment, and the potential usefulness of PtDA in facilitating these discussions. All interviews were audio taped. The recorded interviews were transcribed, analyzed and summarized into themes.

B. Focus group discussions (FGD) among post-menopausal patients

FGDs among postmenopausal patients who received treatment for their care were conducted to obtain information on the osteoporosis treatments they received at diagnosis, the information they wished they had known before making a decision, their opinions about their participation in decision-making, and their views on the use of PtDA. Nineteen postmenopausal patients who satisfied the inclusion criteria were recruited via convenience sampling from the Endocrinology outpatient clinics of the Philippine General Hospital and participated in one of the 2 focus group discussions. Inclusion criteria were: (1) postmenopausal women 50 years of age and above, (2) have experienced medical treatment for osteoporosis aside from calcium and/or vitamin D, (3) able to participate verbally in a group discussion, and (4) fluent in Filipino. Informed consent was obtained prior to starting the FGDs. The FGDs were conducted in a quiet room to ensure privacy, video recorded, and transcribed verbatim.

Phase 2: Development of the PtDA

An iterative process was employed in designing the PtDA. First, evidence on the effectiveness and safety of the different osteoporosis treatments were reviewed and summarized. Second, a prototype PtDA was designed that contained information on the route of administration, method of administration, efficacy, safety and cost of the osteoporosis drugs. This was shown to expert panels that included physicians (a rheumatologist, geriatrician, an orthopedic surgeon who is the head of the Fracture Liaison Service of the hospital, and a family medicine physician who has experience in developing a culturally adapted PtDA on diabetes) and patients to obtain feedback on appearance, understandability, content, ease of use. Finally, the PtDA was revised according to the feedback. This process was repeated until no new feedback was obtained.

Phase 3: Pilot Testing in an Actual Clinical Encounter

Six physicians, who were knowledgeable in osteoporosis medications, and were not part of the expert panel, were selected via convenience sampling and oriented on the nature of the study. The prototype PtDA was tested in 6 actual clinical encounters among 6 postmenopausal patients who were candidates for the treatment of osteoporosis in order to obtain feedback on the length, appearance, understandability, content, ease of use and acceptability of the PtDA. Recommendations for improvement were also inquired. The PtDA was then revised according to the feedback obtained from the interviews and the process was repeated, each time with new patients, until no further revisions were needed.

RESULTS

Phase 1: Needs Assessment

A. Key informant interviews with physicians

Key informant interviews were conducted among 8 physicians who were from endocrinology (n=4), rheumatology (n=1), orthopedics (n=1), family medicine (n=1) and adult medicine (n=1). The main focus of the interviews were challenges postmenopausal women face in making decisions on osteoporosis treatment, and the potential usefulness of PtDA in facilitating these discussions.

Initiation of treatment

Once physicians diagnosed their patients with osteoporosis, there were no issues in initiating pharmacologic management to the patients. Majority of the physicians offer treatment options to the patients, mostly starting with alendronate due to its availability, ease of administration and cost. They discuss the other forms of medications in passing, focusing more on the frequency of administration and cost.

Physicians' priorities

The top consideration of physicians when initiating treatment is cost. Since most of their patients are from families of low socioeconomic status, the physicians did not offer the other medications, such as denosumab and teriparatide, due to their perceived limited financial capacity of their patients. On the other hand, 2 physicians offer these medications because of available support from funding agencies. Accessibility is another consideration, as other medications aside from bisphosphonates are usually not available in pharmacies. In contrast, 2 physicians offer only alendronate. The first physician acknowledged unawareness of the newer medications in the market, while the other physician found it difficult to present all the options to his patients due to time constraints.

Use of PtDA in osteoporosis

When a locally adapted PtDA on diabetes was shown to the physicians, all were receptive to using a similar tool when discussing treatment options for osteoporosis with their patients. Reasons cited include the usefulness of the PtDA in: (1) facilitating and shortening the discussion on treatment options because the important points are already provided, (2) helping patients understand the information better than just listening to a verbal explanation, and (3) engaging the patient in a conversation. In addition, physicians also consider efficacy, method and frequency of administration, cost and side effects as important issues in initiating treatment. One physician emphasized that for the tool to be effective, the patient has to be willing to participate in decision-making, as there are some who would leave the decision to their physicians.

B. Focus group discussion with patients

Nineteen postmenopausal patients who received treatment for osteoporosis participated in the FGD. The average age of the participants was 66 years (range, 51 to 94 years), while the average time on treatment with an anti-osteoporosis drug was 17 months (median, 12 months; range, 1 to 60 months). More than half of the participants were on alendronate (11/19) followed by zoledronic (5/19), while 3 patients were using denosumab. Majority of them finished high school and college, while 5 patients completed elementary school. All of the patients had a household income of less than PhP 15,000/month (Table 1).

Table 1. Characteristics of focus group discussion patient participants

Characteristic	Total n = 19
Mean age, year	66
Mean age at diagnosis, year	64
Medication timeline, month	17
Medications taken	
Alendronate	11
Zoledronic acid	5
Denosumab	3
Education	
No formal education	0
Elementary school	5
High school	7
College degree	7
Postgraduate degree	0
Vocational	0
Employment	
Employed	4
Retired	15
Household income per month	
Less than PhP 15,000	19
PhP 15,000 to 30,000	0
PhP 30,000 to 45,000	0
PhP 45,000 to 60,000	0
More than 60,000	0

Osteoporosis consultation

Once patients were diagnosed with osteoporosis, majority based on bone densitometry, their physicians offered pharmacologic treatment to prevent fractures. There was no difficulty in initiating treatment since most patients understood their condition and the importance of fracture prevention. Pharmacologic options were discussed with the majority of the patients, but a subset (7/19) were not offered options at all. These patients would have wished to be involved in decision-making if given the chance. For patients who were offered pharmacologic management, they were mostly asked to choose among the drugs based on frequency of administration and cost of treatment.

Factors influencing patient choice of osteoporosis treatment

Since most patients pay for their medications out-of-pocket, cost was the main consideration in selecting osteoporosis treatment for majority of the patients (8/19). However, some (3/19) were able to procure medications such as denosumab and zoledronic acid from government funding agencies. The next priority of the patients was drug efficacy in terms of preventing fractures. The frequency and convenience of administration of the drug were also important considerations. One patient preferred yearly treatment with zoledronic acid due to polypharmacy and convenience issues. On the other hand, other patients preferred weekly administration due to the fear of a one-time administration of the drug.

Information clarification

Majority of the patients said they wished they had received more information about the side effects of medications from their physicians. Some reported that it was only after they developed symptoms after taking the drug that they learned that these were actually side effects. Costs of the medications should also have been mentioned during the consultation. One patient emphasized the need to explain how the drug will be administered since only a prescription was given to her.

Use of PtDA in osteoporosis

A sample of a locally adapted PtDA on diabetes was shown to the patients and they were told that a similar tool will be developed for osteoporosis. Almost all of them were receptive to the idea of incorporating the tool in the consultation. A tool that uses graphics would facilitate their understanding of the information about the different drugs and help them in choosing which medication to start. The content that they wanted to see included efficacy, cost, frequency and method of administration, and duration of treatment. One patient was satisfied with the physician's choice of medication and did not see the need for a PtDA.

Phase 2: Drafting of the PtDA

A. Prototype development

We based the content and format of the initial prototype on the information gathered from the needs assessment phase. The included the drugs alendronate, ibandronate, risendronate, zoledronic acid, raloxifene, denosumab and teriparatide, which are all approved by the Food and Drug Administration of the Philippines and locally available. The PtDA was developed as paper-based, laminated flashcards since there is no readily available access to computers in the outpatient clinics in our setting. The flashcards were divided into the priorities of the patients when choosing a drug: efficacy, method of administration, frequency of administration, side effects and cost. The tool is intended to be used during an actual clinical consultation with the physician.

In order to provide quality and up-to-date data, we performed a systematic literature search on different anti-osteoporosis medications. Data on the route of administration and frequency were extracted mainly from the National Osteoporosis Foundation's Clinician's Guide to Prevention and Treatment of Osteoporosis.[4] The side effects of each class of drug with its corresponding probabilities of occurrence were mainly based on the National Osteoporosis Society's data.[16-22] A network meta-analysis comparing the efficacy of the different classes of bisphosphonates was the basis for the relative risk reduction in the efficacy card.[23] Additional data on risk reduction were obtained from the landmark trials of denosumab and teriparatide.[24,25] Lastly, the range of costs of the different classes of drugs were based on local pharmacy prices.

The flashcards were printed on laminated paper sized 7.5 in x 4 in each. The font sizes were at least 12 pt and non-cursive to allow easy user readability among elderly patients. Dark fonts were contrasted to a white background to allow the eyes to relax. The flashcards were color coded to easily differentiate each aspect of the drug. The researchers also used visual aids in the form

of icons to communicate information. We also presented information using illustrations as well as pictograms in communicating risks and risk reduction.

B. Iterations with expert panel

Walkthroughs of the initial prototype were done for the physician and patient expert panels. Each flashcard was discussed including content, design, format, and presentation of data. Revisions were made based on the recommendations of both groups. A total of 4 iterations were performed until the final prototype tool was formed.

During the first iteration, the physician expert panel agreed to use flashcards for ease of access and reproducibility with a larger size format (10.8 in x 5.4 in). Improvements in the presentation of cost, method and frequency of administration were made. We decided to present the 5 most common side effects of the different medications and to arrange it based on frequencies of natural occurrences. Rare side effects such as osteonecrosis of the jaw (ONJ) and atypical fracture were included to offer a balanced presentation.

On the second iteration, the presentation of the efficacy card was changed from the initial bar graph comparing relative risk reduction per medication to a colored pictogram of the spine and hip. Each colored figure represents a 10% risk of fracture. An introduction card was also added, containing non-pharmacologic osteoporosis prevention. Minimal revisions in grammar and layout were made in the third and fourth iterations.

When shown to the patient expert panel, the tool received positive responses. The group commented that the PtDA was easy to understand, visually appealing, used clear language and was engaging to the patients. They also appreciated the introduction card which contained non-pharmacologic management, as was a frequently asked question among patients. They wished they had a similar tool when they were initially deciding which medication to start.

Several recommendations were made during the discussion. Physicians should have a standardized way of explaining the cards, prompting the development of a clinician's guide. Physicians, when using the PtDA, should clearly communicate the risk of side effects to avoid alarming the patients. A comment was made to include the duration of use of medications, but it was decided that it will be discussed separately by the physician.

Phase 3: Testing in actual clinical scenarios

The revised PtDA was tested for acceptability among 6 patients who were candidates for treatment and 6 physicians who used it in actual clinical encounters in the outpatient services (Figures 2 to 8). Clinicians were oriented on how to use the PtDA cards prior to use in a patient consultation.

The patients' ages ranged from 56 to 66 years old with varying educational backgrounds, from elementary to college graduates. The physicians were all endocrinologists. The range of time using the tool ranged between 8 to 14 minutes, with an average time of 10 minutes.

A. Patient insights

Overall, patients were receptive to using the PtDA during clinic consultation. They all agreed that the PtDA made the options more clear and also recommended its use to all candidate patients.

The length of presentation was enough in order to explain the vital information needed by the patients. However, for one patient, it seemed longer than the usual consultation but was "necessary" in order to discuss the medications in detail. Another patient, an elementary degree graduate, had the longest time of presentation of 14 minutes. She needed more time to understand the flashcard on cost because she could not grasp that some of the drugs are paid once a week while the others were once a year.

Moreover, the amount of information was sufficient enough to enable the patients to choose their medication at the end of the consultation. One of the patients appreciated that the aspect of cost was discussed since she was surprised at how much it will cost her in addition to her other maintenance medications (Figure 8). The side effects card was initially intimidating and raised anxiety in some of the patients (Figure 7). One patient had an issue with the rare adverse event of ONJ from zoledronic acid after seeing the flashcard. However, the patient eventually said she will take the risk after sufficient explanation from the physician about the rarity of ONJ as an adverse event. We observed that the PtDA was able to stimulate conversation between the patient and physician by encouraging patients to ask questions based on the information presented to them. Likewise, it enabled clinicians to clarify important points in the treatment plan.

Figure 2. Introduction card on osteoporosis. It contains a brief description of osteoporosis, the cost of having a fracture and an overview of management.

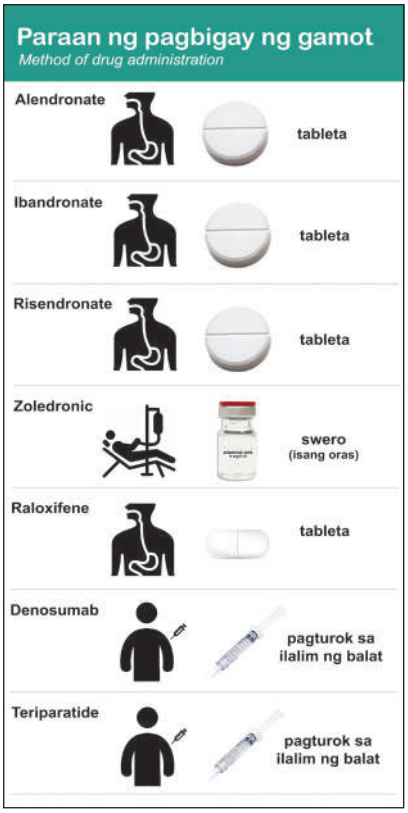

Figure 3. Flashcard on method of drug administration.

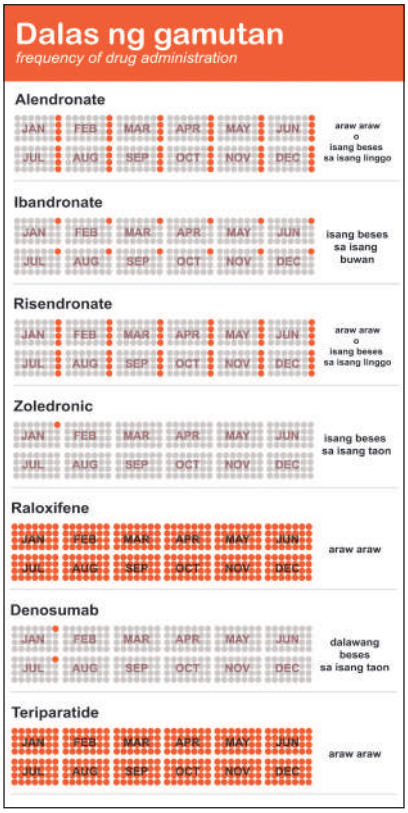

Figure 4. Flashcard on frequency of drug administration.

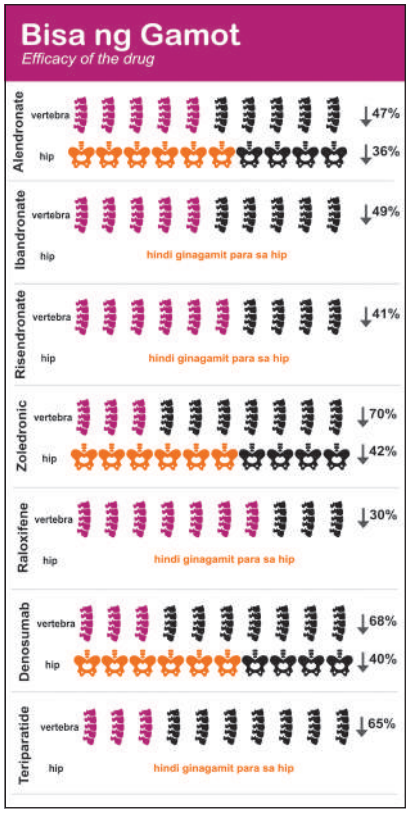

Figure 5. Flashcard on efficacy of other treatments.

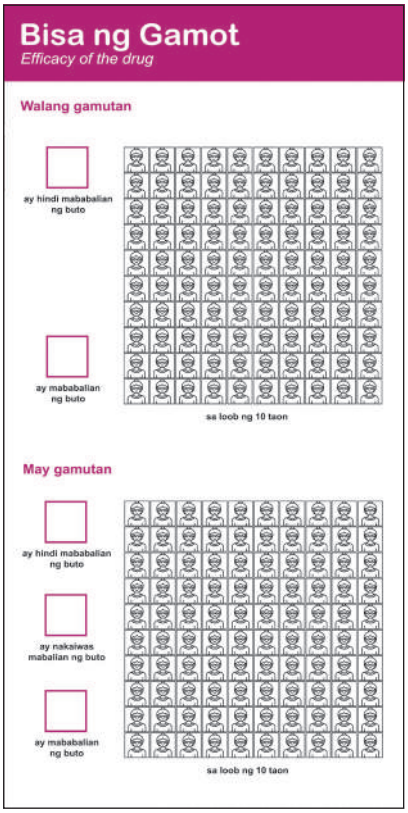

Figure 6. Patient-specific absolute fracture reduction worksheet.

Figure 7. Flashcard on side effects of the different agents.

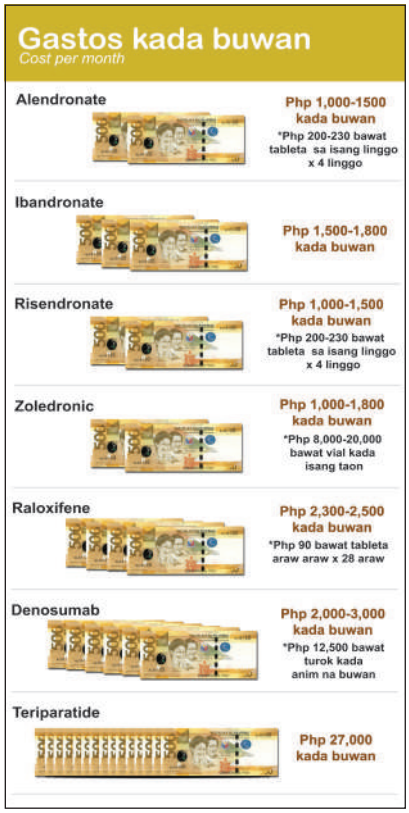

Figure 8. Flashcard on cost of treatment per month.

Similarly, the patients related that the graphics made it easier for them to understand information on the medications. Although some of the pictograms, particularly the efficacy card, needed more clarification, physicians were able to sufficiently explain risk reduction for patients to understand the concept. Nonetheless, a separate worksheet was added to further illustrate patient-specific absolute fracture risk reduction (ARR) when the medication is taken (Figure 6). Both physicians and patients agreed that this way of presenting ARR more clearly illustrated medication efficacy.

Overall, the patients preferred using the tool over the usual consultation. As one of the patients aptly remarked, "*Mas maganda na may nakikita* (It's better to have visuals)." A patient also wished that her other doctors had a similar tool to guide her treatment decisions for her other conditions.

B. Physician insights

Similarly, all physicians were receptive to using the PtDA because it made the consultation more interactive. They were able to elicit the aspects of medication that were important to patients, which allowed them to arrive at an informed decision. The cards were clear and easy to understand for both the patients and physicians. On the other hand, one physician noted that it will take some practice explaining the cards to the patients.

Furthermore, although the use of PtDA by some of the physicians increased consultation time by a few minutes, the trade-off was a more well-informed patient. On the other hand, one physician related that the PtDA even shortened consultation time because the tool provided a more directed yet comprehensive discussion of the treatment options. In addition, physicians also appreciated that they were provided with evidenced-based information as well as key points when explaining the different aspects of the medications.

DISCUSSION

The paper describes the systematic development of an evidence-based, illustrated PtDA on the treatment of osteoporosis among Filipino postmenopausal women. After testing in clinical encounters, we found the use of PtDA in osteoporosis treatment was well-received and encouraged conversation between Filipino physicians and patients. The integration of decisional needs, clinical expertise and user preference helped the creation of an easy-to-understand PtDA consisting of 5 colored, graphic, easy to understand flashcards consisting of the different aspects of the drugs: efficacy, method of administration, frequency of administration, side effects and cost.

In this study, we have seen that patients were more willing to participate in decision-making when given the opportunity by their primary physician. This is consistent with a systematic review that found that through the years, there has been an increase in patient preference to be involved in decision-making.[26] There has been a shift in the theoretical model on medical decision-making from paternalistic to shared. It is only in the latter where two-way information communication occurs.[27] The patient's participation cannot be undervalued because decisional regret, often a result of uninformed decisions or the lack of choices, is associated with lower satisfaction, poor adherence, and reduced quality of life.[28,29] One of the ways to enhance SDM is through the use of a PtDA.

The development of this PtDA involved several phases. The most challenging of these was the information content, specifically on the side effects of the drugs. It was a recurrent theme among patients that the possible side effects of the drugs might discourage them from taking these drugs. This is similar to one of the qualitative studies done in Iran, wherein some physicians believed that explaining the side effects could raise patient anxiety and subsequently make them quit treatment.[30] Likewise, a PtDA on osteoporosis treatment that was developed in the Netherlands also had concerns on mentioning serious but usually rare side effects.[31] To date, it has not yet been established how best to communicate risk of side effects. However, since the goal was to offer a balanced presentation of the benefits and risk of the drugs, it was decided to still highlight these risks in order for patients to have an informed decision.

Another challenge was presenting the data on drug efficacy. We decided to portray the efficacy based on relative risk reduction, as studies have shown that this conveyed better understanding than the number needed to treat.[32] Given that using relative risk reductions may be perceived to be larger treatment effects, we also presented the baseline risk based on the Fracture Risk Assessment Tool (FRAX®) score and the absolute risk reduction with treatment in order to balance risk communication.[33] A separate worksheet was formed in order to better illustrate the efficacy of the drug (Figure 6). This method was also used by Montori et al when they created the Osteoporosis Choice trial. They showed the patient-specific absolute reduction of fracture risk with alendronate using a worksheet, assuming a treatment-related reduction in overall osteoporotic fracture risk of 40%.[13]

Notably, our osteoporosis PtDA tool was adapted to serve patients from low socioeconomic settings with varied educational backgrounds. The patient who was an elementary school graduate particularly had the most difficult time understanding the PtDA. Communication of health information in simple language is one of the challenges of PtDAs among patients with low literacy and numeracy levels. The use of imagery in the form of icons and probabilistic information expressed in natural frequencies (e.g. 1 in 100) have been acceptable ways to help them understand information better.[32,34] In addition, PtDA has been shown to benefit disadvantaged people including those from low socioeconomic status and literacy level. In a systematic review investigating the impact of SDM interventions on disadvantaged groups and health inequalities, there was a significant increase in knowledge and a reduction in decisional conflict and uncertainty post-intervention among disadvantaged groups. The participation of patients also increased as they were more involved in discussing options with their physicians.[35] Although we have not tested the tool in the general population, based on the interviews with patients, the tool made the options more clear, hence the decisions more informed. According to the patients, they would like to have this tool in their future consultations. Similarly, when a decision aid on osteoporosis treatment in Canada was tested, results showed a statistically significant decline in mean decisional conflict scores after using the PtDA.[12]

A limitation of this study is that this tool was only tested on a small population of patients and physicians in a tertiary government hospital that caters mostly to patients from low socioeconomic backgrounds. Feasibility studies of the tool in the private setting and for use by other subspecialties involved in the care of osteoporosis will provide a richer information that could be used to further refine the tool. Based on the needs assessment phase, we also emphasize that not all patients are ready to participate in decision-making and would rather leave it to the physician. Some patients are used to the paternalistic model of the physician-patient relationship. Studies have also shown that patients with low literacy levels were less likely to be involved in health decisions and would rather leave it to the decision of the physician.[32] In the same way, we must also assess the readiness of the physician in incorporating the tool to their usual clinical encounter. Although all agreed that this tool will be helpful in making the options more clear to the patient, it takes skill and practice to incorporate SDM and use of PtDA in the clinic. While the concept of SDM is acknowledged by both parties, it is not yet integral in our daily clinical practice. Therefore, further studies to assess readiness to participate in SDM must also be evaluated in our setting.

In the future, the tool will be tested in an actual field setting in a bigger population with heterogeneous educational and socioeconomic backgrounds to assess its feasibility and eventually implementation. Randomized controlled trials comparing the PtDA versus usual clinical scenario will be conducted to assess transfer of knowledge, level of SDM, decisional conflict, and eventually adherence to treatment.

CONCLUSION

We were able to develop an illustrated PtDA on the treatment of osteoporosis among Filipino postmenopausal women through the integration of decisional needs assessment, clinical expertise, user preference and iterative revision testing. The tool was acceptable for patients and physicians for their use in the actual clinical setting.

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All authors certified fulfillment of ICMJE authorship criteria.

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CASE REPORT

A Case of Appendiceal Goblet Cell Carcinoid Tumor: Getting it right under the Microscope

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Abstract

Goblet cell carcinoid (GCC) is a rare neoplasm of the vermiform appendix and can be mistaken as a typical neuroendocrine tumour (TNET). The natural history of this disease is more aggressive compared to TNETs and requires a more aggressive approach. We report a case of a 37-year-old male who was initially diagnosed with TNET, but subsequently revised as Tang's A GCC. He underwent appendectomy and right hemicolectomy. Aside from a persistently elevated carcinoembyrogenic antigen (CEA) result, his ^{18}F-fluorodeoxyglucose (FDG) PET/CT and a 68-Gallium DOTATATE PET/CT scan showed no FDG or DOTATATE avid lesions.

Key words: goblet cell carcinoid, mixed neuroendocrine-non-endocrine neoplasm, MiNEN, histopathology

INTRODUCTION

Goblet cell carcinoid (GCC) is a rare neoplasm of the vermiform appendix, and is often diagnosed in less than 1% of appendectomy specimens.[1,2] They are often diagnosed incidentally during a histopathological examination after an appendectomy for "suspected appendicitis." GCCs often present as classical acute appendicitis (right iliac fossa pain and tenderness), or even as vague abdominal complaints. GCCs present more commonly in the 50-60 years old age group, with no gender predilection, and a majority of the cases are reported in the Caucasian population. Distinctive histopathological features of a GCC are the presence of both goblet cells (glandular components) and neuroendocrine components. Due to its rarity, it may be misinterpreted as a neuroendocrine tumor. This case describes a patient who was initially diagnosed as TNET, but later the diagnosis was revised as GCC and underwent a more aggressive management approach.

CASE

A 37-year-old healthy male presented to a private hospital with right iliac fossa pain and was diagnosed to have acute appendicitis. He underwent a laparoscopic appendectomy uneventfully and the histopathological examination of the appendix was reported as a neuroendocrine tumour of the appendix with lymphovascular infiltration.

The patient denied symptoms suggesting of a carcinoid tumour, such as diarrhoea, flushing or wheezing. He denies any constitutional symptoms and there was no family history of malignancy. Clinical examination was uneventful. He was subsequently referred to our centre for further evaluation.

Revised histopathological examination (HPE) showed mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) of intermediate grade (goblet cell carcinoid) as there were two morphologically distinct tumour components. The conventional group, composing of nests and cords of tumour cells, exhibited round uniform nuclei with salt and pepper chromatin and scanty eosinophilic cytoplasm (NET appearance). The second group of cells displayed irregular infiltrating nests of goblet cells with abundant univacuolated cytoplasm and peripheral compressed nuclei. Both tumour groups (Figures 1 and 2) encompass >30% of tumour volume each. Mitotic figures were not seen. Immunohistochemical studies showed both tumour groups being positive to synaptophysin and chromogranin. Only the goblet group shows positivity to CK20. The Ki-67 proliferation index is <2% (Figure 3).

Based on the HPE results, he was classified as Tang's classification group A (classic GCC and underwent right hemicolectomy. The histopathological examination of the colon and its surrounding lympho-vascular are showed no local invasion.

His whole body ^{18}F-fluorodeoxyglucose (FDG) PET/CT and a 68-Gallium DOTATATE PET/CT scan showed no FDG or DOTATATE avid lesions. His post-operative CEA was elevated despite his being asymptomatic. At the moment the patient is still under close surveillance with routine CEA measurement and FDG PET/CT Scan.

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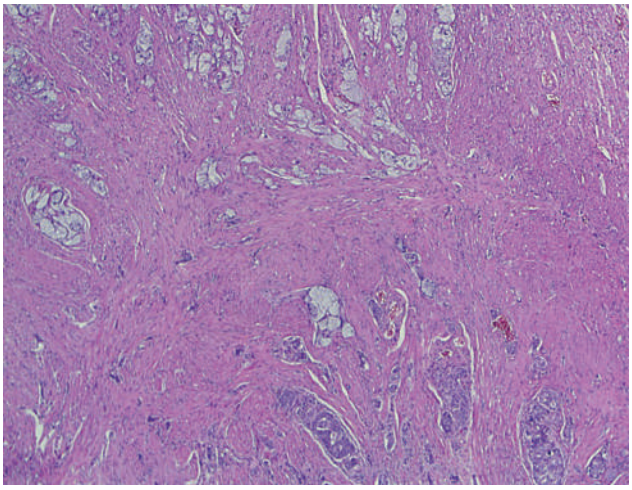

Figure 1. Microscopic findings of the resected appendix showed tumour cells infiltration into the muscularis propriae, with two distinct components identified (H&E, 40x).

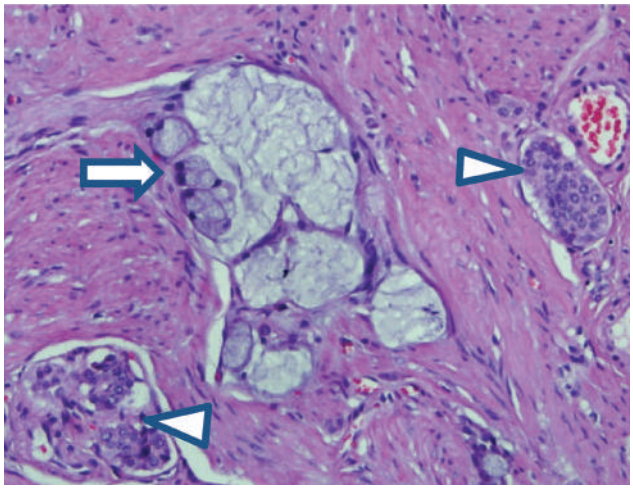

Figure 2. First component: nests of tumour cells exhibiting uniform, round nuclei with salt and pepper chromatin (arrow head). Second component: goblet cells displaying univacuolated cytoplasm and peripherally compressed nuclei (arrow) (H&E, 200x).

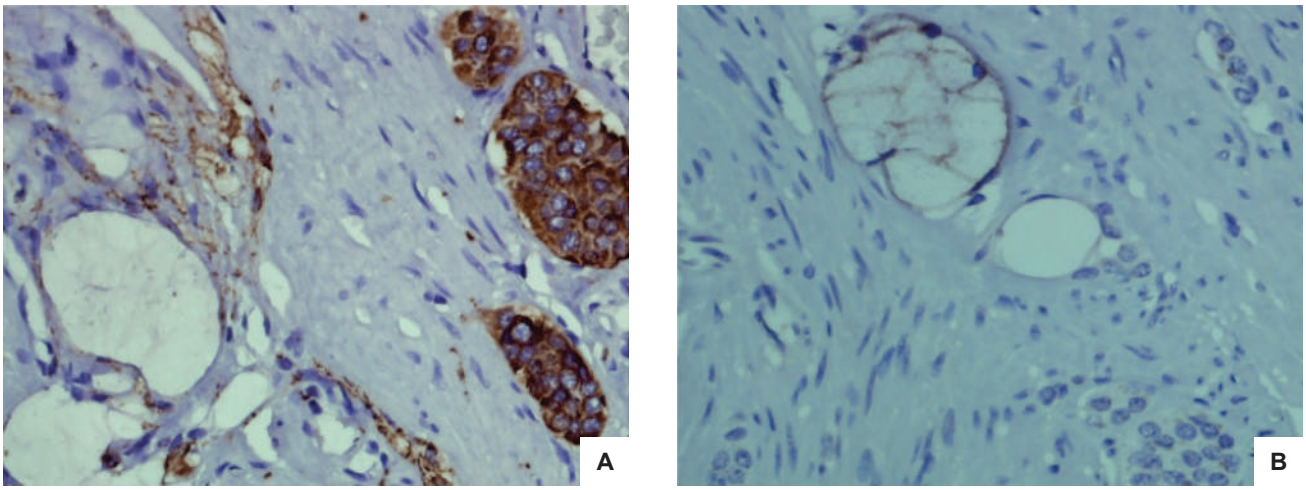

Figure 3. Immunohistochemical findings revealed both components are positive for synaptophysin **(A)**. However, only the goblet cells are positive for CK20 **(B)** (400x).

DISCUSSION

Our patient was diagnosed to have Tang's A GCC and underwent an appendectomy followed by right hemicolectomy. Often diagnosed post-operatively during histopathological examinations, GCCs can sometimes be mistaken as a neuroendocrine tumour (NET). The diagnosis is vital as GCCs exhibit more aggressive behaviour compared to the typical appendiceal neuroendocrine tumours (TNET), which are often managed conservatively.[3] In other words, the overall prognosis of GCCs are poorer compared to NETs, and a more aggressive plan of management and surveillance is essential for these patients.

GCCs are distinctive from the other appendiceal tumours as they have both neuroendocrine differentiation and goblet cell type morphology. The cells stain weakly positive for classical neuroendocrine tumour markers, i.e., chromogranin A and synaptophysin, and they simultaneously produce mucin, pathognomonic for colorectal adenocarcinomas.

The natural history of GCCs is intermediate in its aggressiveness between classical adenocarcinomas and carcinoids, with reported 5-year survival rates of 58%-83%. Due to its natural history and malignant nature, treatment recommendations are in general similar to adenocarcinomas rather than classical carcinoids, with the role of right hemicolectomy in non-extensive GCCs still being debated.

Staging of GCCs include both the 2010 World Health Organization (WHO) classification for appendix tumours, the 2010 AJCC (TNM classification) staging, and Tang et al., classification.[2,4] The Tang classification divides the tumours into three distinctive group based on histological features such as degree of atypia, degree of desmoplasia and arrangement of goblet cells.

The cornerstone of treatment for non-metastatic disease is surgical resection, yet the extent of resection is still debatable. Contrary to the TNETs, there is no consensus among the European Neuroendocrine Tumour Society

(ENETS) and North American Neuroendocrine Tumour Society (NANETS). Despite ENETS's recommendation to proceed with a right hemicolectomy and/or salphingo-oopherectomy after appendectomy, the evidence is still scarce due to absence of randomized controlled trials.[3,5,6] A review by Gilmore et al., quoted a meta-analysis of 13 studies by Varisco et al., showing no benefits of right hemicolectomy in patients with localized disease with low grade histology, while other studies also show no benefits of right hemicolectomy in those with small (<1 cm), localized, low grade tumours without high risk features such as a positive resection margin.[7]

Retrospective analysis of Surveillance, Epidemiology, and End Results (SEER) data evaluating 3137 patients with appendiceal NETS, showed only statistically significant benefit of right hemicolectomy in appendiceal NETs with signet ring cell adenocarcinoma histology, while there were no significant surgical benefits for right hemicolectomy versus appendectomy for typical NETS, after adjusting for age, stage and histology.[6] Tang et al., noted in their analysis that tumour of higher grades benefit more with right hemicolectomy, suggesting that tumours <2 cm, locally advanced stage, positive margins, group B and C histologically, or pT3 and pT4 tumours warrants a right hemicolectomy.[4,7]

Treatment of advanced GCCs mainly includes chemotherapy, but currently, there are no randomized control trials or evidenced-based guidelines. In view of its resemblance to a colon adenocarcinoma, 5-FU based chemotherapies have been suggested despite the scant evidence. Theranostic therapies may not be appropriate, since GCCs are not Ga-DOTATE avid.

Monitoring of recurrence with biochemical investigations (serum CgA or urinary 5-HIAA) are not useful, as these tumours are often non-functional. Contrast CT or MRI scans are sensitive to detect recurrence, whilst the FDG PET/CT scan is sensitive for advanced GCCs. Ga-DOTATATE PET/CT scans in these patients are often negative as GCCs rarely possess somatostatin 2 receptors. Conventional tumour markers of adenocarcinoma of the colon such as carcinoembryonic antigen (CEA), CA125, CA-19-9, may have better value for surveillance for recurrence.[2]

Overall prognosis of GCCs depends on the staging and histology of the tumour. Tang et al., reported that the 5-years disease-specific survival reduces according to the groups, with 100% (group A), 36% (group B), and 0% (group C) respectively.[4] Patients with a major adenocarcinoma component (>50%) have a poorer prognosis compared with those with minor (<50%) component.[1]

CONCLUSION

GCC tumours are more aggressive than classical neuroendocrine tumours even if they do not exhibit malignant properties of adenocarcinomas. Thus, they should be identified promptly as their further definitive therapy differs from the other gastrointestinal NETs. The cornerstone treatment for GCCs are surgical removal of the tumour, yet the value of right hemicolectomy in localised diseased is still unknown.[8] To date, there are still no consensus on the follow-up algorithm of GCCs. In the future, collaborative multi-centre studies will be integral in identifying the best treatment and monitoring options.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

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Debilitating Pain and Fractures: A Rare Case of Hypophosphatemic Osteomalacia with Concomitant Vitamin D Deficiency in Neurofibromatosis Type 1

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Abstract

Hypophosphatemic osteomalacia is a rare form of metabolic bone disorder in neurofibromatosis type 1 (NF1). The exact disease mechanism of this disorder in NF1 is yet to be established. We present a 44-year-old female known to have NF1, who presents with debilitating bone pain, weakness and multiple fractures. Laboratory investigations showed persistent hypophosphatemia with renal phosphate wasting suggestive of hypophosphatemic osteomalacia. She also had concomitant vitamin D deficiency which contributed to the disease severity. Medical therapy with oral phosphate and vitamin D improved her symptoms without significant changes in fracture healing or phosphate levels.

Key words: NF1, hypophosphatemia, osteomalacia, FGF23, Vitamin D deficiency

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder resulting in mutation to the tumor suppressor gene, neurofibromin. It is associated with numerous skeletal abnormalities and disorders of the bone metabolism. Skeletal abnormalities in NF1 are common, it has been well described in literature ranging from dysplasia of the tibia and long bones, dystrophic scoliosis, chest wall deformities, sphenoid wing dysplasia and many more. In contrast, the disorders of bone metabolism in these patients are poorly understood.[1] Hypophosphatemic osteomalacia is amongst the rare disorders associated with NF1, with less than 40 cases reported to date. It usually has a later onset in adulthood with persistent hypophosphatemia, renal phosphate loss and multiple pseudofractures.[2]

CASE

We describe a 44-year-old female who presents with multiple long bones and axial skeleton fractures from a trivial fall in the bathroom. She was referred to the endocrine team for suspected pathological fractures with persistent hypophosphatemia. Further history revealed generalized bone pain for the last decade with progressive weakness resulting in unstable gait and frequent falls over the last two years. She was diagnosed with NF1 at the age of 17 due to pathognomonic cutaneous manifestations and positive family history. Her mother was diagnosed with NF1 in her 20's with cutaneous features, without multisystem involvement. Apart from the maternal history of NF1, there was no history of skeletal or bone metabolism disorders. She defaulted follow up subsequently, without surveillance for complications. She had no visual or hearing impairment. There were no constitutional symptoms to suggest malignancy. She had no history of renal, liver or gastrointestinal disease. Her diet is predominantly vegetarian, with very poor appetite of late, due to debilitating pain. She spends most of her time indoors, with limited sun exposure due to restricted mobility.

Physical examination revealed a slightly built female (BMI 18) with cutaneous manifestations of NF1, café au lait patches and numerous small neurofibromas, the largest being approximately 1.5 cm predominantly over her trunk. She was found to have skeletal abnormalities of the chest wall, pectus excavatum and marked kyphoscoliosis. Neuromuscular examination was unremarkable except for proximal muscle weakness of the hip and thigh. Slit lamp examination of the eye was normal.

X-rays done showed fractures of the left 6-9th ribs, bilateral superior and inferior rami, left neck and right subtrochanteric of femur (Figure 1). Her thoracolumbar x-ray confirmed marked kyphoscoliosis with compression fracture of L1 (Figures 2 and 3). Her blood biochemistry showed a persistently low phosphate (0.31-0.56 mmol/L) with a concomitant normal calcium (2.2-2.6 mmol/L). Her other electrolytes, renal and liver function were normal except for an elevated alkaline phosphatase (300-360 U/L). Her 25-OH Vitamin D level was 25 pmol/L, suggestive of deficiency and intact Parathyroid Hormone (iPTH) was elevated at 46.4 pmol/L.

The hypophosphatemia was due to renal loss evidenced by elevated urinary fraction of phosphate excretion, 12.7% and low TMP-GFR (Ratio of Tubular Maximum

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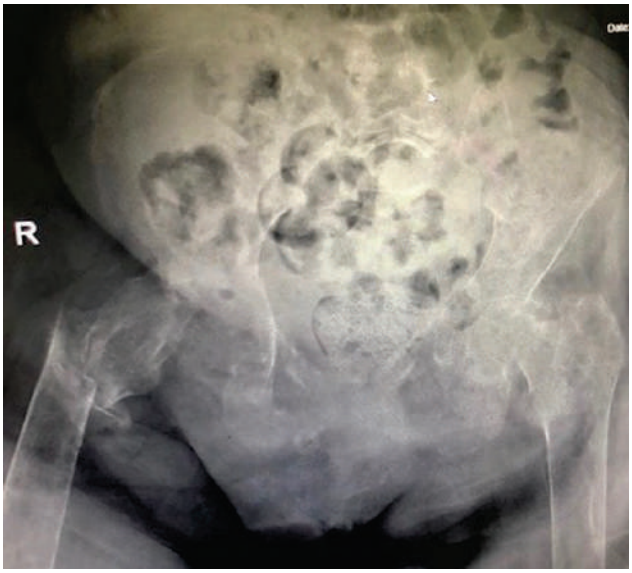

Figure 1. Pelvic x-ray showing bilateral femur fractures with diffuse osteopenia.

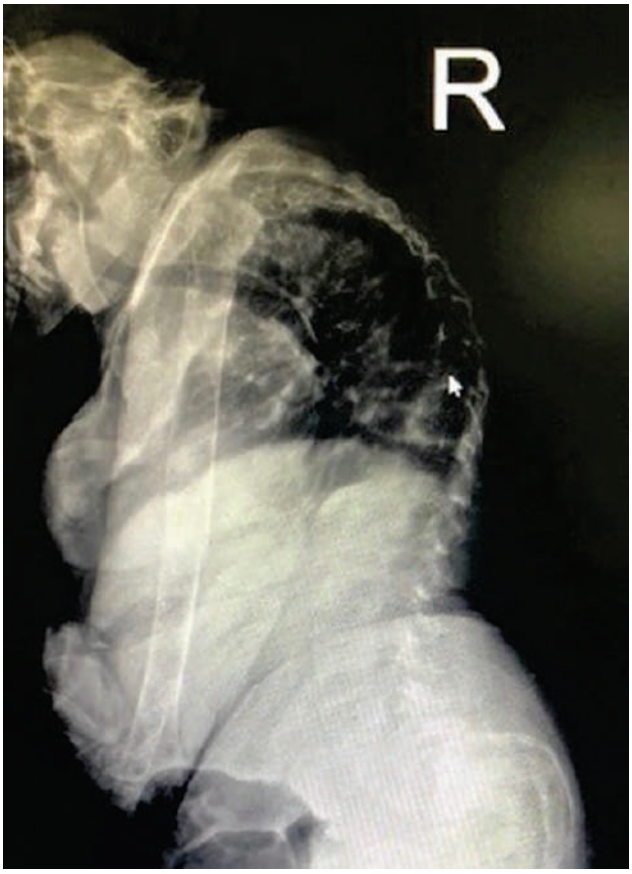

Figure 2. Lateral view of spine showing excessive thoracic kyphosis.

Reabsorption Rate of Phosphate to Glomerular Filtration Rate) of 0.488 (0.88-1.42). There were no abnormalities in the blood acid base balance or urinary biochemistry to suggest renal tubular dysfunction. A full body CT-scan was done to ensure an occult phosphaturic mesenchymal neoplasm resulting in tumor induced osteomalacia was not missed out. She was concluded to have hypophosphatemic osteomalacia secondary to neurofibromatosis with

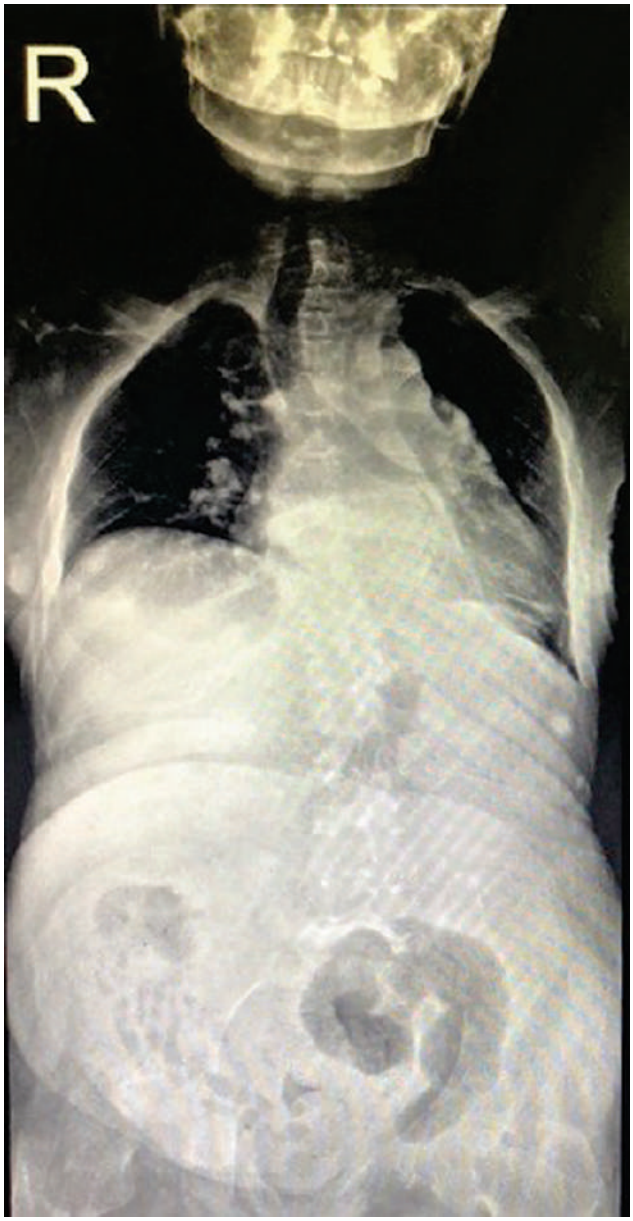

Figure 3. Anteroposterior view of spine x-ray showing marked scoliosis.

concomitant vitamin D deficiency. The elevated iPTH was explained by secondary hyperparathyroidism due to vitamin D deficiency.

She was seen after 8 weeks to assess response to treatment. She reported improvement in symptoms especially bone pain and weakness despite the delay in fracture healing. There was no significant changes in her serum phosphate levels with persistent hyperphosphaturia. Unfortunately, due to the limited availability and cost of vitamin D testing, she was not able to repeat her levels. A clinical decision was made to continue the oral phosphate and to shift her to activated vitamin D, calcitriol 1 mcg a day in divided doses. Her future medical therapy will be titrated mainly based on her symptoms. She will also be monitored closely for complications of treatment with activated vitamin D such as hypercalciuria and nephrolithiasis with routine six -monthly 24 hour urine calcium/creatinine index and renal ultrasound.

DISCUSSION

This patient presented with features suggestive of renal phosphate wasting in adulthood with underlying NF1. Despite the lack of formal diagnosis, her cutaneous stigmata of NF 1 preceded the onset of renal phosphate wasting by at least 20 years whereby she was well, asymptomatic till her mid 30's. Her presentation with multiple fractures and marked skeletal abnormalities with accelerated disease progression over the last few years signifies an active underlying disease pathophysiology.

As mentioned above, the association of hypophosphatemic rickets/osteomalacia with NF1 has been rarely reported in literature. These patients usually develop disease later in adulthood and often present with severe bone pain, muscle weakness and fractures.[3] Their biochemistry typically reflects hypophosphatemia with normal or low calcium levels, elevated ALP, and increased urinary phosphate excretion. It is interesting to note, that despite the chronic urinary phosphate loss, the 25-OH Vitamin D, 1,25 OH Vitamin D and iPTH levels were often reported as normal.[4] However, our patient was deficient in 25-OH Vitamin D resulting in secondary hyperparathyroidism which cannot be solely attributed due to the disease process above. It can be postulated that her vitamin D deficiency is multifactorial due to her dark skin, limited sun exposure and poor nutrition. The concomitant vitamin D deficiency could be a contributing factor to the disease severity resulting in debilitating symptoms and multiple fractures.

There have been multiple hypothesis with regard to the underlying pathophysiology of hypophosphatemic osteomalacia in NF1, however the exact mechanism of disease is yet to be established. Abdel-Wanis et al.,[5] hypothesized in 2002 that melatonin deficiency in NF-1 may be driving the underlying mechanism of hyperphosphaturia by a complex mechanism involving decreasing the sodium-phosphate cotransport, increasing the level of cyclic adenosine monophosphate (cAMP) and the unantagonized effect of dopamine on phosphate reabsorption. Secondary hyperparathyroidism as a result of osteomalacia may augment the dopamine effect resulting in worsening phosphaturia. Melatonin deficiency also results in excess corticosteroids secretion which in turn may further inhibit melatonin secretion. This results in a vicious cycle of phosphate loss causing progressive bony deformities and osteomalacia.

In recent times, it has been suggested that excess fibroblast growth factor-23 (FGF-23) is responsible for hypophosphatemic osteomalacia in NF1.[2,3] FGF-23 is a protein secreted by osteocytes which functions as the central regulator of phosphate metabolism. It mainly acts on the kidneys where it inhibits reabsorption of phosphate by the sodium–phosphate co-transporters in the proximal tubules. It also decreases 1,25$(OH)_2$Vitamin D production by suppressing the 1-alpha hydroxylase enzyme. Excess activity of FGF-23 has been proven to be responsible for various hypophosphatemic bone disorders including inherited forms of rickets and tumor induced osteomalacia.[6] Where neurofibromatosis is concerned, there is still insufficient evidence to conclude if FGF-23 drives the pathogenesis of the disease. In a single center study in India, it was found that only one out of three NF1 patients with persistent hypophosphatemia had marginally elevated level of plasma FGF23.[7] In 2019, Sahoo et al.,[2] had reported the first unequivocally elevated FGF-23 in a NF-1 patient with skeletal dysplasia, neurofibroma and hypophosphatemia. It was initially postulated that the excess FGF-23 is produced by neurofibromas resulting in a tumor induced osteomalacia like syndrome.[3,8] However, recent literature has disputed this theory by showing absent FGF-23 staining in histopathological examination of neurofibroma of a NF1 patient with hypophosphatemic osteomalacia who had elevated circulating levels of FGF23.[2] It has been proposed that the bone may be source of excess FGF-23 in NF-1 patients. This was supported by a study done on mice, where the NF1 gene deficient osteocytes in conditional knock out mice (NF1cKO) produced excess FGF-23 in their bones and exhibited an osteomalacia- like bone phenotype. This is attributed to the upregulation of PI3K intracellular signalling pathway in these neurofibromin deficient osteocytes.[9] Unfortunately, in our patient, we were not able to send her FGF-23 levels due to logistic and financial caveats.

CONCLUSION

In conclusion, hypophosphatemic osteomalacia in NF-1 is a rare but important bone metabolism disorder. The disease process can result in debilitating pain and multiple fractures in patients, affecting their quality of life and longevity. The current consensus for treatment of this disorder is medical therapy with phosphate and activated vitamin D based on symptoms. There is no definitive therapy to treat the underlying disease itself in current practice. There has been recent interest in FGF-23 mediated hypophophatemic rickets and osteomalacia due to the development of burosumab, a human monoclonal antibody against FGF-23. Burosumab has been proven as a novel therapeutic agent in management of both children and adults with X-linked hypophosphatemic rickets.[10,11] An on- going open label phase 2 study using burosumab in patients with Tumor Induced Osteomalacia (TIO) syndrome and Epidermal Naevus Syndrome (ENS) has shown biochemical and symptoms improvement in these patients.[12] If the hypothesis of excess FGF-23 can be confirmed in hypophosphatemic osteomalacia in NF-1, it unlocks a possible therapeutic opportunity to use burosumab as definitive treatment in these patients.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

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The Perilous PPI: Proton Pump Inhibitor as a Cause of Clinically Significant Hypomagnesaemia

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Abstract

Proton pump inhibitors (PPIs) are the mainstay of therapy for all gastric acid related diseases and are commonly used in current clinical practice. Although widely regarded as safe, PPIs have been associated with a variety of adverse effects, including hypomagnesaemia. The postulated mechanism of PPI-related hypomagnesaemia involves inhibition of intestinal magnesium absorption via transient receptor potential melastin (TRPM) 6 and 7 cation channels. PPI-induced hypomagnesaemia (PPIH) has become a well recognized phenomenon since it was first reported in 2006. Clinical concerns arise from growing number of case reports presenting PPIH as a consequence of long-term PPI use, with more than 30 cases published to date.

In this article, we report 2 cases of PPIH associated with the use of pantoprazole. Both patients presented with severe hypomagnesaemia and hypocalcaemia. One of them had associated hypokalemia and cardiac arrhythmia. A casual relation with PPIs postulated and supported by resolution of electrolyte abnormalities after discontinuation of PPIs.

Key words: Proton pump inhibitors, hypomagnesaemia, hypocalcaemia, hypokalemia

INTRODUCTION

Proton pump inhibitors (PPIs) are the mainstay of therapy for all gastric acid related diseases and are commonly used in current clinical practice. Although widely regarded as safe, PPIs have been associated with a variety of adverse effects including interstitial nephritis, pneumonia, *Clostridium difficile*-associated diarrhea, vitamin B12 deficiency, osteoporosis and fractures.[1] More recently, long-term use of PPIs has been suggested as a potential cause of hypomagnesaemia[2] Magnesium is the second most abundant intracellular cation and its homeostasis is intricately regulated by intestinal absorption and renal excretion. The postulated mechanism of PPI-related hypomagnesaemia involves inhibition of intestinal magnesium absorption via transient receptor potential melastin (TRPM) 6 and 7 cation channels.[3,4] Severe hypomagnesaemia can be associated with malignant cardiac arrhythmias, tetany, generalized seizures, and other metabolic disturbances such as hypokalemia and hypocalcaemia.[5]

PPI-induced hypomagnesaemia (PPIH) has become a well recognized phenomenon since it was first reported in 2006.[6] Clinical concerns arise from growing number of case reports presenting PPIH as a consequence of long-term PPI use, with more than 30 cases published to date.[6-22] In 2011, United States Food and Drug Administration released a safety concern on PPIs, stating that it may cause hypomagnesaemia if taken for prolonged periods of time.[23] This announcement alerted healthcare professionals to the risk of hypomagnesaemia among chronic PPI users, with the consideration of obtaining baseline and regular follow-up serum magnesium concentrations over time. In this article, we report 2 cases of PPIH associated with the use of pantoprazole.

CASE 1

Patient 1 was a 59-year-old female with a background history of diabetes mellitus and hypertension. Her medications included perindopril, amlodipine, metformin and gliclazide. She was diagnosed with pulmonary tuberculosis one month prior to admission (PTA), having presented with 3-month history of fever, cough and constitutional symptoms. She was started on anti-tuberculosis treatment. Unfortunately, she developed epigastric pain and vomiting and was started on pantoprazole a month later. She requested at-own-risk discharge from hospital on two days after starting the PPI.

Three days later, she was admitted again due to persistent vomiting and epigastric pain. On her 1st hospital day (HD) she developed an episode of narrow-complex tachycardia with prolonged QTc and went into respiratory distress. She required intubation and was transferred to the intensive care unit. Her blood investigations showed multiple electrolyte abnormalities, including hypomagnesaemia, hypocalcaemia, hypophosphatemia and hypokalemia. She was given multiple doses of parenteral magnesium sulfate, calcium gluconate and potassium chloride to correct those deficiencies. However, the serum magnesium,

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potassium and calcium levels failed to return to normal despite multiple corrections given.

On the 3rd HD, pantoprazole was discontinued. Thereafter, the serum levels of magnesium, potassium and calcium started to respond to the IV corrections and slowly returned to normal. (Table 1 and Figure 1). Unfortunately, the patient developed hospital-acquired pneumonia and succumbed to septicemia two weeks later.

CASE 2

Patient 2 is a 71-year-old female. She had underlying diabetes mellitus, hypertension, chronic kidney disease (CKD) stage V (not on renal replacement therapy) and bilateral knee osteoarthritis. She was diagnosed with peptic ulcer disease in 5 months PTA after an episode of upper gastrointestinal bleeding. She was prescribed pantoprazole since that admission. On the day of admission, she presented with lethargy and bilateral hand numbness. Blood investigations showed she had severe hypocalcaemia and hypomagnesaemia. Her pantoprazole was withheld on her 2nd HD and substituted with oral ranitidine. She was given a few intravenous calcium and magnesium corrections. Her serum magnesium and calcium levels slowly returned to near normal levels after the pantoprazole was discontinued (Table 2 and Figure 2). She was discharged on her 6th HD with oral calcium carbonate supplement. When she followed up one month later, her blood magnesium and calcium levels had normalized. Vitamin D level was not available due to reagent shortage.

DISCUSSION

We describe two adult patients presenting with severe hypomagnesaemia and hypocalcaemia while using PPIs. Patient 1 developed hypomagnesaemia and hypocalcaemia after short-term use of pantoprazole of 7 days while patient 2 experienced the same side effects after 4 months. This is consistent with the findings in a systematic review published by Hess et al, in which the time to onset of hypomagnesaemia is highly variable and ranged from 14 days up to 13 years (mean 5.5 years).[7] This finding suggests that serum magnesium and calcium levels should be frequently monitored in patients taking PPIs, regardless of the duration of medication given.

Recent studies postulated that the potential mechanism for PPIH is not due to renal magnesium wasting, but rather decreased gastrointestinal absorption, evidenced by reduced urinary excretion of magnesium in the setting of PPIH.[6-9] Few recent mechanistic studies which have focused on the potential effect of PPI use on the TRMP6 transporter, the main pathway of magnesium absorption in the intestine, supports the above clinical observations. TRPM6 activity is regulated by intracellular magnesium along with pH.[24,25] A more acidic environment will increase TRPM6 activity. PPI therapy decreases gastric acid secretion, increasing lumen pH, and therefore decreases TRPM6 activity, which results in decreased intestinal magnesium absorption.[26-28] Our patient 1 showed similar pattern, in which during the hypomagnesaemia state, the urine excretion of magnesium was reduced to conserve magnesium. For patient 2, unfortunately, no 24-hour urine magnesium was sent.

Table 1. Patient 1 blood investigations

	Baseline	On pantoprazole		Pantoprazole discontinued				
Date	27/8/17	19/9/17	20/9/17	21/9/17	22/9/17	24/9/17	27/9/17	29/9/17
Corrected calcium (2.18-2.6 mmol/L)	2.22	1.5	1.5	1.46	2.0	2.02	1.96	2.26
Magnesium (0.53-1.11 mmol/L)	0.75	0.35	–	0.74	0.85	0.78	0.74	0.65
Phosphate (0.78-1.65 mmol/L)	0.83	0.7	0.48	0.12	0.66	0.86	1.01	0.57
Potassium (3.5-5.1 mmol/L)	4.6	3.0	3.3	3.6	4.1	4	3.3	4.4

iPTH:	7.45 pmol/L	(1.58-6.03)
24 hour urine calcium:	0.15 mmol/24hour	(2.5-7.5)
24 hour urine magnesium:	3.4 mmol/24 hour	(4.0-5.0)
Total 25-hydroxyVitamin D:	46.94 nmol/L	(<25 Deficient) (25-75 Insufficient) (75-250 Sufficient) (>250 Possible intoxication)

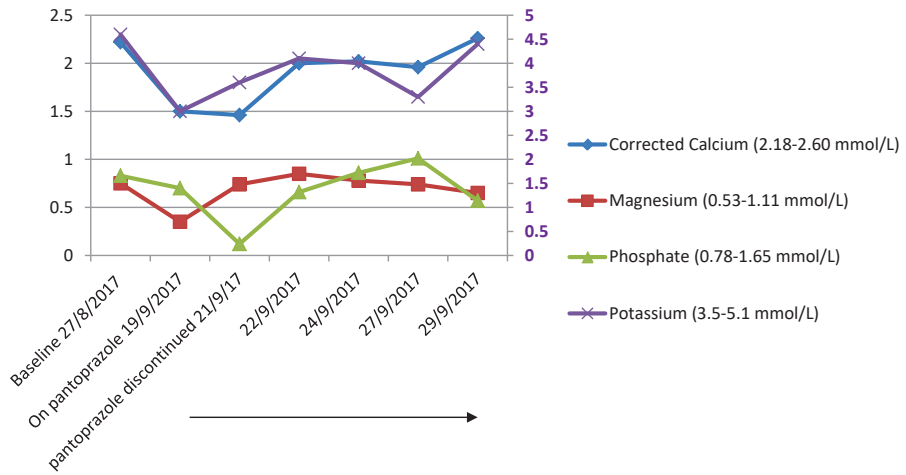

Figure 1. Course of laboratory parameters over time in patient 1.

Table 2. Patient 2 blood investigations

		Pantoprazole discontinued					
Date	11/9/18	13/9/18	14/9/18	15/9/18	16/9/18	17/9/18	17/10/18
Corrected calcium (2.18-2.6 mmol/L)	1.35	1.54	1.63	1.73	1.91	1.96	2.29
Magnesium (0.53-1.11 mmol/L)	0.42	0.48	0.53	0.46	0.52	0.77	0.81
Phosphate (0.78-1.65 mmol/L)	1.47	1.44	1.33	1.58	1.63	1.58	–
Potassium (3.5-5.1 mmol/L)	4.3	–	–	4.4	4.6	4.6	–
iPTH: 22.78 pmol/L (1.58-6.03)							

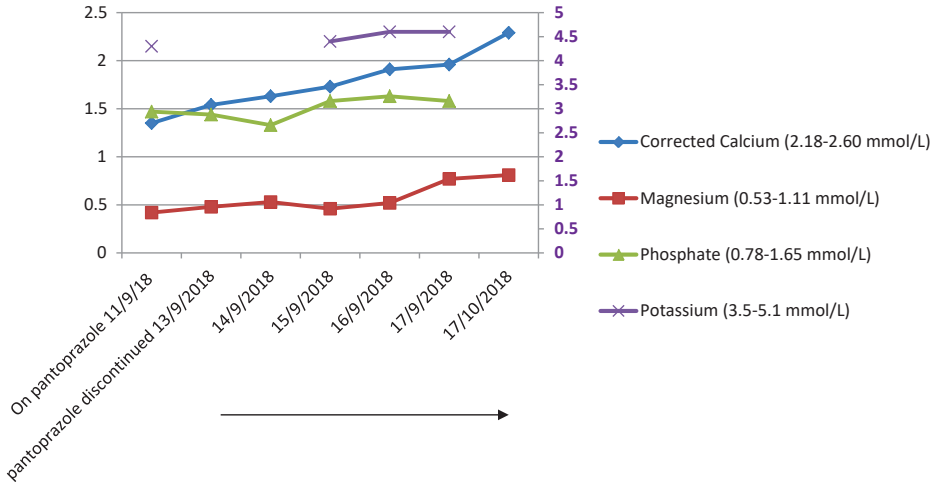

Figure 2. Course of laboratory parameters over time in patient 2.

Hypomagnesaemia is commonly asymptomatic and the most common signs of magnesium deficiency are hypokalemia and hypocalcaemia. Patients with symptomatic hypomagnesaemia will most commonly present with neuromuscular irritability or cardiac arrhythmia[29] as was the case with our patient 1 who presented with a narrow complex tachycardia with prolonged QT.

As mentioned above, the most classical sign of severe hypomagnesaemia is **hypocalcaemia.** Adequate amount of magnesium is essential for vitamin D and calcium homeostasis[30] and function of the parathyroid glands. Magnesium deficiency affects the function of phosphatidylinositol system and adenylate cyclase activity in parathyroid glands and in target tissues.[31-36] As a result, this will lead to:

1. Reduced secretion of parathyroid hormone (PTH), leading to reduced bone resorption, reduced intestinal calcium absorption, and increased renal calcium loss. Collectively, these will lead to hypocalcaemia.
2. Reduced target tissue sensitivity to PTH. When bone and kidney tissues are resistant to PTH, PTH mediated 1α-hydroxylation of vitamin D decreases.[37] This will lead to a decrease in intestinal absorption of calcium and result in hypocalcaemia.

In patient 1, we noted magnesium-dependent PTH suppression with development of transient hypoparathyroidism and severe hypocalcaemia (the iPTH level 7.45 pmol/L is only mildly increased, which is inappropriate in the setting of severe hypocalcaemia in patient 1). After the magnesium level was corrected, hypocalcemia in patient 1 slowly resolved. This confirmed that hypomagnesaemia is the cause of the transient hypoparathyroidism and hypocalcaemia in patient 1. On the other hand, in patient 2, the iPTH level was high (22.78 pmol/L) instead of low. Patient 2 had CKD stage 5, she might have concurrent secondary hyperparathyroidism due to CKD and therefore the iPTH level was elevated.

Patient 1 was noted to have concurrent vitamin D deficiency. This is not an uncommon finding among Malaysian women as the prevalence of vitamin D deficiency is high in Malaysia.[38] Concurrent vitamin D deficiency in patient 1 could also be contributing to her hypocalcaemia. For patient 2, unfortunately no vitamin D level was sent.

Hypokalemia is a common event in patients with hypomagnesaemia, occurring in 40 to 60 percent of cases.[39] Hypomagnesaemia is associated with a reduction in intracellular magnesium concentration, which may then lead to a decline in adenosine triphosphate (ATP) activity. This decline removes the ATP inhibition of potassium (ROMK) channels, leading to an increase in the number of these channels. The uninhibited potassium channels will therefore increase potassium secretion from the cell into the lumen in the cells of the thick ascending limb and cortical collecting tubule, and cause renal potassium wasting and eventually lead to hypokalemia.[40-42] As a result, hypokalemia is resistant to potassium supplement and can be treated only by correcting the magnesium deficit. In patient 1, the hypokalemia was initially resistant to potassium correction. After pantoprazole was discontinued and the magnesium deficit corrected, the potassium level normalized. In patient 2, no hypokalemia was noted, possibly because patient 2 had advanced chronic kidney disease with reduced kidney excretion of potassium, which neutralized the hypokalemia caused by magnesium deficiency.

The treatment of PPIH is similar to that of other forms of hypomagnesaemia, in which parenteral magnesium is indicated in severe hypomagnesaemia. However,

intravenous magnesium replacement is only partially effective and provides only short-term relief, while PPI therapy is maintained. This is because PPI-induced blockade in magnesium absorption cannot be overcome by magnesium supplement alone. The struggle to reverse the hypomagnesaemia in these 2 patients while still on pantoprazole improved after pantoprazole was discontinued. This finding is consistent with previous case reports and systematic review.[6-22] The only effective way to reverse PPIH is discontinuation of PPIs.

PPIH is observed for all currently available PPIs and appear to be a class effect. Discontinuation of PPIs leads to fast recovery from PPIH. However, it reappears invariably when rechallenged with the same or a different PPI. Fortunately, it does not occur with other acid suppressants such as H2 receptor antagonists (H_2RA)[6-22] as seen in patient 2. Her pantoprazole was substituted with ranitidine. During her clinic follow up a month later, her magnesium and calcium levels remained normal. Therefore, in patients with gastric acid related disease that is complicated with PPIH, H_2RA should be considered and we should avoid rechallenge with the same or a different PPI.

The prevalence of PPI-induced hypomagnesaemia is not known. Case reports and case series to date only represent the tip of the iceberg. Symptoms of hypomagnesaemia are either non-specific or could be misinterpreted. Therefore, proper identification and treatment of PPIH mainly rests on 3 principles:

1. The need for long-term PPI therapy in patients should be kept under regular review.
2. If PPI therapy is required on a long-term basis, serum magnesium monitoring should be performed on a regular basis. If PPIH develops, discontinuation of PPIs, supported by magnesium supplement, will lead to rapid normalization of serum magnesium.
3. Patients with PPIH can avoid hypomagnesaemia by using alternative acid suppressants. Therefore, H_2RA should be considered in the event of PPIH.

CONCLUSION

In conclusion, known risks of long-term PPI administration must be considered in clinical practice and judicious use of PPIs is important to avoid potentially fatal complications.

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CASE REPORT

45,X/46,XY Mosaicism in an 18-year-old Girl with Primary Amenorrhea: A Case Report*

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Abstract

45,X/46,XY mosaicism is a rare disorder with a wide heterogeneity in its manifestations. An 18-year-old girl was referred to the endocrine clinic for investigation of her primary amenorrhea. Clinical examination was unremarkable. Hormonal profile was consistent with primary ovarian insufficiency and human chorionic gonadotropin (hCG) stimulation did not show evidence of active testicular tissue. Karyotyping studies by G-banding revealed a 45,X/46,XY karyotype. She was diagnosed with mosaic Turner syndrome with Y chromosomal material and investigation was performed to identify the presence of male gonads due to the risk of gonadal malignancy. Magnetic resonance imaging (MRI) of the pelvis did not show evidence of gonads. Laparoscopic exploration was proposed but the patient and parents refused opting for conservative management. This case highlights the challenges in the management of this rare condition.

Key words: Mixed gonadal dysgenesis, Turner syndrome, Y chromosome, sex chromosome aberrations, 45,X/46,XY mosaicism

INTRODUCTION

Disorders of sexual development (DSD) consist of congenital conditions in which development of the chromosomal, gonadal or anatomic sex is atypical.[1] Gonadal dysgenesis is part of the subset of DSD and is characterized by incomplete or defective gonadal development as a result of either structural or numerical anomalies in the sex chromosomes or mutations in the genes involved.[2] This is further divided into complete (Swyer syndrome) and partial gonadal dysgenesis depending on the morphology of the gonads. In partial gonadal dysgenesis, the percentage of cells with intact XY genotype determines the degree of testicular differentiation.[3] Deficiency of Müllerian inhibiting substance and testosterone results in incomplete internal and external genital masculinization.[3] An X-linked molecule, DAX1 (duplicated in adrenal hypoplasia congenita on the X chromosome) has also been proposed to play a role in suppressing testicular differentiation.[3] A common karyotype is 45,X/46,XY although 46,XY or other forms of mosaicism can be seen.[2] 45,X/46,XY mosaicism is rare with estimated detection rates of 1.7 per 10,000 newborns and most reports are from case series.[4] In Turner syndrome, Y chromosome material has been reported between 5 to 12 percent of patients.[5,6] Individuals may present with a wide spectrum of manifestations ranging from phenotypic females with or without virilization, ambiguous genitalia or Turner features to phenotypic males and are typically short or of normal height although the reason for this is unclear.[7] This condition may go unrecognized into adulthood unless there are gross features of Turner syndrome, growth retardation, pubertal delay or sexual ambiguity. Adult males may present during investigation for infertility. Traditionally, gonadectomy has been recommended in all individuals with presence of Y chromosome material.[8] In complete gonadal dysgenesis, there is a high risk of gonadal malignancy. Bilateral gonadectomy is recommended as soon as the diagnosis is established.[2] In contrast, the evidence is inconsistent for partial gonadal dysgenesis. In light of more recent studies, there has been a move towards a more individualized and conservative approach to decision-making in these individuals, taking into account their phenotype and certain risk factors.[2,9] There is also lack of evidence regarding the utility of imaging and tumour markers as part of surveillance in those who decide for conservative management.

CASE

An 18-year-old girl of Chinese descent was referred to the adult endocrine clinic for further investigation of her primary amenorrhea. She had an uneventful antenatal history and was born with normal female external genitalia. She is an only child and there was no history of consanguinity. There were no major childhood illnesses or admissions to hospital. According to her parents, her developmental milestones were normal and academic performance was average. Among her peers in class, she was on the shorter side but otherwise did not have any issues with her social interactions and was a reasonably well adapted child. Academic performance was average. She had an aunt on her mother's side who had delayed menarche, hence the delay in seeking medical treatment.

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A year prior, she had visited a gynaecologist and had been given a trial of oral contraceptive pills leading to commencement of her menstrual periods which stopped upon cessation of the pills. She is not sexually active and denies use of any other medications or substances.

She is 145 cm tall with a mid-parental height of 152 cm. Her weight is 48 kg with a body mass index of 22.8. She has no acne, hirsutism or deepening of voice. There were no dysmorphic or obvious Turner features. External genitalia appeared female. Breast development was Tanner 3 and pubic hair was Tanner 2. There was no clitoromegaly or palpable gonads. Cardiovascular examination was normal.

Blood investigations reveal hypergonadotropic hypogonadism with normal prolactin, thyroid function test and insulin like growth factor-1 (IGF-1) (Table 1). HCG stimulation test was performed showing no increase in serum testosterone post-stimulation (Table 1) suggesting that there is no active testicular tissue. These were taken after the hormonal pills were stopped. Bone age was 14 years of age. Magnetic resonance imaging (MRI) of the pelvis was done which showed a small and atrophic uterus (Figure 1). No structures resembling ovaries or testicular tissue were identified. An echocardiogram was performed to screen for cardiac malformations showing a normal aortic valve and aortic root. Standard chromosomal analysis by G-banding on peripheral blood revealed 2 different cell types, one with single X chromosome (4 spreads) and one with XY chromosome (60 spreads). Careful discussion was carried out with the patient and her parents disclosing her diagnosis, gonadal status, consequences on fertility and the possibility of gonadal malignancy in view of the presence of Y chromosome material. The patient is comfortable with her gender identity as a female and did not express any gender dysphoria. Fertility was not an active concern at the time as she was still single, however it was explained that she would be unable to conceive normally. Laparoscopic exploration was recommended for assessment of any atypical gonads followed by gonadectomy. However, the patient and her family were not keen for an invasive procedure and opted for conservative management for the time being. She was started on hormonal replacement therapy for prevention of the long-term consequences associated with primary ovarian insufficiency and is under regular follow-up and monitoring for medical and endocrine complications related to Turner syndrome. Option for interval imaging for surveillance for gonadal malignancy was also discussed with the family.

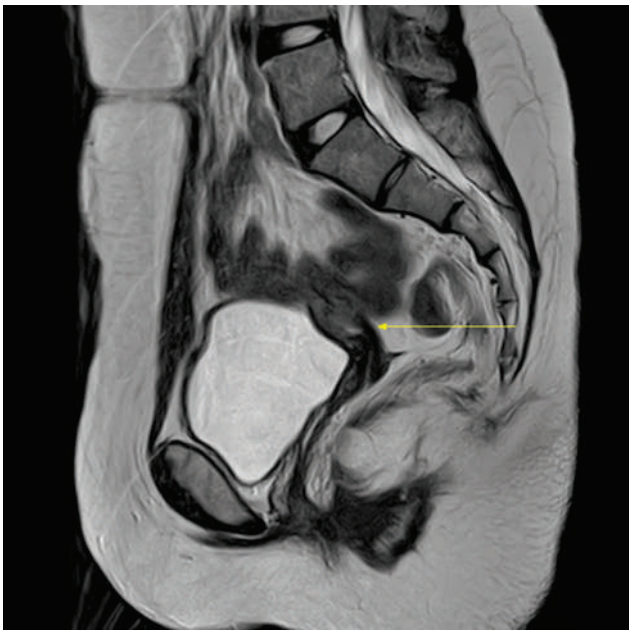

Figure 1. MRI pelvis. Image shows small and atrophic uterus (yellow arrow).

Table 1. Hormonal profile

Serum oestradiol	<70.0 pmol/L (follicular phase 70.0-670.0)
Serum follicle-stimulating hormone	101.7 IU/L (follicular phase 3.5-16.0)
Serum luteinizing hormone	36.4 IU/L (follicular phase <15.0)
Serum Insulin-like growth factor-1	245.0 ng/ml (14.0 - 483.0)
Serum testosterone (baseline)	0.52 nmol/L (0.30 - 2.00)*
Serum testosterone (post hCG)	0.59 nmol/L (0.30 - 2.00)*
Serum Prolactin	411.4 mIU/L (108.78 - 557.13)
Free T4	13.0 pmol/L (9.0-19.1)
Thyroid stimulating hormone (TSH)	1.63 mIU/L (0.35 - 4.94)

* Normal laboratory reference ranges for testosterone in females. No specific cutoffs available for hCG stimulation.

DISCUSSION

In partial gonadal dysgenesis, there is wide heterogeneity in phenotype ranging from males with varying degrees of masculinization of the external genitalia to females with or without features of Turner syndrome. Imaging findings can range from absent to fully developed Müllerian structures, depending on the degree of testicular dysgenesis.[2] Prior studies have shown that the proportion of the cell lines in the blood karyotype does not appear to accurately reflect the phenotype.[7] However, there is evidence to suggest that the mosaicism ratio in various tissues may explain the variability in the phenotypes.[10] The ratio exhibited in different tissues can vary widely, hence tissues with a higher ratio of 45,X/46, XY fragments may be more likely to exhibit Turner syndrome phenotype.

In our patient, we were unable to perform the analysis on the gonads, however a higher mosaicism ratio and consequent lack of Y chromosome in the gonadal tissues could explain her predominantly Turner phenotype. A study evaluating 16 Chinese patients with 45,X/46,XY mosaicism demonstrated that most of the female patients had persistent Müllerian structures with streak or unidentified gonads which present as an infantile or rudimentary uterus with 2 patients having a normal-sized uterus.[7] These findings are consistent with those of our patient. In one case series, absence of gonadal tissue was noted in 18% of patients with 45,X/46,XY mosaicism who underwent gonadectomy.[11] It is hypothesized that the gonadal anlage, when unable to develop to mature stage, regressed by apoptosis.[11] Similar to our patient, patients with partial gonadal dysgenesis usually demonstrate hypergonadotropic hypogonadism with decreased levels of serum testosterone and minimal or no elevation in testosterone response to hCG stimulation as well as reduced anti-Müllerian hormone levels.[7]

In the past, prophylactic gonadectomy has been routinely recommended, although it has been debated whether this may constitute over-treatment. Presence of Y chromosome material increases the risk of gonadal malignancy with gonadoblastoma being the most common germ cell

tumour seen in individuals with XY gonadal dysgenesis.[12] For individuals with 45,X/46,XY (with or without Turner stigmata) and its variants, the estimated tumour prevalence is between 15 to 40%.[13] Notably, the rate was lower in Turner syndrome girls with Y chromosome material, estimated to be between 7% to 10% in one study.[14] Furthermore, no cases of gonadoblastoma or dysgerminoma were identified in a study of the Danish Cancer Registry.[15] Possible explanations include the lack of regulatory Y chromosome genes on the X chromosome affecting the level of potential oncogenes like the H-Y transplantation antigen and other potential carcinogenic oncogenes resulting in a lower incidence of gonadoblastoma in Turner syndrome females with Y chromosome material compared to XY females.[13] Studies have suggested that the degree of virilization of the external genitalia may reflect gonadal differentiation and thus the risk of tumour in 45,X/46,XY mosaicism.[2,11] The risk of developing a tumour was noted to be highest in individuals with ambiguous phenotype, 52% compared to 2.2% in females without signs of virilization.[11] Other proposed risk factors for development of malignancy include intra-abdominal location of gonads and the presence of various immunohistochemical markers on gonadal tissue in particular expression of OCT 3/4 (octamer binding transcription factor 3/4) and TSPY (testis-specific protein-Y).[16] Plescakova et al., proposed a malignancy risk stratification criteria by placing OCT3/4 positive gonads at intermediate to high risk, TSPY expression at high risk and normal gonads or negative OCT3/4 as low risk categories.[9] Our patient has no evidence of virilization with no identifiable gonads on imaging. Taking this into consideration, it could be argued that she may be at a low or intermediate risk category and a "watch and wait" strategy may be plausible.

Imaging is generally used to evaluate presence and type of Müllerian structures, localize gonads and detect any malignant features.[16] However, small tumours or dysgenetic gonads may be missed due to the heterogeneity of their size and appearance.[16] Although limited, studies have shown that there is poor correlation between preoperative imaging and gonadal pathology. Pelvic ultrasound is the most easily accessible, non-invasive and quick imaging study to perform, although it may be highly dependent on transducer resolution and operator experience. Ultrasound rates for identifying intra-abdominal gonads in individuals with DSD range from 47 to 54%.[16,17] An MRI may have better sensitivity compared to ultrasound scan being able to identify gonads in 29% to 57% of DSD individuals.[2,18] However MRI scans were not good at identifying pre-malignant changes.[18] Hence, the only definitive way to identify a gonadal tumour is gonadectomy. In view of the limited accuracy and potential differences in imaging equipment and technique between smaller centers and tertiary referral centers with paediatric trained radiologists, imaging surveillance for patients who wish to defer gonadectomy remains a challenging aspect of care. In our patient, imaging failed to reveal presence of gonadal tissue. This may be consistent with other studies showing absence of gonads in some patients, but we were unable to completely rule out small tumours, dysgenetic or streak gonads. Whilst tumour markers have been used for diagnosis and follow-up of some germ cell tumours, use of markers such as alpha fetoprotein, lactate dehydrogenase and beta-human chorionic gonadotropin for early detection of gonadal tumours in patients with XY partial gonadal dysgenesis has not been well established. However, positive tumour markers in the setting of a gonadal mass with or without discordant pubertal characteristics would warrant a staged surgical procedure which would involve a laparotomy rather than laparoscopy.[19]

A careful review of the physical features, hormonal evaluation, karyotype, imaging and assessment of malignancy risk should be undertaken and the findings discussed between the health care provider with the patient and family. Ethical dilemmas regarding future gender identity and hormonal and fertility preservation have to be balanced with the risk and benefit of surgery, bearing in mind the challenges faced for future surveillance in those who decide to defer gonadectomy. Our patient is phenotypically female and has been reared as a female for her whole life and is thus comfortable with her gender identity. However, earlier gender assignment or reassignment may be a significant issue and may require detailed psychosocial assessment. Follow-up for the patient should also encompass monitoring of physical health including possible Turner complications, hormone replacement and addressing future fertility concerns. In Asian cultures, female infertility may preclude future marriage prospects and carry a stigma. Where available, involvement of an experienced multidisciplinary team is key to ensure the best management for the patient and family.

CONCLUSION

We present a rare disorder of 45,X/46,XY with heterogenous manifestations. Work-up revealed a diagnosis of mosaic Turner syndrome with Y chromosomal material. This case highlights management challenges of a rare endocrine condition.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

Thyroid Storm with Acute Flaccid Quadriparesis due to Thyrotoxic Myopathy: A Case Report

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Abstract

Thyrotoxicosis is a well-recognized cause of myopathy, but rarely presents as acute flaccid quadriparesis. We report a 25-year-old female with underlying uncontrolled Graves' disease who presented with thyroid storm and acute flaccid quadriparesis due to thyrotoxic myopathy. She showed marked clinical improvement with subsequent normalization of her thyroid parameters. Besides highlighting this rare association, this report underscores the importance of considering thyrotoxic myopathy in the evaluation of patients with acute flaccid quadriparesis.

Key words: Thyroid storm, quadriplegia, thyrotoxic myopathy, Graves' disease

INTRODUCTION

Thyroid storm is a potentially life-threatening condition characterized by multi-organ failure due to severe thyrotoxicosis. Neuromuscular weakness often occurs in thyrotoxic state presenting as chronic myopathy. An acute form of myopathy on the other hand is much rarer, manifesting as acute flaccid quadriparesis with respiratory failure.[1] We report a case of thyroid storm with acute flaccid quadriparesis due to thyrotoxic myopathy, highlighting the importance of rapid diagnosis to prevent further morbidity.

CASE

A 25-year-old female presented with fever, breathlessness, palpitation and rapidly progressive generalised body weakness rendering her bedridden over a period of 3 days. She has a background of Graves' disease, diagnosed 6 months earlier when she presented with weight loss, palpitation and heat intolerance. Initial investigation revealed severe thyrotoxicosis with thyroid stimulating hormone (TSH) level of <0.008 mIU/L (normal range: 0.35–4.94), free thyroxine (FT4) level of >75 pmol/L (9.01-19.05) and TSH receptor antibody (TRAb) level of 19.3 IU/L (<1.0). She was started on oral carbimazole but her thyrotoxicosis was suboptimally controlled due to poor compliance. She was otherwise well and did not have any previous muscle weakness.

Upon assessment, she appeared agitated with a blood pressure of 102/50 mmHg and respiratory rate of 32/min. She was also febrile at 38°C and had an irregular pulse rate of 150 beats/min. Clinical examination revealed a diffuse grade 3 goiter with thyroid bruit and bilateral exophthalmos with inactive thyroid eye disease. She also had generalised hypotonia, areflexia and diminished power of Medical Research Council (MRC) grade 2/5 in her upper limbs and 1/5 in her lower limbs both proximally and distally. Her cranial nerve examination and pinprick sensation were normal. Her condition was further complicated by decompensated cardiac failure with poor peripheral perfusion, raised jugular venous pressure, bibasal lung crepitations and gallop rhythm. Electrocardiography showed atrial fibrillation and chest X-ray revealed signs of pulmonary congestion and cardiomegaly.

Her thyroid function test (TFT) demonstrated overt hyperthyroidism with TSH level of <0.01 mIU/L and FT4 level of 43.56 pmol/L. Her serum potassium level was normal, 4 mmol/L (3.5- 5.1). Her serum bilirubin level was elevated at 53.5 umol/L (3.4–17.1) and she had severe transaminitis with alanine aminotransferase of 748 U/L (0-55) and aspartate aminotransferase of 1755 U/L (5-34). t Subsequent investigations including blood culture, lumbar puncture and antiganglioside antibodies were normal. Her nerve conduction study (NCS) showed reduced compound motor action potential (CMAP) amplitudes with normal conduction velocities and distal motor latencies (Figure 1). Her sensory nerve action potentials (SNAP) were within normal limits and this relative sparing of SNAP was suggestive of underlying myopathy. Her electromyography (EMG) showed small amplitudes, short duration motor unit action potential with early recruitment. There were also increased insertional activities with complex repetitive discharges, in keeping with recent onset generalized myopathy (Table 2). Repetitive nerve stimulation was not performed in view of the positive EMG findings.

Her Burch-Wartofsky score was 85, highly suggestive of thyroid storm (Table 1). A diagnosis of thyroid storm

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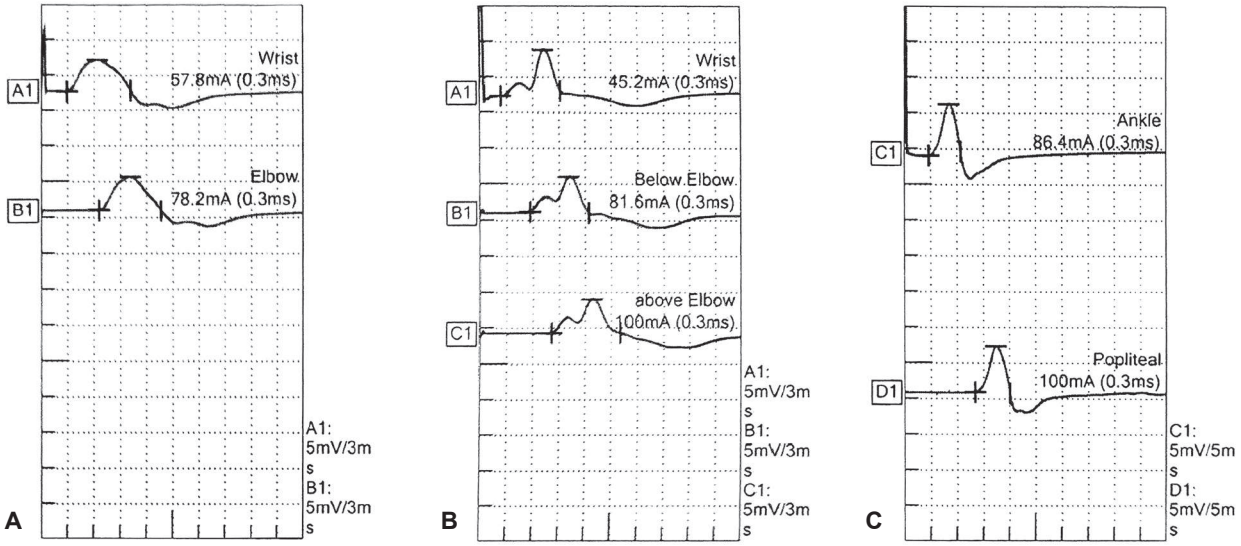

Figure 1. Motor NCS of the patient showed reduced compound motor action potential (CMAP) amplitudes of **(A)** median, **(B)** ulnar and **(C)** tibial nerve.

Table 1. Burch-Wartofsky score of the patient

	Diagnostic Parameters	Scoring points
Thermoregulatory dysfunction	Temperature 38ºC	10
Central nervous system effects	Agitation	10
Gastrointestinal-hepatic dysfunction	Jaundice	20
Cardiovascular dysfunction:		
Tachycardia	Heart rate: ≥140 beats per minute	25
Congestive heart failure	Moderate	10
Atrial fibrillation	Present	10
Precipitating events	Absent	0
Total score		85*

*Total score of more than 45 suggestive of thyroid storm

Table 2. EMG of the patient

Muscle group	Insertional Activity	Complex Repetitive Discharges	Amplitude	Duration	Recruitment
Deltoid	Normal	–	0	Short	Early
Biceps brachii	Normal	–	0	Short	Early
Illiopsoas	Normal	–	0	Short	Early
Vastus lateralis	Normal	–	-1	Short	Early
Tibialis anterior	Increased	+2	0	Short	Early
Gastrocnemius	Increased	+2	0	Short	Early

complicated with decompensated cardiac failure, severe hepatitis and acute thyrotoxic myopathy was made. She was intubated for type 1 respiratory failure and was started on intravenous hydrocortisone 100 mg three times daily, oral Lugol's iodine 8 drops three times daily, oral cholestyramine 4 g four times daily and oral propranolol 40 mg four times daily. Oral carbimazole 20 mg twice daily was subsequently started after 3 days when the liver function tests (LFT) improved. Within 3 days, her condition improved tremendously and she was extubated. Following one week of treatment, her muscle power improved partially to MRC grade 3/5 coinciding with an improvement in her TFT with FT4 of 15.32 pmol/L and TSH <0.01 mIU/L. Total thyroidectomy was performed during the same admission and she was then started on thyroxine replacement. She required assisted ambulation with walking frame initially upon discharge but gradually regained full muscle power over three months following biochemical remission.

DISCUSSION

Neurological complications of thyrotoxicosis can manifest in the brain all the way down to the muscle, causing encephalopathy, seizures, neuropathy and neuromuscular disorders. Varying degrees of muscular weakness with different aetiologies were reported in up to 82% of patients with hyperthyroidism.[1] Acute thyrotoxic myopathy has been long described but is rarely reported, presumably due to the low incidence. This condition usually presents with severe proximal and distal weakness, and rarely quadriplegia with bulbar and respiratory muscle involvement.[2] Due to the rarity of the condition, the acute weakness is thought to be due to concomitant myasthenia gravis instead of pure myopathy.[3] The presence of reports in whom myasthenia gravis was excluded however, suggests otherwise.[2,4]

Before reaching a diagnosis of acute myopathy, it is crucial to exclude other causes of lower motor neuron weakness

in thyrotoxic patients as the treatment differs significantly. Myasthenia gravis (MG) should be the first consideration, especially in patients with bulbar symptoms. The rate of MG was found to be higher in Graves' disease (0.18%) than in the general population (0.01%).[5] However, MG was unlikely in this patient as there were no ocular signs, clinical fatiguability and her EMG was consistent with myopathic changes. Her spontaneous improvement without definitive treatment for MG also was against this diagnosis.

Another differential to consider, Guillain-Barr*é* Syndrome, was also unlikely with the absence of cranial nerve involvement, normal cerebrospinal fluid protein, negative antiganglioside antibody and non-suggestive NCS findings. Hypokalemic periodic paralysis and rhabdomyolysis are widely reported causes of acute paralysis in thyrotoxic patients. Our patient had normal potassium and creatine kinase levels, making these diagnoses improbable. In an intensive care setting, the metabolic derangement associated with hyperthyroidism and intravenous glucocorticoids can increase the risk of critical illness myopathy (CIM) or critical illness polyneuropathy (CIP).[6] The onset of our patient's weakness which preceded admission and hydrocortisone commencement excludes these 2 conditions.

We arrived at the diagnosis of acute thyrotoxic myopathy in this patient in view of the EMG findings and the marked clinical improvement following normalization of thyroid function. In patients with thyrotoxic myopathy, serum creatine kinase and myoglobin concentrations are usually normal despite muscle wasting and this does not correlate well with the degree of muscular weakness.[1] The EMG in these patients demonstrate myopathic findings of increased polyphasic, low-amplitude motor unit action potentials and there is usually no spontaneous electrical activities.[1] Muscle biopsy is rarely required, but if done would reveal various findings, which include normal, non-specific structural alteration and type 2 fiber predominance.[1]

The pathophysiology of muscle disease in thyrotoxicosis is probably multifactorial. Contributing mechanisms may include increased cellular metabolism and energy utilization, increased catabolism and protein degradation, and inefficient energy utilization.[7] The likelihood of developing weakness is correlated with the duration of the hyperthyroid state but the severity of the myopathy dose not correlate with the degree of thyrotoxicosis.[8] The risk factors associated with severe acute thyrotoxic myopathy remains unknown as the reported cases are limited to date.

Treatment of the underlying hyperthyroid state is usually sufficient to reverse the myopathy and symptoms may improve over several months following return to a euthyroid state.[9]

In this case, a combination of hydrocortisone, Lugol's iodine, carbimazole, cholestyramine and propranolol controlled the thyrotoxic state promptly. For patients with thyroid storm, delay iodine initiation for at least one hour **after** loading a thionamide to prevent the iodine from being used as substrate for new thyroid hormone synthesis, especially in patients with toxic adenoma or toxic multinodular goiter. However, due to severe transaminitis and the possibility of carbimazole-induced hepatotoxicity, carbimazole was only started 3 days after Lugol's iodine in this patient. Subsequent rapid improvement in her LFT made the diagnosis of ischaemic or congestive hepatitis more likely in this case. Carbimazole was then started without any worsening of LFT.

Therapeutic plasma exchange (TPE) is also an option when conventional treatments fail or in case of thyroid storm with severe neurological symptoms including severe myopathy.[10] However, this was not required in this patient as she improved with our initial treatment.

Definitive therapy with either radioactive iodine (RAI) or thyroidectomy should be considered in cases with thyroid storm or severe complications stemming from uncontrolled thyrotoxicosis. Thyroidectomy was preferred over RAI in this case because of the emergent need to achieve biochemical control rapidly and administration of Lugol's iodine precludes rapid RAI treatment. Besides that, a transient increase in FT4 is noticed in 30-50% of the patients 2 to 6 weeks post RAI irrespective of whether the patient was pre treated with thionamides or not, and this may potentially worsen the patient's condition.[11] RAI may also lead to worsening of pre-existing Graves' orbitopathy and should be considered cautiously in this patient as she had the risk factor of high TRAb levels.[12] Hence, thyroidectomy was performed in the same confinement to prevent recurrence of this life-threatening thyroid storm and to improve muscle recovery.

CONCLUSION

Acute thyrotoxic-induced myopathy should be considered in uncontrolled thyrotoxicosis presenting with flaccid quadriparesis. Early definitive therapy with RAI or thyroidectomy is necessary: with the aim of achieving rapid long term biochemical control and with that, prevent future occurrence of acute thyrotoxic-induced myopathy and improve muscle recovery.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

Delayed Puberty and Anosmia in CHARGE Syndrome: A Case Report*

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Abstract

A 26-year-old female presented to the paediatric clinic at 11 years of age with poor growth. The detection of delayed puberty, anosmia, coloboma and hearing impairment led to a diagnosis of CHARGE syndrome. This was confirmed by a heterogenous *de novo* pathogenic variant c.6955C >T:p.(Arg2319Cys) detected in the CHD7 gene. Detailed assessment, including olfaction, ophthalmic and auditory examination should be part of the evaluation framework in children with delayed growth and puberty.

Key words: anosmia, delayed puberty, CHARGE syndrome

INTRODUCTION

Congenital hypogonadotropic hypogonadism is a disorder of gonadotropin releasing hormone (GnRH) secretion or action, leading to an insufficiency of the hypothalamo-pituitary-gonadal-axis. It can present as lack of mini-puberty during infancy, absence of onset of puberty or arrested puberty, and infertility. The presence of hypogonadotropic hypogonadism and anosmia has been classically associated with Kallmann Syndrome (KS). CHARGE syndrome, which is a differential diagnosis for this clinical entity is less well recognised.

CHARGE syndrome constitutes coloboma, heart defects, choanal atresia, retarded growth and development, genital abnormalities and ear abnormalities. It has an incidence rate of 1 in 10-15,000 live births and results from loss-of-function variants in the *CHD7* gene which is *de novo* in the majority but can also be autosomal dominant in inheritance.[1] The major diagnostic criteria for a diagnosis of CHARGE syndrome proposed by Verloes et al., in 2005 were coloboma, choanal atresia and semi-circular canal agenesis/hypoplasia.[2] Minor criteria proposed were rhombencephalic dysfunction (cranial nerves VII to XII palsies, brainstem dysfunctions), hypothalmo-pituitary dysfunction, heart or oesophageal anomalies, external or middle ear anomalies and intellectual disability.[2] A clinical diagnosis of typical CHARGE syndrome could be made if a patient fulfilled 3 major criteria or 2 major with 2 minor criteria.[2] Since the availability of newer molecular genetic testing techniques for pathogenic *CHD7* variants, the phenotypic spectrum of CHARGE syndrome had broadened. New diagnostic criterion proposed by Hale et al., in 2016 has enabled individuals with fewer and atypical features to be diagnosed with CHARGE syndrome.[3]

CASE

Our patient was first seen at 11 years old in the general paediatric clinic for poor growth and followed up for possible familial short stature or constitutional delay in growth and puberty (CDGP). She was born at full term, with a birth weight of 2.45 kg. She was always small-sized and grew below the 3rd centile since childhood. She had no known medical illnesses. She had previously undergone an operation to correct a left eye squint and lazy eye secondary to an underlying left optic disc coloboma. She had a normal dietary intake. She is an only child of non-consanguineous parents. Her mother had late menarche at 15 years of age and father had late growth spurt after 16 years of age. Her father's height is 169 cm and her mother's height is 150 cm. Mid-parental height is 153 cm. She grew up under normal social circumstances and was good in her studies.

She was referred for paediatric endocrine assessment at age 13 years due to absence of puberty onset and further faltering of her growth. Probing into history revealed that she had no sense of smell since birth. There were no other family members with anosmia or infertility. On physical examination, her weight was 25.6 kg and height was 134.2 cm, both below the 3rd centile. She had poor growth velocity of 3.7 cm in the past 1 year and her height had fallen to below her genetic target height range. On physical examination, she was not dysmorphic and there was no cleft lip or palate. She was pre-pubertal with no breast,

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axillary hair or pubic hair development. Other systemic examination was unremarkable.

Her karyotype was 46XX, thus ruling out mosaic Turner syndrome as the cause of her short stature and delayed puberty. Bone age was markedly delayed corresponding to 8 years. Her Insulin-like growth factor 1 (IGF-1) was 172.8µg/L (normal for bone age of 8 years old). A combined pituitary function test revealed isolated hypogonadotropic hypogonadism. Luteinising Hormone (LH) and Follicular Stimulating Hormone (FSH) responses were poor with peak responses of 0.34 IU/L and 2.62 IU/L respectively while serum estradiol was <37 pmol/L (low). Peak growth hormone (GH) was 19.2 mIU/L (normal >20) and peak cortisol was 665 nmol/L (normal >500). She had normal thyroid function tests (thyroid stimulating hormone (TSH) 0.92 mIU/L, free thyroxine (fT4) 13.2 pmol/L) and normal TSH response to TRH (TSH of 9.74 mIU/L at 30 min and 7.72 mIU/L at 60 min). MRI pituitary findings were normal. Nasoscopy was also normal and ruled out occlusion of the nasal passages.

The patient was treated with conjugated estrogen (Premarin) and Norethisterone was added after 3 years. She is presently on Femoston (1/10). She achieved a final height of 152 cm, which approximates her midparental height. She subsequently complained of hearing difficulties at the age of 19 years. Pure tone audiometry revealed bilateral moderate conductive hearing loss (Figure 1). A CT scan of the temporal bones showed absence of all the semi-circular canals bilaterally (Figure 2A). Figure 2B shows the temporal bones of a normal patient used for comparison. On retrospective re-examination, she was found to have a marginally reduced elevation of the right mouth due to a lower right 7th cranial nerve palsy. The clinical diagnosis of CHARGE syndrome was made as the patient fulfilled 2 major criteria of CHARGE syndrome i.e., coloboma and absent semi-circular canals and 2 minor criteria i.e., hypogonadotropic hypogonadism and right 7th cranial nerve palsy. This was later confirmed by a heterogenous *de novo* pathogenic variant c.6955C >T:p.(Arg2319Cys) detected in the *CHD7* gene by whole exome sequencing.

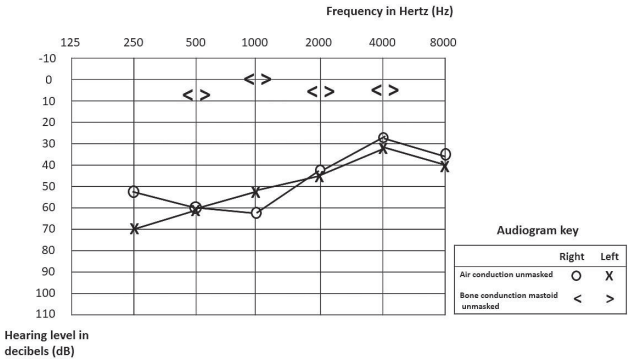

Figure 1. Pure tone audiometry.

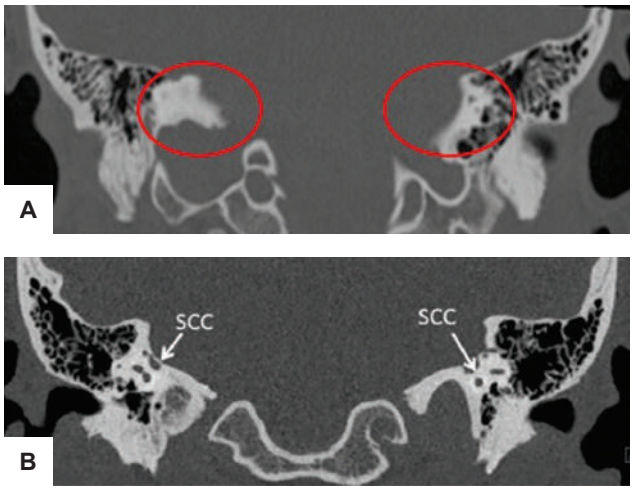

Figure 2. (A) CT temporal bones coronal view showing bilateral absence of all semi-circular canals (SCC); **(B)** The temporal bones of a normal patient for comparison.

DISCUSSION

Constitutional Delay of Growth and Puberty (CDGP) is an extreme late end of normal pubertal timing and occurs in up to 30% of girls and 65% of boys.[4] Many children with this condition have co-existing familial short stature. It is a far more common cause of delayed puberty compared to congenital hypogonadism, e.g., Kallmann Syndrome (KS) or CHARGE syndrome and often a positive family history of delayed puberty in either parent is present. Girls with no spontaneous puberty beyond the age of 13 years warrant further investigation. In this case, the presence of coloboma, anosmia and hearing impairment pointed to congenital hypogonadism rather than CDGP. Earlier detection of these red flag signs would have enabled earlier diagnosis, earlier screening of other comorbidities and timely pubertal induction at 11-12 years of age.

The multitude of malformations associated with CHARGE syndrome stems from abnormalities in the formation of multipotent migratory neural crest cells in the presence of *CHD 7* haploinsufficiency.[5] The *CHD7* gene encodes the Chromodomain Helicase DNA binding (CHD) protein 7 which is important in regulation of embryonic stem cell pluripotency and remodelling of chromatin.[6] *CHD7* is widely expressed in neural crest derived mesenchyme, undifferentiated neuroepithelium, auditory, nasal and pituitary epithelia, cranial nerves and neural retina.[7] The most common endocrine abnormality found in CHARGE syndrome is hypogonadotropic hypogonadism, occurring in 60-80% of patients.[8] This manifests as micropenis and/or cryptorchidism in boys which is readily detectable at birth. In contrast, girls do not have external genitalia abnormalities. Gonadal defects are only detectable when they fail to enter spontaneous puberty. The frequent coexistence of hypogonadotropic hypogonadism and anosmia in these patients suggests a disruption in the embryonic neuronal migration of the GnRH neurons which share the same pathway with the olfactory neurons to the hypothalamus.

The classical phenotypes of hypogonadotropic hypogonadism and anosmia are both also well recognised features in KS due to defect of the GnRH migration pathway. *CHD 7* mutation is not only unique to CHARGE syndrome but has also been reported in both patients with KS and normosmic hypogonadotropic hypogonadism.[9,10] Many of these patients were however found to have extra features of CHARGE syndrome on retrospective reevaluation.[9,10] As the *CHD7* gene affects chromatin structuring and gene expression during embryonic development, it is possible that it could also influence the action or genetic

expression of *KAL1, FGFR1, FGF8, PROKR2 and PROK2* which are the genes involved in KS.[9] Since Kallmann syndrome is one of the constituent phenotypes seen in CHARGE, some authors recommend performing *CHD7* analysis in KS patients without known mutations when additional CHARGE features are present.[9,10]

The KAL 2 genetic form of KS ie *FGFR1* and *FGF8* gene mutation shares a lot of similar features with CHARGE syndrome as cleft lip or palate, external ear malformation, hearing impairment, corpus callosum agenesis and colobomas can also be present.[11] The most discerning feature which pointed to a diagnosis of CHARGE syndrome rather than KS in this patient was the absence of semi-circular canals which is a feature found in over 95% of patients with CHARGE syndrome but is unusual in other syndromes.[12,13] This patient was also found to have a lower right 7th cranial nerve palsy which is atypical of KS upon re-evaluation. A complete evaluation with dilated eye examination, renal ultrasound, echocardiogram as well as imaging of brain, pituitary gland, temporal bones, olfactory bulbs and choanae has been recommended by The Atlantic Canadian CHARGE syndrome team in patients with suspected CHARGE syndrome for the purpose of diagnosis and medical management.[14] Establishing a diagnosis with genetic testing is also important for genetic counselling regarding reproductive options and recurrence risk. Fertility induction by exogenous gonadotropins or pulsatile GnRH to obtain ovulation is possible in these individuals.[15] It should however be made known to these patients that the risk of having an offspring with CHARGE syndrome is 1/2 (50%) for each pregnancy with an unaffected partner and severity in phenotype is indeterminate due to intra-familial variability seen in this condition.

CONCLUSION

Detailed clinical assessment, including olfaction, ophthalmic, auditory and ear/teeth/palate examination should be part of the evaluation framework in children with delayed growth and puberty. The presence of non-reproductive anomalies including anosmia, coloboma and hearing defects, are red flag indicators of possible underlying congenital hypogonadism. While KS has an incidence of 1 in 8000 in males, the prevalence is much lower in females, estimated to be 1 in 40000.[11] CHARGE syndrome is a major differential diagnosis for KS, especially in females. Additional CHARGE features should be screened for in patients who present with delayed puberty and anosmia.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

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Severe Developmental Delay, Epilepsy and Neonatal Diabetes (DEND) Syndrome: A Case Report*

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Abstract

Developmental delay, Epilepsy and Neonatal Diabetes (DEND) syndrome is the most severe form of Permanent Neonatal Diabetes with KCNJ11 gene mutation which accounts for most of the cases. We report the first DEND syndrome in Malaysia with heterozygous missense mutation Q52R at KCNJ11 (Kir6.2) gene with delayed presentation beyond 6 months of age and failure to transition to glibenclamide. This report signifies the phenotypical variability among patients with the same genetic mutation and the different response to treatment.

Key words: DEND syndrome, glibenclamide, congenital diabetes

INTRODUCTION

Permanent Neonatal Diabetes Mellitus (PNDM) is defined as insulin-dependent diabetes with the onset of presentation in infant less than 6 months of age.[1,2] There is a wide spectrum of neonatal diabetes with developmental delay, epilepsy and neonatal diabetes (DEND) syndrome being the most severe form within the spectrum. DEND syndrome is caused by gain of function mutation of either one of the proteins that made up the ATP-sensitive K+ (K+ATP) channel, the pore-forming subunit (Kir6.2) or sulfonylurea receptor protein (SUR1).[3] The Kir6.2 protein is encoded by KCNJ11 gene located at chromosome 11p15.1.[4] The K+ATP channel is present in pancreatic β-cell, brain synapses and muscles. To date, there are at least 32 KCNJ11 gene mutations that can cause permanent neonatal diabetes.[5] Most of these mutations occurred sporadically and involved single amino acid substitution due to missense or nonsense mutation.[5,6] Among all, Q52R mutation has the most severe phenotype.[3]

In normal physiology, the K+ATP channel will close in the presence of ATP. However, in DEND syndrome, the K+ channel is persistently activated and remains open despite the presence of ATP.[1] Sulfonylurea can bind to sulfonylurea receptor and inhibit the ATP-sensitive K+ channel leading to its closure. This will trigger membrane depolarization that leads to the release of insulin.[3,7] Due to this, sulfonylurea has been widely used in the management of patient with congenital diabetes to replace insulin. Patient with DEND syndrome that responded well to sulfonylurea showed improvement in the neuro-developmental outcome.[8,9]

Here, we report the first case of DEND Syndrome in Malaysia due to Q52R single amino acid substitution mutation of KCNJ11 gene with late diagnosis beyond 6 months of age and failed transition from insulin to glibenclamide.

CASE

ZH is a Malay boy, the first child from non-consanguineous marriage. He was born at 41 weeks gestation via spontaneous vaginal delivery with birth weight 2500g (below 10th percentile), head circumference of 31cm (below 3rd percentile) and length of 50cm (at 50th percentile). The antenatal period was uneventful. There was no maternal diabetes or hypertension, no polyhydramnios, reduced fetal movement or risk of sepsis throughout the pregnancy. Postnatally, he was well and was discharged home on the same day.

At 8-month old, ZH was referred to our hospital for severe Diabetic Ketoacidosis. He had hyperglycaemia with blood glucose level of 21 mmol/L and severe metabolic acidosis with blood pH 6.9 and serum bicarbonate ($HCO3^-$) level of 4.7 mmol/L. He was ventilated for 48 hours for airway protection. The ketonemia and acidosis resolved after 24 hours of insulin infusion and hydration therapy. Insulin infusion was then converted to subcutaneous NPH human insulin 1 u every 12 hours. The boy had two other past hospital admissions not related to diabetes. The first admission was for abdominal distention at the age of 3 months in which he was suspected to have possible Hirschsprung disease; while the second admission was at the age of 6 months for acute gastroenteritis.

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Initial investigation of diabetes revealed negative anti-insulin, anti-islet cells, anti-glutamic acid decarboxylase (anti-GAD) and anti-Islet Antigen 2 (anti-IA2) antibody with low C-peptide level. HbA1c was high at 16.5%. Karyotyping was 46XY. Clinically, patient showed some facial dysmorphism with low set ears, micrognatia, short neck, and triangular mouth with thin lips. Other systemic examinations were unremarkable. The boy presented with global developmental delay: he had limited head control, he was not reaching for objects, he only smiled responsively, and just started vocalizing. With the clinical history, negative diabetes autoantibody, early onset of DM and the associated developmental delay, the boy was suspected to have DEND syndrome.

Since diagnosis, his development was globally arrested at around 4-6 months. Currently, at 5-years old, he has good head control but is still unable to roll over. His fine motor skills were significantly delayed since he is only able to reach for objects and bang 2 cubes. He is able to smile and laugh spontaneously, turn to loud sound and babble but does not respond to name-calling. There is no meaningful word except for monosyllables. On top of the developmental arrest, ZH also has poor linear growth. His latest height and head circumference were below the third percentile for age while his weight is at third percentile for age (Figure 1). He never had any seizure episodes. Electroencephalography (EEG) showed slowing of background wave with no epileptic discharges. The MRI brain showed normal brain structure. DNA sequence analysis to confirm the specific mutation causing the neonatal diabetes was sent to Exeter Clinical Laboratory when the child was two-and-a-half years old.

Heterozygous missense mutation Q52R was found at KCNJ11 (Kir6.2) gene at Exon 1 DNA. This missense mutation caused single amino acid substitution, Glutamine to Arginine at position 52 (p.Gln52Arg) of the protein. The genetic mutation together with severe global developmental delay and neonatal diabetes confirmed the diagnosis of DEND.

Switching of treatment from insulin to sulfonylurea was attempted at 3 years and 7 months old once the genetic diagnosis confirmed. The 'Inpatient Protocol for the Transfer of Patients with Kir6.2 and SUR1 Mutations from Insulin to Sulfonylurea in Patients with PNDM' developed by Prof Andrew Hattersley and team from University of Exeter was used as reference.[10] In-patient low dose oral glibenclamide at 0.1 mg/kg/day was given in twice daily divided dose. Insulin was gradually weaned off whilst the glibenclamide dose was slowly escalated daily throughout 10 days to the maximum dose of 2 mg/kg/day. Regular 4 hourly post prandial capillary blood glucose monitoring was continued throughout his hospital stay. The blood sugar remained high despite an increasing dose of glibenclamide. At the dose of 2 mg/kg/day, the patient developed diarrhea and became lethargic while the blood glucose level remained above 20 mmol/L. Insulin was restarted and glibenclamide was then withheld. The side effects wore off. The repeat HbA1c was also increased compared to baseline during the trial period. At present, patient still has marked global developmental delay with HbA1c of 7.1% and is on maintenance basal and prandial insulin.

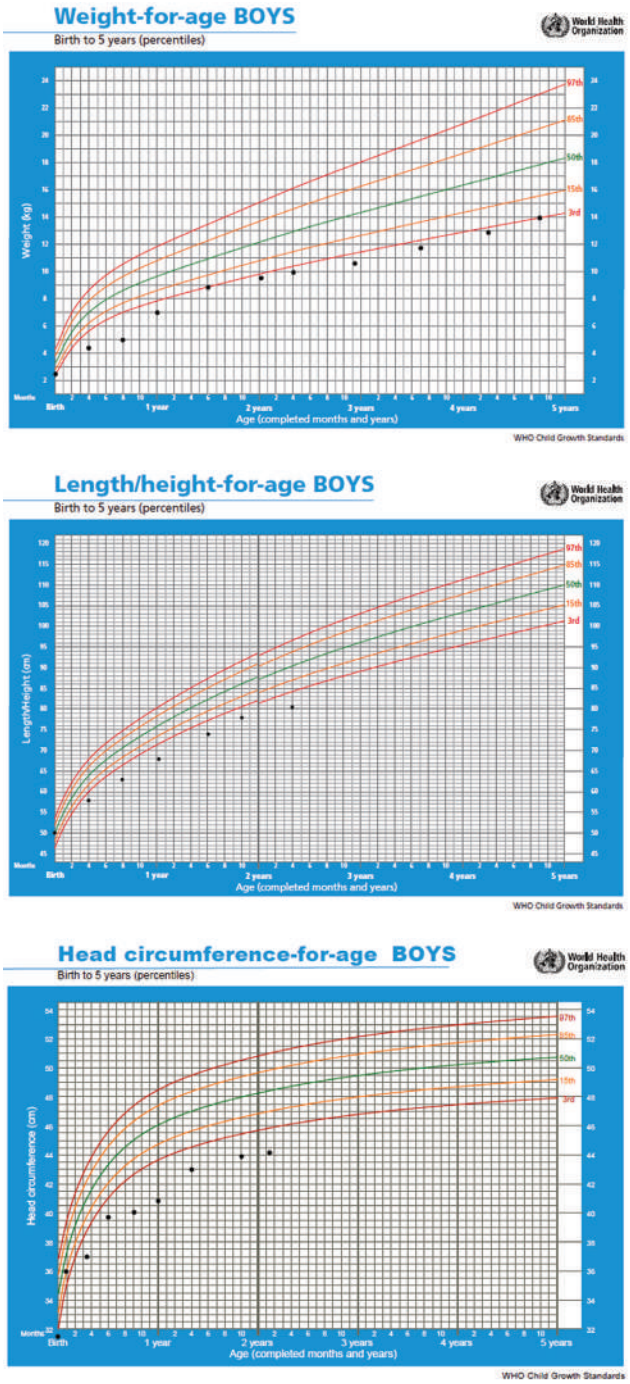

Figure 1. Weight, length and head circumference of ZH. There was a poor linear growth noted from birth as plotted on WHO growth chart for weight, length and head circumference for age.

DISCUSSION

Based on our literature search up to this date, this is the first reported case of DEND Syndrome in Malaysia. Among all the mutations of the KCNJ11 gene that cause DEND syndrome, Q52R mutation has the worst clinical outcome.[1,3] This particular mutation involves the substitution of amino acid Glutamine with Arginine at position 52 of the Kir6.2 protein. This leads to reduction in sensitivity of the channel to ATP without affecting its affinity.[1,3] To date, there are 4 reported cases of patient with Q52R mutation. Among them, only 1 patient successfully

switched from insulin to sulfonylurea, 1 patient partially responded to sulfonylurea but is still insulin dependent, while 1 patient died at infancy. All these patients first presented and were diagnosed under 6 months old (ranges 2 days to 4 months old) and all except for 1 had developmental delay and seizure at initial presentation. ZH was diagnosed with diabetes mellitus at the age of 8 months when he presented with DKA. No hyperglycemia was noted during the two earlier admissions. There are a few reported cases of patient with genetic mutation on either the Kir6.2 or the SUR1 protein who were diagnosed after 6 months of age.[6,11] However, the reason for the delayed presentation remains unexplained.[3]

Patients with this particular genetic mutation are known for sulfonylurea resistance and insulin dependency.[12] Sulfonylurea works synergistically with ATP to close the K channel. The former inhibitory action can only exert its full effect if the Kir6.2 protein sensitivity to ATP is intact. Therefore, in patients with Q52R mutation, the substitution of Glutamine by Arginine at distal position of the protein alters the structure of the pore of the protein leads to insensitivity of the channel to ATP binding.[8] This partially explains the failure to respond to sulfonylurea therapy in this patient. Even though there are reported cases of successful sulfonylurea therapy in patients with Q52R mutation, this phenomenon is to date not fully explained and might represent the variability of expression within the same genetic mutation.[8]

Other factors leading to failure of insulin replacement include low birth weight and delay in introduction of sulfonylurea.[12] In this case, ZH had birth weight below 10th percentile and sulfonylurea was introduced rather late at the age of 3 years and 7 months old due to the delay in the confirmation of genetic mutation. In a case report, Greeley et al, 2016 reported that the number of β-cells in a 2-year-old female with KCNJ11 mutation was significantly less compared to normal age-matched children.[13] Over time, there is a reduction in β-cell numbers in the pancreas of patients with KCNJ11 mutation DEND syndrome that might explain the inverse proportion of successful transition with age and the need for a higher dose of sulfonylurea.[3] The only patient successfully treated with glibenclamide monotherapy was given glibenclamide 2.6 mg/kg/day in 4-8 divided doses. However, since glibenclamide has a half-life between 12 to 24 hours with peak concentration achieved in 2 to 4 hours post ingestion, giving 12 hourly of high dose glibenclamide should exert optimal effect.[14] In our case, increasing frequency of glibenclamide dosing may be beneficial. However, since our patient was unable to tolerate the high dose of glibenclamide, this is not an option.

CONCLUSION

In conclusion, this case report describes the variability of presentation in patients with the same genetic mutation and the challenges in managing DEND syndrome patients with severe genetic mutation such as Q52R mutation. Prompt genetic analysis is vital to avoid delay in diagnosis and trial of glibenclamide therapy. The transition to sulfonylurea from insulin should be the main aim in the treatment of patients with DEND syndrome as it may reverse neurodevelopmental delay and seizure. Since patients with KCNJ11 mutation require high doses of glibenclamide, newer drugs with similar modes of action but with better side effect profiles may be alternative therapy for this population of patient. However, more studies are required to prove this hypothesis.

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Ethical Consideration
Patient consent was obtained before submission of the manuscript.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Hypoparathyroidism in a Case of Transfusion Dependent Thalassemia

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Abstract

Repeated blood transfusions in transfusion dependent thalassemia (TDT) leads to iron overload-related endocrine complications. Hypoparathyroidism (HPT) with severe signs of hypocalcemia is a recognized complication among these patients.

A 14-year-old thalassaemic boy, on regular transfusion and on anticonvulsant therapy with a presumptive diagnosis of epilepsy for the last 1 year, was admitted with high fever and severe muscle cramps with positive Trousseau's sign. He was diagnosed as a case of primary HPT and magnesium deficiency on the basis of low serum calcium, high phosphate, normal alkaline phosphates, very low intact parathyroid hormone (iPTH), normal serum vitamin D and very low serum magnesium level. His calcium, magnesium and phosphate level normalised following treatment with intravenous magnesium and calcium. His iPTH improved but remained at low normal. He was discharged from hospital with oral calcium, calcitriol, and magnesium supplementation. The anticonvulsant (Phenobarbitone) was successfully withdrawn gradually over the next six months without any recurrence of seizure in the subsequent 3 years of follow up.

Acquired HPT (apparently from hemosiderosis) is a common cause of hypocalcemia; and magnesium depletion further complicated the situation leading to severe hypocalcemia with recurrent episodes of convulsion. Magnesium replacement improved the parathyroid hormone (PTH) value proving its role in acquired HPT. Very high phosphate level on admission and poor PTH response with respect to the low serum calcium, indicates intrinsic parathyroid pathology. Metabolic abnormalities should always be evaluated in thalassaemic subject with seizure disorder and it appears that the initial convulsive episodes were due to hypocalcemia.

Muscle pain, cramps or convulsion may occur from HPT and simultaneous magnesium deficiency in transfusion dependent thalassaemic subjects. Metabolic correction is more important than anticonvulsant medication. Calcium and magnesium should both be assessed routinely in transfusion dependent thalassemic patients.

Key words: hemosiderosis, hypomagnesemia, hypoparathyroidism, thalassemia

INTRODUCTION

Thalassemias are inherited blood disorders due to genetic defect in alpha globin (alpha thalassemia) or beta globin (beta thalassemia) protein chains of normal hemoglobin (hemoglobin A). Beta thalassemia results from several mutations in the beta globin gene in the short arm of chromosome 11[1] and presents as non-transfusion dependent thalassemia (NTDT) or transfusion dependent thalassemia (TDT), its most severe form. Clinical management of TDT consists of lifelong red blood cell transfusions and iron chelation therapy, to combat iron overload from excessive blood transfusions. The only definitive cure is bone marrow transplantation.[1] However, potentially curative gene therapy to treat transfusion-dependent β-thalassemia has recently been approved.[2]

Repeated blood transfusion therapy leads to iron overload-related complications including endocrine complications (growth retardation, failure of sexual maturation, diabetes mellitus, insufficiency of the parathyroid, thyroid, pituitary, and less commonly, of adrenal glands), dilated cardiomyopathy, liver fibrosis and cirrhosis.[3]

HPT in TDT is not an infrequently observed complication and is estimated in about 4.5% of thalassemia patients.[4] HPT is thought to be the consequence of iron deposition in the parathyroid glands but it has no clear relationship with serum ferritin levels and rarely presents with severe signs of hypocalcemia.[4]

CASE

A 14-year-old boy was admitted in the hospital with high fever, pain in throat and cough associated with muscle cramps and generalized body pain for one week. He was a known case of transfusion-dependent β-thalassemia (detected at 9 months old), was regularly receiving packed red blood cell (RBC) transfusion (starting from 18 months old) and requiring, on average,

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4 units per month. He was maintained on Deferiprone (500 mg thrice daily) for a long time and was also put on deferoxamine mesylate since his serum ferritin went above 10000ng/dl one year prior to admission.

He was also treated conservatively for fever and muscle cramps about a year prior to admission, but no details were available. He had recurrent convulsive seizure at that time. Electroencephalography (EEG) showed nonspecific changes and Magnetic resonance imaging (MRI) brain was normal. Anticonvulsant therapy (Phenobarbitone 60 mg daily) was given since then, with a presumptive diagnosis of epilepsy along with other regular treatments for thalassemia.

Following this admission in the hospital for high fever, he experienced several episodes of severe muscle cramps and generalized body pain. He was conscious, febrile, anaemic and sick. The examination of the patient's pharynx revealed mild erythema with pharyngeal exudates. He was flushed, had hepatosplenomegaly, with no local muscle tenderness in limbs and positive Trousseau's sign. He had no other focal neurological deficit.

Laboratory evaluation showed hemoglobin: 10.5 gm/dl (13-16), leucocyte: 12,400/cumm (3500-9000), erythrocyte sedimentation rate: 44 mm (0-20), potassium: 2.45 meq/l (3.5-5.0), urea: 16 mg/dl (3.5-7.0) and creatinine: 0.83 mg/dl (0.7-1.3), serum ferritin: 8976 ng/dl (7-140), serum calcium: 3.8 mg/dl (9-10.5), phosphate: 11.53 mg/dl (2.7-4.5), alkaline phosphates: 86 U/L (53-141), serum albumin: 3.9 mg/dl, albumin corrected serum calcium: 3.98 mg/dl and repeat serum calcium: 4.1 mg/dl (9-10.5). His liver function test was abnormal with raised indirect bilirubin of 2.41 mg/dl (0.1-0.9) but normal direct bilirubin of 0.4 mg/dl (0-0.4) and normal aspartate transaminase 17 IU/L(8-40). His fasting plasma glucose and thyroid function test was normal.

Throat swab was obtained and was cultured. Gram-positive cocci suggestive of Streptococcus pyogenes grew in chains. No blood culture was done. His iPTH was very low: <2.5 (14-70 pg/ml) and serum vitamin D level was 34.62 ng/ml (30-100). The patient was diagnosed as a case of primary hypoparathyroidism and was evaluated for serum magnesium (Mg) which was also very low: 0.53 mg/dl (1.5-2.5).

He was treated with an antibiotic from day 1 for the fever and congested throat. Magnesium replacement (20 mmol/day for 6 days in intravenous route) along with calcium replacement (Ca-gluconate in intravenous route) was started on the second day of admission and daily monitoring of calcium, phosphate and magnesium was done. Calcium level and Magnesium level gradually improved from 2nd day to 6th day while serum phosphate level gradually declined (Table 1). Hypomagnesaemia contributes to hypokalemia and he was closely monitored in the Intensive Therapy Unit. However, his serum potassium gradually improved from 2.45 meq/l (on admission) to normal levels (4.30 meq/l) on 6th day without potassium supplementation.

Table 1. Changes in biochemical parameters during treatment of HPT

	Day-1	Day-2	Day-4	Day-6	Day-8	Day-12
Calcium (mg/dl)	3.8	5.57	6.08	6.59	6.7	8.7
Magnesium(mg/dl)	0.53	0.87	1.04	1.09	1.14	1.24
Phosphate(mg/dl)	11.53	8.09	5.79	4.97	4.9	4.4
Potassium (meq/l)	2.45	2.57	2.63	4.30	4.2	4.3
iPTH (pg/ml)	< 2.5	–	–	–	16.5	

His episodes of severe muscle cramps and pain all over the body gradually improved, as well as the fever and congested throat. Intravenous calcium and magnesium replacement was stopped after 6th day and oral calcium (1000 mg daily), calcitriol (0.5 ug) and oral magnesium (400 mg daily) were started. On the 8th day, two days after oral supplementation was started, serum calcium was 6.7 mg/dl, magnesium 1.14 mg/dl and phosphate 4.9mg/dl. The iPTH was repeated and was at a low normal value of 16.5 (14 – 70 pg/ml). The dose of oral calcium (1500 mg daily) and calcitriol (1.5 ug) was then increased. Biochemical parameters improved further (Serum calcium 8.7 mg/dl, magnesium 1.24mg/dl and phosphate 4.4mg/dl) on the 12th day (Table 1). He had no further seizure and was discharged from the hospital. Repeat serum ferritin before his discharge came down to 7795 ng/dl.

On follow up, he was maintained on blood transfusions, deferiprone, deferoxamine mesylate, oral calcium and calcitriol without any history of muscle cramps or convulsion. The anticonvulsant (Phenobarbitone) was gradually withdrawn over the next six months. He did not have any further episode of convulsion over 3 years of follow up.

DISCUSSION

Reduced or absent synthesis of the beta globin chains of the hemoglobin tetramer is the basic pathology of beta-thalassemia.[1] Regular red blood cell transfusions and iron chelation therapy to remove excess iron introduced with transfusions are the standard therapeutic interventions. Despite early establishment of chelation therapy, elevated ferritin is commonly due to iron overload from multiple blood transfusions; and in the long term may lead to cardiac, hepatic, or endocrine dysfunctions.[3] The patient presented with fever and very high serum ferritin (8976 ng/dl) level. Fever was due to throat infection which improved with antibiotic. Being an acute-phase reactant, serum ferritin settled down to 7795 ng/dl from 8976 ng/dl at the time of discharge from hospital. This high serum ferritin (7795 ng/dl) at the time of discharge indicates significant iron over loading. The clinical picture of TDT is often dominated by endocrine system abnormality, a consequence of iron overload and chronic hypoxemia.

As the survival of the TDT subjects improved with modern management, most (88.4%) suffer from at least one endocrine complication, the most common being hypogonadotropic hypogonadism (about 70% among male and 39.1% among female).[5] Type 1 Diabetes (18.6%), impaired glucose tollerance (34.8%), HPT (11.6%), subclinical hypothyroidism (20.9%), overt hypothyroidism (2.3%), central hypothyroidism (4.6%), and growth hormone deficiency (20%) are other common endocrine complications. Even some of them (11.6%) can have multiple (>3) endocrine complications simulteneously. Interestingly primary and secondary adrenal insufficiency appears very rare. [5]

Oxidative damage by reactive oxygen species (ROS) is responsible for endocrine organ damage in patients with thalassemia. ROS generation is caused by two major mechanisms (Figure 1). The first is iron overload and the second, chronic hypoxia resulting from chronic anemia. Iron overload develops not only from secondary to regular transfusions but also from increased intestinal iron absorption. Normally about 1–2 mg of iron is lost daily and is balanced by intestinal absorption of 1-2 mg daily. On the other hand, each unit of transfused packed red blood cells contains 200 to 250 mg elemental iron and loads 400 mg to 1000 mg per month (13 to 33 mg per day) in the TDT patients with assumed monthly transfusion rate of 2 to 4 units. Moreover, the rate of intestinal iron absorption is much higher (3-4 times) among both TDT and NTDT due to ineffective erythropoiesis and chronic hypoxia.[6] Senescent transfused red blood cells are phagocytized by the macrophages and the labile cellular iron is released into the plasma to bind transferrin. As loading continues, the capacity of transferrin binding with released iron and intestinal absorbed iron get saturated and results in nontransferrin-bound iron fraction within plasma. Iron toxicity is primarily from non-transferrin bound iron which cannot be regulated, and hence, potentially damaging. It is avidly captured by hepatocytes and other parenchymal cells including endocrine glands and continues to accumulate in the cells and damage cell membranes, mitochondria, nuclei and other intracellular organelles by its propensity to generate ROS.[6]

In response to hypoxia from chronic anemia, several mechanisms are triggered to adapt cells to a low oxygen environment. As mitochondria are the major consumers of oxygen in the cell, they are severely affected by decreased oxygen availability. Mitochondria are also potential source of ROS. In response to hypoxia they modify cellular metabolism, especially lowering of the citric acid cycle. Intermediates of the citric acid cycle regulate hypoxia inducible factors (HIF), the key mediators for ROS-production by the HIF-pathway.[7] ROS are capable of causing oxidative damage to macromolecules leading to protein fragmentation and DNA damage. Cumulative oxidative damage produced both by iron and hypoxia lead to organelle collapse and dysfunction.

HPT is well known among the transfusion-dependent patients with beta-thalassemia[4,8] and commonly seen in iron-overloaded patients and is often accompanied by other endocrinopathies.[9] Acquired HPT from hemosiderosis (due to repeated blood transfusion) is always the first consideration for hypocalcemia in patients with TDT. However, the concentration of ferritin is not a valuable tool in the prediction of the development of HPT, as no significant differences have been reported in serum ferritin level in patients with HPT in the background of thalassemia in many studies.[10] Other factors, such as individual susceptibility to iron toxic effects and the hematological phenotype of the disease might play some roles in the development of HPT.[11,12]

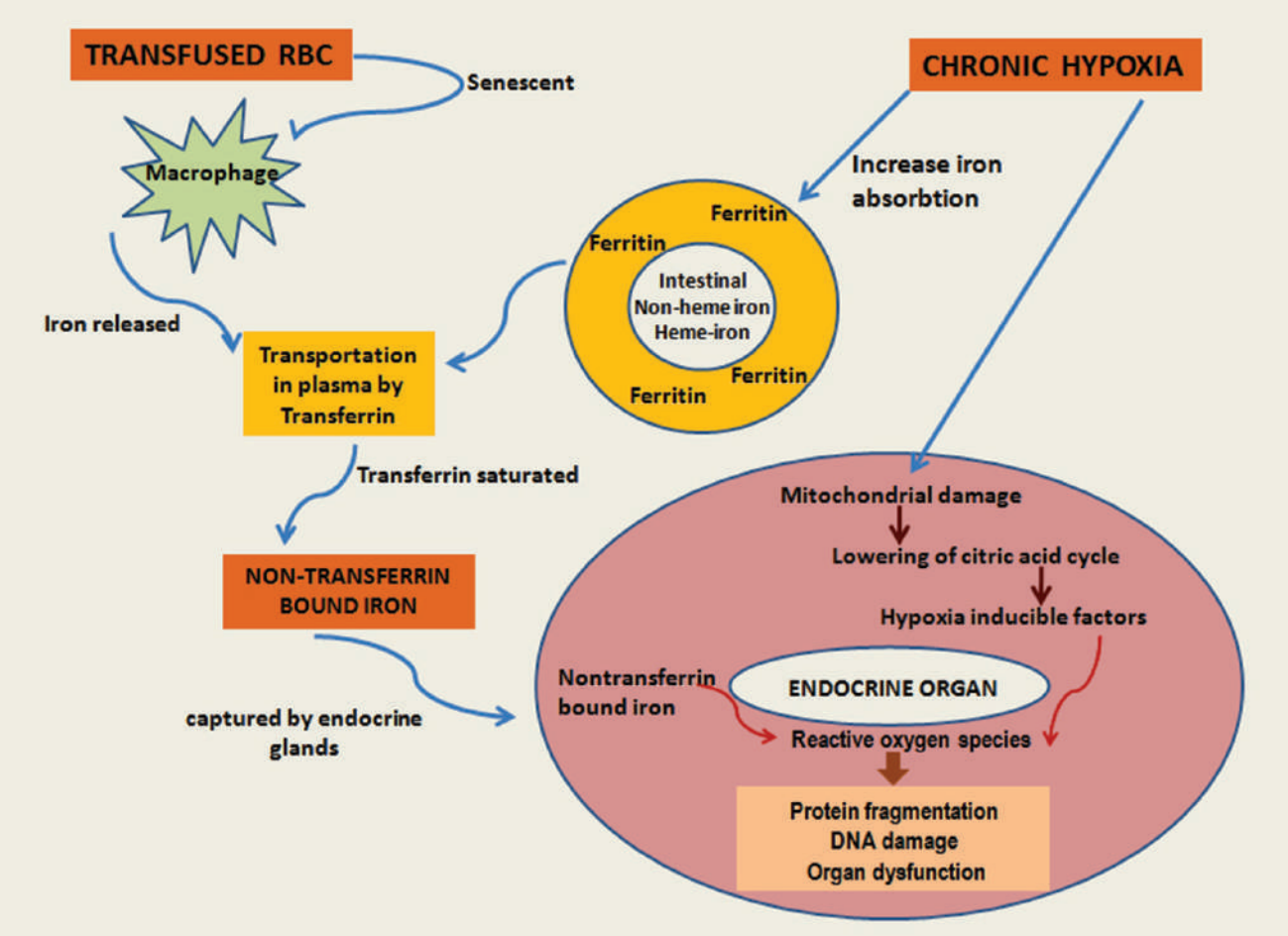

Figure 1. Mechanism of organ dysfunction from iron overload and chronic hypoxia in TDT.

Magnesium depletion is also associated with impaired PTH secretion, common among TDT subjects and is often present even in younger asymptomatic children,[13] Magnesium replacement in this patient improved the serum PTH value (from <2.5 pg/ml on admission to 16.5 pg/ml on 8th day) proving magnesium depletion as an important contributing factor for the acquired HPT. However, the PTH response was inappropriately low (16.5 pg/ml) in respect to the low serum calcium level (6.7 mg/dl), indicating intrinsic parathyroid pathology, probably from hemosiderosis. Moreover, phosphate level is usually not elevated (because phosphate deficiency is frequently associated with magnesium deficiency) in isolated magnesium deficiency states and very high phosphate level (11.53 mg/dl on admission) in this patient indicates significant intrinsic parathyroid defect. Magnesium deficiency further complicated the hypocalcemic state.

Hypokalemia is common in most hypomagnesemic subjects as both potassium and magnesium are the major intracellular cations. Excess renal potassium wasting in hypomagnesemic patients leads to hypokalemia.[14] Potassium secretion from the renal collecting tubular cells is mediated through luminal potassium channels and is inhibited by intracellular (collecting tubules) magnesium concentration. Hypomagnesemia leads to reduction in intracellular magnesium and releases this inhibitory effect on potassium efflux. This promotes potassium secretion from renal tubules and enhances urinary losses. Correction of the magnesium deficit and not potassium supplementation can reverse this effect as we have observed in our case.[14] Though the childhood seizure is mostly treated with anticonvulsant therapy,[15] metabolic abnormalities should always be looked into while evaluating a thalassaemic subject with seizure disorder. Anticonvulsant therapy was successfully withdrawn without any recurrence of seizure till last follow up and it appears that the initial convulsive episodes in this patient were probably due to hypocalcemia.

CONCLUSION

Transfusion related hemosiderosis in thalassaemic subjects can cause HPT state with severe signs of hypocalcemia. Simultaneous magnesium deficiency may aggravate the HPT state. Muscle pain, cramps or convulsion can occur from these metabolic alterations and metabolic correction is more important than anticonvulsant medication. Assessment of both calcium and magnesium should be done routinely in the care of transfusion-dependent thalassemic patients.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declare no conflict of interest.

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CASE REPORT

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Case Report of a Pituitary Metastasis from Lung Adenocarcinoma Masquerading as Pituitary Adenoma

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Abstract

Metastasis to the pituitary gland is an unusual situation in clinical practice and is typically observed in those with underlying malignancy with breast and lung being the commonest primary site. However, we report a case of an apparently well 49-year-old female with metastatic lung adenocarcinoma who presented with visual disturbance and diabetes insipidus related to pituitary metastasis as an initial presentation.

Key words: pituitary metastasis, diabetes insipidus, lung adenocarcinoma

INTRODUCTION

Cancers metastatic to the pituitary gland are uncommon and account for only 1.8% of all metastases and 1% of all pituitary cancers.[1] The breast and lung are the most frequent primary sites. Although the majority of patients are asymptomatic and often diagnosed at autopsy, two of the largest reported series noted that symptoms from the pituitary metastasis were the initial manifestation of metastatic disease in over half of the patients.[2,3] Diabetes insipidus was by far the most frequent symptom, occurring in 45% of patients, followed by optic nerve dysfunction (28%); anterior pituitary dysfunction (24%); palsies of cranial nerves III, IV, or VI (22%); and headache (16%).[4]

CASE

A 49-year-old female with no significant medical history presented with one-month history of progressive peripheral vision loss and headache. She had also experienced polydipsia with polyuria and further history revealed that she was amenorrhoeic for one year. Otherwise, she has no respiratory or constitutional symptoms. Physical examination was unremarkable except that visual field examination confirmed bitemporal hemianopia (Figure 1). A subsequent cranial magnetic resonance imaging (MRI) scan displayed a lobulated heterogeneous enhancing mass approximately 1.7 x 1.9 x 2.0 cm arising from the sella turcica with suprasellar extension and

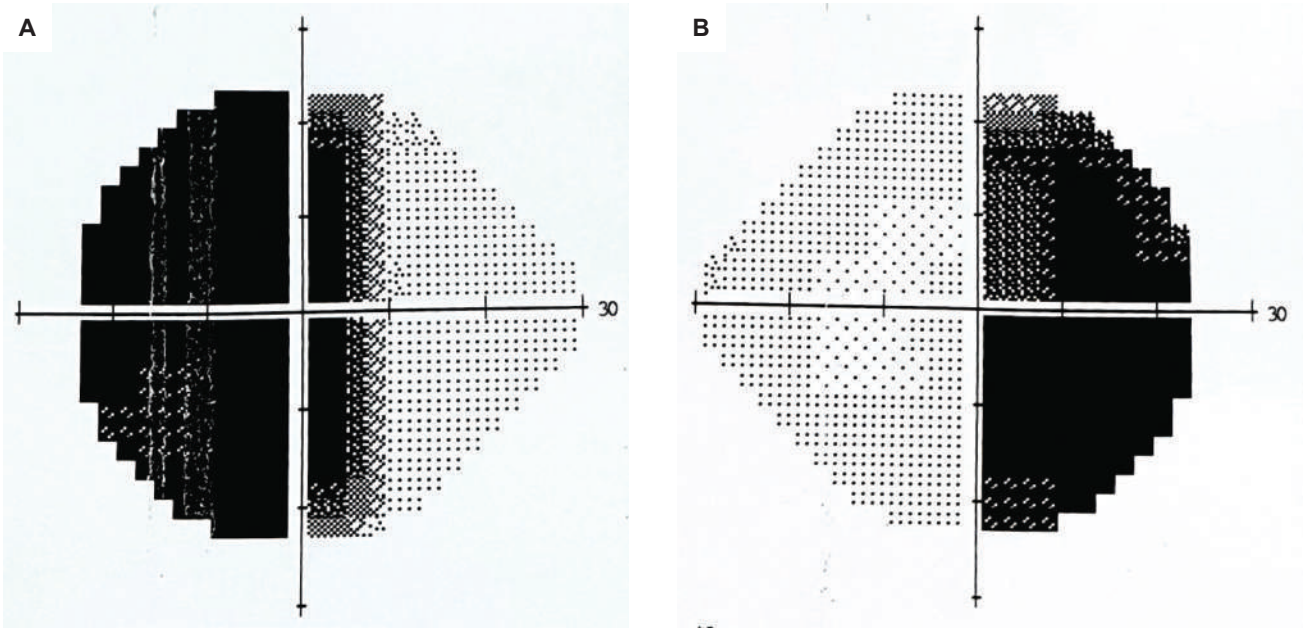

Figure 1. Humphrey visual field test results for patient's left **(A)** and right **(B)** eyes, confirming a dense bitemporal visual loss.

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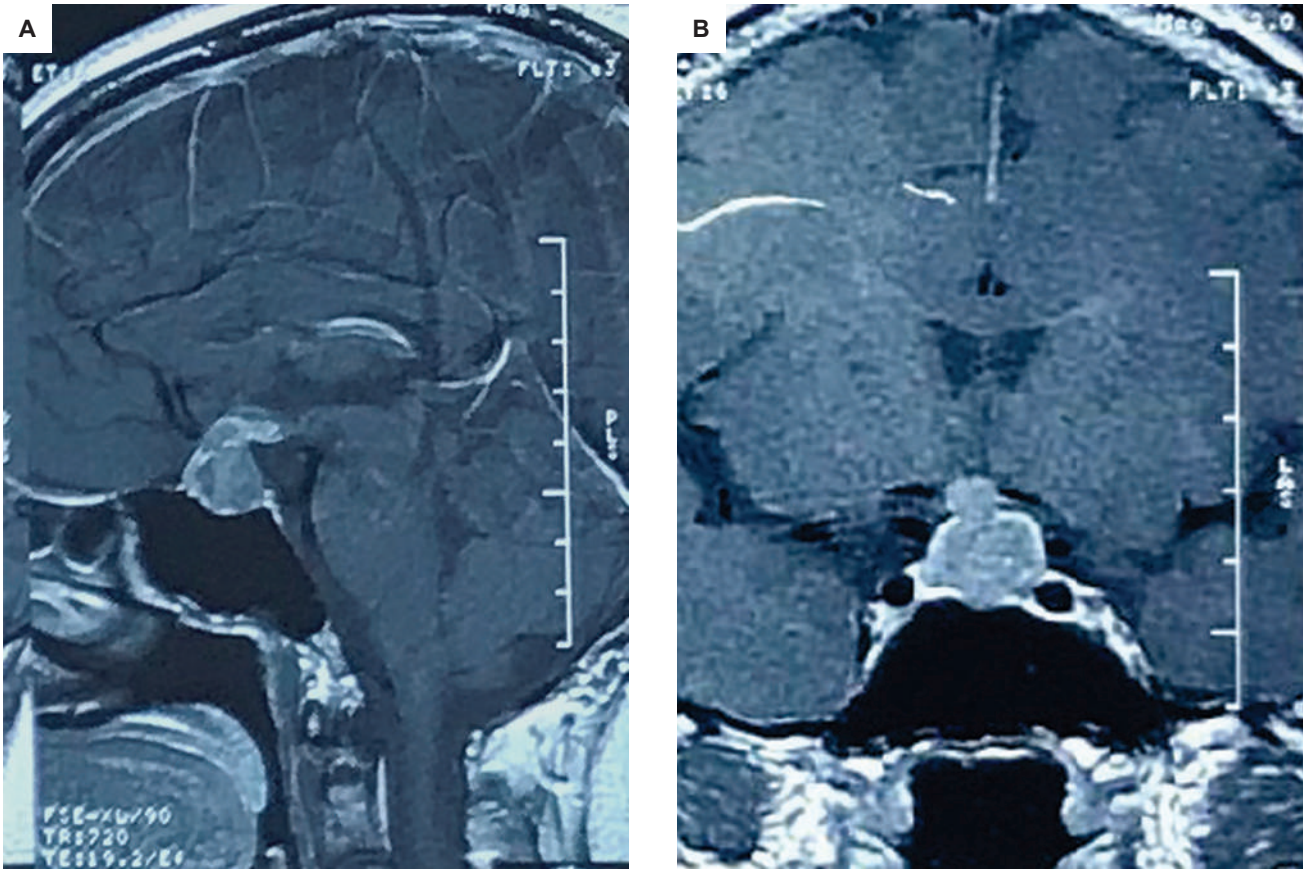

Figure 2. Magnetic resonance imaging of the pituitary showing lobulated heterogenous sellar mass with suprasellar extension and compression of optic chiasm, sagittal view in **A** and coronal view in **B**.

compression of the optic chiasma (Figure 2). Initial laboratory tests showed normal blood count, Na: 144 mmol/L (reference value [RV]:136-145), K: 4.1 mmol/L (RV: 3.5-4.4), and creatinine: 52 umol/L (RV: 44-80). Serum osmolality: 365 mOsm/kg (RV: 275-295) and urine osmolality: 66 mOsm/kg (RV: 300-900) taken during the polyuric phase were consistent with diabetes insipidus. Hormonal evaluation demonstrated insufficiencies of the corticotropic, thyroid and gonadotropic axis. (Table 1). She was started on hormonal replacement therapy (T. Hydrocortisone 10 mg BD, L-Thyroxine 25 mcg OM and T. Desmopressin 0.1 mg BD).

Table 1. Initial hormonal evaluation

Hormone (unit)	Results	Reference Value
LH (IU/L)	0.1	2.4-12.6
FSH (IU/L)	1.4	3.5-12.5
PRL (ug/L)	6.73	4.79-23.30
IGF-1 (ug/L)	93	103-310
ACTH (pmol/L)	<1.1	<10.2
Cortisol (nmol/L)	43.6	171-536
FT4 (pmol/L)	10.8	12-22
TSH (mIU/L)	0.18	0.27-4.2

LH: luteinizing hormone, FSH: follicle-stimulating hormone, PRL: prolactin, IGF-1: insulin like growth factor -1, ACTH: adrenocorticotropic hormone, T4: thyroxine, TSH: thyroid stimulating hormone

The patient underwent endoscopic transsphenoidal pituitary surgery with resection of the mass. The postoperative recovery was uneventful and was discharged well with hormonal replacement therapy. She was seen in clinic one week postoperatively with the complaint of left shoulder pain. Left shoulder x-ray showed pathological fracture of the left proximal humerus (Figure 3) and

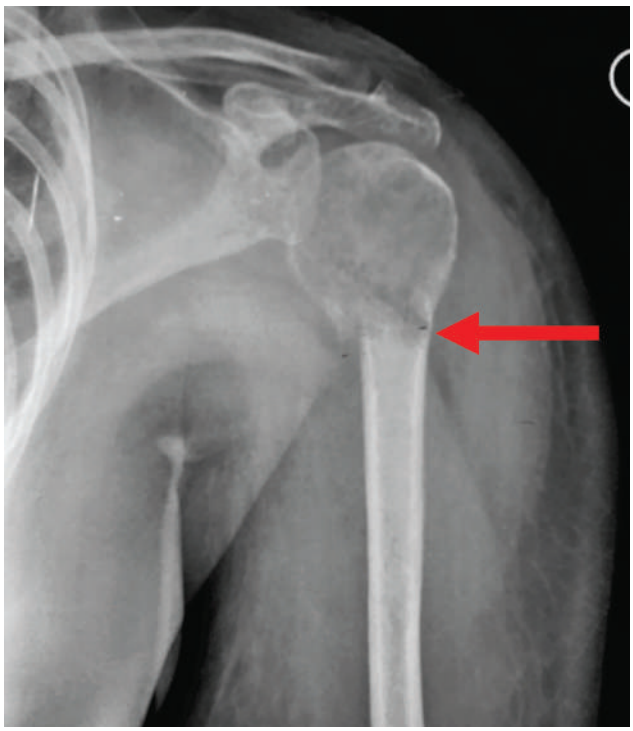

Figure 3. Pathological fracture of the left proximal humerus.

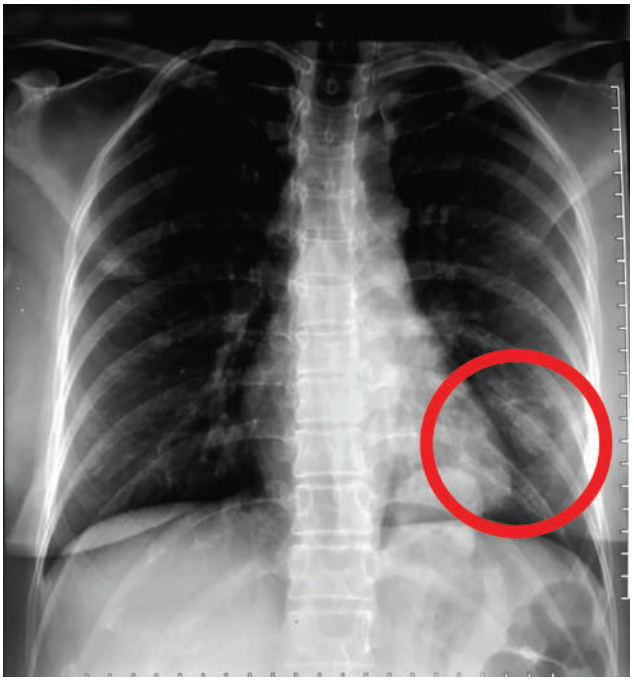

Figure 4. Suspicious left lung nodule.

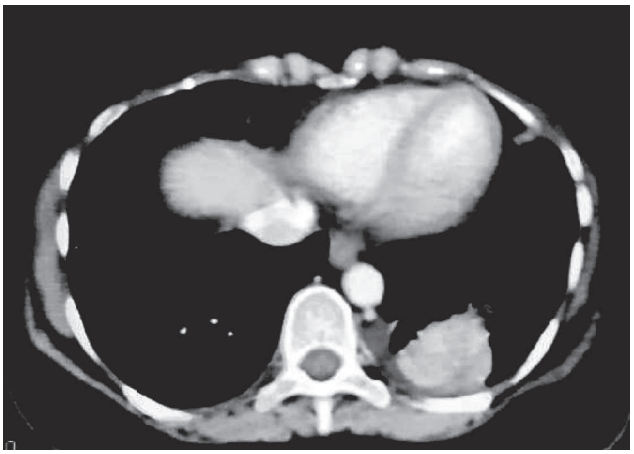

Figure 5. CT scan of the thorax revealed a mass (3.3 x 4.9 x 3.6 cm) at the posterior basal segment of left lower lobe.

chest radiography (Figure 4) showed suspicious left lung nodule. A chest radiography was not done pre-operatively as there were no prior clinical indications. Pituitary histopathological analysis was later reported as metastatic adenocarcinoma. CT of the thorax, abdomen and pelvis revealed a mass (3.3 x 4.9 x 3.6 cm) at the posterior basal segment of left lower lobe (Figure 4) with multiple lung nodules of varying size noted bilaterally, enlarged mediastinal and hilar lymph nodes, and lytic lesion at proximal humerus and L5 vertebral body.

Subsequently, patient underwent CT guided biopsy of the left lung mass. The histopathological analysis was consistent with pulmonary adenocarcinoma and the immunohistochemistry results were positive for cytokeratin 7 (CK7) and thyroid transcription factor 1 (TTF1) and negative for CK20 and thyroglobulin. Patient underwent stereotactic radiation therapy to the pituitary mass and was started on oral chemotherapy gefitinib.

DISCUSSION

Pituitary adenoma is the most common cause of pituitary masses, constituting approximately 10% of all intracranial neoplasms. Pituitary gland metastasis accounts for only approximately 1% of all pituitary tumours in previous serial studies.[5] Breast and lung tumours are the most common primary sites of malignant metastases to the pituitary gland, but other sites such as the gastrointestinal tract, prostate, kidney, thyroid, and pancreas have also been reported.[6]

Majority of the pituitary metastases are clinically silent and only 6.8% of cases are symptomatic.[7] The most common presentations include diabetes insipidus (DI), visual field defects and hypopituitarism. DI is much more common in cases of pituitary metastases than in pituitary adenoma. Nearly 70% of symptomatic patients with pituitary metastases present with DI, whereas the rate of diabetes insipidus in patients with pituitary adenomas is less than 1%.[8]

Differentiating a pituitary metastasis from a pituitary adenoma is often difficult, as the clinical and radiologic findings are often nonspecific.[9] Clinically, one helpful differentiating factor is the presence of DI, which is much more common in pituitary metastases than pituitary adenomas. The most characteristic imaging feature of a pituitary metastasis is enlargement or enhancement of the pituitary stalk with a pituitary mass.[10]

In our patient, she had pituitary metastases from lung adenocarcinoma and her initial presentation was visual field defect and diabetes insipidus. Her imaging showed typical snowman shape appearance of a pituitary adenoma. However, with no previous malignant history, clinical suspicion of pituitary metastases was low.

CONCLUSION

Pituitary metastases are rare but should be included in the differential diagnosis of invasive sellar lesions with pituitary stalk involvement, especially if it is associated with diabetes insipidus.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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At least 3 keywords but no more than 6, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

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4. All measurements and weights should preferably be in System International (SI) units.
5. If appropriate, information should be provided on institutional review board/ethics committee approval.
6. Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

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3. All references should provide inclusive page numbers.
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Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. JTranslational Med. January 20, 2004;2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the US. JAMA. 2001;286(10):1195-1200.

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Authors Representing a Group

Moher D, Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-1991.

Book

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5. Font should be Arial Narrow size 8.
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5. Up to a maximum of five (5) tables are allowed.

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- ☐ (2) drafting the work, revising it critically for important intellectual content; AND
- ☐ (3) that we are all responsible for the final approval of the version to be published; AND
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