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Diabetes Care Models

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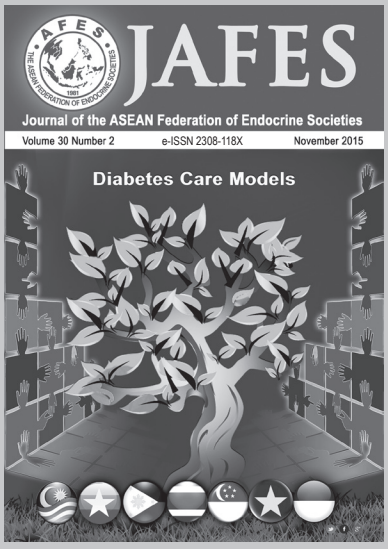

About the Cover

Cover Design by: **Mia C. Fojas, MD**
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Diabetes continues to plague every region in the world and every region, including Southeast Asia, will have to face this disease with action plans or care models that are as diverse as the cultures that make up the ASEAN respective member nations. The region shares a commonality, the production and consumption of rice and the widespread use of coconut cream and oil. These staples make up the foundation of their diet, yet every ASEAN country is distinct in its food heritage. Each has had its share of western influence on diet and healthcare delivery, some American, some European. Yet there is, to a variable degree in each, the Chinese heritage as well as an Indian influence on culture and culinary arts that even predate the western colonial concepts. And every country has its unique politics, specifically how much of the healthcare delivery is subsidized by the national government. Indeed it is a jigsaw puzzle for the stakeholders to solve. What are they each to do to know more about the profile of those afflicted with diabetes in their country? What treatment plans succeed, who will compose the multidisciplinary team? And very important, what resources are available and who will pay? Most ASEAN countries share another commonality, a treatment gap between rural and urban areas. How does each nation trickle down diabetes care to far flung rural areas and what interventions are feasible and acceptable to poor rural dwellers? Every ASEAN country has its healthcare system that has evolved in time, incorporating both traditional and scientific know how in healthcare delivery to battle this juggernaut of a puzzle called diabetes.

JAFES
Journal of the ASEAN Federation of Endocrine Societies
Vol. 30 No. 2 NOVEMBER 2015

JAFES congratulates

Vietnam Association of Diabetes and Endocrinology (VADE)

on its 15th Year Anniversary

VADE was established on June 21st, 2001. Since its establishment to present, under the leadership of the Ministry of Health and supervision of the Vietnam Medical Association, VADE has operated actively, developed continuously, obtained many encouraging achievements in the cause of people's health protection, and taken an important part in the overall development of Vietnam's Health sector. VADE has hosted Congresses in Hanoi (2001), Hue City (2005), Ho Chi Minh City (2011). The new Executive Committee has 43 members with the present **Chairman-Professor PhD Hong Quang Thai** at the helm.

JAFES
Journal of the ASEAN Federation of Endocrine Societies

Full Circle

Five years. Ten issues. Now, we have come full circle. The commitment of the Philippine Society of Endocrinology, Diabetes and Metabolism to take the lead in nurturing JAFES in 2010 has become a regional reality with the continued support of the societies of member nations. *"Were we successful in this endeavor?"* is the question. For the moment, we may use such tentative metrics as manuscript acceptance and rejection rates, number of pages, article downloads, and website views, among others. But such figures feel so objective, so bound in numbers, that they cannot sufficiently describe the editorial team's journey.

We feel nostalgic looking back at the work accomplished and the work at hand. With unwavering passion, we reared the journal like our child, full of ambition and hope, celebrating small victories, committing some mistakes in the process, but learning, continually learning, as we go. Each issue, a genuine product of sleepless editorial nights, was like a milestone, from learning to sit to learning to crawl, from crawling to pulling to stand, from standing to finally taking one step, two steps then three.

We watched the JAFES progress from humble beginnings to international aspirations. In five years, we learned to appreciate the importance of publication ethical standards, authentic open access and a stable online platform to grow. For half a decade, we were learning to follow international guidelines; we were actively networking with editors, editor societies, and journals from other countries; we were emulating journal standards and best practices in journal management and editorial operations. We, too, have matured with the publication.

Have we transformed the JAFES into a self-sustaining, peer-reviewed, English language journal? Have we promoted the exchange of knowledge? Have we encouraged research initiatives to facilitate collaborative research? Have we published high quality research work in a timely and focused manner? Have we advanced endocrine research in the ASEAN region? What seemed too ambitious then, now appears within reach.

And now, as we began with diabetes clinical practice guidelines in 2010, we cap our five-year country commitment by featuring national diabetes clinical care models. It was at the IDF-WPR meeting at Singapore in November 2014, when various Asian countries came together at a plenary

meeting to describe each country's diabetes care models. These models are featured in this issue. Asian neighbors can take the opportunity to learn from each other and set up collaborative efforts to effectively control diabetes and its complications.

The AFES meeting in December 2015 will dedicate time to discussions on the status and future of JAFES. It will give the editorial team great pleasure and honor to present the progress that the journal has made to the societies of member nations who have acted as its parents.

It has indeed been a full circle, after five years and ten issues. On behalf of the Editorial Team, I express our heartfelt thanks to the international Peer Reviewers and many others who support JAFES. It has been a great growing process and we all are blessed to have been part of it.

Elizabeth Paz-Pacheco
Editor-in-Chief

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Contents

JAFES
Journal of the ASEAN Federation of Endocrine Societies

CASE REPORTS

BRIEF COMMUNICATIONS

SPECIAL FEATURE

FEATURE ARTICLE

JAFES Journal of the ASEAN Federation of Endocrine Societies

Diabetes Care in Singapore

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Abstract

Singapore, like her ASEAN counterparts, faces a human and economic burden of chronic diseases such as diabetes. The Singapore diabetes care model features a mixed financing and mixed care delivery model, with an increasing focus on integration of care across traditional boundaries, through information technology, clinical engagement, robust clinical governance and financing schemes, and patient education and self-management.

Key words: health services needs and demands, delivery of healthcare, Singapore

INTRODUCTION

Excellent and efficient healthcare delivery must surely be the aim of any healthcare system around the world. As our Prime Minister Lee Hsien Loong expounded at the Universal Health Coverage Ministerial Meeting in February 2015, good health is fundamental to the happiness, fulfilment and dignity of every human being and good health is a public good.[1]

Disease burden

Diabetes (including type 1 diabetes, but predominantly type 2 diabetes) accounted for 10.4% of the total disease and injury burden in Singapore in 2010.[2] Demographic epidemiological modelling places the estimate at 15% in 2050, with a similar prevalence of obesity at 15.9%; and that ethnic Malay and Indians will continue to bear a disproportionate burden compared with the Chinese majority.[3]

Between 2004 and 2010, there was a 4.6% increase in total disease burden: 15.9% increase in disability burden and decline of 59.9% in premature mortality burden. However, both crude and age-standardized overall burden per head of population decreased by 3.3% and 11.6%, respectively. Less than one-tenth (6%) of the burden were from premature mortality. Eighty percent of the total diabetes burden resulted from diabetes *per se* (i.e. the experience of being diabetic regardless of complications), and the remainder due to complications (neuropathy, diabetic foot, peripheral vascular disease, nephropathy, amputation and others). Diabetes was the second most important cause in overall disease-adjusted life years (DALYs), and was ranked first in overall DALYs for women. It was the second leading cause of DALYs for men. Total diabetes burden increased to 14.2% when the increased risk of ischemic heart disease and stroke attributed to diabetes was included.[2]

Singapore also has a high burden of pre-diabetes (impaired fasting glucose and impaired glucose tolerance), with 14.4% of its population between the ages of 18 and 69 having pre-diabetes. Pre-diabetes is associated with an increased risk of developing diabetes mellitus. Diabetes was the 8th most common cause of hospitalization in 2013.

Current structure and financing

The Singapore Healthcare system is constantly evolving, as it adapts to more chronic diseases like diabetes. Compared with 50 years ago, as disease patterns and practices have changed, we are now dealing with more diseases of lifestyle and affluence, and less with communicable diseases and ailments of poverty and sanitation.

Our system is perhaps best described as a sometimes uneasy marriage between a privatized healthcare system and a single-payer model, effected through a mixed financial system. The twin philosophies are individual responsibility and affordable healthcare for all, and the devil is in the details. In a majority of cases, Singaporeans have to co-pay for each medical service, treatment and prescription drug that they utilize or receive.

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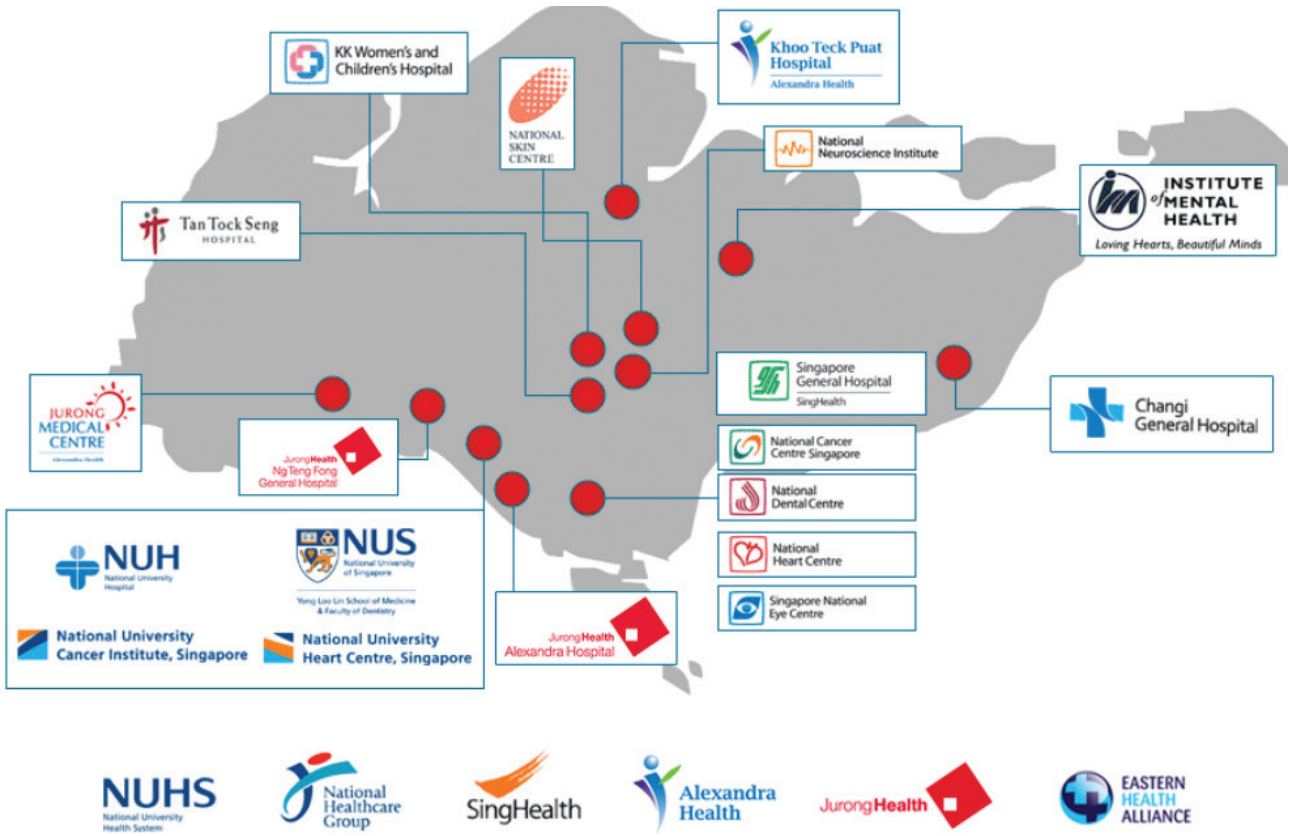

Figure 1. Restructured hospitals in Singapore.

The healthcare system is divided into two: the private and public (known as 'restructured') sector. The majority of hospital beds are owned by the restructured hospitals which continue to be owned by the government and supervised by the Ministry of Health, but function as non-profit operating and accounting entities (Figure 1). Eighty percent of acute care is serviced by the restructured sector, but primary care is dominated by private providers.[4] About 2000 private General Practitioners provide 80% of primary healthcare services, while public outpatient polyclinics provide 20% of the care.

Many community-based programs come under the purview of the Health Promotion Board (HPB), a World Health Organization Collaborating Centre for Health Promotion and Disease Prevention. The HPB conducts a myriad of programs addressing the public health concerns on diabetes, including a Pre-Diabetes Intervention Program offering three individual counselling sessions for 45 minutes at each time in community centers/clubs (CCs) or General Practice (GP) clinics. HPB also offers an interactive diet and activity tracker known as iDAT and blood glucose/blood pressure recording templates. As the lead agency spearheading health promotion and disease prevention, it has embarked on a multi-prong approach to target obesity, active living, smoking cessation, low-salt consumption, workplace health and community wellness.

Singapore has a compulsory medical savings scheme known as Medisave, launched in 1984. The underlying rationale is that the current workforce of active wage-earners should save for their healthcare needs instead of relying on tax revenues from future generations and government handouts. Funds in Medisave accounts can also be used to pay for certain hospital-related expenses of immediate family members, in line with the principle of promoting the primacy of family in care-giving. Government subsidies are also based on price discrimination, allowing subsidies to be directed to poorer users in the lowest ward class. In the period of July 2014 to June 2015, the 50th percentile bill size for admissions related to uncomplicated diabetes in a C-class (lowest ward class, least add-ons) was in the range of S$162 to 216 per day, with an average length of stay of 2.5 to 4.3 days.[4] In comparison, a hospitalization episode in a B1-class ward, which receives a lower level of subsidy, the 50th percentile bill size is S$785 per day. Items such as blood glucose monitoring and insulin pumps are entirely out-of-pocket expenses.

In the restructured/public healthcare system, patients receive subsidies for pharmacotherapeutic agents on a tiered basis depending on their paying status (maximum subsidy for the lowest payment class) and type of medication (maximum subsidy for drugs on the standard list such as generic glipizide and human insulin, and zero subsidy for SGLT2-inhibitor).

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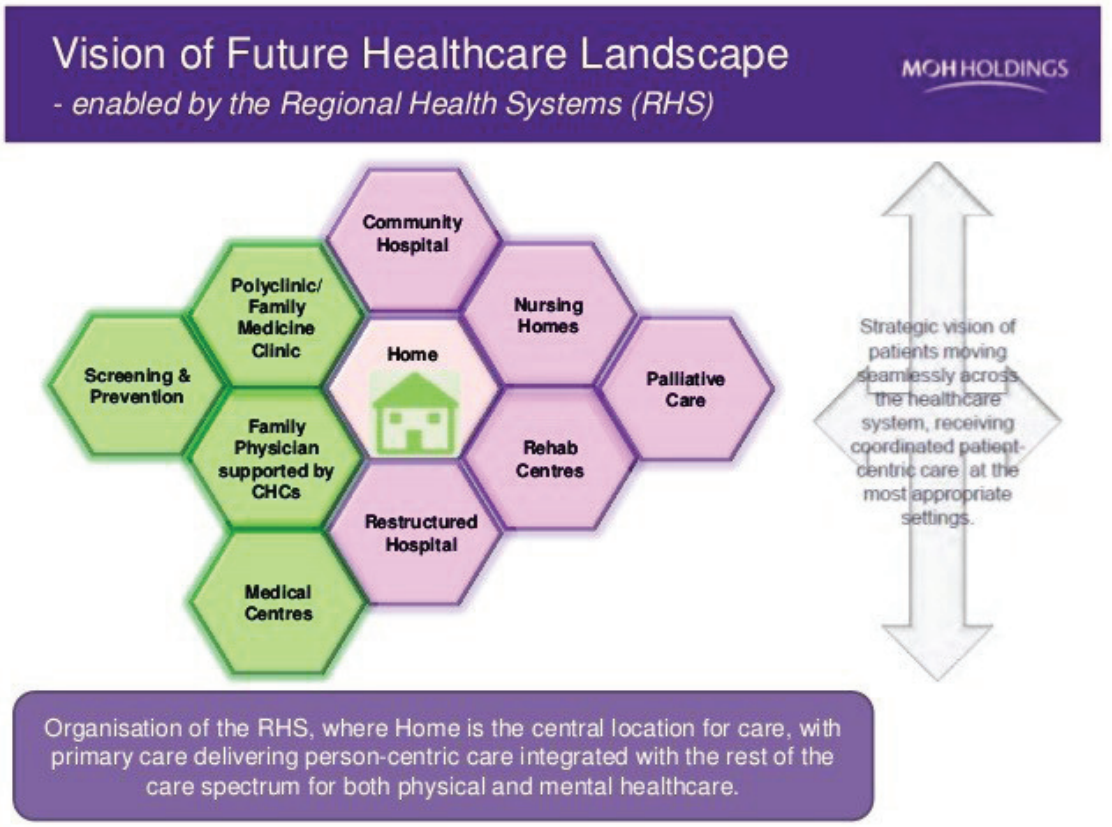

Figure 2. Interface between general practice, community-based programs and secondary/tertiary services, under the Regional Health Systems.

The Chronic Disease Management Programme (CDMP) was first introduced in October 2006 for diabetes mellitus, hypertension, hyperlipidemia and stroke, permitting the use of a family member's or one's own Medisave (up to 10 accounts) of up to S$400 per account per year. Each claim is subject to a 15% co-payment in cash. The scheme has also incentivized the involvement of private GPs in managing chronic diseases.

In recent years, the Ministry of Health has also launched the Community Health Assist Scheme (CHAS), a scheme that enables Singapore Citizens from lower- to middle-income households to receive subsidies for medical and dental care at participating GP and dental clinics near their homes.

Hopes and aspirations

Interface between general practice, community-based programs and secondary/tertiary services

More than ten years ago, Singapore realized that the traditional tiers of primary, secondary, tertiary and quaternary care centers were too rigid for effective chronic disease management. Two terms have been bandied about: right-siting and integrated care. Integrated care refers to the organizational process of coordination which seeks to achieve seamless and continuous care, tailored to the patient's needs and based on a holistic view of the patient.[5] True integration of care often requires a painful demolition of old rigid structures, working across traditional health service boundaries. Functional integration needs information technology support, clinical integration needs distinct work processes, and virtual integration needs a coordinating body such as a Chronic Disease Management Office to orchestrate patient and information transition across different care settings as well as the monitoring of clinical quality indicators (Figure 2).

In 2004, the concept of right-siting was first used to describe the principle that chronic disease patients should be managed in primary care instead of specialist settings. In 2005, the National Healthcare Group developed the Chronic Disease Management System (CDMS), a region-wide disease register that synchronizes clinical health records.[6] In the same year, the Singapore Health Services (SingHealth) regional cluster initiated the Delivering On Target (DOT) Programme, leading to positive health outcomes in diabetic patients. The aim of the DOT Programme was to right-site chronic patients to primary care, benchmarked against evidence-based best practice clinical guidelines. It expanded into a nation-wide program in 2008.

In July 2011, the National University Hospital (NUH) and Frontier Healthcare, an eight-clinic private GP chain, announced a collaboration to fine-tune the shared care model. Stable diabetes patients are referred to Frontier clinics by NUH doctors for co-management. Patients under the program are assured of the same level of care when they consult the family physicians at Frontier clinics.

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The family physicians will follow the same set of care components for diabetic patients practised by the specialists at NUH. The partnership aims to ensure patients receive timely care for their conditions at greater convenience, at clinics nearer their homes.

In 2014, in line with the government's Primary Care Master Plan which promotes the participation of public and private sectors in providing comprehensive and integrated care to patients with stable chronic conditions, SingHealth set up a similar service with a Family Medicine Clinic at Chinatown Point.

Facilitating multi-disciplinary care

The first diabetes center for one-stop patient care was established in 1990 in Singapore General Hospital (SGH). Since then, every restructured hospital/regional healthcare system has established a multi-disciplinary diabetes center. In the primary healthcare sector, government polyclinics also have on-site foot and retinal screening and access to diabetes nurse educators and dieticians.

The co-location of outpatient services with interests in diabetes management (endocrinology, renal medicine, internal medicine, vascular surgery and podiatry from SGH and vitreo-retinal service from Singapore National Eye Centre) in 2015 provides an opportunity to establish a new diabetes model of care under a unifying umbrella of the Singhealth-Duke Diabetes Centre. We are also working to streamline clinical services across the continuum of diabetes care including pediatric and adolescent care, dental services and cardiology/ cardiothoracic care.

Improve accessibility and quality of diabetes self-management education

We have moved to broaden delivery of care by expanding the healthcare team to include several types of healthcare professionals. Team care can minimize patients' health risks by assessment, intervention, and surveillance to identify problems early and initiate timely treatment.

One area for improvement is the use of effective behavioral interventions to lower the risk of diabetes and improve glycemic control and cardiovascular risk profiles. Patients' participation in treatment decisions, personal selection of behavioral goals, patient education and training, and active self-management can all improve diabetes control. This, in turn, can lead to increased patient satisfaction with care, better quality of life, improved health outcomes, and ultimately, lower healthcare costs. We recognize that there is plenty to do in this arena. We were glad to include a new chapter addressing psychosocial needs and self-management in the most recent edition of our local Clinical Practice Guidelines for diabetes mellitus.[7]

The National Electronic Health Record (NEHR)

The NEHR was operationalized in the end or 2011, to integrate and share medical records nationwide to support the seamless delivery of patient care. Patients served by the public sector healthcare institutions already have a single health record shared among our institutions, such as hospitals, specialist outpatient clinics and polyclinics. All community hospitals, 56 community healthcare providers and close to 40% of GP clinics have access to NEHR. The Ministry of Health is actively working with the remaining private healthcare providers not yet on board to encourage their participation.

The NEHR will continue to develop new IT functions and provide information to support the integration of care services for the patient across the healthcare sector. This includes the development of the Continuity of Care Record (CCR) functionality which would provide a mechanism for institutions to share the patient's active problem list and care plan, with the end state being a seamless integration with hospital electronic medical record (EMR) systems. Future developments will also include the use of data analytics to support both point-of-care decision making and national planning for the Ministry of Health.

The Health IT Master Plan (HITMAP) was developed in 2015 with public and private sector stakeholders to anticipate and meet emerging challenges and growing healthcare needs.

Harnessing technology

Another objective of the Singapore Diabetes care model is the use of technology to improve service coordination for better outcomes and more efficient care. An excellent example can be seen in the retinopathy screening services. Diabetic retinopathy is the leading cause of new blindness in working adults in developed countries, including Singapore. Before the advent of a national screening program, patients in the primary care sector had to travel physically to designated polyclinics or centers for an appointment. Retinal images were interpreted by family physicians housed within the polyclinics, with a turnaround time of two to four weeks for grading. Inherent weaknesses with this system were inconsistencies in the grading outcomes, cumbersome quality assurance maintenance, and poor cost-effectiveness especially in terms of manpower costs.[8]

The Singapore Integrated Diabetic Retinopathy Programme (SiDRP) was thus conceptualized and launched in 2010, based on telemedicine and centralized reading centers. All retinal images captured are routed electronically to the Singapore Eye Research Institute (SERI) ocular reading centre for same-day reading and reporting. A remarkable 90 to 95% of images are read and reported in a one-hour time frame. Appropriate referrals are made to ophthalmologists for further assessment and treatment, if necessary, for the same visit at the polyclinic. Patient accessibility has been greatly increased, with image capture sites established beyond conventional touchpoints like polyclinics, to include mobile screening

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vans and optometrists. With these patient volumes, there is also the opportunity to generate a powerful cohort of patients with retinal phenotyping for outcome studies.

CONCLUSION

The main aim of the Singapore model is to configure a system that is efficient and cost-effective, in order to prevent and delay the onset of diabetes and diabetes-related complications, and to improve the quality of life of people who have diabetes.

This is done through a mixed financing system and a mixed delivery model, underpinned by dual principles of affordability and individual responsibility. Any model of care, not just Singapore's, involves prescribers, patients, regulators, influencers and payers. There is already a conscious effort to structure our decision trees and algorithms on evidence-based medicine drawn from an Asian population. However, there is a paucity of real-world data to help make effective decisions on the value propositions of diabetes therapies that are currently available.

Integration of care for patients with diabetes is a noble and worthwhile aspiration. We must remember that integration is a means to an end, and not an end in itself. We need flexible, networked solutions to bring about positive change, especially in the areas of GP-coordinated prevention programs, ready and targeted availability of new technology in diabetes diagnostics and therapeutics, and patient self-management and self-care.

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FEATURE ARTICLE

Diabetes Care Model in Malaysia

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Abstract

With the highest prevalence of diabetes in the region, Malaysia faces a massive task ahead to care for its people afflicted with the disorder. For a successful Diabetes Care model to work, it requires a well-established functioning multidisciplinary team comprising Endocrinologists/Physicians/Family Medicine Specialist Physicians, Diabetes Nurse Educators, Dietitians, Pharmacists, and others such as Podiatrists are needed to provide broad ranging services. Although we have many such individuals trained and working independently, these services are fragmented. What is required is coordination and integration of these services to enable patients' access in a timely manner. The Disease Control Division, Ministry of Health continues to play a central role – coordinating and funding these initiatives. What is desperately needed are more certified Diabetes Nurse Educators to manage the overall care of the patients as well as to provide key diabetes education that enable patient-empowerment to improve self-care, compliance, and ultimately result in better lives.

Keywords: diabetes care, diabetes educator, integrated service, patient empowerment

INTRODUCTION

Diabetes is the classic chronic disease that requires a multidisciplinary care team approach to provide comprehensive management to reduce complications, both acute as well as in the long-term.

The Diabetes Care model in Malaysia is continuing to evolve. Approximately 80% of people with diabetes seek treatment from the Ministry of Health. As such, it is appropriate that the Malaysian Health Ministry, Disease Control Division, is spearheading the initiative to develop a functioning Diabetes Care model and will continue to drive its establishment and success. Before moving forward, it is important to recognise where we are at this moment. Several points need to be considered, that include:

- Burden of disease
- Structure of the healthcare system
- Where are the people seeking care
- How are we doing (recent audits, including DiabCare, etc.)
- Diabetes care team – what is already in place and what needs to be done
- National guidelines for diabetes management
- Strategies for prevention

Burden of disease

Malaysia continues to progress as a nation, both socially and economically. Concomitant with this progress, disease patterns and burdens have changed to reflect these changes in lifestyle and dietary patterns. Unfortunately, of all the countries in the ASEAN region, Malaysia probably has the distinction of having the highest prevalence of diabetes. The recent National Health and Morbidity Survey conducted in 2011,[1] found that 20.8% of Malaysians above the age of 30 years had diabetes (10.7% known and 10.1% undiagnosed). With a population of 30 million, that would mean that there are approximately 2.6 million Malaysians with diabetes.

Structure of the healthcare system and where are the people seeking care

As in most developing nations, the healthcare system is broadly divided into hospital-based and outpatient, primary care-based facilities.

In order to plan proper diabetes care managements to address the needs of this population of individuals, we need to know where they are seeking their medical care.

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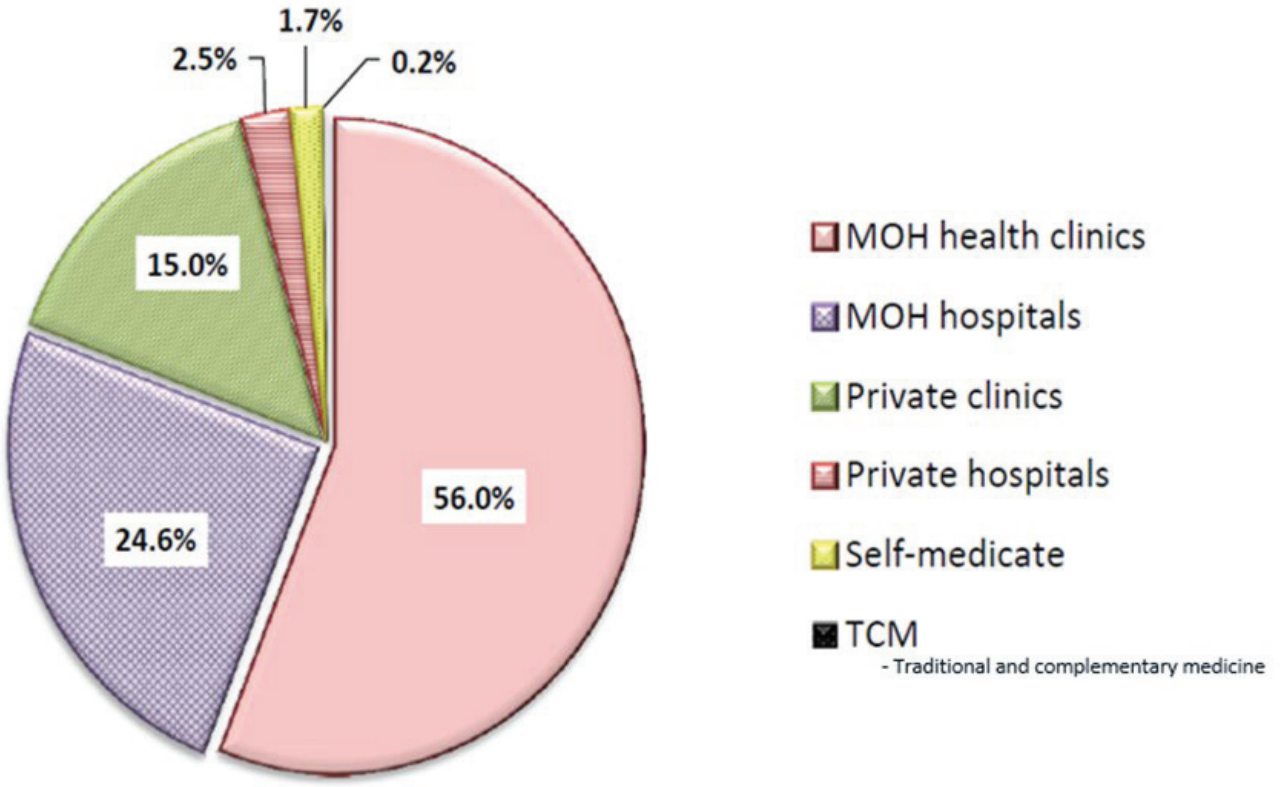

Figure 1. Usual place of treatment for patients with diabetes in Malaysia.

In Figure 1, we recognise that 80% of people with diabetes are seeking care in the primary care health clinics (56%) and hospital-based clinics (24.6%) in the Ministry of Health (MOH). As such, much of the Diabetes Care model has to be designed around the Ministry of Health, in particular, the primary care clinics, that are carrying much of the burden.[2]

How are we doing? National Diabetes Registry[3] and DiabCare[4]

The national diabetes registry started in 2009 and went web-based on January 2011. It supported the implementation of the annual "Diabetes Clinical Audit" amongst patients with Type 2 Diabetes attending the MOH health clinics/primary care facilities. Over 2009-2012, ~650,000 patients' data were added into this registry. Mean age of the patients was 59.7 years. HbA_{1c} was performed in 78% of the patients (in 2012), with the mean HbA_{1c} of 8.1% for T2DM,[1] of which 37.9% of patients achieved target HbA_{1c} <7.0%. The mean BMI was 27.4 kg/m^2 and only 16.6% achieved BMI <23 kg/m^2. Among these patients with T2DM, 70.1% had hypertension and 55.1% had dyslipidaemia. The most common DM-related complications were nephropathy (7.8%), retinopathy (6.7%), and ischaemic heart disease (5.3%).

For tertiary hospital-based diabetes management, Diabcare 2008[2] assessed ~1549 patients with T2DM attending the outpatient diabetes clinics of the general hospitals and institutional academic hospitals, the mean HbA_{1c} was 8.66%, of which only 22.0% had HbA_{1c} <7.0%. In the latest 2013 Malaysian DiabCare audit, 1668 patients with T2DM assessed from the same hospital-based diabetes clinics had a mean HbA_{1c} of 8.52%, with a similar 23.7% achieving HbA_{1c} <7.0% (unpublished data).

These results continue to emphasise the fact that achieving glycaemic control in our diabetic population remains a challenge.

Diabetes Care Team – what is already in place and what needs to be done

There are many models of integrated diabetes care. The main objective of these Diabetes Care models is to establish pathways to provide improved patient care and allow appropriate and timely referral of patients between different parts of the healthcare system. However there remain significant barriers that need to be overcome.

Key members of the multidisciplinary team needed to ensure success of the Diabetes Care model, include diabetologists or endocrinologists / internal medicine physicians / family medicine specialists (FMS) / medical officers, certified diabetes nurse educators / nurse practitioners, pharmacists, as well as dietitians. Other members (if available) include podiatrists, optometrists, dental care professionals and mental health professionals. Currently, in Malaysia, there are endocrinologists / internal medicine physicians in every state general hospital offering specialist diabetes care services. For the smaller hospitals, there are internal medicine physicians handling that aspect. Each of these main general hospitals

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have established diabetes resource centres, where there are diabetes nurse educators helping to deliver patient-centered education to inpatients as well as outpatients. The Ministry of Health pharmacists have also initiated services that offer education focusing primarily on medications, how the medications work with emphasis on the importance of adherence / compliance. This initiative was started in 2006, with formation of the Diabetes Mellitus Treatment Adherence Clinics (DMTAC),[5] coordinated and operated by pharmacists. After being shown to improve glycaemic control on follow-up,[5] these services have been expanded from the major public hospitals to the primary care clinics.

Family medicine specialists (FMS) form the backbone of the health clinics that look after ~60% of the diabetes population. The Ministry of Health (MOH) has 960 primary care clinics; and there are only ~280 trained and certified FMS' "manning" these clinics. There is a continuing need to train more FMS' to fill this huge void. These trained FMS' further improve care by providing downstream educational courses to update trainee medical officers. They also continue to audit diabetes care and initiate patient educational initiatives. There is also no official integration or pathways between these health clinics and the major public hospitals or institutional hospitals where many of the physicians and endocrinologists practice to enable more timely and seamless transfer of patients requiring complex care between these systems.

Certified diabetes educators (DNEs) are an essential member of this diabetes care team. On an individual basis, they are able to educate patients on medications, particularly insulin injection techniques, timing of injections; and in addition, organise small group educational initiatives to allow for broader coverage of patients attending the outpatient diabetes facilities. Currently, only the major urban hospitals have such DNEs, while there are no such individuals to help drive a systematic diabetes service in smaller hospitals and rural healthcare facilities.

Dietitians are also important members of the team, and for best results, they should be available at the diabetes outpatient clinics so that patients can be seen and appropriate advice given with input from the doctors. There are currently approximately 39,000 registered dietitians working in the MOH primary health clinics. Unfortunately, there are still some areas and clinics, particularly in the rural areas, that have no dietitian support. The Malaysian Dietitians' Association has been actively supporting the management of patients with diabetes. With this in mind, they have helped develop the nutrition chapter of the Malaysian Clinical Practice Guideline (2009,[6] with an update expected in December 2015). They have also developed 2 guidelines; Medical Nutrition Therapy guidelines for Type 2 diabetes mellitus, in 2005,[7] updated in 2013.[8] Of course, training specialist dietitians with in-depth knowledge of dietetic management for Type 1 diabetes, diabetes in pregnancy / gestational diabetes or concomitant renal dysfunction will enhance their contribution to the Team.

There are no certified trained podiatrists available to help in the important aspect of diabetes foot care. Several of the main hospitals have diabetes foot services, largely manned by orthopaedic surgical units and orthopaedic surgical doctors. This lack needs to be addressed.

Important role of Disease Control Division, Ministry of Health

The MOH has a unit in the Non-communicable Disease (NCD) Section of the Disease Control division (DCD), which plans initiatives for the management of chronic diseases like diabetes. They have a team that is dedicated to planning strategies, implementation of appropriate programs, educational initiatives and obtaining funding; with the end result – setting-up of a successful chronic care model for diabetes. The NCD section developed a National Strategic Plan for Non-communicable Diseases in 2010,[9] presented and approved by the Cabinet of the Government of Malaysia. This provided a framework for strengthening NCD prevention and control in Malaysia. In addition, systematic management of NCDs at the community level (that included diabetes) was implemented – with 7 goals / targets, including: screening, registration, clinical management, complications screening, rehabilitation, defaulter tracing, and self-care / patient empowerment.

In addition, the disease control division has recognised the importance of improving healthcare delivery; as well as aligning finances. This division works toward obtaining funding allocation for human resource development e.g. Diabetes Nurse Educators as well as funding to enable timely availability of medication to achieve glucose targets.

Newer modalities of anti-diabetic medications, including oral dipeptidyl-peptidase inhibitors (DPP-4i), sodium glucose co-transporter 2 inhibitors (SGLT2-inhibitors), modern insulin analogs (insulin aspart, lispro insulin, insulin glargine, etc.) have all been registered in a timely fashion in the national drug formulary for use; and budgets were made available for prescription to appropriate patients attending the public MOH clinics.

With regard to patient empowerment, modules for patient health education, including pre- and post-test questionnaires, have been developed and published by the Disease Control Division, MOH. Further development of a Peer Support Group educational initiative has been developed and trial runs have proven its success. It remains for this initiative to be rolled out to the wider public.

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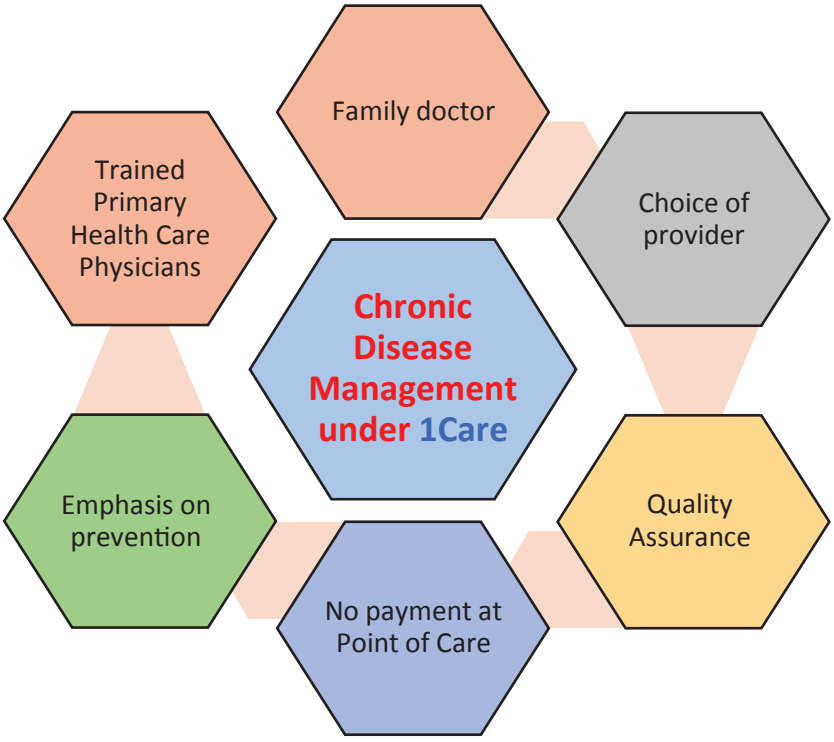

Figure 2. Proposed structural reform to integrate public and private healthcare sectors (Malaysia).

Recognising that majority of patients with diabetes are accessing care from primary care facilities in the MOH, there are also proposed reforms to integrate public and private healthcare sectors, as shown in Figure 2. This will devolve some of the healthcare burden to the private clinics that are abundant in the whole country and further improve overall healthcare.

Unfortunately, despite having many of the members of this multidisciplinary team as mentioned above, there remains significant fragmentation of these services. These services need to be integrated to allow for timely referrals to improve patient experiences and outcomes.

Malaysia has been extremely fortunate in that the MOH-DCD has been very supportive, working closely with other stakeholders in diabetes, e.g. NGOs and academic diabetes fraternity to drive change for the improvement of diabetes care in the country.

Much of the initiatives, programs, developments described above have been driven by the Ministry of Health, with some minor assistance from the endocrinologists, physicians, dietitians and pharmacists, helping with clinical audits and the clinical practice guidelines.

National Guidelines for Management of T2DM

Clinical Practice Guidelines (CPGs) have been developed over the past 15 years and in December 2015, the latest 5th CPG for T2DM will be rolled out. Updated CPGs are required to allow timely changes to recommendations for improving diabetes care and aligning clinical decision making according to prevailing evidence. These guidelines are endorsed by the MOH and made available to all practising physicians. In addition, there is a specific insulin initiation guideline to assist primary care doctors.

Strategies for Prevention

Of course, prevention strategies cannot be excluded from any future plans for diabetes care. Again, the Ministry of Health recognizes this and has initiated collaborative efforts with a "Whole-of-Government" strategy to engage relevant ministries such as Ministry of Environment / Infrastructure, Ministry of Transport as well as local governments to modify behaviour of the population toward a healthy lifestyle. These are spelt out in the NSP-NCD.[9]

SUMMARY

The burden of diabetes has increased exponentially in Malaysia and achieving glycaemic control remains a challenge. There is an increasing challenge in providing satisfactory, consistent quality of care across a broad range of patients. Many of the specialized services are located in the urban areas, in the major public hospitals and institutional centres. Referrals to specialists are delayed due to late diagnosis and sub-optimal control. Timely referrals with more seamless transition within the healthcare system need to be established. Patient-related factors, i.e. patient empowerment, need to be addressed. Continued close collaboration between the MOH and

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.30.02.09

other key stakeholders, such as non-governmental organisations (e.g. Diabetes Malaysia / Malaysian Diabetes Educator Society / National Diabetes Institute) as well as corporate partners – will help drive many of these changes required to further establish a successful Diabetes Care model in Malaysia.

After decades of establishing a comprehensive healthcare system, Malaysia continues to work toward improving its chronic disease care models, in particular, for the management of people with diabetes. The component that needs urgent attention would be the recognition of the Certified Diabetes Nurse Educator (DNE) – to recognise the DNE as a specialised field of nursing, allowing definitive career opportunities and appropriate remuneration. These steps would encourage more healthcare professionals to embark on training as DNEs.

CONCLUSION

Being a developing nation, Malaysia has come a long way toward providing quality medical care to its populace. After establishing good acute care services, attention is needed toward chronic disease management. With the high prevalence of diabetes, it is essential that an Integrated Diabetes Care model be put in place to handle the demands and to improve patient outcomes. What is desperately required are more well-trained certified diabetes nurse educators to help drive these initiatives through, with emphasis on patient education and patient self-empowerment.

The Disease Control Division (Non-communicable Disease Section) of the Ministry of Health has been supportive and will continue to drive change and progress toward achievement of this goal.

Acknowledgement

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FEATURE ARTICLE

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Myanmar Diabetes Care Model: Bridging the Gap Between Urban and Rural Healthcare Delivery

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Abstract

There has been significant magnitude of problems of diabetes in Myanmar, according to the estimates of International Diabetes Federation (IDF) and the recent National Survey on the prevalence of diabetes. There has been a wide gap of equity between the urban and rural healthcare delivery for diabetes. Myanmar Diabetes Care Model (MMDCM) aims to deliver equitable diabetes care throughout the country, to stem the tide of rising burden of diabetes and also to facilitate to achieve the targets of the Global Action Plan for the Prevention and Control of NCDs (2013-2020). It is aimed to deliver standard of care for diabetes through the health system strengthening at all level. MMDCM was developed based on the available health system, resources and the country's need. Implementation for the model was also discussed.

Key words: diabetes care, NCDs, equity

INTRODUCTION

Diabetes represents a significant public health burden worldwide by decreasing quality of life and causing death and disability at great economic cost.[1] Diabetes in all its forms imposes unacceptably high human, social and economic costs on countries at all income levels.[2]

International Diabetes Federation (IDF)'s most recent estimates indicate that 8.3% of adults - 382 million people - have diabetes and the number of people with the disease is set to rise beyond 592 million in less than 25 years. Yet, with 175 million of cases currently undiagnosed, a vast amount of people with diabetes are progressing towards complications unawares. Moreover, with 80% of the total number affected living in low- and middle-income countries, where the epidemic is gathering pace at alarming rates.[2]

Myanmar is included in the Western Pacific region among the six IDF regions. IDF estimated that the national prevalence of diabetes in 2013 was 5.7% and total numbers of people with diabetes were 1,988,850 in Myanmar. Numbers of people with diabetes in urban and rural area were estimated as 1,100,380 and 888,460 respectively.[2]

STEP survey for Yangon Division (2003-3004) reported the prevalence of diabetes as 11.8% and prevalence of diabetes in urban and rural areas as 13.9% and 7.3% respectively.[3] It was the regional survey conducted in the most populous area of the country, when the Yangon was the capital of the country. There were twice as many people with diabetes as in urban than in rural areas.

National STEP Survey (2009) recorded associated risk factors for diabetes and the prevalence of smoking was 33.6% in males and 6.1% in females, the prevalence of hypertension was 31% in males and 29.3% in females; the prevalence of overweight was 21.85% in males and 23.07% in females; the prevalence of obesity was 4.35 in males and 8.45 in females among the sample population.[4] Although it was a national survey it included only the survey on the behavioral and physiological risk factors and could not report the prevalence of diabetes which required laboratory measurement of blood glucose.

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National Survey on the prevalence of diabetes and risk factors for non-communicable conducted in 2013-2014 reported the prevalence of diabetes as 10.5% for the adult population aged between 25 and 65 years.[5] It also reported the prevalence of risk factors for major non-communicable diseases. The prevalence of hypertension for both sexes was 26.4%. Percentage who currently smokes tobacco was 26.1% whereas percentage who currently drinks alcohol was 19.8%. The prevalence of overweight (BMI >25 kg/m^2) and obesity (BMI >30 kg/m^2) were 22.4% and 5.5% respectively.[5] This survey was an extensive survey showing the magnitude of the problem of diabetes and risk factors for major NCDs for the whole country. The survey showed the higher prevalence of diabetes than the estimated prevalence of diabetes by the IDF. Based on this prevalence the total number of diabetes can be more than 2.5 million in Myanmar.

Diabetes mellitus is one of the major non-communicable diseases which also include cardiovascular disease, cancers and chronic respiratory disease. These major non-communicable diseases share four behavioral risk factors: tobacco use, unhealthy diet and physical inactivity and harmful use of alcohol. Current global mortality from non-communicable diseases remains unacceptably high and is increasing. Thirty-eight million people each year die from non-communicable diseases. Over 14 million deaths from NCDs occur between the age of 30 and 70 of which 85% are in the developing countries.[6]

In 2011 September, world leaders adopted the Political Declaration on the non-communicable diseases at the United Nations General Assembly in New York and committed to develop national multi-sectoral action plan for the prevention and control of NCDs and to consider the development of national targets to focus efforts and assess progress made. At the same time, 2011 Political Declaration gave the WHO leadership role along with many time bound assignments.[7]

The World Health Assembly endorsed the WHO Global Action Plan for the Prevention and Control of NCDs 2013-2020 in May 2013. The Global Action Plan provides Member States, international partners and WHO with a road map and menu of policy options which, when implemented collectively between 2013 and 2020 will contribute to progress on 9 global NCD targets (Appendix 1) to be attained in 2025.[8-10]

A primary healthcare approach is essential to address NCDs effectively and equitably,[11,12] and the need to strengthen primary care (PC) has been recently highlighted in the political declaration of the United Nations high-level meeting for NCD prevention and control.[13] There are many cost-effective and high-impact interventions that are feasible to be delivered in PC in low-resource settings by physician as well as non-physician healthcare providers.[11] These include cardiovascular risk assessment and management to prevent heart attacks and strokes using hypertension and diabetes as entry points, detection, and follow up of diabetes to prevent diabetes complications such as chronic renal disease, smoking cessation counseling to prevent progression of chronic respiratory disease, among others.[14-16]

In Myanmar, WHO Package of Essential Non-Communicable Diseases (PEN) implementation was conducted in two pilot townships in 2012-2013 successfully. Diabetes and hypertension were used as entry point for the screening of high risk persons for cardiovascular diseases at primary care level by Basic Health Staffs who were regularly supervised by township medical officers. Lifestyle modifications like consumption of healthy diet, promotion of physical activity and cessation of tobacco were counseled according to the WHO protocol. Initiation of treatment for diabetes and hypertension to those with high risk of cardiovascular diseases as identified by using WHO/ISH risk score according to the protocol and regular follow up of these patients with counseling on healthy lifestyle and checking the response to treatment with scoring of cardiovascular risk were carried out fortnightly. For successful implementation, community mobilization was undertaken through advocacy of the aim and process of the NCD intervention to the local administrative authorities, community leaders and local NGOs. After three months of implementation, there were improvements in the cardiovascular risk scores with reduction of risk in those patients with high risk of cardiovascular diseases. This pilot project proved the feasibility of implementation of Package of Essential NCD intervention in the low-resource settings in Myanmar. Most importantly there was a building of trust between the community and BHS, which led to the success in undertaking of other public health activities also in the community.[17]

The health system of Myanmar comprises a pluralistic mix of public and private systems both in financing and provision. The network of hospitals and health centers (which extends down to village level) provides preventive and curative services ranging to primary to tertiary care. There are challenges to overcome the limitations of the past (e.g. low investment in rural health services), inadequate funding for expansion of universal coverage and to address health inequities is paramount importance, needing a major reform that will ensure healthcare services to reach the poor and the disadvantaged groups, through the effective functioning of township health system.[17]

Prevention, early detection, diagnosis, and management of NCDs are compromised due to critical health system gaps at PC level. They include deficiencies in equitable health financing, access to medicines and technologies, reliable health information and referral systems, and the health workforce. There is a growing consensus that health

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system strengthening, particularly at PC level is a prerequisite for scaling up prevention and control of NCDs in resource-constrained settings.[18]

The situation of delivery of diabetes care to the public in Myanmar is far from satisfaction. Major challenges in the diabetes care service in Myanmar are public health seeking behaviour issues, presence of traditional medicine, lifestyle and diet issues and issues pertaining to religion and environment.[19] There is also a wide gap in the equity of delivery of diabetes care between the rural and urban areas. Standard of care for diabetes is available only in cities where majority of physicians and diabetologists work. Essential medication and diagnostic facilities are not available in primary health centers in rural areas where 70% of the population reside. As the health system is mainly orientated towards prevention and control of communicable diseases and delivery of care for maternal and child health, medical officers and Basic Health Staff needs capacity building for the delivery of standard of diabetes care. Apparently, to improve the delivery of equitable diabetes care to the public, it is utmost important to strengthen the health system with emphasis on the primary healthcare level.

It is imperative to develop Myanmar Diabetes Care Model not only to stem the tide of rising prevalence of diabetes along with its health and socio economic burden but also to achieve the targets set in the Global Action Plan for the prevention and control of NCDs 2013-2020, as a Member State of the World Health Organization as well as the United Nations. Myanmar Diabetes Care Model will be based on the experience of PEN intervention in primary care, using diabetes as the starting point for the screening for high risk for cardiovascular diseases. Moreover, health system strengthening at all level of care will be undertaken and narrowing the gap between the rural and urban delivery of health services with particular focus on the improvement in the diabetes care and integrated approach for the major NCD.

Literature review

Diabetes can be found in every country. Without effective prevention and management programmes, the burden will continue to increase worldwide.[20] Diabetes is a complex, chronic illness requiring continuous medical care with multifactoral risk-reduction strategies beyond glycemic control.[21]

American Diabetes Association (ADA) has recommended "standards of medical care in diabetes." ADA position statements on "Standards of Medical Care in Diabetes" provides key clinical practice recommendations which are viewed as important resources for healthcare professionals who care for people with diabetes.[21]

Though quality diabetes care is essential to prevent long-term complications, care often fails below recommended standards regardless of healthcare setting or patient population, emphasizing the necessary for system change.[22]

The chronic care model (CCM) is a multifaceted framework for enhancing healthcare delivery. The model is based on a paradigm shift from the current model of dealing with acute care issues to system that is prevention based.[23] The premise of the model is that quality diabetes care is not delivered in isolation and can be enhanced by community resources, self-management support, delivery system redesign, decision support, clinical information systems, and organizational support working in tandem to enhance patient -provider interactions.[24-26] The CCM has been shown to be an effective framework for improving the quality of diabetes care.[27] Currently, few efforts exist to improve quality of care in diabetes despite studies that demonstrate their proven effectiveness.[28]

A group of external and WHO experts have developed a guideline for diagnosis and management of type 2 diabetes in primary healthcare in low-resource settings. The primary goal of the guideline is to improve the qualities of care and the outcome for people with type 2 diabetes in low-resource settings. It recommends a set of basic intervention to integrate management of diabetes into primary healthcare (Table 1).[29]

Effective approaches to reduce the noncommunicable disease burden in low- and middle-income countries (LMIC) include a mixture of population-wide and individual interventions. Such cost-effective interventions are already available and include methods for early detection of NCDs and their diagnosis using inexpensive technologies, non-pharmacological and pharmacological approaches for modification of NCD risk factors and affordable medications for prevention and treatment of heart attack, strokes, diabetes, cancer and asthma. The WHO Package of Essential Non-communicable Disease Interventions (WHO PEN) for primary care in low-resource settings is an innovative and action-oriented response to the above challenges. It is a prioritized set of cost-effective interventions that can be delivered to an acceptable quality of care, even in resource-poor settings.[14]

In Myanmar, WHO Package of Essential non-communicable Diseases (PEN) implementation was conducted in two pilot townships in 2012-2013 successfully. Diabetes and hypertension were used as entry point for the screening of high risk persons for cardiovascular diseases at primary care level by Basic Health Staffs who were regularly supervised by township medical officers. Lifestyle modifications like consumption of healthy diet, promotion of physical activity and cessation of tobacco were counseled according to the WHO protocol. Initiation of treatment for diabetes and hypertension to those with high risk of cardiovascular diseases as identified by using WHO/ISH

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Table 1. Recommendations for the management of diabetes in primary healthcare[29]

No.	Recommendation	Quality of evidence	Strength of recommendation
1	Point of care devices can be used in diagnosing diabetes if laboratory services are not available.	not graded	strong
2	Advise overweight patients to reduce weight by reducing their food intake.	very low	conditional
3	Advise all patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.	moderate	conditional
4	Advise all patients to practice regular daily physical activity appropriate for their physical capabilities (e.g. walking).	very low	conditional
5	Metformin can be used as a first-line oral hypoglycaemic agent in patients with type 2 diabetes who are not controlled by diet only and who do not have renal insufficiency, liver disease or hypoxia.	very low	strong
6	Give sulfonylurea to patients who have contraindications to metformin or in whom metformin does not improve glycaemic control.	very low	strong
7	Give a statin to all patients with type 2 diabetes aged ≥ 40 years.	moderate	conditional
8	The target value for diastolic blood pressure in diabetic patients is ≤80mm Hg.	moderate	strong
9	The target value for systolic blood pressure in diabetic patients is <130mm Hg	low	weak
10	Low-dose thiazides (12.5 mg hydrochlorothiazide or equivalent) or ACE inhibitors are recommended as first-line treatment of hypertension in diabetic patients. They can be combined.	very low for thiazides, low for ACE inhibitors	strong
11	Beta blockers are not recommended for initial management of hypertension in diabetic patients, but can be used if thiazides or ACE inhibitors are unavailable or contraindicated.	very low	strong
12	Give patients health education of patients on foot hygiene; nail cutting, treatment of calluses, appropriate footwear.	low	strong
13	Educate healthcare workers on assessment of feet at risk of ulcers using simple methods (inspection, pin-prick sensation)	low	strong
14	Persons with type 2 diabetes should be screened for diabetic retinopathy by an ophthalmologist when diabetes is diagnosed and every two years thereafter, or as recommended by the ophthalmologist.	low	conditional
15	Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 should be given hypertonic glucose intravenously. Food should be provided as soon as the patient can ingest food safely.	strong	strong
16	Unconscious diabetic patients on hypoglycaemic agents and/or blood glucose ≤2.8 mmol/L administer intravenously 20 to 50ml of 50% glucose (dextrose) over 1 to 3 minutes. If not available, substitute with any hypertonic glucose solution. Food should be provided as soon asthe patient can ingest food safely.	very low	strong
17	If blood glucose ≥18 mmol (refer to hospital with i.v. drip 0.9% NaCl 1 litre in 2 hours, continue at 1 litre every 4 hours until hospital.	very low	strong

Sources: Modified from World Health Organization: Prevention and control of non-communicable diseases: Guidelines for primary healthcare in low-resource settings

risk score according to the protocol and regular follow up of these patients with counseling on healthy lifestyle and checking the response to treatment with scoring of cardiovascular risk were carried out fortnightly. For successful implementation, community mobilization was undertaken through advocacy of the aim and process of the NCD intervention to the local administrative authorities, community leaders and local NGOs. After three months of implementation, there were improvements in the cardiovascular risk scores with reduction of risk in those patients with high risk of cardiovascular diseases. This pilot project proved the feasibility of implementation of Package of Essential NCD intervention in the low-resource settings in Myanmar. Most importantly there was a building of trust between the community and BHS, which led to the success in undertaking of other public health activities also in the community.[30]

Myanmar Diabetes Care Model (MMDCM)

The Diabetes Model of Care provides a framework for comprehensive, accessible and efficient provision of coordinated diabetes prevention and management services for both rural and urban areas throughout the country. It is based not only on the country specific situation especially health system, diabetes, NCDs epidemiology, and the need of the country but also on the literature review in particular on the best practices in the diabetes care and experience with PEN implementation in primary care in pilot townships. It is aimed to deliver comprehensive and equitable healthcare service to those people with pre-diabetes or diabetes. The unique features of the care model are: empowering the basic health staffs in the diabetes care, community mobilization and participation in the care plan, and application of concepts of Universal Health Coverage (UHC) and WHO's list of essential drugs and integration of diabetes care to the prevention and control of other major non-communicable diseases. It is an effort to fulfill the Myanmar's obligation to the targets and indicators for diabetes as endorsed in the Global Action Plan for the prevention and control of non-communicable diseases (2013-2020). It is expected that the successful implementation of the MMDCM will also assist in achievement of other targets through the adoption of healthy life style throughout the whole country.

Vision

A nation free of the avoidable burden of diabetes mellitus.

Mission

Effective and equitable care for people with diabetes both rural and urban areas throughout the country.

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.16

Goal

To reduce the preventable and avoidable burden of diabetes by delivering the comprehensive healthcare to the people with diabetes through the community mobilization and empowering of basic health staff in the diabetes care throughout the country equitably.

Objectives

1. Prevention and delay the onset of diabetes in the community by facilitating the adoption of healthy life style;
2. Early detection of diabetes patients by offering screening for asymptomatic patients;
3. Delivery of standard of care for diabetes to those patients equitably throughout the country to prevent and slow the progression of diabetes complications;
4. Establishing the proper referral system for diabetes patients with complications.

Structure of the Diabetes Care Model

Myanmar healthcare system evolves with changing political and administrative system and relative roles played by the key providers are also changing although the Ministry of Health remains the major provider of comprehensive healthcare. It has a pluralistic mix of public and private system both in the financing and provision. Healthcare is organized and provided by public and private providers.[12]

Structure of the Diabetes Care Model is planned to be aligned with the structure of Myanmar healthcare system which comprises primary, secondary and tertiary care level (Figure 1).

Primary healthcare level consists of townships and rural health centers. There are more than 300 townships throughout the country. Each township has 5-6 rural health centers. Township health center is taken care by township medical officer who is responsible for administration works, clinical care of both outpatients and inpatients, and supervision of public health activities. There are 4-6 medical doctors working in township hospital under the supervision of township medical officer. The main responsibility of township medical center is to offer the general clinical care service and the public health activities such as surveillance and prevention of infectious diseases, maternal and child healthcare, immunization of community according to the extended program of immunization of the country. There is no specialist medical care service available at the township medical health center. Function of the rural health centers are carried out by Basic Health Staff like Health Assistants, Midwives and Public Health Supervisors.

Secondary healthcare level is provided at the district level where specialists medical care services are available. Each district hospital has specialists such as physicians, obstetricians and gynecologists, pediatricians and general surgeons. There are also private clinics and private hospitals in some of the districts.

Tertiary healthcare level is provided at the States and Regions and major cities like Yangon, Mandalay and Naypyidaw. University teaching hospitals are situated mainly in Yangon, Mandalay, Magway and Taunggyi where ultra-specialists care like cardiology, endocrinology, oncology, nephrology etc. are available. Private hospitals with specialist medical care are also available at tertiary healthcare level.

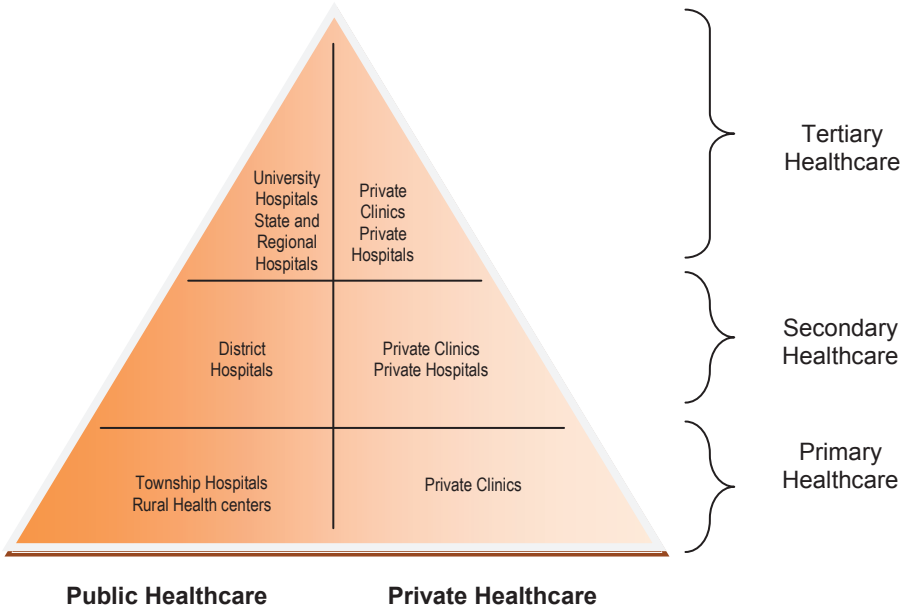

Figure 1. Structure of Myanmar Healthcare system.

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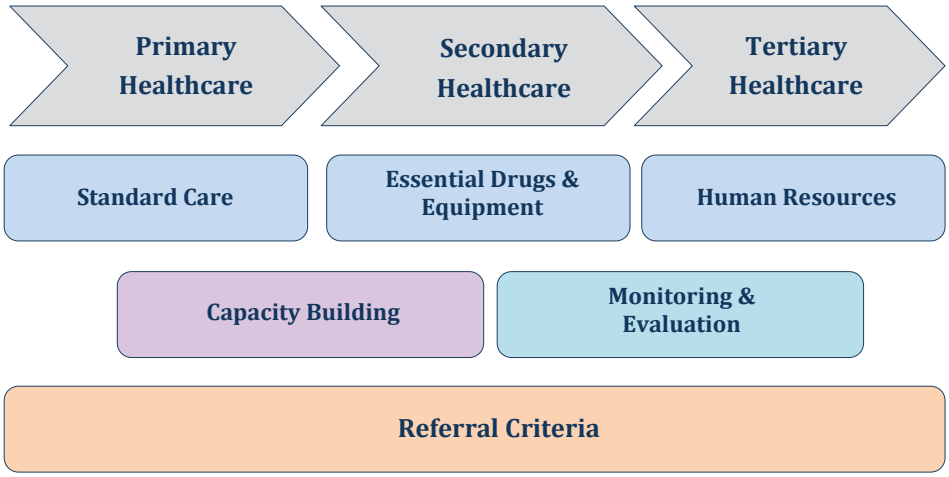

Figure 2. Myanmar Diabetes Care Model.

Diabetes care services will be made accessible from rural health center to tertiary level. Each level will have to perform specified functions for delivery of care in accordance with the guidelines for delivery of standard of diabetes care at different healthcare level. Each level of care will be supported by specified lists of essential drugs and equipment, and required human resources. Private clinics and private hospitals will also be included in the delivery of standard of diabetes care according to the level of healthcare. Basic health staff and medical doctors from township medical hospital, station medical hospital and private clinics will be strengthened their capacities to deliver the standard of care to diabetes patients. Guidelines for proper referral for appropriate care for the diabetes patients will also be included in the capacity building program. Each healthcare center including private clinic will be provided with a set of minimal data for monitoring and evaluation (Figure 2).

At the primary healthcare level, in rural health centers, work done by basic health staff will be supervised by Health Assistants who will in turn be under the supervision of designated medical officer from the township medical center. There are also private clinics which mainly deliver ambulatory care to the community. TMO will overall supervise the activities and monitor the progress of all healthcare centers including private clinics in the township.

Physician of the district hospital will supervise the activities of diabetes care service in the hospital and District Medical Officer will supervise the activities of the delivery of diabetes care in the private clinics in the district.

At the tertiary healthcare level, diabetologists or the senior consultant physicians of the hospital will supervise the activities of diabetes care of the hospitals and public health officers of the States and Region health Office will supervise the activities diabetes care of the private sectors.

Function of diabetes care centers

Each healthcare center delivering standard of diabetes care will perform the specified functions according to the level of healthcare (Table 2). Management of diabetes and cardiovascular risk factors will be performed according to the set protocol for the primary care (Appendix 2).[18] At each level of care, health education and counseling on healthy behavior (healthy diet, physical activity, cessation of consumption of tobacco and avoidance of harmful use of alcohol) will be given to all persons attending the health center according to the set protocol (Appendix 3).[18]

Each level of care will be provided with lists of essential drugs and equipment (Table 3) and required health personnels (Table 4).

Implementation

Funding

Implementation of the diabetes care model will be in different phases according to the availability of the funding which will be mainly from the government healthcare budget. Resource mobilization will be undertaken from local and international philanthropic organizations and international civic organizations and developmental partners. Since the change in political system to democratic government in 2011 the health expenditure has been increased to 2.4% of GDP, which is still the lowest among the member states in the WHO South East Asia Region. It is expected that with the landslide victory of the National League for Democracy in the recent general election, new government is very likely to reform the health system to meet the needs of the country and people expectation, there will be positive change in the health expenditure and in the implementation for the Universal Health Coverage, and hence, the funding and implementation of diabetes care model will be made feasible through these changes.

Community mobilization

Prior to the implementation at each primary healthcare level, advocacy on the healthy lifestyles, health and socioeconomic burden of diabetes and other major non-communicable diseases, prevention and control of non-communicable diseases including diabetes, and services

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.16

Table 2. Functions of diabetes care according to the healthcare level

Level of Healthcare	Functions

Primary Healthcare Level	• **Rural Health Center**
	  • Health promotion: General Health Education and awareness of Healthy Lifestyle (Diet, Physical Activities, Tobacco consumption and Alcohol consumption)
	  • Screening for diabetes in high risk persons
	  • Glycemic management
	  • Cardiovascular Risk Factor Management (Management of Hypertension and Hypercholesterolemia, Weight Management, Tobacco cessation)
	  • Diabetes foot (Health education, Wound care)
	• **Township level**
	  • above all + basic cardiovascular disease screening (ECG, Lipid Profile, Urea and Creatinine, eGFR)
	  • in- patient management of acute complications of diabetes

Secondary Healthcare Level	• Above all Plus • Screening for Diabetes Retinopathy and treatment • Screening for Neuropathy and treatment • Screening for Nephropathy and treatment • Screening for cardiovascular diseases and treatment • Diabetes foot (Wound care, Surgery)
Tertiary Healthcare Level	• Above all Plus • Screening for cardiovascular diseases and treatment (Coronary angiogram, Insertion of cardiac stent and CABG) • Screening for retinopathy and treatment(laser therapy) • Screening for Nephropathy and treatment (Renal replacement therapy) • Screening for Neuropathy and treatment • Amputation and Prosthesis

available at each health center for standard of diabetes care, will be conducted to the local administrative authorities, community leaders and local non-governmental organizations. The purpose of the advocacy is to mobilize the community to participate in the prevention and control of diabetes and other non-communicable diseases. Previous experience with the pilot project on the PEN implementation, it was proved that the community mobilization to motivate the public to participate in the activities of the project is feasible. Health seeking behavior of the public can be changed to facilitate the screening for the high risk persons for diabetes and cardiovascular diseases and so is the feasibility of the community participation in the adoption of healthy lifestyles, in particular, increased mass physical activity and raising of local fund for the sustenance of the activities through local donations by generous and philanthropic persons in the localities.

Table 3. Essential drugs and equipment of diabetes care according to the healthcare level

Level of Healthcare	Essential drugs and equipment
Primary Healthcare Level	**Drugs** • Metformin • Gliclazide • Insulin • Hydrochlothiazide • Amlodipine • Atenolol • Atorvastatin • Isosorbide dinitrate • Glyceryl trinitrate • Furosemide • Spironolactone • Aspirin • Equipment • Thermometer • Stethoscope • Blood pressure measurement device* • Measurement tape • Weighing machine • Glucometer • Blood glucose test strips • Lancets and needles • Urine protein test strips • Urine ketones test strips • Electrocardiograph
Secondary Healthcare Level	• Pulse oximeter • Lipid profile assay • Serum creatinine assay • Troponin test strips • Urine microalbuminuria test strips • Tuning fork • Defibrillator
Tertiary Healthcare Level	• Advanced technologies for specialist • Laser therapy • Haemodialysis • Continuous Ambulatory Peritoneal dialysis • Neck Lines • Angiogram • Doppler Ultrasound

Development of IEC materials

It is also necessary to develop the advocacy tool kits for stakeholders, and also information, education and communication (IEC) materials for health education diabetes care for the public. With the widespread

Table 4. Required health personnel for diabetes care according to the healthcare level

Level of Healthcare	Functions
Primary Healthcare Level	• Midwife • Health Assistant • Medical Officer
Secondary Healthcare Level	• Above all PLUS • Specialist (Medicine, Surgery, OG and Pediatrician) • Diabetes educator
Tertiary Healthcare Level	• Above all PLUS • Endocrinologists • Orthopaedic and Vascular surgeons • Diabetes Specialist Nurse • Nutritionist • Podiatrist • Physical Activity instructor • Occupational therapist

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dissemination of information on the diabetes care model and availability of these services at the local RHC and Sub-RHC and township hospitals public can be informed as well as motivated to participate in the project activities and utilize the health services in their local health centers.

Development of guidelines

It is also important to develop guidelines for the delivery of standard diabetes care at different healthcare levels. Guidelines for the BHS and medical officers will be developed differently and these guidelines can be used as manuals for them in daily implementation of the activities of the diabetes care model. A registry with minimal essential data for evaluation, monitoring and reporting is also necessary to be developed.

Capacity building of Health Work Force

It is mandatory to build the capacity of basic health staff from the primary healthcare levels and medical doctors from the private clinic on the standard of diabetes care and proper referral according to the guidelines developed for the diabetes care model. Capacity building workshops for township medical officers will be conducted as training of trainers for each township. TMO will conduct multiplier workshops for the BHS and medical officers from both public and private sectors in their townships. Junior physicians from the district and State and Regional hospitals will also need to strengthen their capacity on delivery of standard of diabetes care.

Monitoring and evaluation

Regular monitoring and evaluation of the progress in each township will be done and findings will also be utilized for further advocacy to the stakeholders to strengthen their sustained collaboration and cooperation in the delivery of diabetes care. The NCD Unit of the Department of Health will collect regular reports and returns from States and Region Health Offices to monitor the progress achieved in the whole country.

CONCLUSION

Since diabetes is one of the major non-communicable diseases with shared common risk factors, implementation of the MMDCM should be carried out in aligned with the national action plan for the prevention and control of other non-communicable diseases, which is already endorsed by the National Health Committee Chaired by the Vice President of Republic of the Union of Myanmar.

The Myanmar Diabetes Care Model aims to reduce the inequity in the delivery of diabetes care in urban and rural population. Ultimately it is aimed to lessen the health and socioeconomic burden of diabetes in Myanmar. Achievement of its goal will certainly contribute to the poverty alleviation and national development of the country. Collaboration and cooperation of all stakeholders involved in the diabetes care is the key for success. Although Ministry of Health will be the focal for the implementation, collaboration of other sectors and partners like academia, civic societies and community is obviously necessary for the successful implementation.

Successful implementation of the care model will certainly facilitate Myanmar to achieve diabetes related targets and indicators set in the Global Action Plan for the Prevention and Control of non-communicable diseases (2013-2020). It is also expected that reduction in the burden caused by diabetes and other major NCD will eventually contribute to the national development of Myanmar.

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Appendices

Appendix 1: Voluntary Global Targets [6]

1. A 25% relative reduction in risk of premature mortality from cardiovascular diseases, cancer, diabetes, or chronic respiratory diseases.
2. At least 10% relative reduction in the harmful use of alcohol, as appropriate, within the national context.
3. A 10% relative reduction in prevalence of insufficient physical activity.
4. A 30% relative reduction in mean population intake of salt/sodium.
5. A 30% relative reduction in prevalence of current tobacco use in persons aged 15+ years.
6. A 25% relative reduction in the prevalence of raised blood pressure or contain the prevalence of raised blood pressure, according to national circumstances.
7. Halt the rise in diabetes and obesity.
8. At least 50% of eligible people receive drug therapy and counselling (including glycaemic control) to prevent heart attacks and strokes.
9. An 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major noncommunicable diseases in both public and private facilities.

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.16

Appendix 2: Protocol for the management of diabetes and cardiovascular risk factors at primary care [18]

When could this Protocol be used?

- **The protocol is for assessment and management of cardiovascular risk using hypertension, diabetes mellitus (DM) and tobacco use as entry points**
- **It could be used for routine management of hypertension and DM and for screening, targeting the following categories of people:**
  - **age > 40 years**
  - **smokers**
  - **waist circumference (≥ 90 cm in women ≥100 cm in men)**
  - **known hypertension**
  - **known DM**
  - **history of premature CVD in first degree relatives**
  - **history of DM or kidney disease in first degree relatives**

Follow instructions given in Action 1 to Action 4, step by step

FIRST VISIT

Action 1. Ask about:

- Diagnosed heart disease, stroke, TIA, DM, kidney disease
- Angina, breathlessness on exertion and lying flat, numbness or weakness of limbs, loss of weight, increased thirst, polyuria, puffiness of face, swelling of feet, passing blood in urine etc.
- Medicines that the patient is taking
- Current tobacco use (yes/no) (answer yes if tobacco use during the last 12 months)
- Alcohol consumption (yes/no) (if `Yes`, frequency and amount)
- Occupation (sedentary or active)
- Engaged in more than 30 minutes of physical activity at least 5 days a week (yes/no)
- Family history of premature heart disease or stroke in first degree relatives

Action 2. Assess (physical exam and blood and urine tests):

- Waist circumference
- Measure blood pressure, look for pitting oedema
- Palpate apex beat for heaving and displacement
- Auscultate heart (rhythm and murmurs)
- Auscultate lungs (bilateral basal crepitations)
- Examine abdomen (tender liver)
- In DM patients examine feet; sensations, pulses, and ulcers
- Urine ketones (in newly diagnosed DM) and protein
- Total cholesterol
- Fasting or random blood sugar (diabetes= fasting blood sugar ≥7 mmol/l (126 mg/dl)) or random blood sugar ≥11.i mmol/l (200 mg/dl))

(Point of care devices can be used for testing blood sugar if laboratory facilities are not available)

Action 3. Estimate cardiovascular risk (in those not referred):

- Use the WHO/ISH risk charts relevant to the WHO sub region (Appendix 4)
- Use age, gender, smoking status, systolic blood pressure, DM (and plasma cholesterol if available)
- If age 50-59 years select age group box 50, if 60-69 years select age group box 60 etc., for people age <40 years select age group box 40
- If cholesterol assay cannot be done use the mean cholesterol level of the population or a value of 5.2 mmol/l to calculate the cardiovascular risk)
- If the person is already on treatment, use pretreatment levels of risk factors (if information is available to assess and record the pretreatment risk. Also assess the current risk using current levels of risk factors)
- Risk charts underestimate the risk in those with family history of premature vascular disease, obesity, raised triglyceride levels

FIRST VISIT

Action 4: Referral criteria for all visits

- BP >200/>120 mm Hg (urgent referral)
- BP ≥140 or ≥ 90 mmHg in people < 40 years (to exclude secondary hypertension)
- Known heart disease, stroke, transient ischemic attack, DM, kidney disease (for assessment, if this has not been done)
- New chest pain or change in severity of angina or symptoms of transient ischemic attack or stroke
- Target organ damage (e.g. angina, claudication, heaving apex, cardiac failure)
- Cardiac murmurs
- Raised BP ≥140/90 (in DM above 130/80 mmHg) while on treatment with 2 or 3 agents
- Any proteinuria
- Newly diagnosed DM with urine ketones 2+ or in lean persons of <30 years
- Total cholesterol >8 mmol/l
- DM with poor control despite maximal metformin with or without sulphonylurea
- DM with severe infection and/or foot ulcers
- DM with recent deterioration of vision or no eye exam in 2 years
- High cardiovascular risk

If referral criteria are not present go to Action 5

FIRST VISIT

Action 5. Counsel all and treat as shown below

Risk < 20%	• Counsel on diet, physical activity, smoking cessation and avoiding harmful use of alcohol • If risk < 10% follow up in 12 months • If risk 10 - < 20% follow up every 3 months until targets are met, then 6-9 months thereafter	**Additional actions for individuals with DM:** • Give an antihypertensive for those with BP ≥ 130/80 mmHg • Give a statin to all with type 2 DM aged ≥ 40 years • Give Metformin for type 2 DM if not controlled by diet only (FBS>7mmol/l), and if there is no renal insufficiency, liver disease or hypoxia. • Titrate metformin to target glucose value • Give a sulfonylurea to patients who have contraindications to metformin or if metformin does notimproveglycaemic control. • Give advice on foot hygiene, nail cutting, treatment of calluses, appropriate footwear and assess feet at risk of ulcers using simple methods (inspection,pin-prick sensation) • Angiotensin converting enzyme inhibitors and/or low-dose thiazides are recommended as first-line treatment of hypertension. Beta blockers are not recommended for initial management but can be used if thiazides or angiotensin converting enzyme inhibitors are contraindicated. • Follow up every
Risk 20 to 30%	• Counsel on diet, physical activity, smoking cessation and avoiding harmful use of alcohol • Persistent BP ≥ 140/90 mm Hg consider drugs (see below ** Antihypertensive medications) • Follow-up every 3-6 months	
Risk >30%	• Counsel on diet, physical activity, smoking cessation and avoiding harmful use of alcohol • Persistent BP ≥ 130/80 consider drugs (see below ** Antihypertensive medications) • Give a statin • Follow-up every 3 months, if there is no reduction in cardiovascular risk after six months of follow up refer to next level	
	Consider drug treatment for following Categories • All patients with established DM and cardiovascular disease (coronary heart disease, myocardial infarction, transient ischaemic attacks, cerebrovascular disease or peripheral vascular disease), renal disease. If stable, should continue the treatment already prescribed and be considered as with risk >30% • People with albuminuria, retinopathy, left ventricular hypertrophy • All individuals with persistent raised BP ≥ 160/100 mmHg; antihypertensive treatment • All individuals with total cholesterol at or above 8 mmol/l (320 mg/dl); lifestyle advice and statins	
	** Antihypertensive medications • If under 55 years low dose of a thiazide diuretic and/or angiotensin converting enzyme inhibitor • If over 55 years calcium channel blocker and/or low dose of a thiazide diuretic • If intolerant to angiotensin converting enzyme inhibitor or for women in child bearing age consider a beta blocker • Thiazide diuretics and/or long-acting calcium channel blockers are more appropriate as initial treatment for certain ethnic groups. Medications for compelling indications should be prescribed, regardless of race/ ethnicity • Test serum creatinine and potassium before prescribing an angiotensin converting enzyme inhibitor	

Advice to patients and family

- Avoid table salt and reduce salty foods such as pickles, salty fish, fast food, processed food, canned food and stock cubes
- Have your blood glucose level, blood pressure and urine checked regularly

Advice specific for DM

- Advise overweight patients to reduce weight by reducing their food intake.
- Advise all patients to give preference to low glycaemic-index foods (e.g.beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet)
- If you are on any DM medication that may cause your blood glucose to go down too low carry sugar or sweets with you
- If you have DM, eyes should be screened for eye disease (diabetic retinopathy) by an ophthalmologist at the time of diagnosis and every two years thereafter, or as recommended by the ophthalmologist
- Avoid walking barefoot or without socks
- Wash feet in lukewarm water and dry well especially between the toes
- Do not cut calluses or corns, and do not use chemical agents on them
- Look at your feet every day and if you see a problem or an injury, go to your health worker

SECOND VISIT

Repeat

- Ask about: new symptoms, adherence to advise on tobacco and alcohol use, physical activity, healthy diet, medications etc.
- Action 2 Assess (Physical exam)
- Action 3 Estimate cardiovascular risk
- Action 4 Refer if necessary
- Action 5 Counsel all and treat as shown in protocol

Appendix 3: Protocol for Health Education and Counseling on Healthy Behaviours [18]

Educate your patient to

- Take regular physical activity
- Eat a "heart healthy" diet
- Stop tobacco and avoid harmful use of alcohol
- Attend regular medical follow-up

Take regular physical activity

- Progressively increase physical activity to moderate levels (such as brisk walking); at least 150 minutes per week
- Control body weight and avoid overweight by reducing high calorie food and taking adequate physical activity

Eat a heart healthy diet

Salt (sodium chloride)

- Restrict to less than 5 grams (1 teaspoon) per day
- Reduce salt when cooking, limit processed and fast foods

Fruits and vegetables

- 5 servings (400-500 grams) of fruits and vegetable per day
- 1 serving is equivalent to 1 orange, apple, mango, banana or 3 tablespoons of cooked vegetables

Fatty food

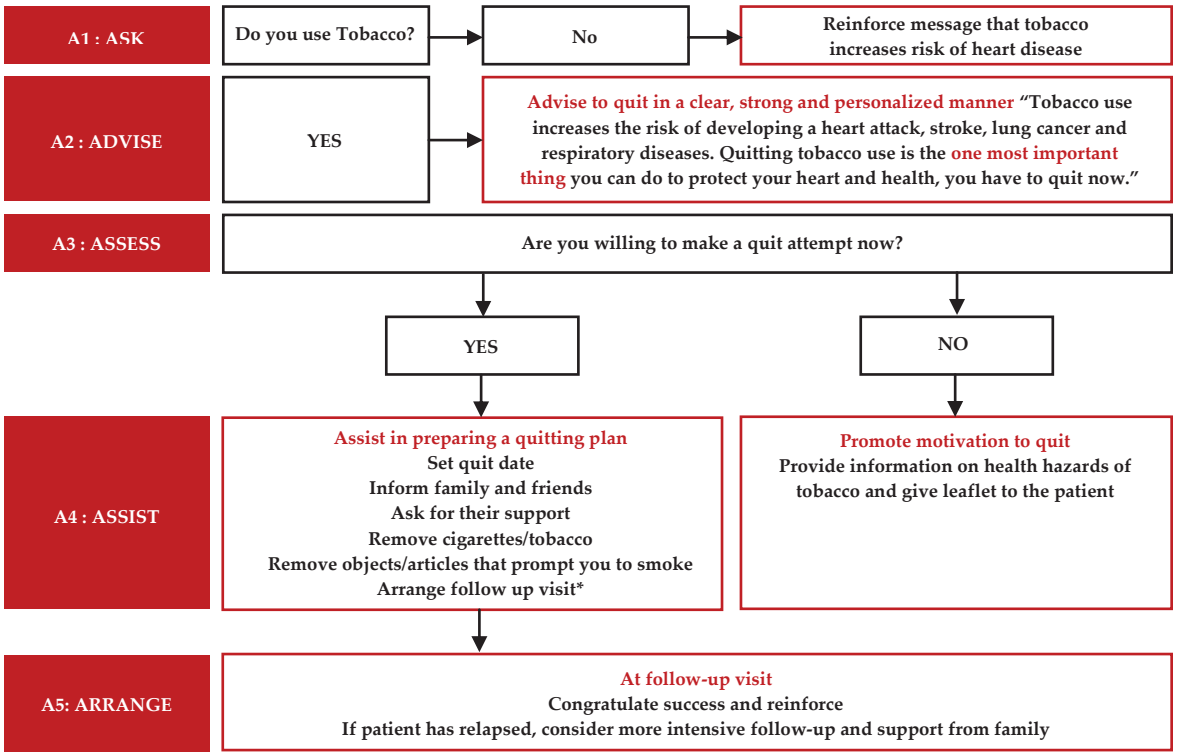
- Limit fatty meat, dairy fat and cooking oil (less than two tablespoons per day)
- Replace palm and coconut oil with olive, soya, corn, rapeseed or safflower oil
- Replace other meat with chicken (without skin)

Stop Tobacco and avoid harmful use of Alcohol:

- Encourage all non-smokers not to start smoking
- Strongly advise all smokers to stop smoking and support them in their efforts
- Individuals who use other forms of tobacco should be advised to quit
- Alcohol abstinence should be reinforced.
- People should not be advised to start taking alcohol for health reasons
- Advise patients not to use alcohol when additional risks are present, such as:
  - driving or operating machinery
  - pregnant or breast feeding
  - taking medications that interact with alcohol
  - having medical conditions made worse by alcohol
  - having difficulties in controlling drinking

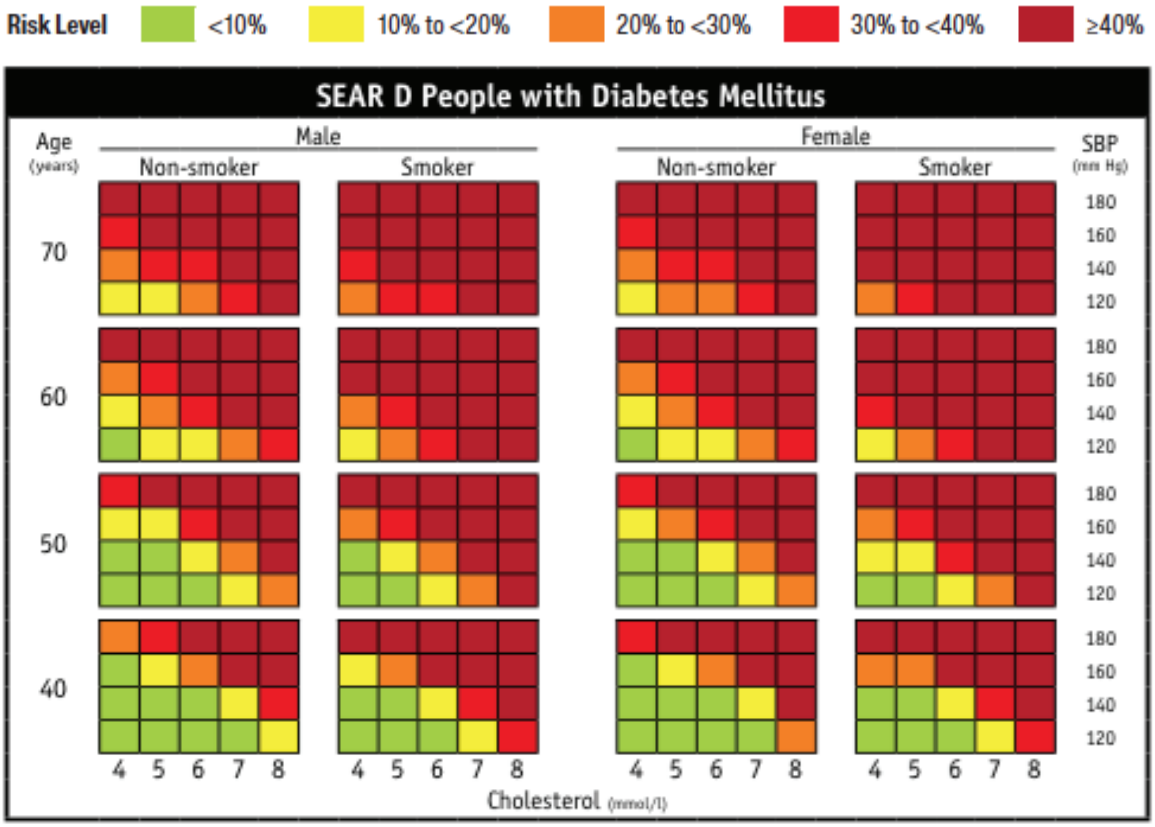
Adherence to treatment

- If the patient is prescribed a medicine/s:
  - teach the patient how to take it at home:
  - explain the difference between medicines for long- term control (e.g. blood pressure) and medicines for quick relief (e.g. for wheezing)
  - tell the patient the reason for prescribing the medicine/s
- Show the patient the appropriate dose
- Explain how many times a day to take themedicine
- Label and package the tablets
- Check the patient's understanding before the patient leaves the health centre
- Explain the importance of:
  - keeping an adequate supply of the medications
  - the need to take the medicines regularly
  - as advised even if there are no symptoms

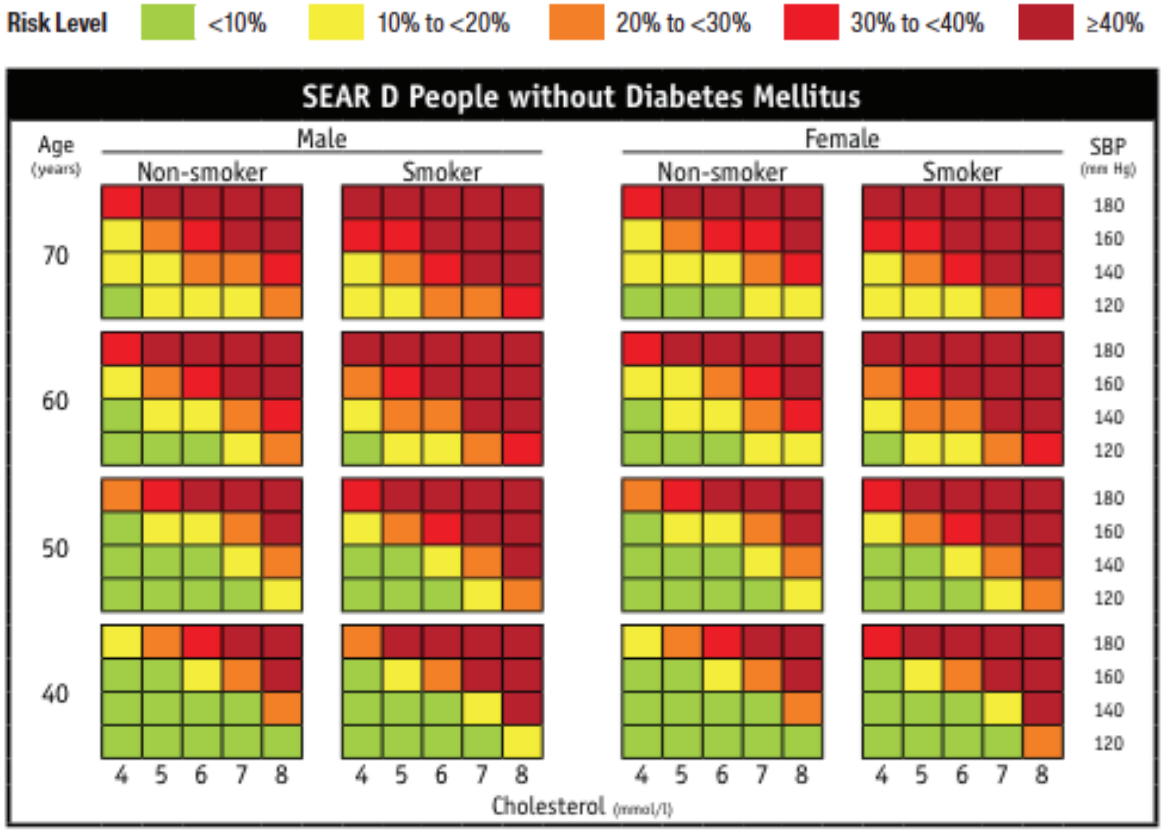


Source: World Health Organization Implementation tools, Package of Essential Noncommunicable (PEN) disease interventions for primary healthcare in low-resource settings

Appendix 4-a: WHO/ISH risk prediction chart. 10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence of diabetes mellitus [18]



Appendix 4-b: WHO/ISH risk prediction chart. 10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and absence of diabetes mellitus [18]



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FEATURE ARTICLE

Diabetes Care in the Philippines

Elizabeth Paz-Pacheco and Cecilia Jimeno

Philippine Society of Endocrinology, Diabetes and Metabolism

Abstract

The global burden of diabetes and its accompanying risk factors is upon us. Asia is the focus of this burden, owing to huge population numbers and increasing prevalence rates. The Philippines National Health and Nutrition Survey (NNHeS) of 2013, has provided the latest health and disease score with prevalence rates of the major risk factors among adults ≥20 years of age: diabetes (5.4%), hypertension (22.3%), dyslipidemia, low HDL (71.3%), obesity, BMI >25 kg/m^2 (31.1%), and smoking (25.4%). Metabolic syndrome as of the 2008 survey reports a 27% prevalence rate (unpublished data). Efforts have to be directed to achieve improvement in prevention, survival, and quality of life for all diabetics. The health infrastructure under the leadership of the Department of Health, in partnership with governmental and non-governmental organizations has to provide a cohesive plan engaging all partners in various aspects of care. Strategies to enhance outcomes include: 1) a national screening program, 2) implementation of practice guidelines that will elevate the quality of care for all, 3) access to healthcare, medications, 4) development of an environment for research in institutions to allow a better understanding of these conditions among Filipino patients and 5) enhancement of training, education and service to benefit the Filipino diabetic. Indeed, the challenge is upon all of us as a nation, and we need to stand up and move forward with an organized and accessible system of care, as we aim to combat the epidemic of diabetes and its complications.

Key words: diabetes care, chronic care model

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic disease characterized by hyperglycemia brought about by defects in insulin secretion (beta cell dysfunction) and insulin action (insulin resistance). Diabetes is the leading cause of devastating complications such as cardiovascular events, strokes, end stage renal disease, blindness and lower extremity amputation.[1] The global burden of diabetes with its accompanying risk factors and complications, is upon us.[2] Asia is the focus of this burden, owing to huge population numbers and increasing prevalence rates.[3] The Philippines is an archipelago consisting of 7,100 islands. As of 2015, the projected population is 102,965,300.[4] The challenges presented to us relate with increased Westernization of diets and decrease in physical activity, leading to obesity. Lifestyles of majority of Filipinos revolve around food. Celebrations and gatherings put emphasis on a bountiful table of food. Physical activity generally consists mostly of house work for the women and a few meters of walk and work-related activities as form of usual exercise for working men and women. Sadly in the Philippines, while under-nutrition continues to be a major health problem, obesity is an emerging concern.[5]

Burden of Disease and Etiology

The latest Philippines' National Health and Nutrition Survey (NNHeS) 2013[6] as compared to 2008[7] has provided the health and disease score with identification of the major risk factors among adults ≥20 years of age, respectively: diabetes (5.4%, 6% using OGTT); hypertension (22.3%, 24.6%); dyslipidemia, low HDL (71.3%, 72%); obesity, BMI >25kg/m^2 (31.1%, WHR of 0.85 in females 65.6%); smoking (25.4%, 31%) and metabolic syndrome, IDF Harmonized Criteria, Alberti et al, 2009 (27% in 2008, unpublished data). The trends are steady for most except for smoking. This reduction in smoking habits may be attributed to the legislative measure, the Sin Tax bill, which has recently been passed.[8]

With regards to gestational diabetes (GDM), the reported prevalence of gestational diabetes was 14% among 1203 pregnant women using the AFES Study Group on Diabetes in Pregnancy (ASGODIP) criteria.[9] Uniformly across various hospital and clinic settings, follow up after gestational diabetes for re-classification using OGTT post-partum is low. Limited data from a private university hospital among 124 women with previous GDM revealed

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that the prevalence of diabetes and pre-diabetes 6-12 weeks post-partum is 7.3% and 34.7%.[10] Although there has been no study on the financial cost of the diagnosis of GDM to the Filipino family, this is probably significant given that gestational DM increases the risk of primary CS (OR=1.79, 95% CI: 1.02-3.16, *p*=0.041) and infant admission to the Neonatal ICU (OR=2.66, 95% CI: 1.3 -5.44), *p*=0.007). A trend for higher risk of LGA, pre-eclampsia, preterm delivery and congenital anomalies was observed in those with GDM, was also found but these did not reach statistical significance.[11] The local guideline advocates routine screening of all pregnant women for GDM using 75-gm OGTT, as well as follow up after delivery to determine glycemic status.

What characterizes diabetes among Asians, among Filipinos?

Data from our region shows emerging data describing an Asian phenotype, somewhat different from our Caucasian counterparts.[12] Asian populations have differing demographic and socio-cultural characteristics in the setting of a genetic susceptibility impacting the development of diabetes. In Asia, India and China will account for the highest numbers (79.4 M and 42.3 M, respectively) by 2030, but South East Asia will have the highest rates worldwide. This increase will affect developing countries substantially as these countries including the Philippines, often have limited resources to cope with the disease. T2DM is seen to develop at a younger age, usually a decade earlier than Caucasians; young onset diabetes is increasing at alarming rates. As diabetes starts early in life, this brings with it an associated increase in morbidity and mortality and a lifetime risk of cardiovascular disease. This was clearly shown in the CANDI Manila study where newly diagnosed adult T2DM patients (mean age of 50 years) showed high prevalence of diabetic complications and cardiovascular risk factors, at the apparent onset of their DM diagnosis. Electrocardiographic findings demonstrating myocardial infarcts and ischemic changes were seen in 5% of study participants, 42% had proteinuria by urinalysis and 12% had retinopathy. Hypertension was present in 42% of individuals (mean BP of 144/88 mm Hg), and dyslipidemia was predominant (80% with LDL $\geq$100 mg/dL, with another 38% with elevated triglyceride $\geq$150 mg/dL).[13]

Characteristics are heterogeneous with high rates of clustering of cardiovascular risk factors. Indeed, metabolic syndrome is manifesting even at a young age. Young onset diabetes in children is common. Both thrifty genotype and phenotype may occur in Asian groups. Several distinctive features are apparent in the pathogenetic factors, ranging from epigenetics, such as maternal imprinting, genetic susceptibility markers to unhealthy lifestyle changes leading to high rates of obesity.[14]

What drives the continued increase in these major risk factors?

Diabetes among Filipinos is not exclusively mediated by obesity per se, as increased rates are seen in relatively lower BMI, as compared to Caucasians. Philippine data show that despite an obesity prevalence that is less than 10%, visceral adiposity as measured by waist-to-hip ratio is 65.6% in females.[7] Clearly, the risk is driven by visceral adiposity. Data from Araneta et al revealed excess visceral adipose tissue accumulation[15] with low adiponectin levels among Filipino-Americans in San Diego, California, USA.[16] The low adiponectin levels were likewise demonstrated among diabetics, as compared with non-diabetic controls from the population based study in the Philippines (NNHeS 2008).[17] In the same survey, lipid profiles among Filipinos revealed a remarkably low HDL, comprising 70% of the population, a consistent finding from surveys as early as 1998.[7]

Despite early studies on genetics of T2DM and its complications[18-20] among Filipinos, there is a need to more comprehensively elucidate this relationship. Relevant questions on distinctive lifestyles, food choices and other preferences have to be clearly understood to form the framework for prevention strategies. The geography of the country led to regions separated by bodies of water, and has created regional preferences and lifestyles. These refer to food preferences for choices that are abundant in the region, as well as activities that are part of the daily chores.

Goals of long-term care for diabetes, a chronic disease

The bottom line is improved survival rates and quality of life for all Filipino diabetics. Chronic care models from various developed countries[21] have demonstrated benefits in reduction of outcomes through an organized system of care.

Prevention is the best investment, as it limits diabetes rates and complications that eventually take its toll on the financial status of families. Diabetic breadwinners have reduced work opportunities and earning capacities. Complicated diabetes is an expensive disease, worsened by lack of government funding support or subsidy for medications, hospitalization and other services. Concurrent coordinated efforts should be directed towards early detection through aggressive nationwide screening and diagnosis of diabetes, obesity and the components of the metabolic syndrome. To date, there is no national screening program for non-communicable disease (NCD) in the Philippines. Efforts by various groups include random screening activities conducted by several health facilities, employers, religious groups and medical organizations. Obesity prevention should begin with children, as this alarming increase in rates will translate to adult diabetes.

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.17

Comprehensive and optimal treatment requires strategies that will allow multi-factor risk control involving hyperglycemia, dyslipidemia, hypertension, weight and smoking cessation. After an initial control, sustainability is an essential goal, that is, to effectively maintain risk control, to reduce complications and outcomes and improve survival and quality of life of all affected individuals.

DiabCare Philippines 2008, a survey on glycemic control among diabetic patients seen by both general practitioners and diabetes specialists showed that less than 20% have good glycemic control (HbA1C of >7%). Mean duration of diabetes was 10 years with the age of onset of DM in the early 50's. Mean BMI was between 24.7- 25.7 kg/m^2. About 10% had some form of nephropathy (6-7% with serum creatinine values greater than 2 mg/dL) and more than 40% of patients already had neuropathy.[22] Future surveys with more strict selection to represent the national average should be conducted to chronicle and plan for the burden of diabetes and its complications on families, the healthcare system, and the economy.

The Infrastructure for Healthcare Delivery in the Philippines

The national healthcare system of the Philippines consists of a three-tiered system similar to other countries. Until 1991, all levels of healthcare delivery from primary to tertiary were under the direct control of the central government through the Department of Health (DOH). Following the implementation of the Local Government Code of 1992, the Philippine government devolved or delegated the management and delivery of health services from the national DOH to the local government units (LGU's). There are currently six "facility levels" managed by different political and administrative units that include: barangay health units (managed by barangay and municipal governments); rural health units (managed by municipal governments); city health offices (managed by city governments); municipal or "district" hospitals (managed by the provincial government); provincial hospitals (managed by the provincial government); and regional hospitals and medical center levels (managed by the DOH). Following the District Health System (DHS) model of the World Health Organization (WHO), facility levels 1-3 correspond to the primary level of care, facility 4 to the secondary level of care and facilities 5-6 to the tertiary level of care.[23] In this decentralized set-up, the DOH serves as the governing agency, and both LGUs and the private sector provide services to communities and individuals. The DOH is mandated to provide national policy direction and develop national plans, technical standards and guidelines on health. The LGUs have autonomy and responsibility for their own health services, but are to receive guidance from the DOH through its regional centers for health and development (CHDs).

In the current system, provincial governments are primarily mandated to provide hospital care through provincial and district hospitals, and to coordinate health service delivery provided by cities and municipalities of the provinces. City and municipal governments are charged with providing primary care including maternal and child care, nutrition services and direct service functions through public health and primary healthcare centers called the city health offices or (municipal) rural health units (RHUs).[24] These city and municipal health centers are linked to the smallest unit of the health delivery that are the peripheral barangay health centers or stations (BHS).

A major share of the national expenditures on health, approximately 60%, goes to a large private sector that also employs over 70% of all health professionals in the country. The private sector consists of for-profit and non-profit providers, which are largely market-oriented. Healthcare is paid through user or professional fees at the point of service, or subsidized by official aid agencies or philanthropy. This sector provides services to an estimated 30% of the population who can mostly afford to pay these fees out of pocket. Although the private health sector is regulated by the DOH and the national health insurance system called the Philippine Health Insurance Corporation, health information generated by private providers is generally absent in the information system of the DOH.[24] Organizational structure and accountability in the Philippine healthcare system is shown in Figure 1.

Health Program for Diabetes in the Philippines

A National Diabetes Prevention and Control Plan has been drafted by the Philippine DOH since the late 1990's, in order to curb the mortality and morbidity from this chronic disease. The management of diabetes subsequently became part of the Integrated Community-Based Noncommunicable Disease (NCD) Prevention and Control Project which were rolled out in the various cities and municipalities of the Philippines. This included the "Healthy Lifestyle (HL)" campaign to increase awareness and consciousness regarding diet, exercise and healthy lifestyles such as smoking cessation.

Other aspects of the integrated NCD program were the development and conduct of training modules for healthcare workers. There is now systemic change through legislation which includes the "Clean Air Act" which prohibits smoking in public buildings, or enclosed public spaces including public vehicles. The country has its own Food Pyramid Guide to curb overweight and obesity among Filipinos, and in 2014, the Food and Nutrition Institute also launched the *"Pinggang Pinoy"* or the Filipino Plate which is similar to the MyPlate concept of the US Department of Agriculture. It uses a locally adapted way to show Filipinos what a healthy balanced diet should look like, complimenting the food pyramid.

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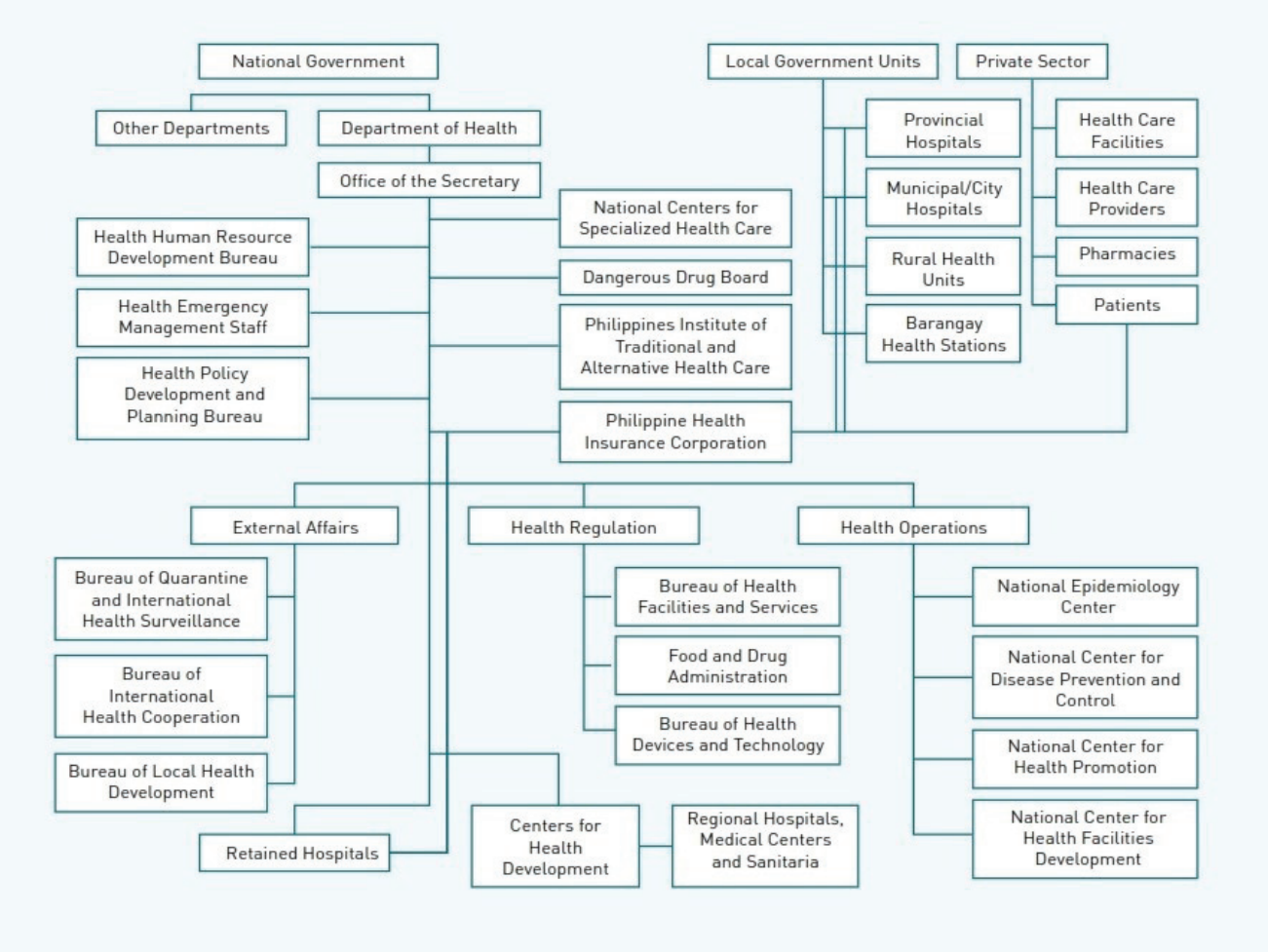

Figure 1. Organizational structure and accountability in the Philippine healthcare system.[24]

Other programs of the DOH include the provision of low cost medications (metformin and sulfonylureas) to the CHO's and RHU's for distribution to indigent diabetic individuals, together with statins and some anti-hypertensives. Access to insulin of indigent patients is also now being expanded through the Insulin (Medicine) Access Program which is active in select DOH-retained hospitals.

Comprehensive strategies to curb the epidemic of diabetes and obesity

The prescription for lifestyle modification is complex. "Reduce intake and increase physical activity" is easier said than done. Proper food choices are a daily challenge for the diabetic and the pre-diabetic, as fast food choices at cheaper prices abound. Fish, fruits and vegetables are not readily available and are often beyond the budgets of ordinary working individuals. Advertising has enticed many to prefer high fat delectable choices. Simple walking as exercise is not readily doable in a busy metropolis where sidewalks have been converted to vending stalls. Gyms and the like with structured exercise programs with equipment are costly and not within reach by many. Proposed strategies include use of designated walking and cycling only streets, walking paths (indoor track) in office buildings, malls; designated exercise rooms and half basketball court at office buildings for lunchtime and end of day exercise classes; keeping the stairways clean and well-lit and encourage exercise breaks. Government has to invest in efficient mass transit systems to reduce traffic and reduce commute (and sitting times) and provide incentives to workers/teams who reach exercise goals.

Education is key to success. As Elliott P. Joslin, an American pioneer on diabetes stated, "The diabetic who knows the most, lives the longest."[25] Regardless of educational attainment, patients at risk for diabetes and the diabetics themselves require an adequate understanding of this condition, the chronicity of care and control and the discipline expected of them to maintain optimal control. Behavioral modification is essential; tailor-fit strategies have to be employed to direct the diabetic to improved lifestyles. For the Filipino, it is a "family affair." Food choices and activity schedules are led by family members; in this matriarchal society often determined by the mother.

Diabetes self-managed education (DSME) is a strategy that has been shown to reduce hyperglycemia and improve outcomes. A pilot study done in San Juan Batangas, an agricultural rural community south of Manila, utilized

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locally modified educational materials and tapped support from peers and *barangay* health workers (BHW) as health educators. This study has shown that health education delivered by peer diabetic educators is effective in achieving important health outcomes for diabetics in the rural setting. Diabetics in the DSME group consistently had better blood sugar control (improved HbA1C levels and greater proportion of diabetics achieving HbA1c ≤7.0%. compared to the standard care group for up to the 6th month). More diabetics now perform foot examination after they have been taught on its importance. There are no consistent significant differences in the other anthropometric, biochemical and other health behavior outcomes in the short-term.[26-27]

Country specific clinical practice guidelines incorporating cost-effective care, appropriate use of oral hypoglycemic agents, insulin and other medications for multiple risk factor control should be widely disseminated. There is a need for partnership with various governmental and non-governmental agencies under the leadership of the DOH to deliver best practices with best use of meager resources to cover a greater number of the diabetic population.[28]

Service for diabetics should also be integrated within in-hospital settings, as costly hospitalization is often not affordable to many. There has to be optimal in-hospital protocols for admitted patients, including insulin administration and patient education.[29-30]

Research is a tool that allows proper understanding of a condition for a specific population. For years, comprehensive epidemiological data in the Philippines was lacking. Practice guidelines and approaches are based on international, mostly American and European data. Our treatment options, drug doses and algorithms are derived from recommendations that are based on predominantly Caucasian populations; that differ greatly in genetic susceptibility, drug responses, as well as variable behaviors and preferences as it relate to nutritional and physical activity prescriptions. With successful collaboration of government with technical input from specialty organizations, there are now data from which Philippine health policy may be derived. The National Nutrition and Health Survey is one such effort that incorporated subspecialty expertise into the mandated Food and Nutrition Research Institute (FNRI) survey for nutritional parameters every 5 years. As a result, a variety of research outputs have been completed and some more awaiting publication. In addition, investigators in other countries studying Filipino populations contribute the needed information. There is also increased research interest from various academic institutions in the Philippines. Research funding for non-communicable diseases has become more readily available, mostly coming from the Philippine Council for Health Research and Development of the Department of Science and Technology (PCHRD) and the DOH with smaller amounts received from other funding agencies such as medical organizations, the Philippine Society of Endocrinology, Diabetes and Metabolism, the Philippine Lipid and Atherosclerosis Society and others. Interest for research is increasing as awareness is seen among medical students and other trainees, initially as course requirement and hopefully, as a career path for many.

Telemedicine can be effective, given the high use of cellphones within the population. Smartphone use is however not as widespread, as cost is limiting. Physicians can network through internet facilities to link with specialists who can provide input to patient care, particularly in underserved areas. Social media through Facebook, Twitter and other platforms may be organized to provide education and links to various resources for a huge number of diabetics especially in remote areas.

It is essential to train others, by increasing subspecialty programs to provide key opinion positions in various regions of the communities. In this way, genuine subspecialty reach to communities may be realized, by providing links with grass-roots practitioners. It is envisioned that these links will provide the needed subspecialty inputs to difficult individual cases, as well as the over-all guidance in achieving improved outcomes in the barrios through feasible well organized programs.

CONCLUSIONS AND RECOMMENDATIONS

The epidemic is upon us. There is no room for complacency. National governmental health agencies should lead with contributions from subspecialist organizations to formulate comprehensive sustainable programs that will detect diabetes early, provide prevention programs, and assist every diabetic in maintaining health and quality of life. Truly we all have to put our act together with the overall aim of reducing the burden of diabetes and other risk factors for every Filipino.

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MANILA DECLARATION ON THE AVAILABILITY AND USE OF HEALTH RESEARCH INFORMATION IN AND FOR LOW- AND MIDDLE-INCOME COUNTRIES IN THE ASIA PACIFIC REGION

We, the participants in the Joint Meeting of the Asia Pacific Association of Medical Journal editors (APAME), the Index Medicus of the South East Asia Region (IMSEAR), and the Western Pacific Region Index Medicus (WPRIM) held in Manila from 24 to 26 August 2015, in conjunction with the COHRED Global Forum on Research and Innovation for Health held in Manila from 24-27 August 2015, drawing on the Pre-Forum Discussions on HIFA from 20 July to 24 August 2015 *"Meeting the information needs of researches and users of health research in low- and middle-income countries"* available at http://www.hifa2015.org/meeting-the-information-needs-of-researchers-and-users-of-health-research-2/ and the BMJ Blogs 20 July 2015 *"How can we improve the availability and use of health research in developing countries?"* available at http://blogs.bmj.com/bmj/2015/07/20/how-can-we-improve-the-availability-and-use-of-health-research-in-developing-countries/:

CONSIDERING

That the WHO Constitution "enshrines the highest attainable standard of health as a fundamental right of every human being," and that "the right to health includes access to timely, acceptable, and affordable healthcare of appropriate quality in tandem with "the underlying determinants of health," including "access to health-related education and information;"

That increasing the availability of quality health research information is fundamental to the successful attainment of global health and progressive realization of the right to health; and that all healthcare stakeholders (individuals, researchers, providers, professionals, leaders and policymakers) need seamless access to peer-reviewed research and information that are relevant to their respective contexts, and presented in a language they can understand;

That despite a growing momentum towards free and open access to research literature, and important initiatives, such as HINARI Access to Research In Health Programme and IRIS Institutional Repository for Information Sharing, that have helped to improve the availability of research in low- and middle-income countries, there continue to be many challenges, limitations and exclusions that prevent health research information from becoming freely and openly available to those who need it;

That the Global Health Library (GHL), Index Medicus of the South East Asia Region (IMSEAR), Western Pacific Region Index Medicus (WPRIM), and Asia Pacific Association of Medical Journal Editors (APAME) are important collaborative initiatives that can promote and uphold the availability and use of health research information especially in and for low- and middle-income countries in the Asia Pacific Region;

CONFIRM

Our commitment to champion and advocate for the increased availability, accessibility and visibility of health research information from and to low- and middle-income developing countries through our Journals, our respective National Associations of Medical Editors, and APAME;

Our commitment to make research information freely and openly available in the right language to producers and users of health research in low- and middle-income countries through IMSEAR, WPRIM, the ASIA Pacific Medical Journal Articles Central Archives (APAMED Central) and other platforms;

Our commitment to improve availability, accessibility and interoperability of the different formats of health information suitable to different users in their respective contexts including through both conventional and alternative channels of research dissemination such as new and social media, mobile and disruptive technologies, blogging and microblogging tools and communities, and communities of practice;

CALL ON

Member States of and governments in the South East Asia and Western pacific Regions, in collaboration with stakeholders from the non-government and private sectors to formulate and implement policies and certification schemes such as the COHRED Fairness IndexTM (CFI) that promote free and open availability of health research information for both its producers and users, especially in low- and middle-income countries;

Stakeholders from the public and private sectors, national and international organizations, universities and academic societies, and discussion groups such as Healthcare Information for ALL (HIFA2015) to support IMSEAR, WPRIM, the GHL, APAMED Central, and develop Integrated Scholarly Information Systems and similar initiatives, in order to ensure the free, open and global accessibility of health research done in the South East Asia and Western Pacific Regions;

The Eastern Mediterranean Association of Medical Editors (EMAME), the Forum for African Medical Editors (FAME), the European Association of Science Editors (EASE), the World Association of Medical Editors (WAME), the International Committee of Medical Journal Editors (ICMJE), the Committee on Publication Ethics (COPE) and other editors' and publishers' associations to support APAME in implementing various activities, guidelines and practices that would improve the quality, availability and accessibility of scientific writing and publications in the Asia Pacific Region and the world;

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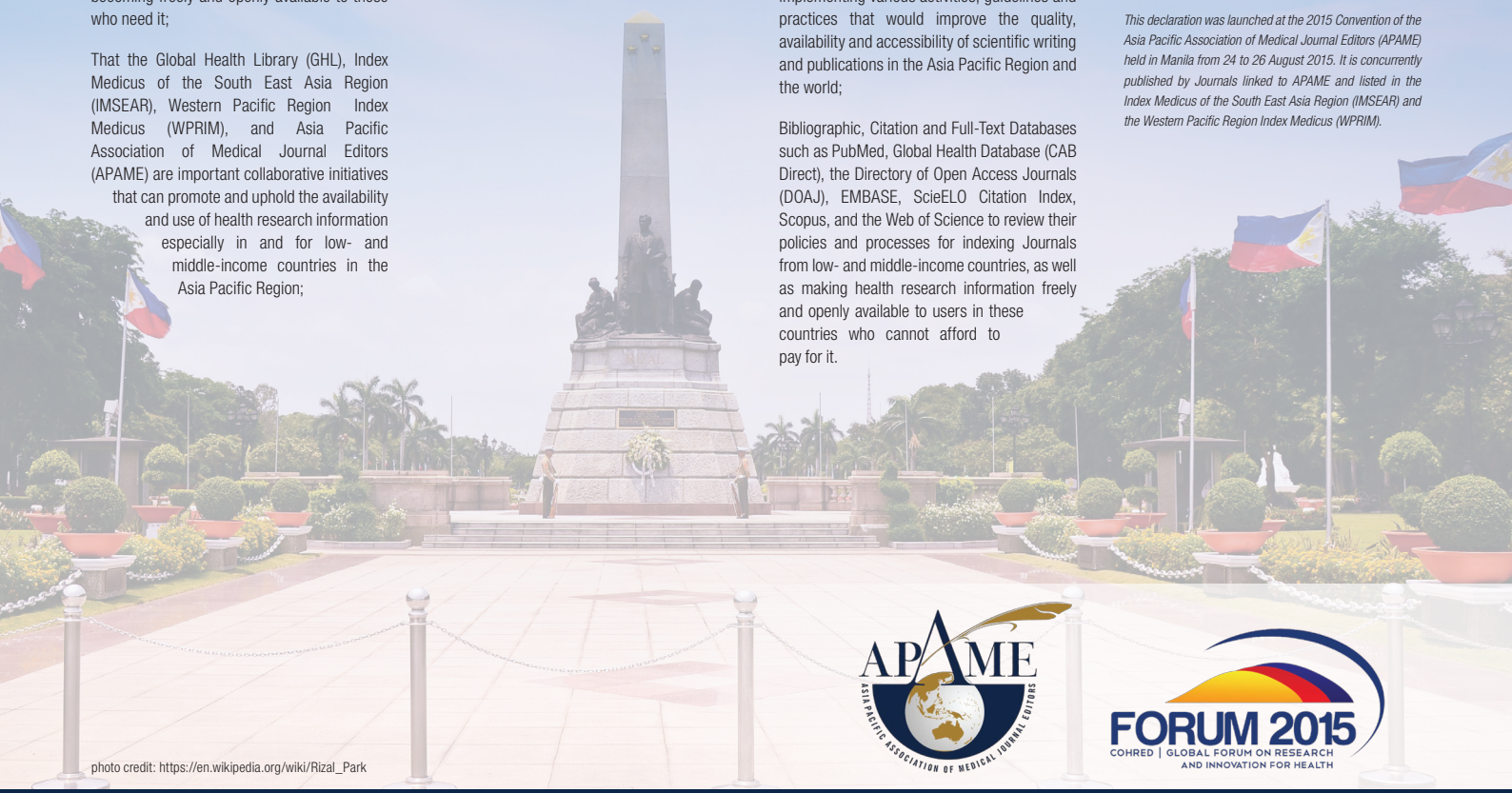

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ORIGINAL ARTICLE

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Clinical Features and Outcomes of Subacute Thyroiditis in Thai Patients

Thewjitcharoen Yotsapon, Krittiyawong Sirinate, Butadej Siriwan, Nakasatien Soontaree, Himathongkam Thep

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Abstract

Objective. To report the clinical characteristics and outcomes of subacute thyroiditis (SAT) patients at the Theptarin Hospital Thyroid Clinic.

Methodology. A retrospective review of medical records of SAT patients in the Theptarin Hospital from January 2007 to December 2013 was conducted. Clinical characteristics, laboratory findings, modes of treatment and complications were recorded.

Results. From January 2007 to December 2013, SAT was diagnosed in 149 patients, with the occurrence of SAT peaking in October and November. Of 115 patients who had complete follow-up data, mean age was 43.8±10.8 years, 88.7% were women, and SAT was preceded by an upper respiratory tract infection in 68.7%. Oral prednisolone was given in 83 cases (72.2%) at a median starting dose of 30 mg/day and was continued for a median duration of 49 days. Recurrence of SAT during the tapering period of oral prednisolone was observed in 12% of patients, resulting in reinitiation of steroid in 13% of patients for late recurrence. Transient and permanent hypothyroidism developed in 6.1% and 8.7% of patients respectively.

Conclusions. SAT in Thai patients showed seasonal clustering during October and November. Recurrences of SAT were common in the course of steroid treatment. SAT patients require careful follow-up during steroid treatment and long-term surveillance for thyroid dysfunction.

Key words: subacute thyroiditis,outcome, Thai patients

INTRODUCTION

Subacute thyroiditis, also called de Quervain's thyroiditis, is the most common cause of thyroidal pain. Symptoms and signs of subacute thyroiditis include a prodrome of myalgia, pharyngitis, low-grade fever and fatigue, followed by a tender, diffuse goiter and neck pain that often radiates to the ear.[1,2] A variety of viruses have been implicated as the cause of SAT, including those that cause mumps, measles, primary human immunodeficiency virus infection and influenza.[3] However, it is regarded as a relatively rare condition as few patients who develop a viral infection ever have thyroiditis. In the early phase of SAT, which usually lasts 3 to 6 weeks, about 50% of patients have an initial thyrotoxic phase due to release of preformed thyroid hormone. About one-third of patients subsequently enter a transient hypothyroid phase that can last up to 6 months.[2] Because permanent hypothyroidism has been reported in 10 to 15 percent of patients, close follow-up after resolution of the early phase is essential.[4]

There is considerable variation in the mode of onset and the severity of SAT. Outbreaks of SAT have been described in reports from Japan and Italy, with highest rates coincident with peak infection rates of echovirus and coxsackie virus groups A and B during summer months.[5,6] In recent years, the number of SAT patients in our clinical practices seems to have markedly increased.

Because of this observation, we sought to characterize the clinical presentation and outcomes in Thai patients with SAT.

METHODOLOGY

We conducted a review of records of all SAT patients who were treated at the Theptarin Hospital, Bangkok, Thailand from January 2007 to December 2013. The diagnosis of SAT was based on clinical features of pain and tenderness in the region of the thyroid gland over one or both lobes, laboratory findings of elevated erythrocyte sedimentation rate (ESR) or elevated C-reactive protein (CRP), elevated serum free thyroxine (FT4) and decreased serum thyroid stimulating hormone (TSH), or suppressed 24-hour radioactive iodine uptake (RAIU). Total triiodothyronine (TT3), FT4, TSH, thyroglobulin autoantibodies (anti-Tg) and thyroid peroxidase antibodies (anti-TPO) were measured using electrochemiluminescent immunoassays

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(Roche Diagnostics, Indianapolis, USA). The onset of subacute thyroiditis was defined as the date at which patients first experienced of thyroid pain. Patients who were lost to follow-up before completion of treatment were excluded from this study. Clinical characteristics, laboratory findings, modes of treatment, and complications were noted. This retrospective study was approved by the Ethical Board Committee of the Theptarin Hospital.

Statistical Analysis

Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were described in a frequency table. Characteristics of patients who developed and did not develop permanent hypothyroidism was compared using unpaired t-test for continuous variables and Chi-square test for categorical variables. The level of significance was set at 0.05. All statistical analyses were conducted using the Statistical Package for the Social Sciences version 17.0 (SPSS, Illinois, USA).

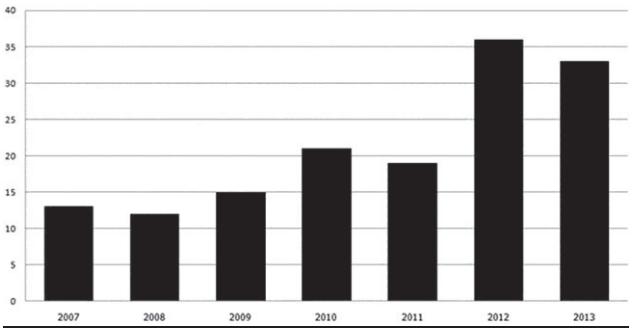

Figure 1. Frequency distribution of subacute thyroiditis patients by year, 2007-2013.

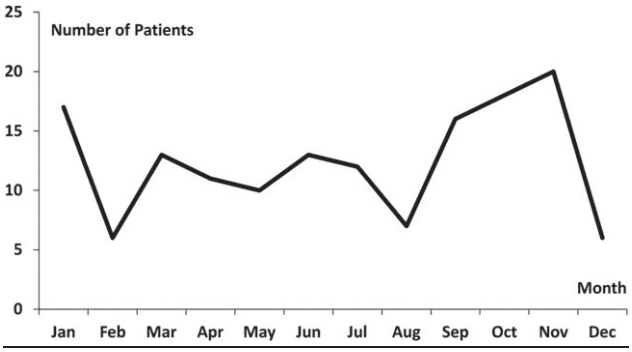

Figure 2. Frequency distribution of subacute thyroiditis in Thai patients by month, 2007-2013.

RESULTS

From January 2007 to December 2013, subacute thyroiditis was diagnosed in 149 patients, with peak occurrence in October and November (32.2%) (Figures 1 and 2). Only 115 patients had complete follow-up data. In these patients, the mean age was 43.8 ± 10.8 years and 88.7% were women. An upper respiratory tract infection preceded SAT in 68.7% of cases. At the onset of SAT, 45.0% of patients experienced unilateral neck pain. 47.0% of patients had temperature readings greater than 38°C. Typical symptoms associated with thyrotoxicosis, including palpitations, increased sweating and weight loss, were reported by 67.1% of patients. On the first visit, thyroid nodules were apparent on physical examination in 29 patients (25.2%), but only 3 of these patients continued to have thyroid nodules after the resolution of SAT. Subsequent fine needle aspiration cytology in these patients revealed benign colloidal nodules.

Anti-TPO levels measured in 69 patients showed positive results in 16% of cases (median titer 382 IU/mL). Positive anti-Tg levels were also seen in 36% of the 83 patients with this test (median titer 280 IU/mL). Clinical characteristics and initial laboratory findings are summarized in Table 1.

A 24-hour RAIU was done in 7 patients with uncertain diagnosis. All 7 showed very low uptake of less than 5%. Thyroid ultrasonography done in 25 patients showed mild thyroid enlargement with homogeneous echotexture and hypoechoic areas consistent with inflammation. Fine-needle aspiration biopsy of the thyroid (FNA) was done in 4 patients with uncertain diagnosis on initial visit. Results showed multinucleated giant cells with thick colloid, typical cytologic results for subacute thyroiditis.

Among 115 patients, 83 (72.2%) received monotherapy with prednisolone at an initial dose of 10 to 60 mg/day, with a median of 30 mg/day. Nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors were given to 25 patients (21.7%), while 7 (6.1%) were observed without any treatment. For the group receiving NSAIDs or COX-2 inhibitors, etoricoxib 90 to 120 mg/day was the most commonly used, followed by ibuprofen 800 to 1,200 mg/day in divided doses. The mean length of time for complete alleviation of pain was 5 days for the successful NSAIDs group (15 patients). The remaining 10 patients who received NSAIDs required

Table 1. Clinical characteristics and initial laboratory findings in Thai patients with subacute thyroiditis

	All patients (N=115)	Euthyroid (N=105)	Permanent Hypothyroid (N=10)	p-value
Age (years)	43.8 ± 10.8	43.6 ± 11.0	45.6 ± 7.4	0.577
Females (%)	88.7%	85.7%	90.0%	0.801
ESR (mm/hour)	71 ± 30	72 ± 30	63 ± 37	0.465
Positive Anti-TPO at baseline (%)	16%	18%	15%	0.875
Free T4 (0.93-1.70 ng/ml)	2.45 ± 1.44	2.36 ± 1.24	3.46 ± 2.66	0.283
Total T3 (61-177 ng/dl)	170 ± 70	167 ± 66	198 ± 94	0.238
Serum TSH (0.27-4.20 µIU/ml)	0.01 ± 0.08	0.02 ± 0.05	0.01 ± 0.04	0.345
Duration of hyperthyroidism (days)	38 ± 28	38 ± 29	27 ± 7	0.340
Treatment of Steroid (%)	72.2%	85.7%	50%	0.221

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prednisolone as rescue treatment. In the group that received prednisolone as initial treatment, continuation and tapering of medication lasted for a median duration of 49 days (range 6 to 194 days). Recurrence of SAT during the tapering period was observed in 14 patients, and late recurrence of SAT necessitated the need to restart steroids in 15 patients. Steroid side effects, such as acne, oily skin, irritability were tolerated well by most patients. One diabetic patient needed to stop steroid treatment because of worsening glycemic control. The steroid-treated patients gained 2 kg on the average during the course of treatment.

Throughout the specified review period, recurrent episodes of SAT after treatment accounted for 7.0% of all cases, with a median interim period of 5.5 years (range 1 to 20 years) between the first and second episodes. Transient and permanent hypothyroidism developed in 6.1% and 8.7% of patients respectively. Interestingly, overt autoimmune thyroid disease occurred following SAT in 3 cases. One case of Graves' disease occurred 2 months after the onset of SAT. There were 2 cases of Hashimoto's thyroiditis following SAT at 2 and 3 months. Unfortunately, baseline thyroid antibody levels were not available in these patients.

DISCUSSION

Subacute thyroiditis is an uncommon inflammatory disease of the thyroid gland which is usually self-limited. The pain typically radiates to the angle of jaw and to the ear on the affected side. Following initial unilateral pain, it may then progress to involve the contralateral side, a phenomenon called "creeping thyroiditis." Tenderness on palpation of the thyroid gland helps differentiate this condition from pharyngitis, a common misdiagnosis during the early stages.[7] The peak incidences of SAT have been reported mostly during the summer and early autumn in regions with four seasons, including North America, Europe and Japan.[5,8] We observed the occurrence of SAT peaked during October and November in Thailand. The significant seasonal cluster and increasing numbers of SAT cases in our clinic is coincides with the increasing rates of influenza observed in recent years in Thailand which demonstrated increased influenza rate from July to September (accounted for one third of annual influenza infection rate). Pandemic of Influenza subtype H1N1 emerged (60.65 of total positive samples) in mid-2009 and persisted in 2010 (53.35 of total positive samples).[9]

It is important to differentiate subacute thyroiditis from other causes of thyroidal pain, particularly acute suppurative thyroiditis, because steroid treatment would be catastrophic in bacterial infections. Acute suppurative thyroiditis is most often caused by gram-positive bacteria in the thyroid gland. Most patients have a preexisting thyroid disorder, typically nodular disease. Accompanying signs usually include infection in structures adjacent to the thyroid, local lymphadenopathy and fever. Chills may also be present if bacteremia occurs. Leucocytosis is seen in acute suppurative thyroiditis, in contrast to a usually normal white blood cell count in SAT. Symptoms are generally more obvious in acute suppurative thyroiditis than SAT.[1]

Other conditions which could mimic symptoms of SAT are hemorrhagic nodules or cysts, painful Hashimoto's thyroiditis, and rare cases of anaplastic thyroid cancer.[2] In our study, the diagnosis of SAT was mostly based on typical clinical features and elevated ESR or CRP. The use of RAIU was only in more difficult cases that presented with thyrotoxicosis needing distinction from Graves' disease. Consistent with a previous study, thyroid nodules observed during the clinical course of SAT resolved spontaneously with resolution of inflammation.[10] SAT may be distinguished from Graves' disease by the relatively smaller increase in triiodothyronine (T3) compared with thyroxine (T4) hormone concentrations. This change reflects T4 elevation from destructive thyroiditis and possibly from impairment of peripheral deiodination of T4 to T3 during acute illness. In previous studies, the total T3 to T4 ratio (calculated as ng/dL divided by μg/dL) is usually less than 20 in SAT, and the ratio of free T3 to free T4 is less than 4.3 in Thai patients.[11,12] While this may aid in supporting the diagnosis of SAT, our study used mostly TT3 and FT4, so that this ratio could not be verified. In general, thyroid antibodies such as anti-Tg, anti-TPO and TSH-receptor antibodies are usually absent in patients with SAT. However, transient low titers of antibodies (mainly anti-Tg) may be found during the initial phase.[4]

Treatment is directed primarily at symptomatic relief of thyroidal pain and tenderness. Symptoms of hyperthyroidism also could be treated with beta-blockers such as propranolol or atenolol, until the FT4 concentration returns to normal.[2]

The American Thyroid Association (ATA) recommends NSAIDs as the initial treatment for SAT. Prednisone may be given at 40 to 60 mg daily, with tapering over 4 to 6 weeks, should NSAIDs fail to provide pain relief.[13] Despite the reluctance of most physicians to use corticosteroids for this usually self-limited disorder, the response is often more rapid and dramatic compared to NSAIDs. Complete alleviation of pain is usually achieved within 24 hours after initiation, compared to several weeks on NSAIDs.[14] In our experience, the use of glucocorticoids has proven to be invaluable in the treatment of a vast majority of patients, most of whom presented with relatively severe symptoms.

In previous studies, steroid treatment did not prevent early- or late-onset thyroid dysfunction after SAT.[4,15] A recurrence of symptoms occurred in about 20% of patients during steroid tapering.[15] We also found a high rate of recurrence of symptoms during the course of steroid tapering in our study. Careful monitoring and tapering of steroid is warranted in order to avoid prolonged steroid exposure.

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Recently, a prospective study from Japan reported that oral prednisolone at an initial dose of 15 mg/day given as the first line treatment in SAT was effective in ameliorating symptoms in 80% of patients within 8 weeks.[16] This interesting finding challenges our current concepts in the treatment of SAT as recommended by the ATA. Further studies should be done to confirm this finding.

SAT generally resolves completely in more than 90 to 95% of patients. However, transient hypothyroidism may occur and may persist for several weeks or months in severe cases.[17] While permanent hypothyroidism is uncommon, it has been reported to occur in 5 to 15% even many years after the diagnosis.[3] In our study population, we found a similar rate of permanent hypothyroidism in less than 10% of patients. The recurrence of SAT is rare, but may happen several years after resolution of the first episode.[18] Familial occurrence of SAT with HLA-B35 has been reported, suggesting that SAT may occur in genetically predisposed individuals.[19] Further studies on patients who develop multiple episodes of SAT may clarify the role of genetics in these exceptional cases.

Another noteworthy finding in our study is the appearance of overt autoimmune thyroid disease (AITD) following SAT in 3 patients within 3 months. It is very rare for SAT to progress to either Graves' disease or Hashimoto's thyroiditis. In previous case reports, most patients had negative baseline thyroid antibodies, so that the autoimmune process was postulated to have been triggered by the release of antigenic material from the inflamed thyroid gland.[20,21]

CONCLUSION

Subacute thyroiditis in our group of Thai patients showed a trend for seasonal clustering during the months of October and November, with considerable variation in the severity of disease. Oral prednisolone provided dramatic improvement of pain, but the recurrence of SAT was common in the course of steroid treatment. The development of AITD following SAT was seen to occur in some patients after the resolution of SAT. These findings emphasize the need for careful follow-up during steroid treatment and long-term surveillance for thyroid dysfunction.

Conflict of Interest

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

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Development and Validation of a Carbohydrate and Insulin Dosing Knowledge Quiz in Adults with Diabetes Mellitus

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Abstract

Objectives. We aimed to develop and validate a carbohydrate and insulin dosing knowledge quiz for adult Asian patients with diabetes mellitus.

Methodology. A self-administered quiz was developed to test carbohydrate recognition; single food carbohydrate estimation; meal carbohydrate estimation and food label reading; and insulin dosing calculation for carbohydrate, blood glucose and for a meal in a multi-ethnic Asian population. The subjects' carbohydrate knowledge and insulin dosing ability were rated by the study dietitian and the subjects' primary physicians, respectively. We compared the quiz scores with the dietitians' and physician ratings and the subjects' HbA1c. Reliability of the quiz was tested by measuring internal consistency and split half reliability.

Results. Seventy-five subjects completed the study. Median (inter-quartile range) quiz score was 71.9 (60.2 to 83.6)%. The quiz score was found to be correlated with the healthcare provider assessments (r=0.652, p<0.001) and the subjects' HbA1c (r=-0.375, p=0.001). Cronbach alpha was 0.897 and Guttman split half coefficient was 0.930.

Conclusions. Our analysis suggested that this newly developed quiz had good reliability and validity for testing carbohydrate and insulin dosing knowledge in a group of Asian subjects with diabetes mellitus. This can be a useful screening tool in clinical practice.

Key words: diabetes mellitus, carbohydrate knowledge, insulin dosing knowledge, Asian

INTRODUCTION

An astounding 382 million people are estimated to be living with diabetes mellitus in 2013, with 72 million in Southeast Asia.[1] In addition, China and India are the two countries with the highest numbers of people with diabetes.

Medical nutrition therapy is a cornerstone of the management of diabetes mellitus (DM). Emphasis is placed on the ability to recognize and estimate the amount of carbohydrate in food, as the intake of carbohydrate has the largest impact on glycemic control.[2] Indeed, for people with type 1 DM, it is recommended that prandial insulin dose should be matched with carbohydrate intake, in addition to pre-meal glucose and anticipated activity.[2] This approach may also be extended to people with type 2 DM on a multiple daily insulin dosing schedule.

There have been numerous tools developed in the Western Hemisphere to evaluate an individual's general diabetes knowledge, diabetes numeracy skills and carbohydrate knowledge.[3-5] In contrast, standardized tools for the study of diabetes knowledge in Asian populations are not common. While quizzes targeted at evaluating general diabetes knowledge and numeracy skills can be applied universally, carbohydrate knowledge quizzes developed for Western populations may not be suitable for Asians. The typical Asian diet is considerably different, with more varied carbohydrate choices. For example, rice and rice products are the staple carbohydrate in most Asian countries including Singapore, whereas cereal, cereal products (including bread) and potatoes account for the bulk of carbohydrate intake in Western countries.[6,7] Furthermore, the conventional way of assessing each individual's

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carbohydrate knowledge by a dietitian is time-consuming and may be fraught with inconsistencies, depending on the experience and training of the dietitian. In the primary care setting, there may also be a lack of access to registered dietitians.

We thus aimed to develop and validate a carbohydrate and insulin dosing knowledge quiz for adult patients with DM who consume a predominantly Asian diet.

METHODOLOGY

Development of the Quiz

The structure of the quiz was based on the PedCarbQuiz, which consists of seven domains: 4 on carbohydrate knowledge and 3 on insulin dosing.[5] The carbohydrate knowledge domains include recognition of carbohydrates in food, estimation of carbohydrates in a single food, food label reading and estimation of carbohydrate in a meal. The insulin dosing domains include use of insulin dose correction based on blood glucose level, use of insulin to carbohydrate ratio in insulin dosing and calculation of total insulin dose for a meal.

Food items were drawn from review of existing patient food logs and from the study dietitians' experience of food that was commonly reported to be eaten during diet counselling sessions.

As a multi-racial country, the average daily diet in Singapore consists of food with Chinese, Malay, Indian, as well as regional Southeast Asian culinary influences. Representative food items commonly eaten by Chinese, Malay and Indian ethnic groups, and available at frequently patronized hawker centers, coffee shops and food courts were selected.[6] Photographs of the food items representing portion size were included for each question to avoid confusion between foods with similar sounding colloquial names.

Most domains contained 8 questions, with the exception of 24 items for recognition of carbohydrate in a single food item and 2 questions for calculation of total insulin dose for a meal. This yielded a maximum total score of 64 for the quiz. The quiz was designed such that the odd-numbered questions mirrored the even-numbered ones. The quiz was then pre-tested in a group of 5 DM patients and non-study dietitians to assess ease of administration and clarity. The final quiz was designed to be self-administered and completed in 15 to 20 minutes. The quiz is appended in the online supplement.

Study Subjects

The study was approved by the National Healthcare Group Domain Specific Review Boards (Singapore). Subjects were sequentially recruited from patients attending a diabetes centre in a single institution. We included English-literate participants who were at least 21 years of age, diagnosed with diabetes mellitus and treated with prandial insulin (short- or rapid-acting, including pre-mixed), regardless of type of diabetes. Informed consent was obtained for all subjects. Subjects who were unable to give or declined consent were excluded.

Study Procedures

The recruited subjects were given the self-administered quiz after informed consent was obtained. Each correct answer was equivalent to 1 mark; for carbohydrate counting domains (single food and in a meal), ½ mark credit was given for answers close to the correct one.

Expert assessment for the carbohydrate domains was performed by the study dietitians (M.Y. and P.K.) who were blinded to the results of the quiz through a semi-structured subject interview. The study dietitians were asked to rate the knowledge of the subject in each of the carbohydrate domains using a 7-point scale, ranging from "not at all" to "very well." For the insulin dosing domains, the usual diabetes physician of the subject, who was also blinded to the quiz results, was asked to rate insulin dosing knowledge for each domain on a 7-point scale.

The expert assessments were correlated with the quiz results by the combined carbohydrate domains, the combined insulin dosing domains and overall total.

Chart review was performed to obtain demographic information (including age, gender and ethnic group), diabetes duration, insulin regimen and HbA1c within 3 months of the quiz administration.

Statistical Analysis

Results are expressed as median (interquartile range) for non-categorical variables and number of patients (percentage) for categorical variables. Respondents were categorized based on the median knowledge quiz score. Comparison of the characteristics of subjects with scores equal to, below and above the median score was done using the Mann Whitney U test for non-categorical variables and chi-square test for categorical variables.

Two methods were used to assess reliability of the quiz by measuring internal consistency: calculation of Cronbach α and determination of split half reliability by Guttman split half coefficient between the two equivalent halves (odd-numbered vs. even numbered halves).

Criterion related validity was assessed by calculating Spearman correlation between the quiz scores and HbA1c, and quiz scores and expert (healthcare provider) assessments (for combined carbohydrate and insulin dosing domains and in total).

ONLINE FIRST | October 1, 2015 | http://dx.doi.org/10.15605/jafes.030.02.04

Wilcoxon signed rank test was used to compare scores between the different carbohydrate domains. The level of significance was set at 5%. Analyses were performed using IBM® SPSS® for Windows (version 21).

RESULTS

Study Subjects

All 75 recruited subjects were able to complete the study. Subject characteristics are shown in Table 1. The study subjects represented all 3 major ethnic groups in Singapore, and included both type 1 and type 2 DM. Majority of the subjects were on multiple daily insulin dosing regimens.

Quiz and Healthcare Provider Scores

The median quiz score was 71.9% (range 60.2 to 83.6), while the median total healthcare provider score was 26 out of a maximum total of 49 (range 21 to 33). The quiz and healthcare provider scores for each domain are shown in Table 2.

The subjects performed better in the simpler carbohydrate compared to the more complex carbohydrate domains. Scores for recognizing carbohydrate in food was significantly higher than estimating carbohydrate in a single food (p<0.001) and estimating carbohydrate in a meal (p<0.001). Food label reading scores were also higher than estimating carbohydrate in a single food (p<0.001) and estimating carbohydrate in a meal (p<0.001). The subjects also scored better in the recognition of carbohydrate in a single food compared to a meal (p<0.001). There was no difference in scores between recognizing carbohydrate in food and food label reading (p=0.386).

Quiz Validity

There was a significant, albeit weak to moderate negative correlation of the total quiz, carbohydrate domain and insulin dosing domain scores with the subjects' HbA1c. Similarly, the total quiz and carbohydrate domain scores had strong and significant positive correlation with the healthcare provider assessments, which was not observed in the insulin dosing domain (Table 3).

Quiz Reliability

Cronbach α was 0.897 for the whole quiz, with a range of 0.641 to 0.866 for individual domains. Guttman split half coefficient was 0.930 for the whole quiz, with a range of 0.700 to 0.866 for individual domains (Table 4). These results indicate good internal consistency and split half reliability respectively.

Comparison of subjects with higher versus lower quiz scores

We used the median of 71.9% as a cut-off to divide the group into higher and lower quiz scores. Subjects who were younger, with type 1 DM, on more complex insulin regimens and with lower HbA1c scored better on the quiz. No significant difference was found between the two groups in terms of gender, duration of diabetes or duration of insulin use (Table 1).

DISCUSSION

Most subjects with type 1 DM are on multiple daily insulin injection regimens for diabetes management. The majority of patients with type 2 DM start with lifestyle measures and oral hypoglycemic agents for glycemic management. Subsequently, many require insulin to maintain good control, frequently starting with basal insulin and then progressing to basal-bolus type regimens similar to that used in type 1 diabetes.[8,9] However, many patients do not practice flexible insulin dosing. This may be due to the lack of carbohydrate knowledge, numeracy skills, education and confidence in self-adjustment of insulin dose, among other reasons.

Table 1. Baseline patient characteristics

Characteristic	All (n=75)	Quiz Score ≤71.9 (n=38)	Quiz Score >71.9 (n=37)	p-value[a]
Age, year	40 (31- 53)	50 (37-58)	36 (28-35)	<0.001
Male (%)	35 (46.7)	20 (52.6)	15 (40.5)	0.294
Ethnic group				
Chinese (%)	46 (61)	16 (42)	30 (81)	0.005
Malay (%)	12 (16)	10 (26)	2 (5)	
Indian (%)	15 (20)	11 (29)	4 (11)	
Others (%)	2 (3)	1 (3)	1 (3)	
Diabetes type				
Type 1 (%)	45 (60)	14 (37)	31 (84)	<0.001
Type 2 (%)	30 (40)	24 (63)	6 (16)	
Diabetes duration, year	12 (5-21)	12 (7-22)	11 (2-19)	0.112
Insulin regimen				
BD[b] (%)	23 (30.7)	20 (52.6)	3 (8.1)	<0.001
MDI[c] (%)	50 (66.7)	18 (47.4)	32 (86.5)	
CSII[d] (%)	2 (2.7)	0 (0)	2 (5.4)	
Insulin use duration, year	6 (1-13)	6 (2-10)	6 (1-19)	0.641
HbA1c, %	8.7 (7.5-9.6)	9.1 (8.0-11.2)	8.1 (6.9-9.3)	0.012

[a]p-value for comparison between subjects with quiz score ≤71.9 and >71.9. Results expressed as median (interquartile range).
[b]BD, twice daily
[c]MDI, multiple daily injection
[d]CSII, continuous subcutaneous insulin injection

ONLINE FIRST | October 1, 2015 | http://dx.doi.org/10.15605/jafes.030.02.04

Table 2. Quiz and healthcare provider scores

Domain	Score
Total quiz score, %	71.9 (60.2-83.6)
Carbohydrate domains, %	70.7 (56.5-79.3)
Recognize carbohydrate in food, %	75.0 (66.7-91.7)
Estimate carbohydrate in single food, %	68.8 (56.3-81.3)
Food label reading, %	83.3 (66.7-83.3)
Estimate carbohydrate in a meal, %	43.8 (37.5-68.8)
Insulin dosing domains, %	86.1 (65.3-94.4)
Calculate correction dose insulin, %	81.3 (62.5-100.0)
Calculate insulin for carbohydrate, %	87.5 (75.0-100.0)
Calculation of total insulin, %	100 (0-100)
Total healthcare provider score[a]	26 (21-33)
Carbohydrate domains	12 (9-17)
Recognize carbohydrate in food	5 (4-6)
Estimate carbohydrate in single food	2 (1-3)
Food label reading	4 (2-6)
Estimate carbohydrate in a meal	1 (1-3)
Insulin dosing domains	14 (10-18)
Calculate correction dose insulin	5 (4-6)
Calculate insulin for carbohydrate	4 (3-6)
Calculation of total insulin	4 (3-6)

Results expressed as median (interquartile range).
[a] Maximum score for each domain is 7, and maximum total score is 49

Table 3. Correlation of quiz scores with healthcare provider scores and HbA1c

	Correlation coefficient	*p*
Correlation with healthcare provider scores		
Total quiz score	0.652	<0.001
Carbohydrate domains	0.663	<0.001
Insulin dosing domains	0.180	0.135
Correlation with subjects' HbA1c		
Total quiz score	-0.375	0.001
Carbohydrate domains	-0.380	0.001
Insulin dosing domains	-0.277	0.020

Table 4. Reliability of quiz

	Cronbach's alpha	Guttman split half coefficient
Total quiz	0.897	0.930
Carbohydrate domains	0.832	0.861
Carbohydrate domain 1 (Recognize carbohydrate in food)	0.796	0.760
Carbohydrate domain 2 (Estimate carbohydrate in single food)	0.710	0.770
Carbohydrate domain 3 (Food label reading)	0.700	0.700
Carbohydrate domain 4 (Estimate carbohydrate in a meal)	0.641	0.792
Insulin dosing domains	0.867	0.911
Insulin dosing domain 1 (Calculate correction dose insulin)	0.745	0.855
Insulin dosing domain 2 (Calculate insulin for carbohydrate)	0.713	0.833
Insulin dosing domain 3 (Calculation of total insulin)	0.866	0.866

Central to flexible insulin dosing would be the ability to estimate the amount of carbohydrates in commonly eaten food, and the numeracy skills to estimate the insulin dose appropriate for the food to be eaten and for the correction dose based on pre-meal glucose. Even with fixed dose insulin regimens, the ability to recognize carbohydrates and estimate carbohydrate amounts in food is important to allow regular distribution of carbohydrates throughout the day. Thus, an objective tool to assess these key knowledge elements is crucial.

To the best of our knowledge, this is the first tool developed and validated for patients consuming a Southeast Asian diet. Some advantages of this tool are that it is brief, allows self-administration and includes visuals by way of food photographs. We also tested the calculation of insulin correction dose based on pre-meal glucose by two different methods: one following a correction scale and another by using an insulin sensitivity factor and a target glucose level. This allowed us to assess subjects with different practices. The PedCarbQuiz only utilized a correction scale.[5]

While attempts were made to include food commonly consumed by the different ethnic groups, it is possible that some items were not commonly eaten by others. However, in the melting pot food culture of Singapore, since we included commonly available foods, most people would be at least be familiar with the different food items. Furthermore, with increasing globalization, international travel and the availability and popularity of many of these food items worldwide, this quiz may also be applied to people with diabetes who enjoy ethnic variety in their food choices.

Overall, the quiz had good reliability (good internal consistency and split-half reliability) and validity (correlation with HbA1c and healthcare provider assessments). However, insulin dosing domains were not significantly correlated with healthcare provider assessment. A possible reason is that many of the study subjects do not routinely adjust insulin on their own, and may not be familiar with how it is done. Accurate assessment of these subjects' numeracy skills may be challenging since they did not self-adjust insulin regularly. Since healthcare provider assessment for the insulin domains were performed by the subjects' usual physicians, wider inter-physician assessment variability may be observed. In contrast, less variability may be seen between the 2 study dietitians for the carbohydrate domains. We attempted to minimize variability in ratings by having detailed descriptions for each point on the rating scale.

We found that subjects with higher quiz scores had lower HbA1c results. This may indicate that better knowledge had translated to better glycemic control. While knowledge alone is insufficient for good glycemic control, it is also clear that the lack of it would preclude the ability to follow a flexible insulin dosing regimen recommended in many guidelines.[10,11] This quiz may then be used as a screening tool to identify subjects who are deficient in the necessary health literacy and numeracy skills for targeted education, with greater attention paid to domains with lower scores. As an example, subjects who do well at identifying carbohydrates in food but fare poorly at carbohydrate counting may attend advanced carbohydrate counting classes, while those who are not able to identify carbohydrates in food or read food labels may be more suited for basic carbohydrate counting classes.

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CONCLUSION

Our study demonstrated the development and validation of a new carbohydrate and insulin dosing knowledge quiz in a multi-ethnic population of diabetic adults with on prandial insulin. It addresses an important gap in the current management of this population of patients. It may be applied within the Southeast Asian region, in migrant Asian populations, as well as to individuals who consume a more cosmopolitan diet. There are numerous potential uses of the quiz, including as a screening tool for knowledge gaps before intensifying insulin therapy and as an objective assessment tool following educational interventions.

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Statement of Authorship

A.K., A.N., M.Y. and P.L. contributed substantially to the conduct of the study, including conception and design, acquisition and analysis of data and drafting of the manuscript. C.S. and K.G. made significant contributions to the critical revision of the article. All authors have given approval to the final version submitted.

Conflict of Interest

All the authors have no conflict of interest to declare with respect to the work carried out in this paper.

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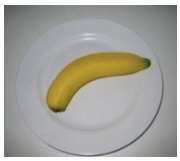
Supplement 1. Carbohydrate and insulin dosing knowledge quiz with answers and scoring notes

Question 1.

Which of the following food(s) contain(s) carbohydrates?
Please choose all the answers that apply.

[x]  Banana

[ ]  Chicken

[x]  Wholemeal bread

[x] 

2-in-1 Instant Coffee mix

Question 2.

Which of the following food(s) contain(s) carbohydrates?
Please choose all the answers that apply.

[ ]  Bittergourd

[x]  White rice

[ ]  Egg

[x] 

Low fat milk

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Question 3.
Which of the following food(s) contain(s) carbohydrates?
Please choose all the answers that apply.

[x]  Potato

[ ]  Olive Oil

[x]  Bee Hoon (Rice vermicelli noodles)

[x]  Peanut Butter

Question 4.
Which of the following food(s) contain(s) carbohydrates?
Please choose all the answers that apply.

[x]  Pumpkin

[ ]  Margarine

[x]  Soya Bean Milk (regular)

[x]  Chee Cheong Fun

Question 5.
Which of the following food(s) contain(s) carbohydrates?
Please choose all the answers that apply.

[x]  Corn

[ ]  Fish

[ ]  Clear Chicken Soup

[x]  Chappati

Question 6.
Which of the following food(s) contain(s) carbohydrates?
Please choose all the answers that apply.

[x]  Oats

[x]  Peas

[ ]  Silken Tofu

[ ]  Diet Soda

ONLINE FIRST | October 1, 2015 | http://dx.doi.org/10.15605/jafes.030.02.04

Question 7.
How many grams of carbohydrates are in this portion of food?

1 cup (250 mL) of low fat milk

(1) 15
(1/2) 30
( ) 45
( ) 60
( ) 75

Question 8.
How many grams of carbohydrates are in this portion of food?

1 bowl of **cooked** white rice

( ) 15
( ) 30
(1/2) 45
(1) 60
(1/2) 75

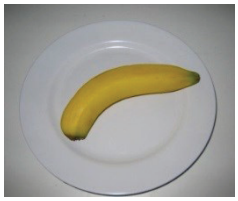
Question 9.
How many grams of carbohydrates are in this portion of food?

3 tablespoons of **uncooked** oats

(1) 15
(1/2) 30
( ) 45
( ) 60
( ) 75

Question 10.
How many grams of carbohydrates are in this portion of food?

1 medium banana (8 inches long)



(1/2) 15
(1) 30
(1/2) 45
( ) 60
( ) 75

Question 11.
How many grams of carbohydrates are in this portion of food?

1 rice bowl of yellow noodles (mee)

( ) 15
(1/2) 30
(1) 45
(1/2) 60
( ) 75

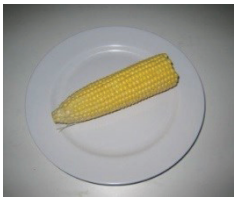
Question 12.
How many grams of carbohydrates are in this portion of food?

1 slice of wholemeal bread

(1) 15
(1/2) 30
( ) 45
( ) 60
( ) 75

Question 13.
How many grams of carbohydrates are in this portion of food?

1 whole corn on the cob (medium, 7 inches long)



(1/2) 15
(1) 30
(1/2) 45
( ) 60
( ) 75

Question 14.
How many grams of carbohydrates are in this portion of food?

1/4 cup barley (uncooked)

(1/2) 15
(1) 30
(1/2) 45
( ) 60
( ) 75

Question 15.
Look at this food label and answer the following questions.

NUTRITION INFORMATION		
Servings per package: 10 Serving size: 3 pieces (25g)		
	Per Serving	Per 100g
Energy	142 kcal	567 kcal
Protein	2.2 g	8.7 g
Total Fat	8.0 g	33.5 g
Carbohydrate	14.0 g	55.8 g
Dietary fibre	1.0 g	4.0 g
Sodium	150 mg	600 mg

What is the serving size? 3 pieces (5 pieces/10 pieces)
How many grams of carbohydrates are there in one serving? 14g (28g/55.8g)
How many grams of carbohydrates are there in the whole packet? (14g/42g/55.8g) 140g

Question 16.
Look at this food label and answer the following questions.

NUTRITION INFORMATION		
Servings per package: 1 Serving size: 1 cup (150g)		
	Per Serving	Per 100g
Energy	153 kcal	102 kcal
Protein	3.8 g	2.5 g
Total Fat	2.4 g	1.6 g
Carbohydrate	30 g	20 g
Dietary fibre	6.0 g	4.0 g
Sodium	74 mg	49 mg

What is the serving size? 1 cup (2 cup/3 cups)
How many grams of carbohydrates are there in one serving? (20g) /30g / (45g)
For one serving, how many grams of carbohydrates should you use to calculate the insulin dose? (24g)/ 27g /(30g/36g)

ONLINE FIRST | October 1, 2015 | http://dx.doi.org/10.15605/jafes.030.02.04

Question 17.
How many grams of carbohydrates are there in the following breakfast?

1 plate of mee siam with
1 glass of kopi-C (coffee with evaporated milk and sugar)
( ) 30g
( ) 45g
( ) 60g
(1/2) 75g
(1) 90g

Question 18.
How many grams of carbohydrates are there in the following lunch?

1 bowl of ban-mien soup + 1 medium green apple + 1 can of isotonic sports drink (e.g. 100 Plus, Pocari)
( ) 60g
(1/2) 75g
(1) 90g
(1/2) 105g
( ) 120g

Question 19.
How many grams of carbohydrates are there in the following snack?

1 piece kuih lapis + 1 cup of kopi-O (coffee with sugar)

( ) 15g
(1) 30g
(1) 45g
(1/2) 60g
( ) 75g

Question 20.
How many grams of carbohydrates are there in the following dinner?

1 plate of fried bee hoon +
1 piece fish otah

( ) 15g
( ) 30g
(1/2) 45g
(1) 60g
(1) 75g

Question 21.
How many grams of carbohydrates are there in the following breakfast?

2 pieces wholemeal bread + 2 tablespoons butter + 2 tablespoons kaya + 2 soft boiled eggs + 1 cup kopi-C (Coffee with evaporated milk and sugar)
( ) 15g
( ) 30g
(1/2) 45g
(1) 60g
(1/2) 75g

Question 22.
How many grams of carbohydrates are there in the following snack?

3 pieces of high fiber crackers +
1 cup of plain malted drink (e.g. Milo, Horlicks) (without milk or sugar)
(1/2) 15g
(1) 30g
(1/2) 45g
( ) 60g
( ) 75g

Question 23.
Look at the insulin scale to determine how much insulin to give for the blood glucose reading.

Blood glucose is 8.6 mmol/L. You should give 3 (2/4/5/6) units of insulin.
Blood glucose is 21.2 mmol/L. You should give 6 (2/3/4/5) units of insulin.
Blood glucose is 12.0 mmol/L. You should give 3 (2/4/5/6) units of insulin.

Question 24.
Look at the insulin scale to determine how much insulin to give for the blood glucose reading.

Blood glucose is 10.8 mmol/L. You should give 2 (~~0~~/~~4~~/~~6~~/~~8~~) units of insulin.
Blood glucose is 5.5 mmol/L. You should give 0 (~~2~~/~~4~~/~~6~~/~~8~~) units of insulin.
Blood glucose is 15.4 mmol/L. You should give 6 (~~0~~/~~2~~/~~4~~/~~8~~) units of insulin.

Question 25.
1 unit of insulin covers 10g of carbohydrate.
Please answer the following questions.

For 30 g of carbohydrate, you should give 3 (1/2/4/5) units of insulin.
For 15 g of carbohydrate, you should give 1.5 (1/2/2.5/3) units of insulin.
For 50 g of carbohydrate, you should give 5 (1/2/3/4)units of insulin.

Question 26.
1 unit of insulin covers 15g of carbohydrate.
Please answer the following questions.

For 30 g of carbohydrate, you should give 2 (3/4/5/6) units of insulin.
For 45 g of carbohydrate, you should give 3 (2/4/5/6) units of insulin.
For 60 g of carbohydrate, you should give 4 (2/3/5/6) units of insulin.

ONLINE FIRST | October 1, 2015 | http://dx.doi.org/10.15605/jafes.030.02.04

Question 27.

1 unit of insulin covers 5g carbohydrate.
1 unit of insulin lowers blood glucose by 1.5 mmol/L. Your **target blood glucose** is **6 mmol/L**.
Your blood glucose before dinner is **11.9 mmol/L.**

Your dinner is:
1 plate of chicken rice with cucumbers + 1 bowl of cheng tng
Fill in the blanks.

The total amount of carbohydrates in this dinner is 105 g.
(1/2 mark for 90g or 120g)
To cover carbohydrates, you should give 21 units of insulin.
To lower your blood glucose to your target, you should give 4 units of insulin.
The total amount of insulin you should give is 25 units.

Question 28.

1 unit of insulin covers 15g carbohydrate.
1 unit of insulin lowers blood glucose by 3 mmol/L. Your **target blood glucose** is **5 mmol/L**.
Your blood glucose before lunch is **8.1 mmol/L.**

Your lunch is:
1 plate of biryani rice + 1 piece curry chicken + stir fried cabbage +
1 small papaya +1 bottle of water
Fill in the blanks.

The total amount of carbohydrates in this dinner is 120 (105)g.
(1/2 mark for 90g or 135g)
To cover carbohydrates, you should give 8 (7) units of insulin.
To lower your blood glucose to your target, you should give 1 unit of insulin.
The total amount of insulin you should give is 9 (8) units.

Quiz Scoring Notes

1. For questions 1 to 6, [x] denotes the food item contains carbohydrates. One (1) mark is given for every correct answer, including correctly identifying that the food does not contain carbohydrates.
2. For questions 7 to 14 and questions 17 to 22 , 1 mark is given for the correct answer (shown as [1]) and ½ mark credit is given for answers close to the correct answer.
3. For questions 15, 16, 23 to 26, the correct answer is underlined. One (1) mark is given for each correct answer.
4. For questions 27 and 28, full credit (1 mark) was given for calculation of insulin for carbohydrates based on the total amount of carbohydrate estimated in the answer and for calculation of total amount of insulin given based on answers for insulin to be given for carbohydrates and correction dose insulin.

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ORIGINAL ARTICLE

Oral Health Status of Children Attending a Summer Camp for Diabetes Children

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Abstract

Objective. The aim of this paper is to examine the oral health of children attending a diabetes camp. Despite studies showing diabetes to be a risk factor for periodontitis on the one hand and periodontitis having been shown to affect glycemic control and increase the risk for developing complications among diabetic patients, oral health is only beginning to receive much needed attention as an important aspect of general health in diabetic patients.

Methodology. A simple count of the number of decayed, missing, and filled teeth was performed and added to come up with the Decayed Missing and Filled Teeth index (DMFT). Periodontal examination was performed using a Community Periodontal Index of Treatment Needs (CPITN) probe. Pocket probing was performed on six sites (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual, and distolingual) on each tooth. The teeth were then scored on a scale of 0–4 similar to the CPITN method of the World Health Organization.

Results. The proportion of participants with dental caries was 72% (18) with a mean number of decayed, missing and filled teeth (DMFT) of 4.6. 5 (20%) of the participants had a DMFT score of 0, meaning that they have no decayed missing or filled teeth while 10 (40%) either already had permanent teeth extracted. or required tooth extraction for non-restorable, severely decayed permanent teeth. Periodontitis (Pockets > 3.5 mm; CPITN = 4) was found in only 1 (4%) patient. 21 (84%) of the participants either had a CPITN score of 1 or 2, meaning bleeding upon probing or calcular deposits were observed. 3 (12%) had a CPITN score of 0.

Conclusions. Diabetes camps are a good place to screen oral health problems among type 1 diabetic patients given the different socio-economic factors, levels of concern for oral health, and availability of dental care providers among families of with type 1 diabetic children. Physicians managing type 1 diabetics should motivate their patients to see the dentist twice a year for preventive visits and strongly encourage them to have treatment when dental diseases are present. An oral exam should be part of the cursory examination performed by physicians handling these patients.

Key words: diabetes, periodontitis, glycated hemoglobin assay, diabetes camp, Diabetes Self-Management Education

INTRODUCTION

The mission of camps specialized for children and youth with diabetes is to facilitate a traditional camping experience in a medically safe environment. The camp setting is an ideal place for teaching diabetes self-management skills. Examples of educational topics tackled in the camp setting include: blood glucose monitoring, recognition and management of hypo-/ hyperglycemia and ketosis, insulin types and administration techniques, carbohydrate counting, insulin dosage adjustment based on nutrition and activity schedules, the importance of diabetes control, healthy lifestyles issues, including integration of healthy eating, physical activity and relaxation, problem-solving skills for caring for diabetes at home versus camp, life skills for independent living, stress management and coping skills, sexual health and preconception issues, diabetes complications and new therapies including technologies.[1]

Just as important, diabetes camps allow children with diabetes to feel less isolated through interaction with other children afflicted with diabetes. It builds self-confidence and fosters independence. Learning is also facilitated through sharing of experience with their peers.

The aim of this paper is to examine the oral health of children attending a diabetes camp. Studies have shown diabetes to be a risk factor for periodontitis on the one hand and periodontitis has been shown to affect glycemic control and increase the risk for developing complications among diabetic patients.[2] In spite of these findings, oral health is

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only beginning to receive much needed attention as an important aspect of general health in diabetic patients.

Project Oral Health for Juvenile Diabetics was organized in 1998 to provide free/discounted dental treatment to children with diabetes 19 years old and below. The mean number of decayed, missing, and filled teeth (DMFT) of the 11–15 age group in the Project Oral Health for Juvenile Diabetics (POHJD) population was 8.5 while the mean DMFT of the 12-year old age group in the 2006 National Oral Health Survey in the Philippines was 2.9.[3,4] The two studies however, used different methods of investigation and therefore, comparisons must be made with caution.

The participants of POHJD have been under the care of a physician for an average of 6 years. In those 6 years, occasions would have arisen to allow the physician a glimpse of the oral problem. However, physicians are also aware of the financial difficulties of type 1 diabetic patients and are not strongly predisposed to recommend preventive or even dental treatment to their patients.[5]

In addition, a study of the periodontal health of POHJD participants found 34% of patients aged 19 and below have pockets greater than 3.5 mm. The youngest patient found with mild periodontitis (pockets 3.5–5.5 mm) was 13 while the youngest patient with moderate periodontitis (pockets > 5.5 mm) was 17.[6]

Type 1 diabetic patients are reluctant to seek dental treatment because of cost, fear, and the lack of dentists who are willing to treat diabetic patients.[5] Medication is the prime concern of the patient and all other concerns have to wait in line until adequate funds become available. Dental insurance is not available in the Philippines and treatment is offered mostly by private practitioners.[3] The development of clinical practice guidelines for the delivery of out-patient dental treatment is also needed in order to relieve the anxiety among dentists when treating diabetic patients.[5]

METHODOLOGY

Study Design

Cross sectional Survey

Setting and Population

Attendees of the 2013 Camp Cope Summer Camp for Juvenile Diabetics.

Materials and Methods

Data regarding the patient's medical and dental history was obtained prior to dental examination. Dental examination was done inside a room with a plastic chair facing the sunlight. A flashlight was used to help examine the posterior teeth. The patients were examined for the presence dental caries and periodontal disease.

A simple count of the number of decayed, missing and filled teeth was performed and added to come up with the Decayed Missing and Filled Teeth index (DMFT).

Periodontal examination was performed using a Community Periodontal Index of Treatment Needs (CPITN) probe. Pocket probing was performed on six sites (mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual and distolingual) on each tooth. The teeth were then scored on a scale of 0–4, which is similar to the CPITN method of the World Health Organization. A score of 0 indicated that no bleeding, calculus, or pockets greater than 3.5 mm was detected. A score of 1 indicated that bleeding was observed during pocket probing but not calculus or pockets greater than 3.5 mm. A score of 2 indicated the presence of calculus but not pockets greater than 3.5 mm. A score of 3 indicated the presence of 3.5 to 5.5 mm pockets. A score of 4 indicated pockets greater 5.5 mm.

During pre-camp orientation the families of the participants were informed that an oral examination will be performed as part of a survey to determine the oral health of the participants. The data and photos obtained for documentation will be presented in a study or a journal article.

Data Analysis

The data were subjected to descriptive statistical analysis and compared with other factors such as age and number of years with diabetes.

RESULTS

Patient profile

A total of 25 type 1 diabetic patients attended the camp. Of these, 14 (56%) were female while 11 (44%) were male. Mean age of the participants was 13 and a mean number of years with diabetes of 8.6. Three (12%) of the patients still had deciduous teeth. Nine (36%) had their first dental examination during the camp, while another 9 (36%) visited their dentist regularly twice a year. The rest, 7 (28%), went to their dentists only when they felt they had problems. Twenty two patients (88%) brushed their teeth at least twice a day and 23 (92%) did not use the dental floss (Table 1).

Caries and Periodontal Disease Profile.

The proportion of participants with dental caries was 72% (18) with a mean number of decayed, missing and filled teeth (DMFT) of 4.6. FIve (20%) of the participants had a DMFT score of 0, meaning that they have no decayed missing or filled teeth while 10 (40%) either already had permanent teeth extracted or required tooth extraction for non-restorable, severely decayed permanent teeth. Only 4 (16%) had fillings or pit and fissure sealants, while 14

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Table 1. Distribution of participants according to demographic and clinical characteristics, N=5

Age (yrs)	
Mean	13
Median	13
Mode	13
Range	10-18
Duration of diabetes (yrs)	
Mean	8.6
Median	8
Mode	8
Range	4-16
Male gender, N (%)	11 (44%)
Female gender, N (%)	14 (56%)
Dentition	
Mixed dentition	3 (12%)
Permanent teeth only	22 (88%)
Preventive Dental Visits	
1st dental visit	9 (36%)
Symptomatic	9 (36%)
Asymptomatic	7 (28%)
Oral Hygiene practices	
Toothbrushing 1/day	3 (12%)
Toothbrushing 2/day	9 (36%)
Toothbrushing 3/day	11 (44%)
Toothbrushing 4/day	1 (4%)
Toothbrushing 5/day	0
Toothbrushing 6/day	1 (4%)
Flossing 0/day	23 (92%)
Flossing 1/day	1 (4%)
Flossing 2/day	1 (4%)

(56%) had a DMFT score derived mainly from the number of decayed teeth. Two (8%) had a DMFT score equivalent to the sum of the number of decayed and missing teeth. Periodontitis (pockets >3.5 mm; CPITN = 4) was found in only 1 (4%) patient. Twenty one (84%) of the participants either had a CPITN score of 1 or 2, meaning bleeding upon probing or calcular deposits were observed. 3 (12%) had a CPITN score of 0.

DISCUSSION

The DMFT scores of the participants showed a high of 16 and a low score of 0, indicating the diverse oral health conditions of the participants. Two (8%) participants have DMFT scores composed only of filled teeth, indicating a high level of concern for the preservation of teeth while 14 (56%) had a DMFT score composed only of decayed teeth indicating the opposite. The high number of participants 10 (40%) who required tooth extraction or already had permanent teeth extracted, however, tilts the balance towards a low level of importance attached to oral health among these participants. This is further evidenced by the number of participants 9 (36%) who had their first dental examination during the camp. This subpopulation had a mean age of 12.9 and had received treatment for diabetes for 7.9 years. This shows a lack of concern for oral health among physician managing children with diabetes. Given the number of concepts that patients are encouraged to learn about their diabetes, this is not surprising. However, the possibility that severely decayed teeth can lead to infection that can trigger hyperglycemia or even diabetic ketoacidosis, should oblige the physician to include oral health as a major component of glycemic control.

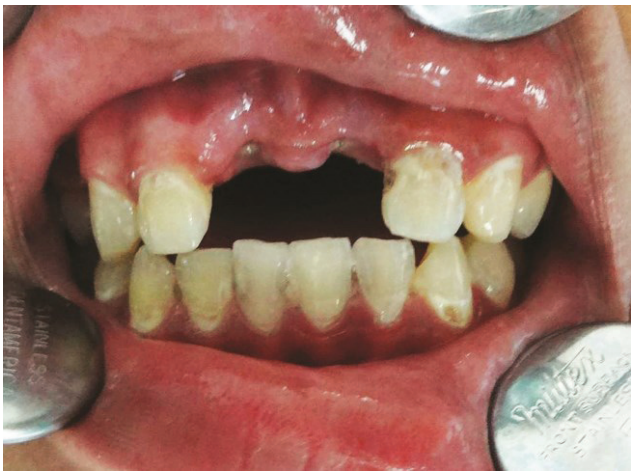

Figure 1. Early loss of anterior teeth secondary to dental caries.

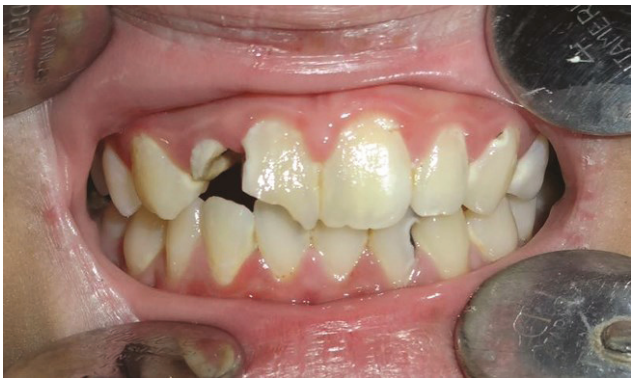

Figure 2. Caries on the interproximal areas.

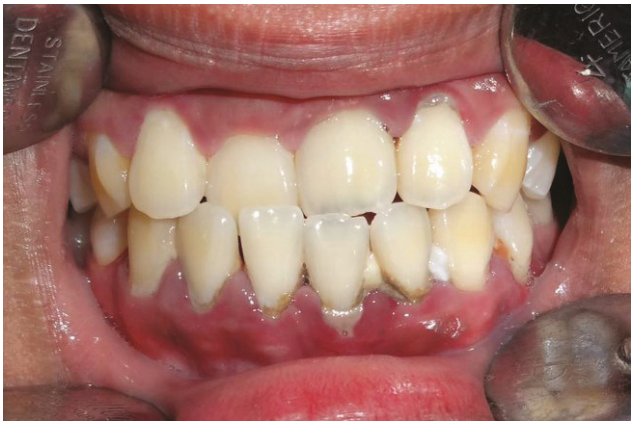

Figure 3. Periodontitis with heavy calcular deposits that extends to the subgingival area with Inflamed gingiva that easily bleeds.

When oral diseases like tooth decay or periodontal disease affect the anterior teeth, it can result in poor appearance, poor social interaction, unwanted attention, and even ridicule (Figures 1-3). This can further add to the isolation most type 1 diabetic patients encounter during the first few years of the disease. The combination of early onset diabetes and poor oral health can lead to delayed educational development in younger patients and inability

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to compete for jobs among older patients. High self-esteem was found to relate to good adherence with exercise regimens and adjustment of insulin doses in type 1 diabetics.[7] Optimum oral health removes additional obstacles that can further impair a young diabetic from overcoming the challenges of her disease.

Limitations

The lack of adequate lighting, a comfortable chair and radiographs during the dental examination could have underestimated detection of the number of caries and periodontal lesions.

CONCLUSIONS

Diabetes camps are a good place to screen oral health problems among type 1 diabetic patients given the different socio-economic factors, levels of concern for oral health and availability of dental care providers among families of with type 1 diabetic children. Physicians managing type 1 diabetics should motivate their patients to see the dentist twice a year for preventive visits and strongly encourage them to have dental treatment when dental diseases are present. An oral exam should be part of the cursory examination performed by physicians handling these patients.

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ORIGINAL ARTICLE

Prevalence and Clinical Profile of Celiac Disease in Patients with Type 1 Diabetes Mellitus in Western Uttar Pradesh, India

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Abstract

Background. Celiac disease is frequently associated with type 1 diabetes mellitus, but is usually ill-defined and not usually suspected until the disease becomes advanced.

Objective. To study the prevalence and clinical profile of celiac disease among patients with type 1 diabetes mellitus in a tertiary care referral centre in north India.

Methodology. Two hundred and fifty six patients were screened (149 males and 107 females) during the study period of two years, patients were evaluated for the clinical signs, biochemical investigations and family history of celiac disease in tertiary care health center in western Uttar Pradesh.

Results. Twenty four (9.37%) patients were diagnosed to have celiac disease; the mean age at diagnosis of diabetes was 9.34 ± 7.3 years. Only 1/24 patients with celiac disease had been diagnosed before detection of diabetes mellitus. The common manifestations were normocytic normochromic anemia (66.6%) followed by diarrhoea (62.5%), abdominal pain/bloating sensation (58.3%) and short stature (58.3%). Some uncommon manifestations were also observed in small number of patients: rickets (20.8%), recurrent hypoglycemia (16.6%), carpopedal spasm (8.3%), and night blindness (8.3%).

Conclusion. Celiac disease was found in about 10% of patients with type 1 diabetes, almost 10-20 times higher than that observed in general pediatric population. Atypical manifestations (rickets, recurrent hypoglycemia, carpopedal spasm and night blindness) were found to be common in patients with type 1 diabetes as compared to the general population. Unexplained anemia, diarrhoea, short stature and rickets should raise suspicion for the possibility of undiagnosed celiac disease in type 1 diabetes mellitus.

Key words: type 1 diabetes mellitus, celiac diseases, short stature, anemia

INTRODUCTION

Type 1 diabetes mellitus is a common autoimmune disorder of the pediatric population and it is frequently associated with other autoimmune conditions, especially with autoimmune hypothyroidism and celiac disease.[1] Celiac disease (CD), or gluten-sensitive enteropathy, is an autoimmune disorder characterized by inflammation, villous atrophy and crypt hyperplasia of the small bowel mucosa after ingestion of dietary gluten and recovers when gluten-containing cereals are withdrawn from the diet.

The mean prevalence rate of celiac disease in type 1 diabetes patients varies in studies but ranges from 1% to 11%,[2] almost 10-20 times higher than that observed in the general pediatric population.[3] It has an incidence of 1 in 96 in north India.[4]

The presentation of celiac disease in Type 1 diabetes patients is extremely variable, less than one third of patients present with gastrointestinal complaints, and some patients remain asymptomatic and are only diagnosed during routine screening procedures.[5] The prominent extraintestinal manifestations of celiac disease are short stature, delayed puberty, poor glycemic control, nutritional anemia, etc.[6-7]

Patients with celiac disease frequently present with growth failure, malnutrition, hypocalcemia anemia, suboptimal growth velocity and poor weight gain and

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pathogenesis appears to be multifactorial A few studies support the role of RANKL/OPG system in the pathogenesis, but the exact cause for it is still unknown.[8]

The main aim of this cross-sectional analytic study is to study the prevalence and clinical characteristics of celiac disease in patients with type 1 diabetes mellitus in Northern India.

METHODOLOGY

Two hundred and thirty six children and adolescents with type 1diabetes, aged 6 to 18 years, presenting to the endocrine OPD or admitted to the endocrinology ward, were enrolled in the study period of two years from July 2011 to June 2013. Ethical clearance for the study was secured from the institution

After explaining the objectives of the study, a written informed consent was obtained from the patients or their parents. Patients were evaluated clinically, biochemically and inquiries were made for family history of other common autoimmune disorders, which are associated with type 1 diabetes.

Physical examination along with Tanner scoring was done by two endocrinologists, which included one pediatric endocrinologist. Blood samples were collected for: anti-TTG immunoglobulin subclass A (IgA) using enzyme-linked immunosorbent assay (ELISA), CBC, iron profile, glycosylated hemoglobin (HbA1C), calcium, phosphorus and albumin.

X-rays of the wrist and knee were done in all patients of celiac disease in the hospital premises and the x-rays were reported first by an experienced endocrinologist and then by radiologists, and if both agreed on a finding, it was accepted. Bone age was assessed using the Tanner Whitehouse 2 system.

Delayed bone age was defined as difference of at least 24 months between chronological age and bone age. Vitamin D level was done when appropriate.

Endoscopic duodenal biopsies were undertaken for those who were negative for anti-TTG antibody after informed consent. Screening for other autoimmune disorders was done only when signs or symptoms or family history suggestive of the disorder were present.

Statistical Analysis

All categorical variables were expressed as percentages and all continuous variables were expressed as mean ± standard deviation. Categorical variables were compared using Fisher's exact test and Chi-square test, whichever is applicable. Continuous variables were compared using independent t–test and ANOVA as applicable. All p values <0.05 were taken as significant. Bivariate correlations were calculated using Pearson's correlation coefficient. Statistical analysis was performed by using software SPSS version 17.

RESULTS

Table 1 shows the comparison between the patients with and those without celiac disease, the age of presentation with celiac disease was almost one year later than the age of presentation of patients without celiac disease.

Patients with celiac disease had much higher HbA1C, FBS and ALP in comparison with patients without celiac disease, which both are significant (<0.05), but had lower hemoglobin, MCV, MCH, serum iron, and serum calcium and all were significant (<0.05). Sex ratio was found to be equal in both, while the incidence of other autoimmune conditions was found to be non- significant.

Table 2 shows the demographic profile of patients with celiac disease and the most common manifestations.

Table 3 shows the prevalence of different laboratory and biochemical abnormalities in the T1DM patients with celiac disease. The data shows that anemia was the most common laboratory finding with an overall prevalence rate of 87.4% (66.6% normocytic normochromic and 20.8% microcytic hypochromic).

Table 1. Demographic and clinical characteristics of patients

Parameters	Patients with celiac diseases (N=24)	Patients without celiac diseases (N=212)	p-value
Age (years)	12.1+4.8	11.5+6.4	-
Age at diagnosis of type 1 diabetes (years)	9.34 ± 7.3	9.6+6.2	-
Female gender (%)	10 (41.6%)	90 (42%)	0.23
HbA1C	11.2+ 1.3	9.1+1.6	<0.05
FBS (mg/dl)	184+ 67.4	143+26.8	<0.05
Hemoglobin (gm/dl)	9.6+1.8	10.6+1.3	<0.05
MCV (fl)	75.9+6.9	80.8+8.6	<0.05
MCH (pg)	23.8+2.1	28.2+1.6	<0.05
Serum Iron (normal 9–30.4 µmol/L)	9.2+4.3	16.8+3.7	<0.05
Serum Calcium (mg/dl)	7.4+ 2.4	8.9+0.9	<0.05
ALP (IU/L)	624+164	189+56	<0.05
Other autoimmune conditions	03 (12.5%)	46 (21.5%)	0.138

Data presented as mean +SD

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Table 2. Clinical profile of children with type 1 diabetes associated with celiac disease, N=24, Uttar Pradesh, India

Clinical features / lab features	Number of Patients (N=24)	Percentage (%)
Short stature	14	58.3
Delayed puberty	07	29.1
Carpopedal spasm	02	8.3
Diarrhoea	15	62.5
Abdominal pain/bloating sensation	14	58.3
Sticky stools	14	58.3
Night blindness	02	8.3
Hypothyroidism with increased dose requirement	01	4.1
T1 DM with recurrent hypoglycemia	04	16.6
Rickets	05	20.8

Table 3. Laboratory results/manifestation of celiac disease

Laboratory results	Number of Patients (N=24)	Percentage (%)
Normocytic normochromic	16	66.6
Microcytic hypochromic	05	20.8
Low Calcium	07	29.1
Increased alkaline phosphatase	07	29.1
X ray s/o rickets, osteomalacia	05	20.8
Hypothyroidism	03	12.4
Sub-clinical hypothyroidism	02	8.3
Anti-TPO positivity	03	12.4
Vitiligo	01	4.1

In bone and calcium metabolism abnormalities, the prevalence of both low calcium and increased alkaline phosphatase was 29.1% while 20.8% of patients had radiological signs of rickets/osteomalacia and hypovitaminosis D. Some 12.4% of patients suffered from overt hypothyroidism with the number of individuals having Anti-TPO positivity but only 8.3% of patients had subclinical hypothyroidism.

DISCUSSION

This is a cross-sectional study carried out in the department of endocrinology and metabolism during the study period of from July 2011 to June 2013. The main aim of the study was to determine the prevalence and various clinical manifestations of celiac disease in type 1 diabetes mellitus.

Celiac disease is an autoimmune-mediated enteropathy precipitated by the ingestion of gluten-containing foods (including wheat, rye and barley) in genetically susceptible persons. Celiac disease is also frequently associated with type 1 diabetes mellitus but less frequently than autoimmune thyroiditis. From last few years, numerous screening studies showed increased worldwide prevalence of celiac diseases in type 1 diabetes mellitus[5] However, data from South Asia is very limited especially in the Indian subcontinent.[9] Its prevalence in children and adolescents with type 1 diabetes ranges from 5 to 7%. In a previous study done by Bhadada et al[10] the prevalence rate was 11.1% among type 1 diabetics. In the present study, out of 236 type 1 diabetics, celiac disease was present in 24 patients, the prevalence is 9.37%. Only one patient was diagnosed with celiac disease before the diagnosis of type 1 diabetes.

Gluten intake varies from population to population and depends upon dietary practices. Wheat is the staple cereal in the northern part of India and flat bread made from wheat flour is one of the most important constituents of almost every meal. In the southern and northeastern part of India, rice is a staple food. A typical North Indian diet, where flat bread is the usual meal, contains about 25–30 g of gluten per day; whereas average gluten intake in the West varies from 10 to 20 g/day.[23]

Although the majority of detected cases of celiac diseases in children with diabetes mellitus are reported to be asymptomatic or silent,[12,13] we have demonstrated that many children do have subtle gastrointestinal complaints that may indicate celiac diseases. Directing specific questions may help increase the yield of gastrointestinal symptoms in these children.

In our study, the common clinical manifestations which were found in type 1 diabetes mellitus with celiac disease are diarrhoea (62.5%), abdominal pain/bloating sensation (58.3%), short stature (58.3%), sticky stool (58.3%) and delayed puberty in 29.1% of patients. Some uncommon manifestations are rickets (20.8%), recurrent hypoglycemia (16.6%), carpopedal spasm (8.3%) and night blindness (8.3%). The most common laboratory findings were normocytic normochromic anemia (66.6%) followed by microcytic hypochromic anemia.

A concern with malabsorptive disease is that it could increase the incidence of hypoglycemia in diabetes, particularly in patients under tight control.[21] About 16% patients presents with hypoglycemia.[21]

Malabsorption may also be linked to vitamin A deficiency which leads to night blindness and treatment failures may be due to inadequate management either of celiac disease or of thyroid disease or both, which may lead to increased dose requirement of levothyroxine.[22]

Numerous studies from all over the world showed the varied manifestations of celiac disease in type 1 diabetes, but these all depend upon the place of study, study population, follow up rate, etc. The most common manifestations in studies is the anemia followed by abdominal complains, short stature, delayed puberty, recurrent hypoglycemia and hypocalcemia.[11,12]

Studies on the impact of celiac diseases on glycemic control and growth in patients with T1D have shown conflicting results.[13-14] Our patients with type 1 diabetes and celiac disease had poor glycemic control and growth parameters as compared to patients without celiac disease as judged by fasting blood sugar and HbA1C.

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We confirmed the observation that children with diabetes who went on to develop celiac disease were younger at diagnosis of DM than other children with DM.[13] The predominance of males with celiac disease in the present study has been observed in few studies,[17] while other studies in different races have shown a female predominance,[16] which likely represents variability of genetic and environmental factors among different races.

While the majority of our patients with celiac diseases were found to have gastrointestinal symptoms, iron deficiency and hypocalcemia, which are indices of malabsorption, were also prominent in the celiac disease patients[15] The potential for early reversal of abnormalities in indices of intestinal malabsorption (iron and calcium deficiencies) is one of the advantages for screening asymptomatic children for early detection of celiac diseases in T1DM patients.

There are many barriers to maintenance of a gluten-free diet (GFD); some of them are universal and some of them are unique to Indian patients with CD. Patients with CD are challenged with barriers in maintenance of a strict GFD primarily due to inadequate information and education about the disease.[23] Insufficient background awareness about CD and its strict dietary restriction in the community creates a problem for the patient and the family of patients with CD. Due to the lack of gluten labeling on food items in India, it is difficult for anyone to know if a particular food product is gluten-free or not. Contamination of food with gluten is another concern. [23]

Adherence to GFD is the most critical factor for remission of CD. Adherence to GFD is complex and is influenced by knowledge, country or region of residence, availability of GF food, determination, and social support. Gluten-containing foods can be replaced by rice, maize, barley grain, millet (Bajra), sorghum (Jowar) and other locally available millet flour or products.[23] Following the introduction of gluten-free diet to patients, a sense of general well-being pervades, weight and height improve and the severity of acute and chronic complications of celiac disease decreases.[22]

CONCLUSION

Celiac disease was found in about 10% of patients with type 1 diabetes, almost 10-20 times higher than that observed in general pediatric population. Atypical manifestations (rickets, recurrent hypoglycemia, carpopedal spasm, and night blindness) were found to be common in patients with type 1 diabetes as compared to the general population. Unexplained anemia, poor glycemic control, diarrhoea, short stature and rickets should raise suspicion for the possibility of undiagnosed celiac disease in patients with type 1 diabetes mellitus. Growth indices and parameters of glycemic control improve considerably on timely detection and management of celiac disease.

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ORIGINAL ARTICLE

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Spot and Morning Cortisol in Comparison to Low Dose Short Synacthen® Test

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Abstract

Objective. While the low dose short Synacthen® test (LDSST) is considered to be the gold standard to evaluate adrenal function, it is labor-intensive, invasive and inconvenient. The aim of the study is to identify cut-offs for spot serum cortisol for in-patients and morning serum cortisol for out-patients. The study also aims to describe the disease spectrum leading to suspicion of adrenal insufficiency in a Chinese out-patient cohort.

Methodology. Adult patients were recruited from a tertiary hospital in Hong Kong. 423 in-patients were included consecutively from July 2013 to December 2013, and 422 out-patients from June 2014 to October 2014. Serum cortisol responses at 0, 20 and 30 minutes were evaluated.

Results. For in-patients admitted for acute illness, a spot serum cortisol of ≤92 nmol/L indicated adrenal insufficiency, and a value of ≥494 nmol/L signaled adequate adrenal reserve. The respective morning cortisol values for out-patients who were ambulatory and not under stress were ≤124 nmol/L and ≥428 nmol/L. The percentage of unnecessary LDSST was higher in the in-patient cohort than the out-patient cohort (43% and 37%, respectively). The most common referral for out-patient LDSST was for suspected iatrogenic Cushing's syndrome (ie: iatrogenic adrenal suppression) from Rheumatology.

Conclusions. The LDSST is of little added value in in-patients with spot serum cortisol of ≤92 nmol/L or ≥494 nmol/L and out-patients with morning serum cortisol of ≤124 nmol/L or ≥428 nmol/L. Spot and morning cortisol levels, for in and out-patients respectively, should be incorporated into endocrine protocols preceding the LDSST in the workup of adrenal insufficiency.

Key words: spot cortisol, morning cortisol, adrenal insufficiency, low dose short Synacthen® test

INTRODUCTION

Accurate assessment of adrenocortical function is essential in the management of patients with suspected adrenal insufficiency (AI). If left untreated, adrenal crisis with features of severe vomiting, shock, confusion, loss of consciousness or even death might result during acute stress. The low dose 1 μg short Synacthen® test (LDSST) is considered to be the gold standard to evaluate adrenal function in such patients. A maximum cortisol response between 400 to 620 nmol/L within 20 to 40 minutes after intravenous administration of 1 μg of synthetic adrenocorticotropin (ACTH) (Synacthen®) are variably used for the diagnosis of adrenal sufficiency.[1-6]

In patients with recent onset ACTH deficiency (e.g. within 2 weeks after pituitary surgery), the adrenal glands may not have become completely atrophic and may still respond to ACTH stimulation.[1,2] For this reason, the insulin tolerance test (ITT) is traditionally seen as the gold standard for investigation of the integrity of the hypothalamic-pituitary-adrenal (HPA) axis in secondary adrenal insufficiency. However, the ITT carries a risk of hypoglycemia, and is contraindicated for patients with epilepsy, ischemic heart disease or recent cerebrovascular accident.[3] The metyrapone test may also be used in evaluating the HPA axis. Its use is limited because metyrapone may precipitate refractory hypotension in some patients, and the measurement of 11-deoxycorticosterone is not readily available in most laboratories.[4,5] Other stimulation tests, such as the glucagon or the corticotropin-releasing hormone tests, are not as sensitive and specific as ITT.[6,7] The LDSST has been validated as a safe and sensitive method for screening abnormalities of the HPA axis in Chinese patients suspected of having secondary adrenocortical

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insufficiency.[8] Earlier studies indicate that LDSST can also detect partial adrenal insufficiency, such as in cases of chronic use of inhaled glucocorticoids or early adrenal destruction by infectious or autoimmune processes. These may be missed by the standard dose short Synacthen® test (SST), which involves a supraphysiologic stimulus that can stimulate a compromised adrenal gland that still has some residual function.[9,10] In our hospital, a peak cortisol response in LDSST at or above 500 nmol/L is accepted as adequate adrenal reserve in a patient with suspected adrenal insufficiency (primary, or secondary if at least 2 weeks post pituitary surgery).

The LDSST procedure involves intravenous administration of Synacthen® and venous blood sample collection at 0, 20 and 30 minutes for measurement of serum cortisol. In our center, cortisol is measured by electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). The test is labor intensive, invasive and inconvenient. The requirement of multiple blood sampling is poorly accepted by patients, especially those who are subjected to the test on a regular basis. A simpler test, such as a spot or morning cortisol, has been evaluated to indicate cortisol reserve.[11,12] In the Caucasian population, a 9 am serum cortisol of <100 nmol/L or >500 nmol/L has been validated as adrenal insufficient or adrenal sufficient, respectively, eliminating the need for further complicated stimulation tests.[13] It was observed that the number of LDSST yielding results consistent with normal adrenal reserve (85%, unpublished data) was more than expected in our hospital as compared to previous studies (69% to 71%).[13,14] This prompted the question as to whether too many patients were put through unnecessary invasive procedures, and whether this could be reduced by measuring spot or morning serum cortisol prior to the stimulation test.

The aims of this study were:

1. To assess the usefulness of spot serum cortisol in the diagnosis of patients with suspected primary or secondary adrenocortical insufficiency, using LDSST as the gold standard diagnostic test, and to identify the optimal cut-off values for spot cortisol in the Chinese population in the in-patient setting; and

2. To assess the usefulness of morning serum cortisol in the diagnosis of patients with suspected primary or secondary adrenocortical insufficiency, using LDSST as the gold standard diagnostic test, and to identify the optimal cut-off values for morning cortisol in the Chinese population in the out-patient setting.

METHODOLOGY

The study was carried out in two phases at the Prince of Wales Hospital, the teaching hospital of the Chinese University of Hong Kong. The first phase was a retrospective analysis of data from 423 in-patients included consecutively from July 2013 to December 2013. All patients were evaluated with LDSST because of suspected disease of the HPA axis for various reasons, such as hyponatremia, hypotension, hypoglycemia or suspected iatrogenic Cushing's syndrome, during their hospitalization for acute illnesses. The LDSST was performed by a house officer at any time of the day, usually within 12 hours from the time the order was placed by a medical officer. One mL (0.25 mg) of Synacthen® was added to 499 mL of normal saline. After mixing thoroughly, 2 mL of the freshly mixed solution (containing 1 μg Synacthen®) was withdrawn into a syringe. Blood was drawn for 0 minute serum cortisol, followed by an intravenous bolus injection of Synacthen® 1 μg. Blood was again sampled for cortisol measurement at 20 and 30 minutes after the injection. Serum cortisol levels were assayed at each time point by electrochemiluminescence immunoassay (Roche Diagnostics, Basel, Switzerland). The lower limit for detection was assessed to be 0.5 nmol/L. The coefficients of variation at different levels for the assay were 3.8% at 104 nmol/L, 2.5% at 700 nmol/L and 2.6% at 1045 nmol/L.

The second phase was a prospective analysis of 422 out-patients recruited consecutively from June 2014 to October 2014. All patients were evaluated with LDSST because of suspected disease of the HPA axis when free from acute stress. The patients were categorized into 4 groups based on the reasons for referral:

Category 1: Patients referred from in-patient at discharge, excluding those in categories 2 and 3;

Category 2: Patients with pituitary lesion or disturbance;

Category 3: Patients who were on exogenous steroid or had adrenalectomy done due to adrenal Cushing's syndrome; and

Category 4: Patients referred for reasons not included in the previous 3 categories.

The LDSST was carried out in the out-patient Endocrine Centre by a specialty nurse at 0900H. The steps of the test and the cortisol assay were exactly the same as those in the first phase of the study.

Receiver operating characteristic (ROC) curves were obtained using the Statistical Package for Social Sciences version 21 (SPSS Inc., Chicago, Illinois).

RESULTS

Phase One (In-patients, retrospective)

423 in-patients with suspected adrenal insufficiency underwent LDSST during their hospitalization for acute illnesses over a 6-month period. Only a small proportion, 15%, failed the LDSST. Both basal and peak cortisol ranges were lower in patients who failed the test

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.10

(Table 1). The peak cortisol of these patients were normally distributed (Appendix 1). There was a significant correlation between basal cortisol values and peak levels during the LDSST (R^2=0.528) (Figure 1). ROC analysis suggested the safest baseline cortisol cut-off point of ≤92 nmol/L as an indication of adrenal insufficiency, resulting in 100% sensitivity and 32% specificity. A cortisol cut-off point of ≥494 nmol/L was found have 100% specificity, but with only 45% sensitivity (Figure 2). Twenty (4.7%) patients had basal cortisol ≤92 nmol/L, while 163 (38.5%) had values ≥494 nmol/L.

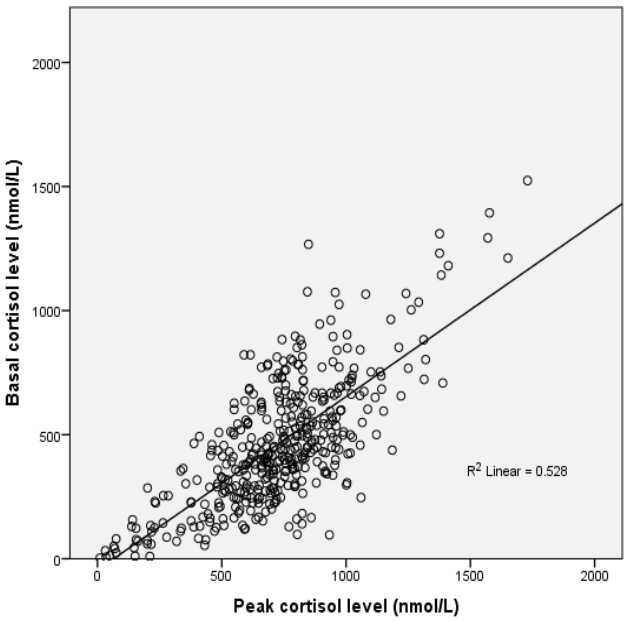

Figure 1. Individual cortisol peak levels in 423 in-patients plotted against basal cortisol during low dose short Synacthen® test.

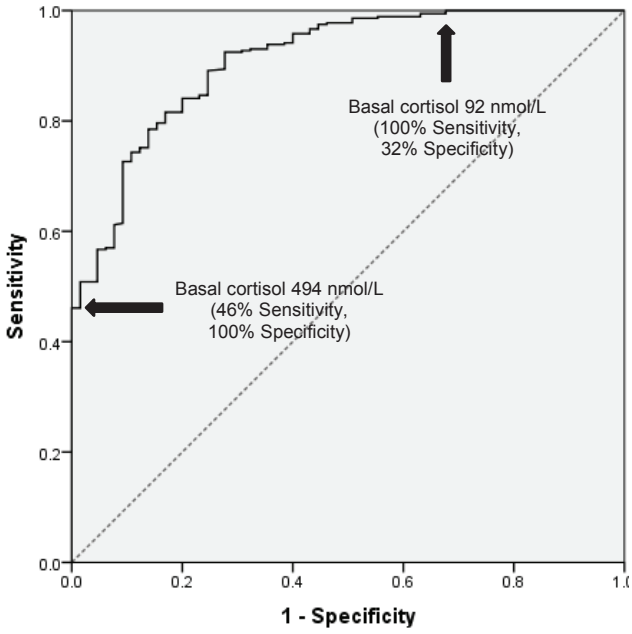

Figure 2. Receiver operating characteristic curve of basal cortisol levels in 423 in-patients with the low dose short Synacthen® test (LDSST) as reference test. Peak cortisol levels in the LDSST less than 500 nmol/L indicate adrenal insufficiency. Area under the curve 0.884 (95% confidence intervals 0.852-0.917).

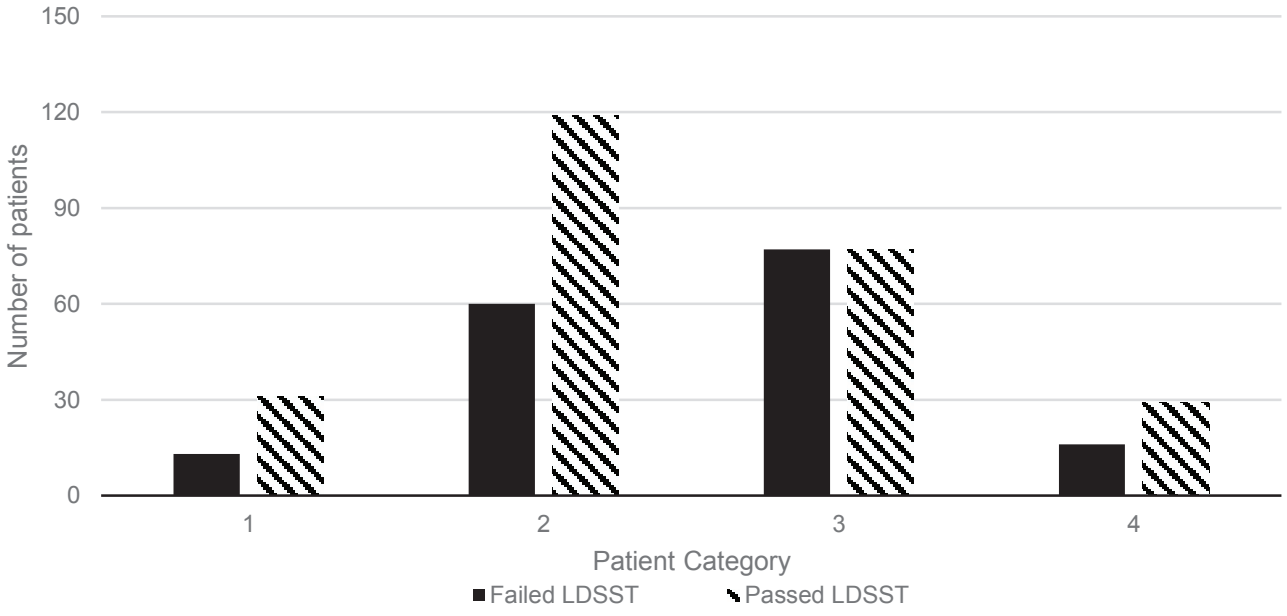

Figure 3. Number of patients in each out-patient category stratified by their responses to low dose short Synacthen® test. Category 1: Patients referred from in-patient at discharge, excluding those in categories 2 and 3; Category 2: Patients with pituitary lesion/disturbance; Category 3: Patients who were on exogenous steroid or had adrenalectomy done due to adrenal Cushing's syndrome; Category 4: Patients referred for other reasons.

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.10

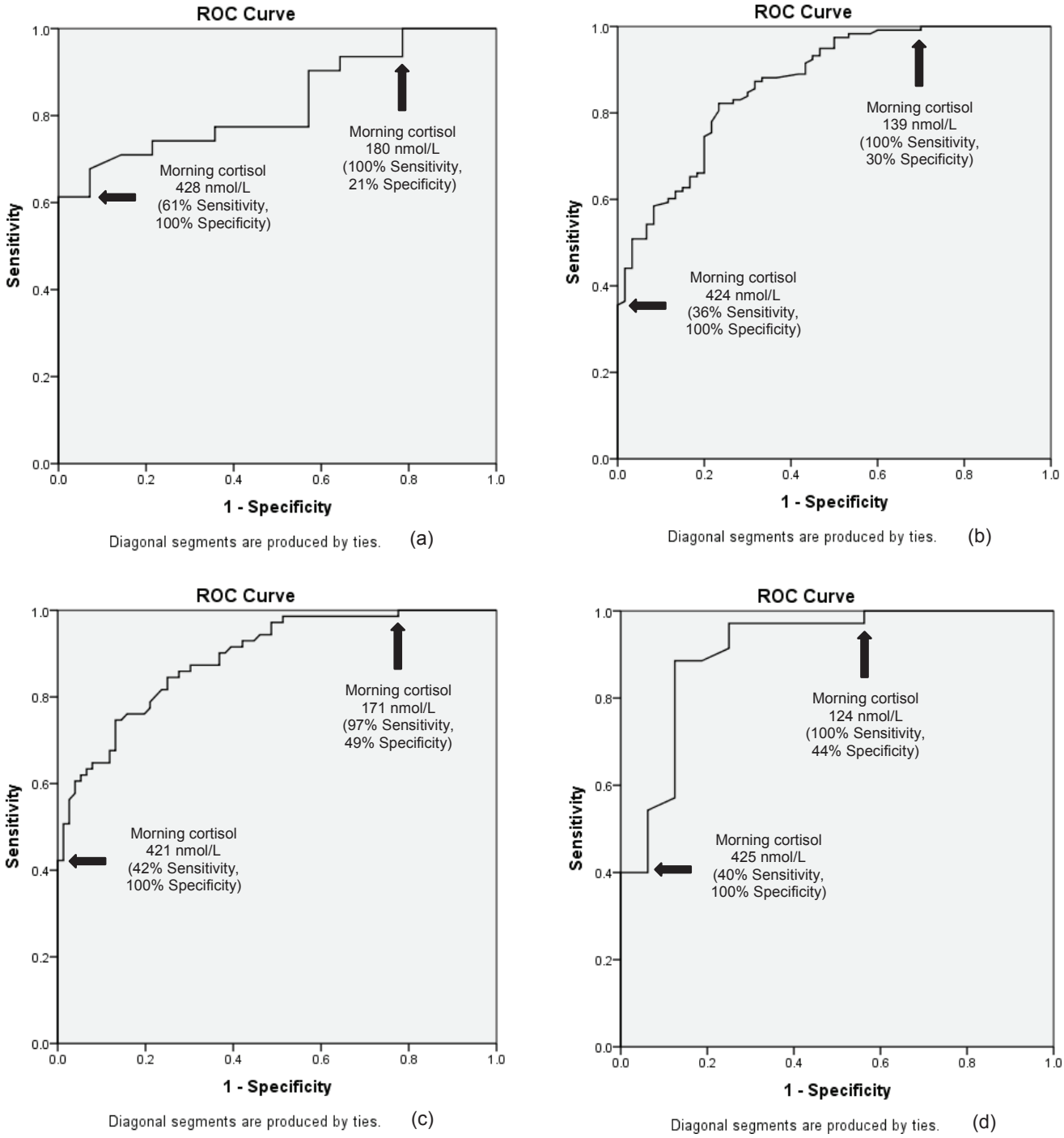

Figure 4. Receiver operating characteristic curves of morning cortisol levels in 422 out-patients with the low dose short Synacthen® test (LDSST) as reference test. Peak cortisol levels in the LDSST less than 500 nmol/L indicate adrenal insufficiency. (a) Category 1: In-patients referred upon discharge, excluding those in categories 2 and 3; area under the curve (AUC) 0.828 (95% confidence intervals 0.711-0.945). (b) Category 2: Patients with pituitary lesion/disturbance; AUC 0.869 (95% confidence intervals 0.817-0.922). (c) Category 3: Patients who were on exogenous steroid or had adrenalectomy done due to adrenal Cushing's syndrome; AUC 0.879 (95% confidence intervals 0.824-0.933). (d) Category 4: Patients referred for other reasons; AUC 0.913 (95% confidence intervals 0.820-1.000).

Phase Two (Out-patients, prospective)

422 out-patients with suspected adrenal insufficiency underwent LDSST in the out-patient Endocrine Centre when they were not under acute stress over a 5-month period. The peak cortisol of these patients were normally distributed (Appendix 2). The number of patients in each out-patient category stratified by their responses to the LDSST is illustrated in Figure 3. Fifty percent of the patients in category 3 failed the LDSST. The proportions of patients who failed the LDSST were similar across category 1, 2, and 4 (30 to 36%). A summary of the responses and reasons for referral for LDSST is presented in Table 2. Most patients were category 2, with radiotherapy to the head and neck region as the most common reason for referral. For both categories 1 and 4, hyponatremia was the most frequently cited reason for referral, followed by postural

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.10

BP drop or hypotension. Suspicion of iatrogenic Cushing's syndrome made up the majority of referrals in category 3 (150 out of 154 patients), most frequently referred from Rheumatology, followed by general medical clinics. Two patients had no clear reasons for referral despite detailed review of their medical records: one in category 1 (referred from in-patient) and one in category 4 (referred from out-patient). A vast variety of reasons for referral were noted in category 4, ranging from abnormal biochemistry results (hyponatremia or hypoglycemia), general signs or symptoms (postural BP drop/hypotension or hyperpigmentation), localized adrenal abnormalities (adrenal abscess, metastasis, calcification, or resection), to endocrine syndromes [polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes (POEMS); or polyglandular autoimmune syndrome (PAS)]. ROC curves for patients in different categories showed that the safest morning cortisol cut-offs as signals of adrenal insufficiency or sufficiency in the out-patient population were different for patients in different categories (Figure 4). Taken as a whole, the most sensitive serum cortisol level indicative of adrenal insufficiency was ≤124 nmol/L, the lowest cut-off across all categories with a sensitivity of 100%. A serum cortisol of ≥428 nmol/L, the highest cut-off across all categories with a 100% specificity, was the most specific level that ruled out adrenal insufficiency. Fifty-three patients (12.6%) had morning cortisol levels ≤124 nmol/L, while 101 (23.9%) had levels ≥428 nmol/L.

Table 1. Cortisol levels of in-patients with low dose short Synacthen® test performed over a 6-month period (N=423)

	Patients who failed[a] LDSST[b]	Patient who passed[c] LDSST[b]
n (%)	65 (15%)	358 (85%)
Basal cortisol range, nmol/L	3-493	96-1524
Peak cortisol range, nmol/L	10-499	504-1730

[a] With peak cortisol <500 nmol/L
[b] LDSST, low dose short Synacthen® test
[c] With peak cortisol ≥500 nmol/L

Table 2. Cortisol levels of out-patients with low dose short Synacthen® test performed over a 5-month period (N=422)

Category	1a	2b	3c	4d	Total
n	44	179	154	45	422
Number of patients who failed LDSSTe (%)	13 (30)	60 (34)	77 (50)	16 (36)	166 (39)

[a] Category 1: Patients referred from in-patient at discharge, excluding those in categories 2 and 3
[b] Category 2: Patients with pituitary lesion or disturbance
[c] Category 3: Patients who were on exogenous steroid or had adrenalectomy done due to adrenal Cushing's syndrome
[d] Category 4: Patients referred for reasons not included in the previous 3 categories
[e] LDSST, low dose short Synacthen® test

Table 3. Category 1[a] reasons for referral

Reason	Frequency
Hyponatremia	23
Postural BPb drop/hypotension	8
Dizziness without change in BPb	3
Hypoglycemia	3
Hyperkalemia	2
Recurrent syncope	2
Low random cortisol	1
Adrenal insufficiency diagnosed in private sector	1
Unknown	1

[a] Category 1: In-patients referred at discharge, excluding those in categories 2 and 3
[b] BP, blood pressure

Table 4. Category 2[a] reasons for referral

Reason	Frequency
Post-radiotherapy to head and neck region	68
Post-transsphenoidal surgery	46
Pituitary tumor on imaging	41
Pituitary apoplexy	5
Empty sella	4
Biochemically cranial diabetes insipidus without lesion on imaging	3
Iron overload	2
Isolated ACTHb deficiency	2
Hyperprolactinemia	2
Post-transfrontal operation	1
Hypogonadotropic hypogonadism	1
Suspected Kallmann syndrome	1
Biochemically hypopituitary without pituitary lesion on imaging	1
Histiocytosis	1
Human immunodeficiency virus infection	1

[a] Category 2: Patients with pituitary lesion or disturbance
[b] ACTH, adrenocorticotrophic hormone

Table 5. Category 3[a] reasons for referral

Reason	Frequency
Post adrenalectomy for adrenal Cushing's syndrome	4
Suspected iatrogenic Cushing's syndrome from clinics	148
Rheumatology	40
General Medical	29
Neurology	18
Renal	18
Respiratory	15
Endocrine	14
Dermatology	7
Hematology	4
Gastroenterology	2
Thyroid	1
Suspected iatrogenic Cushing's upon admission to wards	2

[a] Category 3: Patients who were on exogenous steroid or had adrenalectomy done due to adrenal Cushing's syndrome

Table 6. Category 4[a] reasons for referral

Reason	Frequency
Hyponatremia	17
Postural BPb drop/hypotension	11
Hypoglycemia	3
Hyperpigmentation	2
Adrenal abscess	2
Adrenal metastasis	1
Adrenal calcification	1
Post adrenalectomy for adrenal cortical carcinoma	1
Primary adrenal insufficiency	1
POEMSc	1
Polyglandular autoimmune syndrome	1
Suspected autoimmune disease	1
Hirsutism	1
Post-bone marrow transplant	1
Unknown	1

[a] Category 4: Patients referred for reasons not included in the previous 3 categories
[b] BP, blood pressure
[c] POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes

DISCUSSION

Simpler and non-invasive tests to diagnose adrenal insufficiency, such as spot or morning serum cortisol, could possibly reduce the number of patients having to go through the cumbersome LDSST. In this study, we compared basal cortisol levels with LDSST in a group of in-patients, to determine their utility in being the first step screening test for evaluation of AI. We also compared the morning cortisol levels with the LDSST in a group of out-patients referred for suspected AI, and determined the safest cut-offs for identification of patients requiring further dynamic tests. The disease spectrum leading to suspicion of AI in our Chinese out-patient cohort is described in Table 2.

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.10

Roux studied a cohort of 210 patients with suspected AI to determine the utility of the 9 AM cortisol level prior to SST in out-patient assessment using automated enzyme-linked immunosorbent assay (ELISA) with the Roche Diagnostics ES700 (Lewes, UK). The study found that the SST is of little added value in patients with a 9 AM cortisol of <100 nmol/L or >500 nmol/L. They recommended a 9 AM cortisol level should be included in the appropriate protocols for endocrine workup, since it would have prevented 21% of the patients from going through unnecessary SST.[13] Our investigation of 422 Chinese out-patients revealed similar values: patients with morning cortisol levels ≤124 nmol/L (n=53) and ≥428 nmol/L (n=101) were all adrenal insufficient and adrenal sufficient, respectively. Therefore, further LDSST for these groups of patients (37% of the original 422 patients) would not have been indicated. Similarly, for our in-patient cohort, 43% of the original 423 patients would not have needed the LDSST based on the spot cortisol cut-offs of ≤92 nmol/L (adrenal insufficient) and ≥494 nmol/L (adrenal sufficient). Our higher percentage of unnecessary dynamic test as compared to Roux's study may be the result of a lower clinical threshold for referral in our Centre. However, since the exact reasons for referral were not specified in Roux's paper, we are unable to further examine this hypothesis.

In our study, the cortisol cut-off level for the diagnosis of adrenal insufficiency with the best sensitivity and specificity was lower for in-patients (92 nmol/L) than out-patients (124 nmol/L). The percentage of unnecessary LDSST was higher in the in-patient cohort (43%) than the out-patient cohort (37%). Because the in-patients were under acute stress and the out-patients were ambulatory and not acutely ill, the cortisol levels in these groups cannot be directly compared. The clinical threshold of suspecting adrenal insufficiency is also lower for in-patients, since they are often very ill, leading to a higher number of unnecessary LDSST.

Fifteen percent of the in-patients failed the LDSST. For the out-patients, the percentages of patients failing the LDSST were similar for categories 1, 2 and 4 (30 to 36%). Remarkably, 50% of those in category 3 failed the LDSST. Chronic adrenal suppression, either by exogenous steroid or excessive endogenous steroid from a functioning adrenal adenoma, made them more prone to genuine adrenal insufficiency.

Cushing's syndrome due to exogenous steroid is common, as about 1% of the general population use exogenous steroids for various indications.[15] A recent study from the United Kingdom reported that up to 33.2% of patients on exogenous steroids had a subnormal response to short Synacthen® test when cortisol levels were analyzed with a standard automated competitive immunoassay platform (Roche 114 Modular System, Roche, Lewes, UK).[16] Nasopharyngeal carcinoma (NPC) is a major public health concern in Hong Kong with an annual incidence of 15.4 in 100,000, with radiotherapy being the most commonly used modality of treatment since decades ago.[17] Therefore, it is not surprising that these two groups of patients made up the majority of our out-patient cohort (52%). Both groups are often regularly tested for adrenal function to monitor adrenal recovery in iatrogenic Cushing's and adrenal failure in NPC. Currently, these patients are all being managed by internal medicine specialists in our hospital, taking up a significant share of consults in the internal medicine clinics. Informing the family doctors about the morning cortisol range needing LDSST derived from this study (124 to 428 nmol/L) would help them make rational decisions on who would need follow-up LDSST to diagnose AI, and who would have to be referred to internal medicine clinics when LDSST is needed. This huge number of patients may be managed adequately in the family medicine clinics, while more clinic quota in the internal medicine clinics may be spared for other patients in need.

It should be emphasized that a normal spot/morning cortisol or even LDSST result does not preclude the use of glucocorticoid stress coverage if the clinical picture is strongly suggestive of adrenal insufficiency, especially during extreme physiological stress. While adrenal sufficiency was defined as an adequate serum cortisol response of >500 nmol/L at either 20 or 30 minutes after intravenous Synacthen® for the purpose of this study, this assumption may not always be applicable in clinical practice. LDSST cut-offs were obtained from either 2.5th or 5th percentile values from testing normal individuals, implying an intrinsic error rate when using this test.[18] Physicians ordering spot/morning cortisol or LDSST should always interpret the results within the specific clinical context when making a diagnosis of adrenal insufficiency.

Our study has several limitations. First, the timing of LDSST for in-patients was not standardized. Due to practicability issues within our stretched health-care system, our house officers could only attend to dynamic function tests after completion of all on-hand urgent duties, making it difficult to have tests done at 0900H. As cortisol secretion follows a diurnal rhythm, this lack of standardization might impair the applicability of our analyses. Nevertheless, acute stress is known to affect diurnal rhythm, so that standardizing the timing of LDSST at 0900H for in-patients may not be as important as those performed in out-patients who do not have acute illnesses.[19] Second, concomitant blood glucose levels during cortisol measurements that may influence cortisol responses in acutely ill patients were not accounted for since the data were not captured. Third, since 80% of plasma cortisol is bound by cortisol-binding globulin (CBG), and that many conditions (thyrotoxicosis, hypothyroidism, chronic liver disease, nephrotic syndrome, use of oral contraceptive pills) may affect the levels of CBG and levels of free cortisol, the measurements of CBG with serum cortisol would have improved the

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accuracy of our analyses.[20-22] Fourth, for patients with suspected secondary adrenal insufficiency due to exogenous glucocorticoids, information on the dose, route, potency and duration were not available for assessment of dose-dependent effects. However, the expectation would be intuitive, so that the larger dose, longer duration, more potent the glucocorticoids used, the more likely that secondary adrenal insufficiency would result. Fifth, the duration of pituitary disease was not captured in this study. Sixth, as this is a continual quality improvement project in our hospital, instead of a defined sample size, a designated time period was followed according to the project timeline set by the hospital management team. Lastly, since it has been shown that different assays yield different cortisol cut-offs for confirmation of AI, results and interpretations from our study cannot be directly compared with those from studies using different assays.[23]

Despite these limitations, the clear separation of patients into those with acute illnesses (in-patients) and those without acute stress (out-patients), the relatively large sample size for both the in- and out-patients cohorts, and the detailed categorization of the out-patient cohort are important strengths of this study.

CONCLUSION

We found that he LDSST is of little added value in in-patients with spot serum cortisol of ≤92 nmol/L or ≥494 nmol/L, and out-patients with morning serum cortisol of ≤124 nmol/L or ≥428 nmol/L. Spot and morning cortisol levels, for in- and out-patients respectively, should be incorporated into endocrine protocols preceding the LDSST in the workup of adrenal insufficiency in order to free up manpower, reduce waiting time in specialists' clinics, and to save patients from unnecessary invasive investigations.

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Disclosure Summary
The authors declare the absence of any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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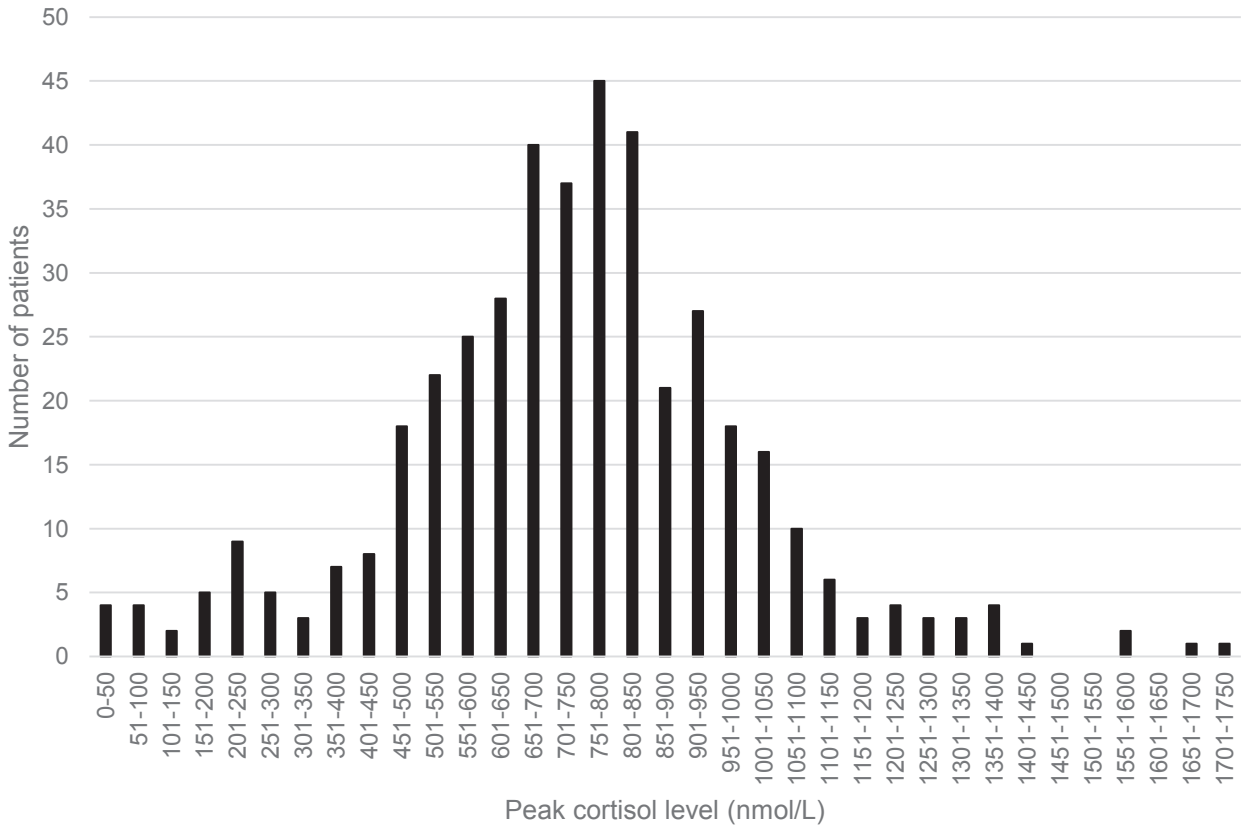
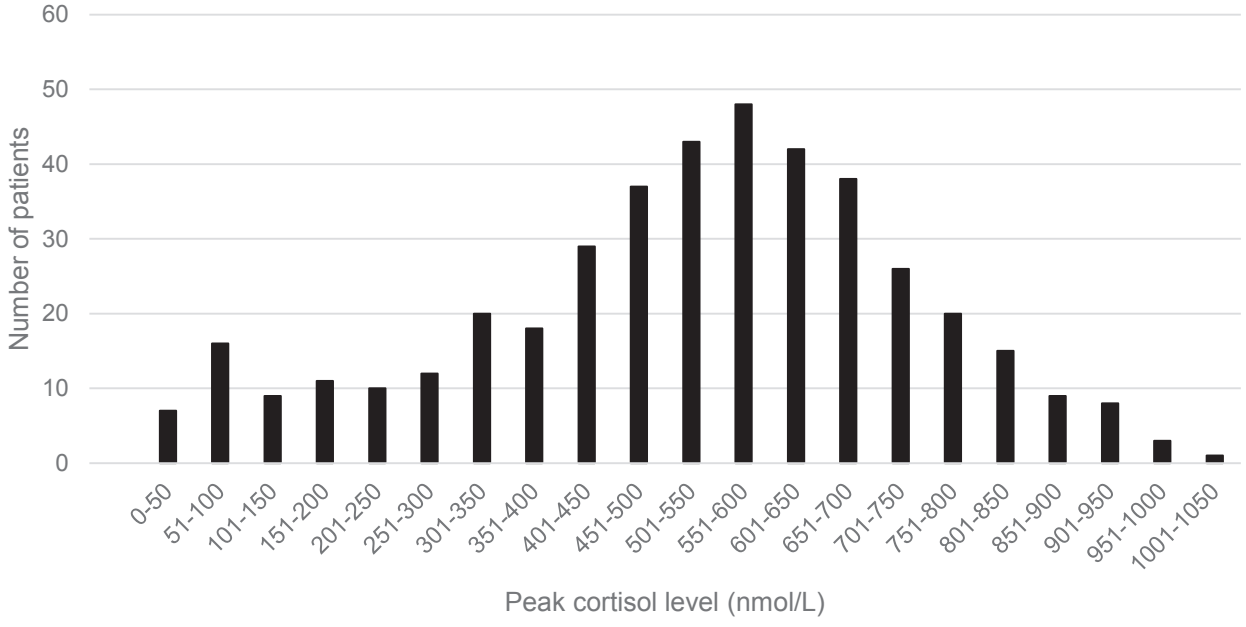
Supplemental material



Appendix 1. Peak cortisol levels in low dose short Synacthen® tests in 423 in-patients.



Appendix 2. Peak cortisol levels in low dose short Synacthen® tests in 422 out-patients.

ORIGINAL ARTICLE

JAFES
Journal of the ASEAN Federation of Endocrine Societies

Prevalence of Thyroid Dysfunction in Young Patients with Type 2 Diabetes Mellitus in Eastern India, Study of 120 Cases from a Tertiary Care Hospital

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Abstract

Objective. The association between thyroid dysfunction and Type 2 Diabetes Mellitus has been reported in several studies. This study was done to explore the prevalence of thyroid dysfunction in young (<40 years) patients with type 2 Diabetes Mellitus in Eastern India.

Methododology. A retrospective chart review of 120 patients with Type 2 Diabetes Mellitus was done. 120 patients (male 81, female 39) of age <40 years, who fulfilled the diagnostic criteria for Diabetes Mellitus according to ADA (American Diabetes Association) were enrolled and investigated through performance of Thyroid Function Tests (FT4,TSH).

Results. Of 120 patients (of less than 40 years of age), 65.83% of patients had the biochemical features of thyroid dysfunction. In descending order of frequency, we found subclinical hypothyroidism in 43.33% of cases (defined by no symptoms or no clinical features of hypothyroidism but with TSH level in the range of above 5 miu/ml but below 10 miu/ml with normal FT4 level), followed by 9.2% of patients with overt hypothyroidism (either clinical features or TSH >10 miu/ml or FT4 below normal), 8.3% with subclinical hyperthyroidism (only biochemically low level of TSH <0.34 miu/ml in this study) and 5% of patients show features of clinical hyperthyroidism (clinical or FT4 level well above normal range along with low TSH).

Conclusion. A high prevalence of thyroid dysfunction in young type 2 DM patients suggests evaluation for thyroid disorder for proper management.

Key words: diabetes mellitus, subclinical hypothyroidism, free levothyroxine, thyroid stimulating hormone

INTRODUCTION

The International Diabetes Federation projects that 592 million individuals will have diabetes by the year 2035.[1,2] The prevalence of type 2 Diabetes Mellitus (DM) is also rising in younger individuals presumably because of increasing obesity and reduced activity levels as countries become more industrialized.[3]

The association between thyroid dysfunction and DM has long been recognized. Thyroid hormones are insulin antagonists; both insulin and thyroid hormones are involved in cellular metabolism and excess and deficit of any one can result in functional derangement of the other. As diabetes is a major public health problem, any disorder that may even be weakly associated with it merits special attention.

Very few studies are reported regarding the relationship of thyroid dysfunction in type 2 DM in young patients. The control of hyperglycaemia in the presence of underlying thyroid dysfunction, even subclinical, poses problems. Correction of thyroid dysfunction may help improve metabolic outcome in type 2 DM patients. As such, thyroid dysfunction and Type 2 DM may be interlinked. Currently there are no internationally accepted guidelines for screening of thyroid dysfunction in Type 2 DM patients. This study therefore is designed to inform the burden of dual pathological prevalence of thyroid dysfunctions in young (less than 40 years) type 2 DM patients.

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OBJECTIVES

1. To assess the thyroid abnormalities in diabetic subjects with or without symptoms of thyroid dysfunction.
2. To assess the prevalence of thyroid dysfunction based on biochemical and/or clinical features.
3. To assess the anti TPO positivity in patients with thyroid dysfunction.

METHODOLOGY

The study includes type 2 diabetics of age less than 40 years. Total of 120 patients were selected who were diagnosed as having type 2 DM in accordance with ADA criteria and evaluated with thyroid function tests (FT4, TSH).

Exclusion criteria

1. Type 1 DM
2. Type 2 DM above 40 years of age
3. Gestational DM
4. Proven thyroid disorder and under treatment
5. Very sick or critically ill patients
6. Patients who had undergone surgery of the thyroid gland
7. Patients who had exposure to radiation of the thyroid gland
8. Patients with drug-induced hyperglycemia

Data Analysis

Data analysis has been done in SPSS 19th software. Chi-square test was used in case of non-parametric value and p-value of <0.05 is considered significant.

Results and Analysis

Of the 120 patients, 81 were males (67.5%) and 39 were females (32.5%). Their average age is 35 years old. The youngest in our study was 26 years old (Figure 1).

Average FBS level in recently diagnosed Type 2 DM population was 137 mg/dl and 95% of the population falls within the range of 130 mg/dl to 161 mg/dl (Figure 2). Average postprandial blood sugar (PPBS) in this population was 223 mg/dl with 95% of them between 190 – 234 mg/dl (Figure 3).

HbA1c prevalence in 95% (2 S.D.) of the population was within 7.5 to 8%.

Normal range for serum FT4 level is 0.7-1.24 μg/dl (standardized for all values). Figure 4 and Figure 5 showed the distribution of FT4 and TSH level in the study population.

The study revealed that 65.8% of patients (79 out of 120) have biochemical features of thyroid dysfunction. Out of the 79 patients, 63 patients have biochemical features of hypothyroidism (79.74% of patients with thyroid dysfunction and 52.5% of the total population). 16 patients have biochemical features suggestive of hyperthyroidism (20.25% of patients with thyroid dysfunction and 13.33% of the total population). Further analysis showed that 43.33% had subclinical hypothyroidism (defined by no symptoms or no clinical features of hypothyroidism but with TSH level in the range of above 5 miu/ml but below 10 miu/ml with normal FT4 level), 9.2% had overt hypothyroidism (either with clinical features or TSH > 10 miu/ml or FT4 below normal), 8.3% had subclinical hyperthyroidism (with only low level of TSH< 0.34 miu/ml) and 5% patients had overt hyperthyroidism (with clinical features or FT4 level above normal range along with low TSH) (Figure 6).

To know the prevalence of autoimmunity in thyroid dysfunction, anti-TPO test was done. The study revealed that 22 patients out of the 79 patients with thyroid dysfunction were positive for anti-TPO antibodies (27.84% of total thyroid abnormality), whereas 57 patients with thyroid dysfunction were anti-TPO negative (72.15%). 7 patients without any thyroid dysfunction showed anti-TPO positivity (17.07%).

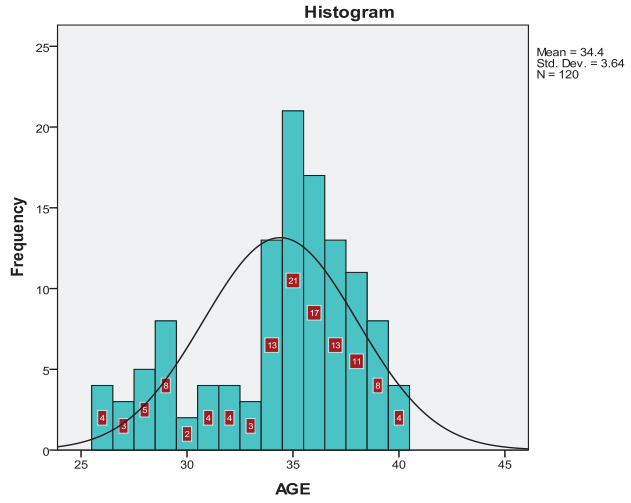

Figure 1. Distribution of age in the study population (n=120).

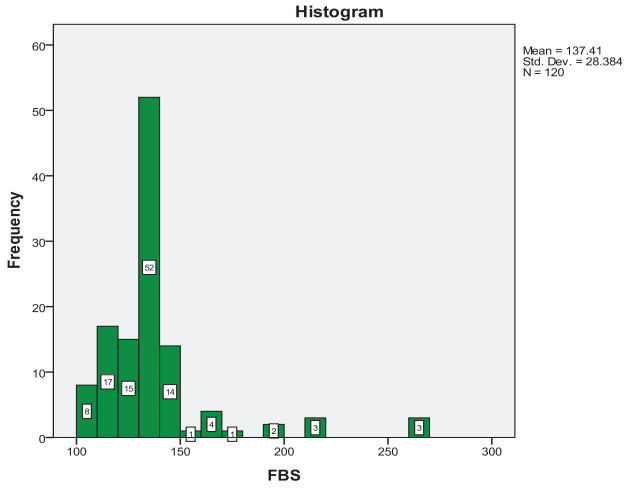

Figure 2. Distribution of FBS in the study population (n=120).

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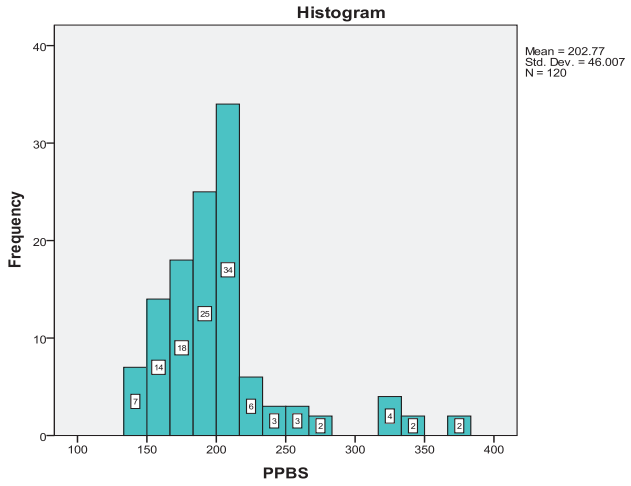

Figure 3. Distribution of PPBS in the study population (n=120).

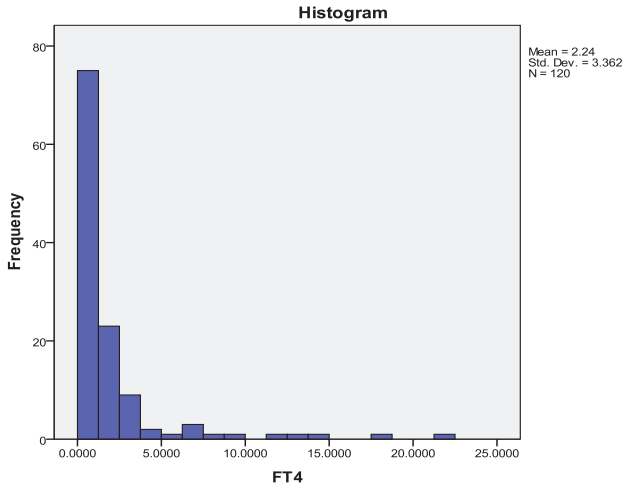

Figure 4. Distribution of FT4 level in the study population (n=120).

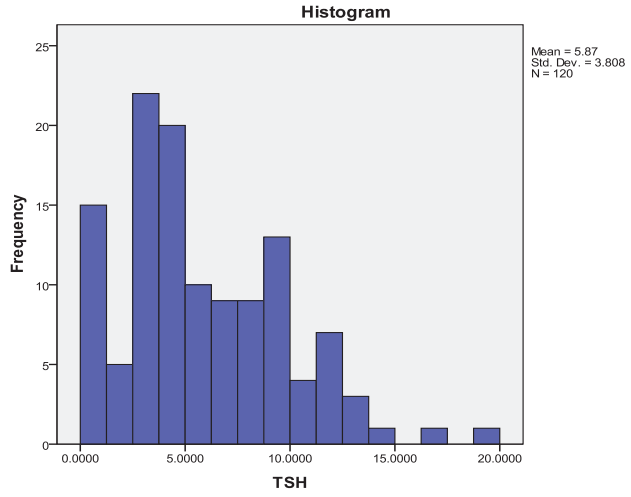

Figure 5. Distribution of TSH level in the study population (n=120).

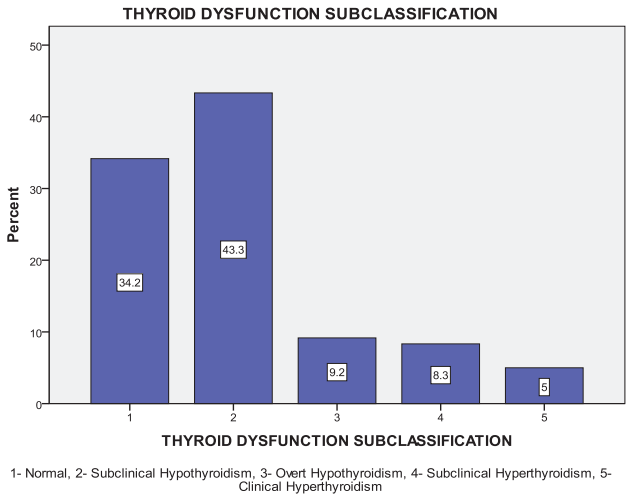

Figure 6. Thyroid dysfunction in the study population (n=120).

DISCUSSION

India will have 109 million diabetics by 2035 as projected by International Diabetes Federation.[2] Sequential surveys from India indicate that the prevalence of diabetes has risen steadily in the last few decades and more so in younger people.[4-7]

In our study, the average age of the study population was 35 years old which is a great burden for the society. Our study results are similar to several recent studies[8] and previous study of our own by Mukherjee S et al[9] in the general population. The mean age of detection of type 2 DM is 35 years in this study. This study reflects a large number of type 2 DM patients with early onset of their disease in contrast to the National Urban Diabetes Survey, carried out in six cities in 2001 in India.[7] However, recent studies like the Chennai Population Study (CUPS) showed similar prevalence in younger generation.[10]

The high fasting blood sugar level in our study reflects higher level of abnormal metabolic status in this part of India which causes more problems in maintaining normoglycaemia in younger individuals. The average PPBS in this study was almost similar to previous studies.[9] Distribution of HbA1c in this study is consistent with several studies.[11] Our study revealed FT4 level has little value in screening for thyroid dysfunction as most of the patients were found to have normal levels of FT4. But TSH level is significantly abnormal in large number of patients reflecting underlying thyroid abnormality in majority of the sample population, which is similar to previous studies.[12]

This study shows that 65.8% of this young diabetic population had thyroid dysfunction which is much higher than several previous studies, though it was in accordance with Mukherjee et al reported from eastern India.[9] This study showed much higher rate of thyroid dysfunction compared to several previous studies which showed lesser prevalence of this association and varied from 1.7% to 23% in different populations.[13-16]

Studies on pediatric population in India had shown higher prevalence of subclinical hypothyroidism (31.2%).[17] A very

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high prevalence has also been noted outside India, from Nigeria, (46.5%).[18] Subclinical hypothyroidism is the most common disorder in our study (43.33%) which is similar to several studies reported.[19-22]

CONCLUSION

This study is the first of its kind in Eastern India, showing very high prevalence of thyroid dysfunction in younger diabetics. As diabetes mellitus is currently increasingly diagnosed in the younger age group, this association has gained a new implication.

The causal association between high prevalence of abnormal thyroid hormone levels in younger diabetics is not fully understood. In our study, very high occurrence of thyroid dysfunction in younger diabetic individuals suggests a dual pathologic prevalence where autoimmunity is playing probably a minor role as evident from previous discussion.

Different studies support a biologically plausible role for hypothyroidism increasing the risk of atherosclerotic cardiovascular disease. Type 2 DM is also an independent risk factor for atherosclerotic cardiovascular disease.

This study suggests routine evaluation for thyroid screening and treatment in younger diabetics in this part of the world to prevent diverse complications of the high dual pathologic prevalence.

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ENDOCRINE SOCIETY

Highlights of ENDO: AFES

Dr. Rachel Gafni

Friday, December 11
- 9:50 – 10:20 *Symposium 3: Paediatric Endocrinology -- Disorders of Phosphate Metabolism: An Update*
- 15:50 – 17:20 *MTP10: Paediatric Calcium Disorders*

Prof. Dr. Mathis Grossmann

Friday, December 11
- 15:50 – 17:20 *MTP6: Male Hypogonadism: Pitfalls and Treatment*

Sunday, December 13
- 8:45 – 9:30 *Highlights of ENDO: Reproduction*

Prof. Dr. Carla Moran

Friday, December 11
- 8:45 – 9:30 *Highlights of ENDO: Thyroid*
- 15:50 – 17:20 *MTP1: Autoimmune Thyroid Disease in the Presence of Resistance to Thyroid Hormone or TSH-secreting Pituitary Tumour: A Diagnostic Challenge*

Saturday, December 12
- 15:40 – 17:10 *MTP2: Pitfalls in the Measurement and Interpretation of Thyroid Function Tests*

Prof. Dr. Lynette Nieman

Friday, December 11
- 15:50 – 17:20 *MTP2: AIMAH, PPNAD and Aberrant Receptors in Adrenal Cushing's*

Saturday, December 12
- 14:45 – 15:30 *Highlights of ENDO: Pituitary*

Prof. Dr. Dolores Shoback

Friday, December 11
- 15:00 – 15:45 *Highlights of ENDO: Calcium & Bone*

Saturday, December 12
- 14:00 – 14:45 *Plenary Lecture 4: Recent Advances in the Management of Osteoporosis*

Prof. Dr. Massimo Terzolo

Friday, December 11
- 9:50 – 10:20 *Symposium 1: Adrenal -- A 2015 Perspective on Treatment of Adrenocortical Carcinoma and the Prognostic Role of Ki67*

Saturday, December 12
- 8:45 – 9:30 *Highlights of ENDO: Adrenal*

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CASE REPORT

Pattern of Weight Loss after Successful Enucleation of an Insulin-producing Pancreatic Neuroendocrine Tumor

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Abstract

We report the case of a patient with hypoglycemic symptoms and weight gain. Biochemical investigations revealed endogenous hyperinsulinemic hypoglycemia. A CT scan and MRI of the abdomen were initially not successful in localizing a pancreatic mass. However, an endoscopic ultrasound was able to demonstrate a pancreatic head mass. Enucleation of the mass resulted in clinical and biochemical improvement. This report also demonstrates the pattern of weight loss after surgery, showing an initial phase of gradual weight loss followed by a rapid loss of weight. This pattern of weight loss after successful removal of an insulin-producing pancreatic neuroendocrine tumor is a novel addition to the existing knowledge we have about this condition.

Key words: hypoglycemia, insulinoma, pancreatic neuroendocrine tumor, weight loss

INTRODUCTION

Insulinomas are rare tumors that produce excessive amounts of insulin causing hypoglycemia and weight gain. These tumors are now more appropriately called insulin-producing pancreatic neuroendocrine tumors (PNET).[1] This case demonstrates the approach to diagnosis of a patient with hypoglycemia and the eventual localization of the cause of endogenous hyperinsulinemic hypoglycemia using 3 various imaging modalities. We have also documented the pattern of weight loss after removal of the pancreatic tumor, new information that this case report adds to our knowledge of this condition.

CASE

A 34-year-old female had an episode of loss of consciousness 10 months prior to admission. During that time, she was brought to an emergency room and was found to have low blood sugar levels. She regained consciousness after intravenous glucose administration. No other diagnostic work-ups were done at that time and she was discharged.

Since then, she has had recurrent episodes of dizziness, disorientation, incoherence, hunger pangs, cold sweats, palpitations and tremors. She developed the frequent urge to eat and she learned to avoid these symptoms by eating every 2 hours. She progressively gained weight as a result.

She denies taking any oral hypoglycemic agent or administering insulin. She has no known illnesses. She is gravida 8 para 2 (2-0-6-2).

Seven months prior to admission she consulted an endocrinologist. Hyperinsulinemic hypoglycemia was considered. A supervised fast was done. When she developed symptoms of hypoglycemia, venous blood was taken and sent for glucose and insulin levels. Serum glucose was low at 2.87 mmol/L (52.1 mg/dL) while the serum insulin was inappropriately unsuppressed at 166.3 pmol/L (normal: 17.8 – 173.0).

Abdominal CT scan did not show any focal lesion in the pancreas. A subsequent abdominal MRI also did not show any focal pancreatic lesion.

With the persistence of symptoms, the patient consulted our institution for further work-up.

Physical examination revealed an obese female with a weight of 107 kg, height of 152 cm and body mass index of 46.31 kg/m^2. Her ideal body weight is 46 kg based on the

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Broca-Devine formula. Vital signs were normal. She was conversant and coherent at the time of examination. There was no acne, hirsutism, violaceus striae nor ecchymoses. There was no goiter. The rest of the PE findings are unremarkable.

A repeat supervised fast was done. Within four hours after the last food intake, the patient developed hypoglycemic symptoms. Capillary blood glucose was 2.5 mmol/L (45 mg/dL). Venous blood was extracted and sent for serum glucose, insulin, C-peptide and cortisol. Serum glucose was low at 3.8 mmol/L (68.83 mg/dL) while insulin and C-peptide were both elevated [serum insulin 25.13 uIU/mL (normal: 4.50 – 20.00); C-peptide 3.60 nmol/L (normal: 0.35 – 1.17)]. Serum cortisol was 253.83 nmol/L (normal: 160 – 620).

Endoscopic ultrasound revealed a 1.5 x 2.0 cm hypoechoic to isoechoic mass at the head of the pancreas (Figure 1). No increased vascularity was noted. There were no peripheral lymphadenopathies. The liver was free of any metastasis but appeared diffusely hyperechoic.

On exploratory laparotomy, a 2 x 2 cm well-circumscribed pancreatic head mass was identified. Intraoperative ultrasound revealed that the mass was more than 3 mm away from the pancreatic duct and it was enucleated. In addition, elective cholecystectomy and bilateral tubal ligation were also performed per patient's preference. Histopathologic examination using H&E stain revealed an islet cell tumor (Figure 2), 2 cm in greatest diameter. Immunohistochemical staining with chromogranin and synaptophysin (Figure 3) are both positive, confirming the neuroendocrine nature of the tumor. Immunohistochemical staining for insulin would be able to morphologically demonstrate that the tumor produces insulin but this test is not available in the Philippines.

Post-operatively, there was no more recurrence of hypoglycemic symptoms and all capillary glucose levels were normal.

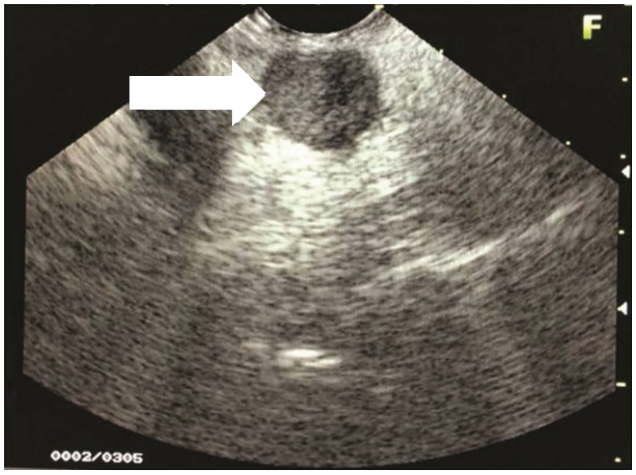

Figure 1. Endoscopic ultrasound shows a 1.5 x 2.0 cm hypoechoic to isoechoic mass at the head of the pancreas.

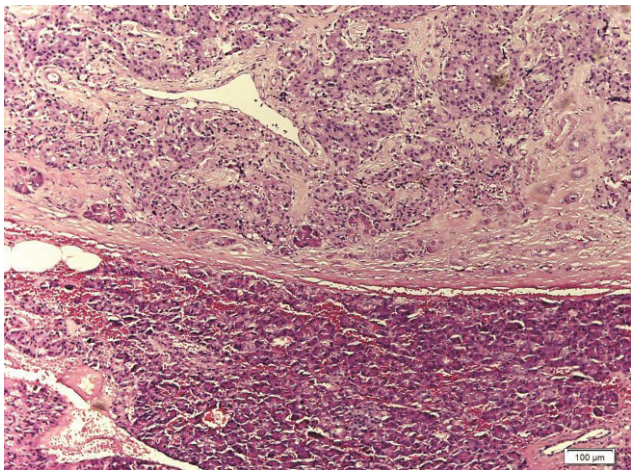

Figure 2. Photomicrograph showing a pancreatic neuroendocrine tumor in the upper area separated from the normal pancreatic tissue below by a fibrous capsule in the middle (H&E stain, x 100).

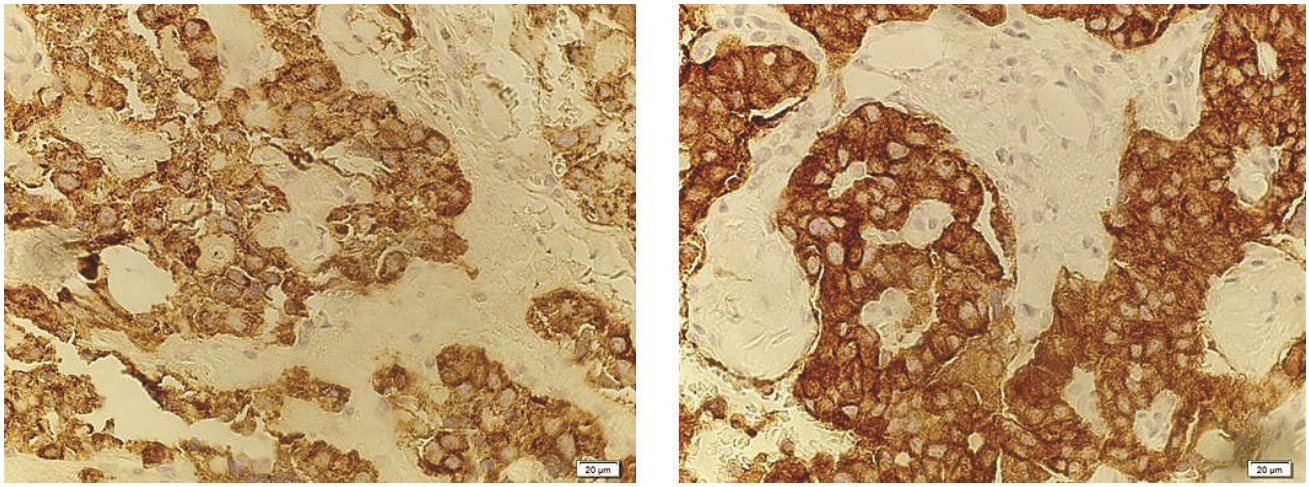

Figure 3. Immunohistochemical staining for synaptophysin (left) and chromogranin (right) are both positive among the neoplastic cells, confirming the neuroendocrine nature of the tumor (x 400).

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After 8 weeks, there was no recurrence of hypoglycemic symptoms. The patient can now tolerate 8.5 hours without food intake and does not experience any hypoglycemic symptoms. Plasma glucose taken after 8.5 hours of fasting was 6.1 mmol/L (110 mg/dL), with a serum insulin level of 22 uIU/mL and serum C-peptide at 1.53 nmol/L.

She also lost a significant amount of weight, losing 18 kg within 8 weeks after surgery (Figure 4). We have documented the pattern of weight loss shown in Figure 5. Weight was first monitored at the 6th post-operative day when the patient did not have any intravenous and urethral catheters in place and when she was already comfortably ambulating with minimal pain. The weight was documented daily until the 56th post-operative day. It appears that weight loss was not linear. There was a gradual weight loss during post-op day 6 to day 19 (3 kg over 13 days; average of 0.23 kg/d). But from post-op day 19 to day 39, there was a rapid weight reduction. She lost 16 kg in this span of 20 days (average of 0.80 kg/d). Subsequently, there was no more rapid weight loss and her weight was maintained within the range of 88-89 kg until the 56th post-operative day.

Figure 4. Appearance of the patient at day 6 post-op and at day 56 post-op.

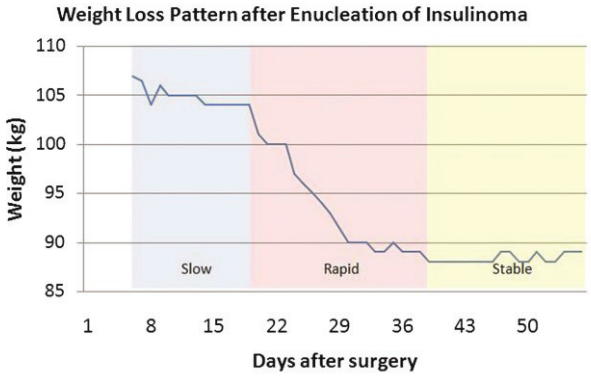

Figure 5. Weight loss velocity graph demonstrating an initial gradual weight loss followed by a rapid loss of weight and eventual stabilization of the patient's weight.

A recall of her 24-hour food intake before and after surgery showed that she consumed much fewer calories after surgery. Prior to surgery, her usual daily intake was as follows: 3,687 kcal comprised of 519 g carbohydrates, 70 g proteins and 135 g fats. After the surgery, her usual daily intake was 1,284 kcal comprised of 132 g carbohydrates, 34 g proteins and 66 g fats.

Levels of physical activity before and after surgery were similar.

DISCUSSION

This patient had symptoms of hypoglycemia, documented low capillary blood glucose levels and resolution of symptoms after the administration of intravenous glucose or food intake. Since the patient already had hypoglycemic symptoms when the capillary blood glucose was determined to be 45 mg/dL, we did not repeat the 72-hour fast even if the serum glucose was 68.83 mg/dL.

After the initial episode, there was no recurrence of syncope since the patient learned to eat larger quantities of food frequently to avoid the symptoms of hypoglycemia, but at the expense of weight gain.

The cause of the hypoglycemia was found to be due to high insulin levels since the measured plasma insulin levels were elevated despite the low level of plasma glucose. The finding of an elevated C-peptide level suggests an endogenous source of the excess insulin. Thus, the combination of low glucose, high insulin and high C-peptide levels is consistent with a diagnosis of endogenous hyperinsulinemic hypoglycemia.

The increased frequency and amount of food intake plus the anabolic effects of insulin both contributed to the patient's significant weight gain.

Differentials of endogenous hyperinsulinemic hypoglycemia include an insulin-producing PNET, sulfonylurea intake, insulin autoantibodies and nesidioblastosis. A PNET is the most common of these causes. Sulfonylurea intake can be determined by history, which the patient denied. Had we suspected surreptitious intake, we could have tested for sulfonylurea in the urine. However, this test is not available in the Philippines.

Insulin-producing tumors are almost always located in the pancreas and imaging tests are done to localize them and plan the necessary surgery to remove them.[2] CT scan and MRI are typically the first imaging tests ordered to visualize such tumors. However, the sensitivity of CT scan is only 78% and that of MRI, 71%, according to a study from Thailand.[3] Endoscopic ultrasound (EUS) has a greater sensitivity at 93%.[3] For our patient, both CT scan and MRI failed to visualize the tumor but it was eventually localized by EUS. There are authors who state that since EUS can detect all tumors by every other

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conventional technique, there is no need for the other imaging tests.[4]

Our patient recovered clinically after the surgery. Her two main symptoms – hypoglycemia and weight gain – have resolved. There was no recurrence of hypoglycemic symptoms despite no food intake for 8.5 hours. Both her insulin and C-peptide levels were already within acceptable values for the prevailing level of serum glucose after surgery.

The patient was also very satisfied with the resultant weight loss. The weight loss was due to decreased food intake as she no longer had to eat frequently to avoid hypoglycemic symptoms. A recall of her food intake for a 24-hour period showed that her total calorie intake decreased after surgery. Among the macronutrients, it was the carbohydrates that showed the greatest reduction in intake: 75% reduction for carbohydrates, 51% reduction for proteins and 51% reduction in fats. Increase in the level of physical activity does not seem to have played a role in her weight loss since she mentioned that her level of physical activity did not change before and after the surgery.

There were case reports that mentioned the amount of weight loss over a specified amount of time after surgery but have not documented the daily change in weight over that period of time. Madathil has reported a 6 kg weight loss over a span of 6 weeks in their patient, while Lemoncito reported a 17 kg weight loss over one month.[5,6] Both however, did not show the daily weight change. A prospective study that followed up 36 patients who underwent surgery for insulinoma did not include weight change as an outcome as well.[7] We have not come across any case report which meticulously documented the daily pattern of weight loss after removal of an insulin-secreting PNET and this is novel information that this case report contributes.

The pattern of weight loss being described here may not necessarily be generalizable to all patients. Meticulous measurement of weight on a daily basis may be done on other patients to see if there is a similar pattern. Knowing the pattern of weight loss may be important to advise patients what to expect after surgery. For this specific patient, she was particularly concerned about her weight gain from the illness and was expecting to lose the excess weight after the operation. If the pattern documented in this case report is true for all patients, then doctors can advise their patients to expect that rapid weight loss occurs on the 19th to 39th day after surgery and that no further weight loss occurs afterwards. However, it is not yet known if further weight loss occurs after the 56th day post-op since the observation in this patient was only until this period.

CONCLUSION

The combination of loss of consciousness, hypoglycemic symptoms and weight gain should raise the suspicion of hyperinsulinemic hypoglycemia. Absence of any focal pancreatic lesions on abdominal CT scan and MRI should not rule out the presence of a pancreatic mass. Endoscopic ultrasound is a more sensitive test to localize these lesions. Surgical removal of the insulin-producing pancreatic neuroendocrine tumor resolves the hypoglycemia and leads to weight loss. The pattern of weight loss after removal of the functioning tumor was documented in this case, with a slow weight loss initially followed by a phase of rapid weight loss.

Acknowledgements

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CASE REPORT

Idiopathic Unilateral Adrenal Hemorrhage

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Abstract

Unilateral adrenal hemorrhages are a rare finding and when discovered they are usually due to a blunt trauma or secondary to anticoagulation therapy. We report a case of a 72-year-old Filipino male presenting with an unsuspected large adrenal mass discovered on abdominal computed tomography that was requested to evaluate a palpable soft, non-tender right lumbar mass. Characteristics of the mass on CT scan pointed to a possible adrenal neoplasm. Endocrine work up revealed a non-functioning adrenal mass. Exploratory laparotomy and resection of the retroperitoneal mass was done with a histopathologic finding of a diffuse adrenal hemorrhage.

Key words: idiopathic adrenal hemorrhage, unilateral adrenal hemorrhage, adrenal hematoma

INTRODUCTION

Hemorrhage to the adrenal glands is a rare finding occurring more frequently in children than in adults. It is classically associated with meningococcal septicemia (Waterhouse–Friderichsen syndrome). In adults, it is mainly caused by trauma, surgical stress, anticoagulation therapy, or a tumor; however, spontaneous or idiopathic adrenal hemorrhage is extremely rare.[1] Two mechanisms that have been proposed in the pathogenesis of idiopathic adrenal hematomas are stress and adrenal medullary venous thrombosis.[2] In a review done by Vella et al at the Mayo Clinic, adrenal hemorrhages (AH) were classified into several categories: incidentaloma (28 cases), spontaneous AH (16 cases), AH associated with antiphospholipid- and heparin-associated thrombocytopenia (20 cases), postoperative AH (14 cases), AH associated with anticoagulation therapy (3 cases), AH associated with trauma (4 cases), and AH associated with severe stress or sepsis (56 cases).[3] The clinical manifestations may vary depending on the amount of hemorrhage, its effect on hemodynamics and the rate of onset. A majority, however, may not have any symptom and the diagnosis may be incidentally discovered through imaging.[1,4] This patient initially had an ultrasound to further investigate a palpable mass over the posterior right upper quadrant area which later revealed a complex mass in the region of the porta hepatis. An abdominal CT scan was done to further investigate the said mass and it showed a retroperitoneal mass with characteristics suggestive of an adrenal neoplasm. In these instances, hormonal work-up is warranted to determine functionality of the tumor in preparation for surgery, as well as to determine any particular hormone excess in an adrenocortical carcinoma. Histopathology remains to be the gold standard in the diagnosis.

CASE

A 72-year-old Filipino male retired lawyer sought consult at his physician's clinic for a routine check-up. On examination, a soft, non-tender mass was palpated over the posterior right upper quadrant area in the lumbar region measuring about 12 x 6 cm (l x w). Patient denied pain over the area of the mass; and there was no history of trauma. He had been experiencing intermittent episodes of generalized weakness and body malaise, and noted an approximate 10-pound weight loss over the past year but otherwise he was ambulant and maintained good functional capacity. The patient has had no previous surgery, no intake of any anti-platelets nor anti-coagulants. He has been diabetic for approximately 5 years with good control, maintained on metformin, acarbose and gliclazide. His hypertension is controlled with indapamide; dyslipidemia is managed with fibrates. Other medications include allopurinol for hyperuricemia, and nitrates for ischemic heart disease.

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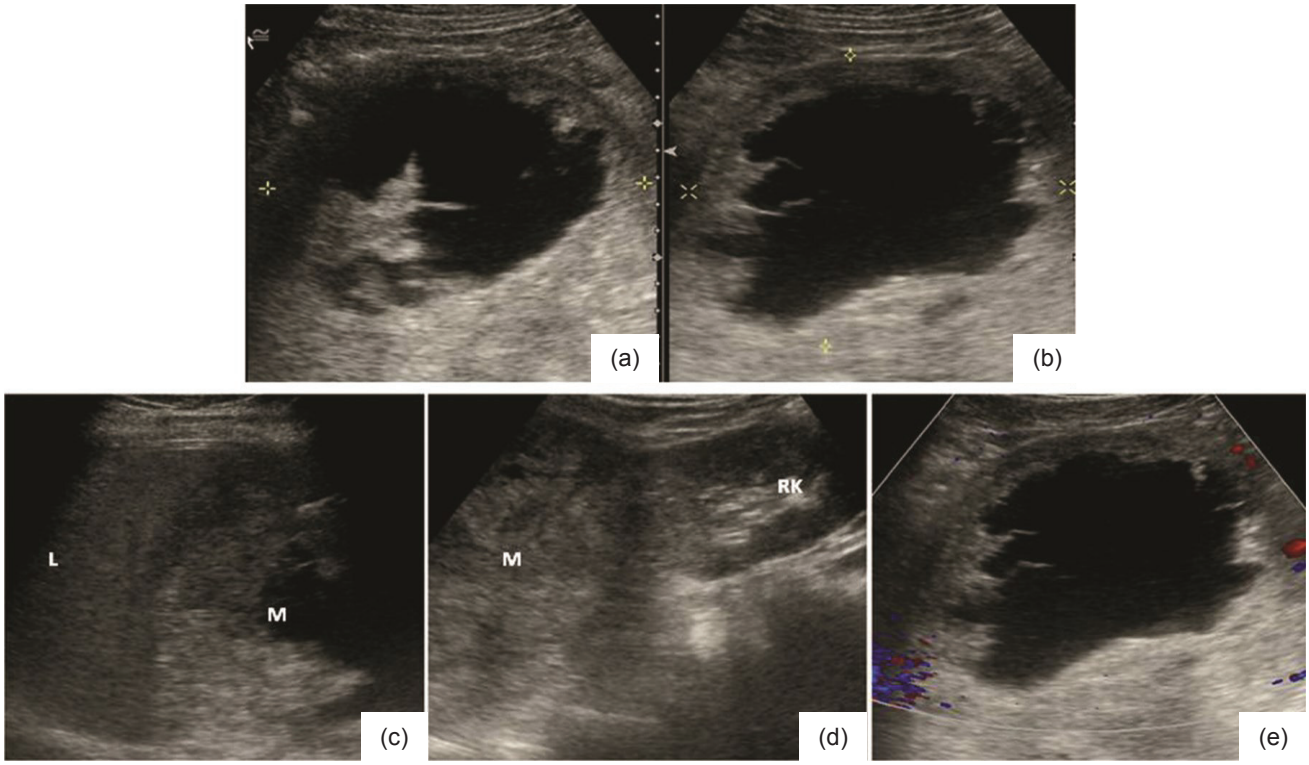

Figure 1a and b. Transverse and sagittal sonographic images revealing a complex mass at the region of the porta hepatis; **c and d.** Sagittal images showing superior displacement of the right hepatic lobe (L) and inferior displacement of the right kidney (RK) by the mass (M); **e.** Minimal peripheral enhancement detected under color Doppler imaging.

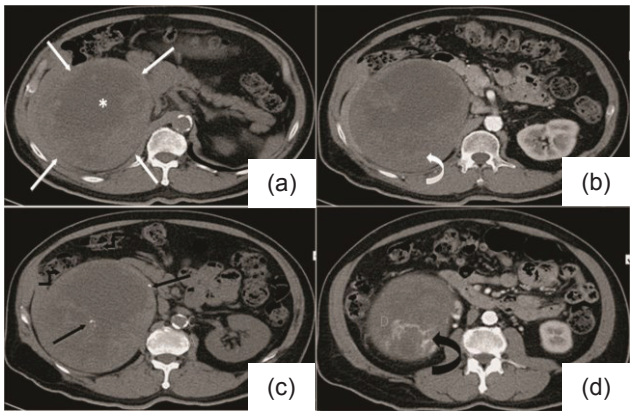

Figure 2. Axial non-contrast (a) and contrast-enhanced (b) CT images showing a large retroperitoneal mass (white arrows) with central hypodensity (*) and peripheral enhancement (curved white arrow); c. Non-contrast axial CT image showing punctate calcifications (black arrows); d. Contrast-enhanced axial CT image showing neovascularization (curved black arrow).

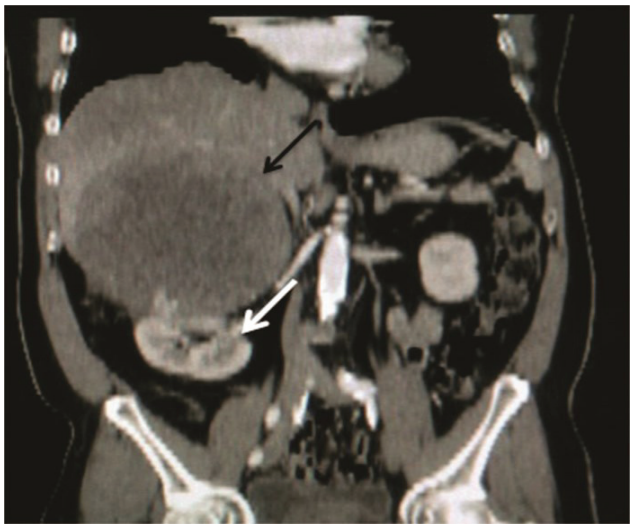

Figure 2b. Coronal contrast-enhanced CT image showing a suprarenal mass (black arrow) causing inferior displacement of the right kidney (white arrow).

Initial consideration for the palpable mass was a lipoma. On ultrasound of the whole abdomen, there was note of a well-defined encapsulated heterogenous mass lesion with central cystic probably necrotic component at the region of the porta hepatis, measuring 11.32 x 11.43 x 10.89 cm. The said lesion appears to displace the right hepatic lobe superiorly and the right kidney inferiorly. Minimal peripheral vascularity is noted under color Doppler evaluation (Figure 1). With the abovementioned findings, a CT scan of the whole abdomen was subsequently done, revealing a large heterogeneous mass lesion with a central hypodense component (likely necrosis) centered in the right retroperitoneal region, with non-contrast Hounsfield units ranging from 15-40 HU (Figure 2a and 2b). It measures 14.2 x 12.5 x 14.7 cm in its maximal craniocaudal x width x anteroposterior dimensions. Neovascularities and small calcific components are identified within the said mass. It displaces the liver superiorly, the right kidney inferiorly, and also splays and compresses the right renal artery and vein. After correlating the ultrasound and CT scan findings, the primary consideration for this lesion was an adrenal neoplasm.

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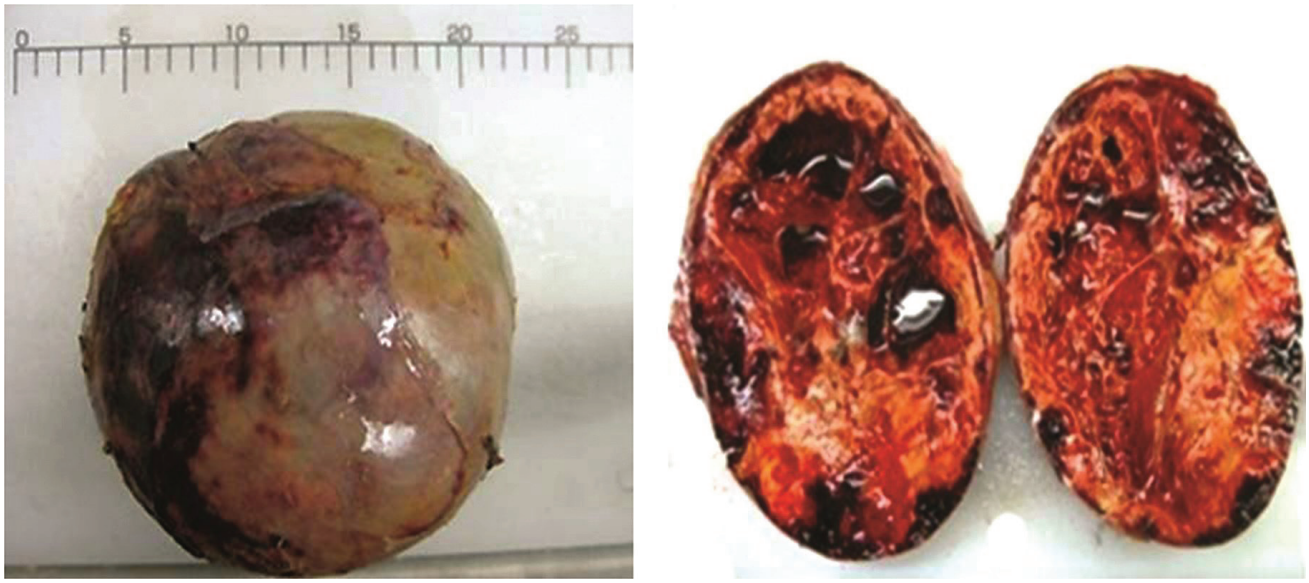

Figure 3a (left). Gross appearance of the thinly encapsulated adrenal mass and measures 16.8 cm in greatest dimension. **Figure 3b** (right). Cross sections of the mass show yellow fibrinous solid areas with variably sized locules containing hemorrhagic fluid.

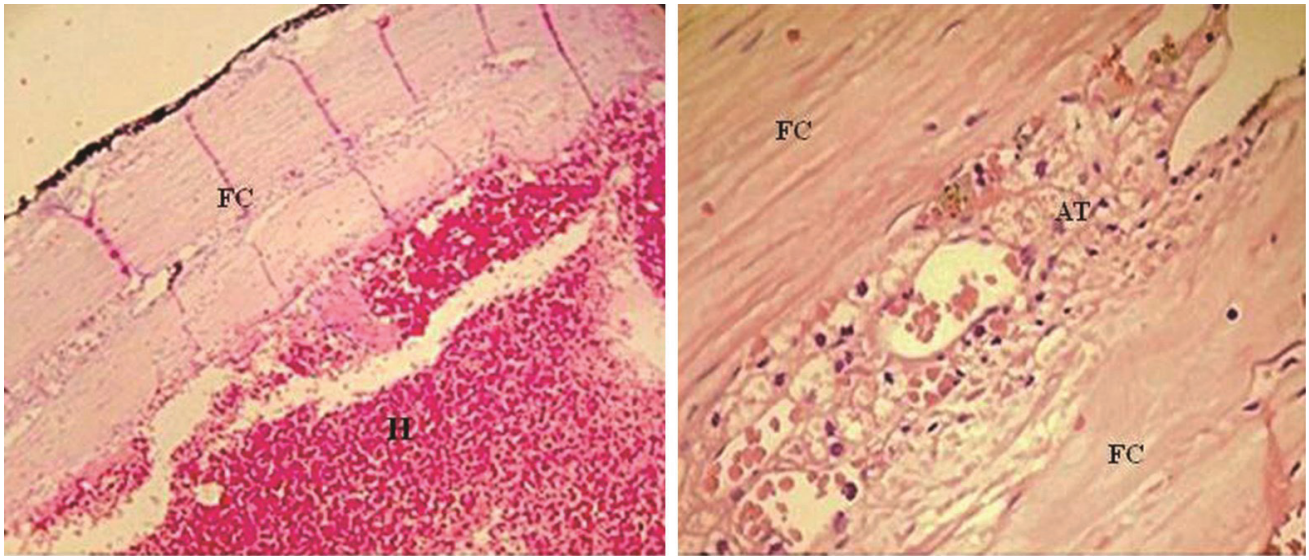

Figure 4. On low magnification [H&E, x 100] (left) the mass shows mostly diffuse hemorrhage (H) capped by a thin fibrous capsule (FC). On higher magnification [H&E, x 400] (right), benign adrenal tissue (AT) is seen compressed within the fibrous capsule with microhemorrhages within the parenchyma.

A hormonal work-up was subsequently done revealing a non-functioning adrenal mass. The results: Plasma Aldosterone-RIA 23.77 ng/dl (NV: 3.0-35.5 ng/dl), Plasma Renin Activity 5.65 ng/ml/hr (0.5-1.9 ng/ml/hr supine; 1.9-6.0 ng/ml/hr upright), ARR: 4.207, Serum Cortisol (8am): 15.7 ug/dl (NV 4.2 – 38.4), 24h urine metanephrine: 1.21 mg/24hr (NV up to 1 mg metanephrine/24 hr); DHEA-S: 69.5 ug/dl (NV 33.6-249); Progesterone: 0.26 ng/ml (NV 0.2-1.31); Testosterone: 3.31 ng/ml (NV 1.95 – 11.38); Estradiol: 29 pg/ml (NV 20-77). A biopsy of the adrenal mass was then done however results were inconclusive. Other sources of a possible malignancy were investigated. Chest x-ray showed an atherosclerotic aorta, CEA was within normal range at 2.10 ng/ml NV 0-3). Prostatomegaly with hypodense nodules were likewise noted on CT scan hence a cysto-TURP was done later on with histopathology findings of a benign prostatic hyperplasia. The patient was not anemic with hemoglobin of 133 g/L and hematocrit of 0.39. The patient was hyponatremic at 127.8 meq/L and hypokalemic at 2.98 meq/L, which was attributed to the patient's anti-hypertensive medication that was then discontinued.

Exploratory laparotomy and resection of retroperitoneal mass on the right with cholecystectomy was done. Histopathologic findings revealed a diffuse adrenal hemorrhage, with no evidence of malignancy seen and chronic cholecystitis with cholelithiasis. Grossly, the specimen was described to be a large globular fluctuant mass weighing 1500 grams, measuring 16.8 x 14.0 x 9.0 cm.

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The external capsule was thin, brown and smooth and covered with small fibrous tags. Cut sections of the mass showed a cream yellow granular to glistening cut surface with multiple locules measuring from 1.3 to 8.0 cm in diameter containing red brown watery to hemorrhagic fluid. The capsule measured 0.4 cm think. Microscopic examination showed mostly diffuse hemorrhage with fibrin surrounded by thin fibrous capsule. The adrenal gland was seen within the fibrous capsule compressed by the hemorrhage material. Delineation of the adrenal zones was not possible due to the compressive effect of the hemorrhage to the affected gland. Serum cortisol was repeated a year later and remained to be in the normal range at 12.6 ug/dl (NV 2.9 – 17.3). The patient continues to follow-up and is well 20 months post surgery.

DISCUSSION

Adrenal hemorrhage is an uncommon condition that is of serious concern as it may result in life threatening adrenal insufficiency and even death. It may be caused by several factors including infection, MI, CHF, anticoagulants, trauma, surgery, and antiphospholipid syndrome. None of these conditions were present in our patient. In most of the reported case it is an autopsy finding and the underlying disease mechanism has not been fully elucidated. The adrenal gland is highly vascular and vulnerable to hemorrhage by nature. Small adrenal branches from the three main adrenal arteries form a subcapsular plexus, and the gland is drained by relatively few venules. The term "adrenal dam" has been ascribed to vascularities within the adrenals, implying the large degree of adrenal vascularities that are susceptible to hemorrhage due to their distinct anatomical attributes. While some have suggested that reduced capillary resistance as a result of aging may be a factor, others have postulated that elevated catecholamines and ACTH as a result of stress increases adrenal vascularity and increases adrenal venous pressure due to vasoconstriction, resulting in intraglandular hemorrhage.[5-7]

Adrenal masses, when discovered, must be further worked up to determine its nature, whether they may be hormonally active or nonfunctional and malignant or benign. A report done by Young included 2005 patients in whom adrenal incidentalomas were detected, adrenocortical carcinoma was found in 4.7% of the patients and metastatic cancer in 2.5%. The size of the mass and its appearance on imaging are the two major predictors of malignant disease.[8,9] Measurement of precontrast Hounsfield units (HU) and contrast washout on computed tomography scan provide useful diagnostic information.[10] Noncontrast CT attenuation coefficient expressed in Hounsfield units (HU) has been increasingly used to differentiate adrenal adenomas from nonadenomas. This is based on the fact that intracytoplasmic fat is often abundant in adrenal adenomas but rare in adrenal metastases, pheochromocytomas, or adrenocortical carcinomas. Threshold values for noncontrast CT HU ranging from 0–20 have been suggested and a 10-HU cutoff value for benign lesions was recommended by a consensus panel organized by the National Institutes of Health.[11] The size of the mass of this patient at 14 cm with compression of its adjacent structures as well as characteristics on CT scan that were indicative of malignancy including a Hounsfield unit (HU) ranging between 15 and 40, was an indication for surgery. Hormonal work-up to determine the malignant potential of the tumor was done including screening for glucocorticoid excess, sexual hormones and steroid precursors, mineralocorticoid excess, as well as the exclusion of pheochromocytoma.[12] Results revealed a non functional tumor.

Majority of the patients with adrenal bleeding do not show any signs of adrenal insufficiency. The most common symptoms are hypotension, confusion, lethargy, nausea, vomiting, tachycardia, and fever. More specific symptoms such as central abdominal pain radiating to the flank are experienced by 45% of the patients. These symptoms together with anticoagulation therapy in an elderly or very young patient should raise clinical suspicion. In these cases, CT is an essential diagnostic tool.[1] On CT scan adrenal hemorrhage appears heterogeneous rather than homogeneous with or without calcification and has a variable density. Adrenal hematomas are usually of soft tissue density but they can also be hypo-attenuated centrally with a peripheral rim of higher attenuation, hyper-attenuated centrally with a rim of hypodensity or hyper-dense. The only specific sign of hematoma, especially with acute hemorrhage, is a spontaneous homogeneous density greater than 50 Hounsfield units. Idiopathic unilateral adrenal hematoma, when diagnosed at a subacute or chronic stage, cannot be distinguished clearly from other lesions on the basis of morphology or density on CT. Findings of a mass with no enhancement or enhancement only in the pattern of a thin peripheral rim agree with the findings of others. This criterion can be valuable in differentiating hematoma from other tumors, with carcinoma and pheochromocytoma almost always have pronounced enhancement.[2]

An MRI is the ideal imaging modality in studying the adrenal mass in that it may determine the age of the hematoma. In the acute stages, the hematoma typically appears isointense on T1-weighted images and markedly hypointense on T2-weighted images, while in the chronic stages a hypointense rim is present in T1 and T2 weighted images.[4]

CONCLUSION

Adrenal hemorrhage is an uncommon condition and is difficult to diagnose because of its nonspecific presentation that the diagnosis is often made at autopsy.[8] The value of imaging modalities with the use of CT scan or MRI allows one to determine certain characteristics of an adrenal mass that can point to a benign or malignant

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tumor. The size and characteristics of the adrenal mass of this patient on CT scan indicated a possibility of malignancy. Further hormonal work-up was warranted and only on post surgical histopathology was the diagnosis of adrenal hemorrhage made. This patient, with no known predisposing factors for bleeding, with no history of intake of anti-coagulant nor history of trauma suffered from an idiopathic adrenal hemorrhage without any hormonal disturbances.

An accurate diagnosis of idiopathic adrenal hemorrhage is quite difficult to make prior to surgery. Some imaging modalities are useful in generating a differential diagnosis, but if the potential for malignancy is not excluded, a thorough hormonal work-up is warranted and surgical resection should be taken into consideration.

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Dr. Adriano Dela Paz from The Section of Cardiology, Department of Medicine, The Medical City, for sharing this case with us.

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CASE REPORT

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Generalized Hyperpigmentation Caused by Addison's Disease in a Patient with HIV/AIDS and Multiple Opportunistic Infections

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Abstract

One of the neglected complications of patients with HIV/AIDS is primary adrenal insufficiency also known as Addison's disease. This condition can be caused by several mechanisms, such as tuberculosis, CMV, cryptococcal, or HIV-related adrenalitis, and also drugs commonly used for HIV/AIDS especially antifungal therapy. This is a case report of a man infected with HIV/AIDS and multiple opportunistic infections. He reported darkening of the skin and reduction of body hair 4 months after diagnosis of HIV/AIDS. From the clinical features and laboratory examinations, he was diagnosed as having primary adrenal insufficiency and was then treated with longterm corticosteroids.

Key words: Addison's disease, opportunistic infection, CMV adrenalitis, HIV/AIDS endocrinopathy, generalized hyperpigmentation

INTRODUCTION

HIV/AIDS is a very important public health problem nowadays. HIV/AIDS pandemic not only leads to morbidity and mortality related to opportunistic infections, but also some forms of AIDS endocrinopathies (AIDS-related endocrine disorders).[1,2] One of the endocrine disorders which is related to immunodeficiency state in HIV/AIDS and opportunistic infections such as tuberculosis, cytomegalovirus (CMV), and fungal infection is primary adrenal insufficiency known as Addison's disease.[1-3] It can be said that hypoadrenalism is one complication that has been well-documented in patients with HIV/AIDS. Addison's disease results from bilateral destruction or dysfunction of the adrenal cortex marked by failure of the adrenal cortex to produce cortisol, aldosterone, and androgen.[4] This disease has broad clinical features from mild to life-threatening conditions. The clinical features depend on the extent of loss of adrenal function and whether mineralocorticoid production is preserved.[5]

Opportunistic infections are known to cause adrenalitis and adrenal insufficiency in patients with AIDS.[2] Several authors have published case reports and findings of CMV adrenalitis in patients with AIDS.[3,6] Other microorganisms involving the adrenals in immunocompromised patients are *Mycobacterium tuberculosis, Cryptococcus neoformans, Histoplasma capsulatum, Pneumocystis carinii,* and *Toxoplasma gondii*.[2] In rare conditions, the adrenals can also be affected by lymphoma and Kaposi's sarcoma in patients with AIDS. Another cause of hypoadrenalism is the use of antifungal drugs for fungal opportunistic infections. Several drugs which can alter adrenal cortex hormone production are ketoconazole, megestrol acetate, rifampin, amphotericin B, trimethoprim, and sulphonamide.[2]

This is an interesting case of a man who was infected with HIV/AIDS and has been treated for multiple opportunistic infections. He experienced generalized hyperpigmentation and reduction in body hair for which he has been diagnosed as having primary adrenal insufficiency from clinical features and laboratory examinations. Treatment with longterm corticosteroids, clinical monitoring, and evaluation of the therapy is mandatory for glucocorticoid replacement, to reduce symptoms, and prevent life-threatening conditions.

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Figure 1. Photographs of the patient: September 2013, February 2014, April 2014, May 2015.

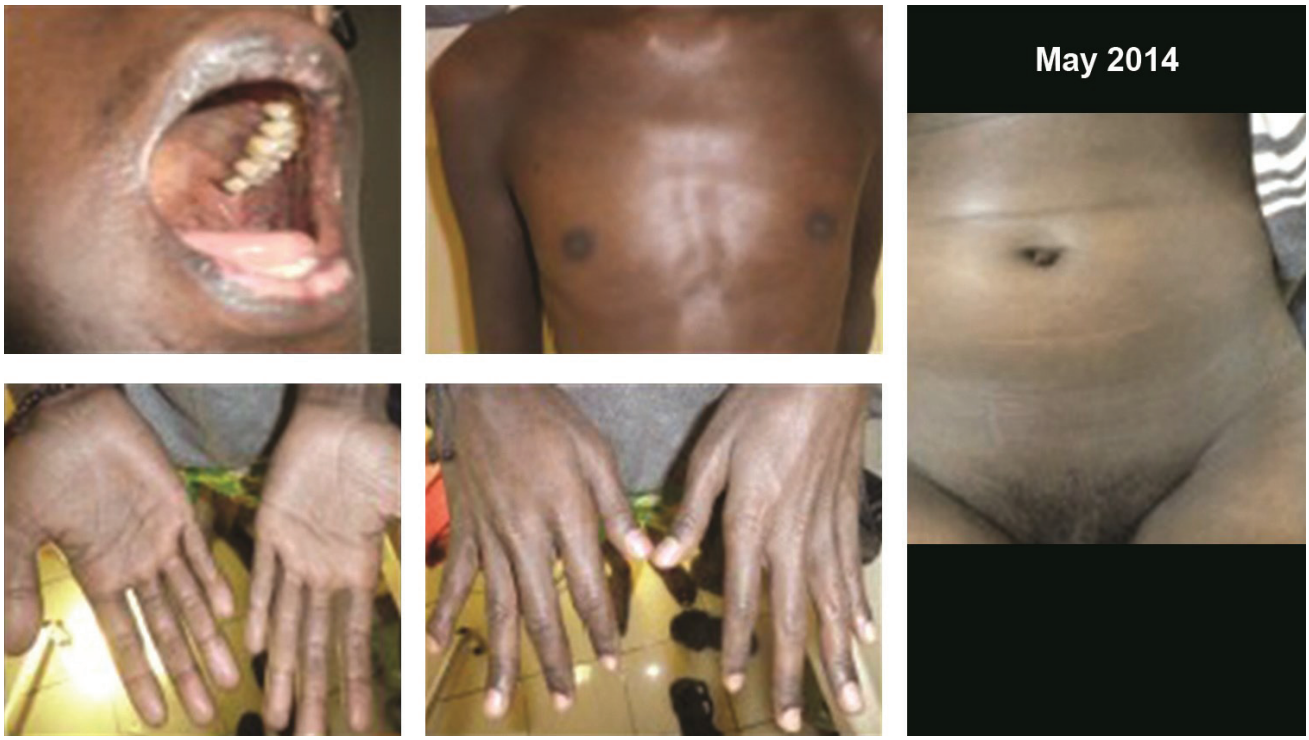

Figure 2. Photographs of the whole body showing hyperpigmentation of oral mucosa and palmar region, and thinning of the body hairs (axillary and pubic hair).

CASE

A 27-year-old man has been diagnosed with AIDS 6 months earlier with multiple opportunistic infections; cryptococcal meningitis, cytomegalovirus retinitis, and pulmonary tuberculosis, treated previously with amphotericin B, anti-tuberculosis drugs, and fluconazole. Later, he also got valganciclovir for cytomegalovirus infection. He reported darkening of the whole skin 2 months prior, accompanied by muscle weakness, chronic fatigue, reduced body weight, and thinning of body hair especially axillary and pubic hair (Figure 1). On physical examination, the whole body was darkened, even in the palmar hand, oral mucosa, along with reduced body hair (disappearance of axillary hair and thinning of pubic hair) (Figure 2).

Routine laboratory examination revealed normal. Anti-HIV was reactive with CD4 count of 46. Morning cortisol was in the lower limit level at 5.6 μg/dL (normal: 4.3 to 22.4 μg/dL) while ACTH (adrenocorticotrophic hormone) level was extremely high at 90.2 pmol/L (normal: 2.2 – 13.3 pmol/L). The adrenal glands on abdominal CT scan were normal. Working together with a dermatopathologist, we did skin biopsy which showed hyperpigmentation caused by systemic disease (suggestive of Addison's disease).

Our patient was finally diagnosed as having primary adrenal insufficiency with differential diagnoses of HIV adrenalitis, opportunistic infection (CMV, TB, cryptoccocal)-related adrenalitis. Medication used in our patient was steroid (prednisone 7.5 mg/day divided into 5 mg in the morning and 2.5 mg in the afternoon following

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the circadian rhythm of cortisol), while HAART (highly active anti-retroviral therapy) which are tenofovir, lamivudine, efavirenz. Longterm regimen for opportunistic infections were likewise continued (valganciclovir, anti-tuberculosis drugs, and fluconazole). After longterm therapy with prednisone, HAART, valganciclovir, anti-tuberculosis drugs, and fluconazole, there was clinical improvement of the patient; chronic fatigue and muscle weakness decreased, the skin became faintly lighter although still dominantly hyperpigmented (Figure 1d). In one year of HAART, CD4 count reached 196 and viral load was not detected. Eventually, valganciclovir, anti-tuberculosis drugs, and fluconazole have been stopped.

DISCUSSION

Primary hypoadrenalism is one of the well-documented manifestations of HIV/AIDS-related endocrine disorders.[1,2] Our patient has multiple opportunistic infections which increase the risk of having disorder in his adrenal glands. In several case reports, it has been noted that either tuberculosis, CMV, or cryptococcal infection in adrenal gland can lead to adrenal insufficiency.[3,6-8] Unfortunately, this patient had all of these opportunistic infections. He had been treated with anti-tuberculosis drugs, amphotericin B, and fluconazole. Later, he was also treated with valganciclovir for CMV retinitis.

His medications can lead to adrenal cortex disturbance inducing adrenal insufficiency. It has been reported in several studies and case reports that the use of azole groups to treat fungal infection is correlated with decrease of adrenal cortical hormones.[9] Use of high-dose fluconazole has been reported to lead to adrenal insufficiency in critically ill patients.[10,11] The basis for adrenal suppression by the azole antifungal agents is by suppression of the cytochrome P-450 enzyme system in the adrenal cells.[9-12] In the culture of normal adrenals, fluconazole suppressed corticosterone, 17-hydroxypregnenolone, and androstenedione levels, whereas concentrations of progesterone, deoxycorticosterone, and 11-deoxycortisol increased.[12]

The clinical features of the patient are typical manifestations of Addison's disease.[5] The generalized hyperpigmentation caused by increased production of pro-opiomelanocortin, a prohormone which is cleaved to ACTH and MSH-α (melanocyte-stimulating hormone-α) which accompanies the secretion of ACTH. ACTH and MSH-α are equally potent stimulators of melanogenesis. It is likely that the combination of increases in ACTH and MSH-α resulted to generalized hyperpigmentation in Addison's patient.[5] Thinning of the body hairs especially axillary and pubic hairs are signs of hypoandrogenism in this patient. It has been published from long time ago the importance of the adrenal factor in the development of secondary sex characteristics.[13]

The patient has decreased morning cortisol level with increased ACTH level. This laboratory examination is matched with the typical finding of primary adrenal insufficiency.[14] Actually, Addison's disease is a term wherein primary adrenal insufficiency is caused by the irreversible destruction or failure of adrenal cortex due to infection. Thomas Addison first described this disorder in patients with destruction of their adrenal glands caused by tuberculosis.[5] Contrasting with the classic presence of hyponatremia and hyperkalemia, our patient didn't develop hyponatremia and hyperkalemia, suggesting that mineralocorticoid is less disturbed than glucocorticoid and androgen.[5,14]

The abdominal computed tomography scan failed to show any gross adrenal pathology. This phenomenon suggested that the adrenalitis is not captured by the radiologic examination, and is unlikely caused by tuberculosis which can be seen in adrenal CT scan (Figure 3).[7] In this situation, biopsy and culture of the adrenal gland is the gold standard to reveal the definitive and etiologic diagnosis of the primary adrenal insufficiency. But, adrenal biopsy is not routinely done in patients with classic clear clinical presentation and matched laboratory examination. Adrenal biopsy is done usually in postmortem examination to study the cause of primary adrenal insufficiency.[6]

In this patient, we did skin biopsy because at the beginning of skin darkening, our multidisciplinary team included a dermatologist who suspected drug eruptions as the etiology of the skin changes of the patient. We found that the hyperpigmented skin is cause by melanin pigment excess in the epidermis layer as seen in the histopathology slides (Figure 4). At routine clinical practice, skin biopsy is not necessary for patients with Addison's disease, except that there are other conditions where histopathology examination of the skin is needed such as in uncommon presentation of drug eruption or skin malignancy.

Primary adrenal insufficiency is considered to be an incurable disease with a need for lifelong glucocorticoid (and mineralocorticoid) replacement therapy.[15] In adrenal insufficiency, DHEA secretion is also decreased resulting to hypoandrogenism. In Europe, review from Grossman A et al[15] summarizes general therapies used for adrenal insufficiency. Choices of glucocorticoid agent are hydrocortisone, cortisone acetate, prednisolone, and dexamethasone, while for mineralocorticoid, it is common to use 9-α-fludrocortisone. DHEA is a precursor for androgen, but not regarded as standard replacement regimen for adrenal insufficiency patient. Our patient was prescribed with prednisone which is a pro-drug converted via hepatic metabolism to prednisolone. It was given in divided dosage in the morning and afternoon following the circadian rhythm of cortisol. HAART and treatment for opportunistic infections were continued.

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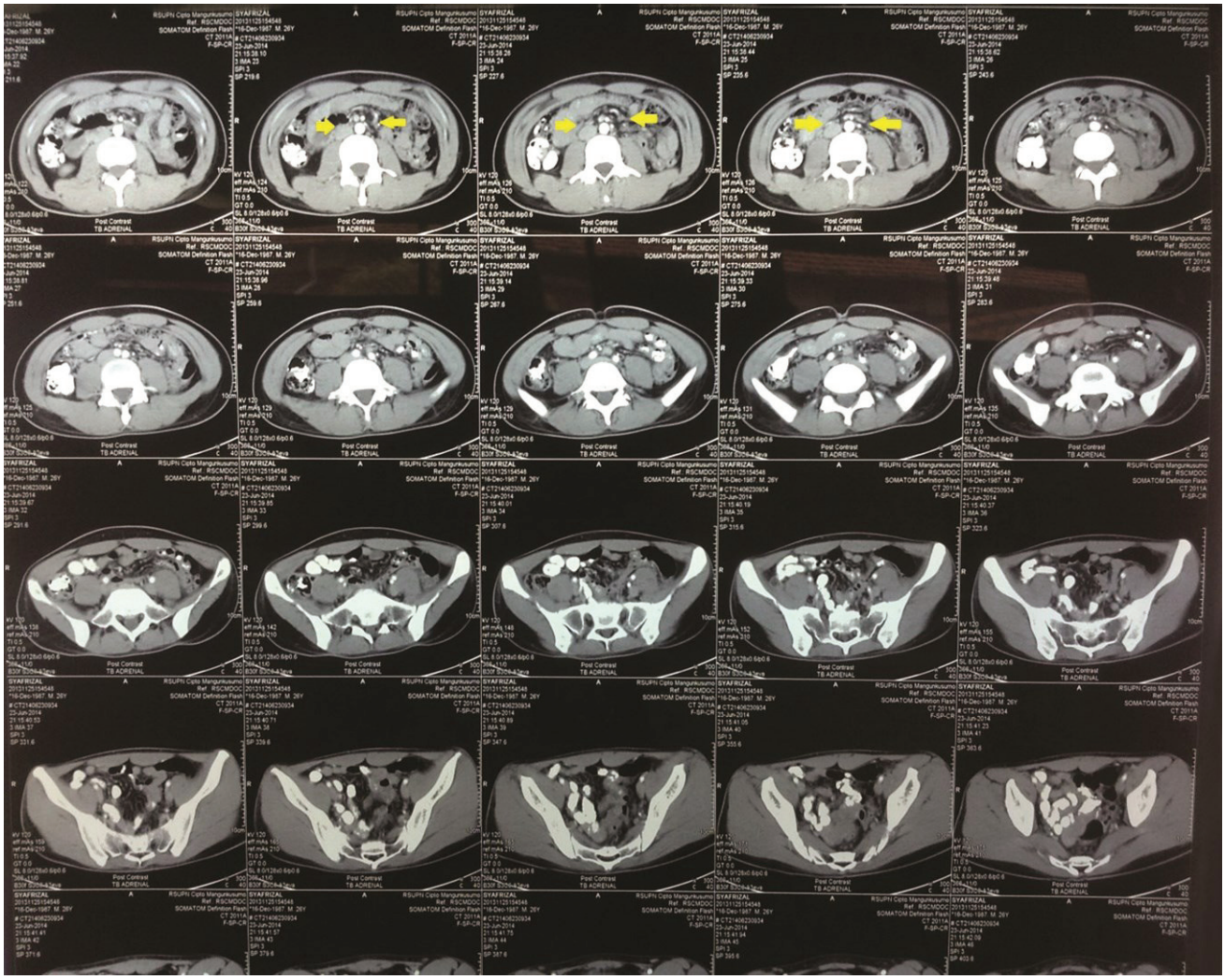

Figure 3. Adrenal CT scan of the patient showing normal adrenals.

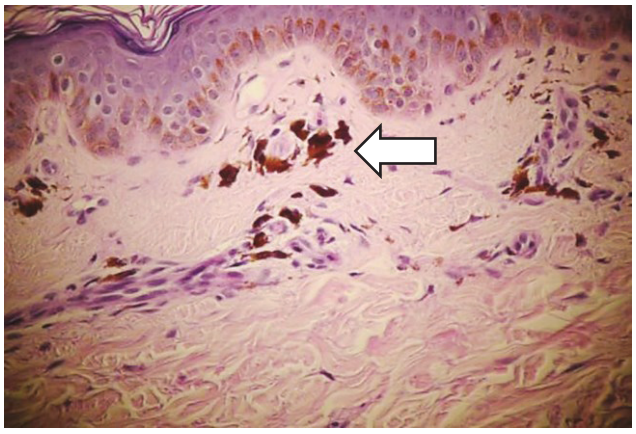

Figure 4. Skin biopsy slide of the patient showing excess of melanin pigment (H&E, x 100).

CONCLUSION

Primary adrenal insufficiency is an AIDS-related endocrinopathy which has a special clinical characteristic marked as darkening of the whole skin (generalized), accompanied by muscle weakness, chronic fatigue, and reduced body weight. Some patients show mineralocorticoid deficiency which manifests with hypokalemia, hyponatremia, and hypoglycemia. This condition can be caused by tuberculosis, CMV, cryptococcal, or HIV-related adrenalitis, and also antifungal therapy commonly used in HIV/AIDS patients. Our patient was finally diagnosed as having primary adrenal insufficiency (Addison's disease) and treated with longterm glucocorticoid replacement therapy using prednisone, while HAART and regimens for opportunistic infections were continued.

Ethical clearance

The patient in this case report has given his permission to publish his case and use his photographs for this case report. The patient also attended the case meeting consisting of internist-endocrinologist, internist-allergologist, clinical immunologist, dermatologist, and dermatopathologist where his medical problems were discussed.

Acknowledgement

We would like to thank Fifinella Raissa, MD (Dermatologist) from the Department of Dermatovenereology, Faculty of Medicine University of Indonesia/Cipto Mangunkusumo Hospital for doing skin biopsy for the patient and also for the histopathology slide used in this article.

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CASE REPORT

Metastatic Glucagonoma Presenting with Weight Loss and Necrolytic Migratory Erythema

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Abstract

A 42-year-old Filipino female was admitted due to weight loss and recurrent abdominal pain over the past ten years. In 2010, she was diagnosed to have disseminated PTB associated with a liver mass. After 1 year of anti-TB treatment, lung condition was treated but her liver mass has enlarged. She also developed diarrhea, diabetes, and skin lesions with biopsy results showing Necrolytic Migratory Erythema (NME). CT scan showed liver and pancreatic tumors that were biopsied revealing a neuroendocrine tumor. Blood glucagon level was elevated. She was treated as a case of glucagon-secreting tumor with liver metastases with everolimus and octreotide. After 3 months of treatment, she gained weight, the skin lesions improved, and the liver mass decreased in size.

Many of the initial symptoms of glucagonoma are nonspecific and subtle. As a result, glucagonoma is often diagnosed relatively late in the course of the disease. NME, the characteristic skin lesion of the glucagonoma syndrome, is often the clue that leads to the correct diagnosis.

Key words: glucagonoma, glucagonoma syndrome, alpha-cell tumor, Necrolytic Migratory Erythema

INTRODUCTION

Glucagonoma is a rare, slow-growing alpha-cell tumor of the pancreatic islets of Langerhans.[1] It is associated with systemic clinical manifestations, referred to as the "Glucagonoma Syndrome" characterized by necrolytic migratory erythema (NME), weight loss, diabetes mellitus, anemia, glossitis, cheilitis, steatorrhea, diarrhea, venous thrombosis and neuropsychiatric disturbances.[2] The incidence of glucagonoma syndrome in the general population is one in 20 million. These clinical findings in association with hyperglucagonemia and pancreatic tumor establish the diagnosis.

CASE

A 43-year-old Filipino woman was admitted in 2014 due to progressive weight loss. In 2001, she was diagnosed with major depressive disorder and 3 years later, in 2004, she started to experience recurrent epigastric pain. Ultrasound of the whole abdomen showed sub-centimeter liver nodules.

Due to the persistence of recurrent abdominal pain, she underwent–gastroscopy in 2005 which showed chronic gastritis. Lipase and amylase were slightly elevated. Magnetic Resonance Cholangio Pancreatography (MRCP) showed unremarkable pancreas and bile ducts with a 0.7 cm focus in hepatic segment II, probably a hemangioma. Tumor markers for liver carcinoma were normal.

From 2006-2011, there was recurrent abdominal pain, now accompanied by loss of appetite and a 20 pound-weight loss over a span of 6 months. Whole abdominal CT-scan done every 6 months revealed stable liver nodule size.

In 2011, she was admitted for fever. Work up showed normochromic normocytic anemia with normal white blood cells (WBC), pneumonia and a nodular opacity on the left lung. Chest CT scan showed multiple pulmonary nodules and nodular pleural thickening in the left lower hemithorax. Consideration was a pleural neoplasm (mesothelioma) with pulmonary metastasis. CT scan guided biopsy of the left pleural-based mass was suspicious for granulomatous process. Acid-Fast Bacilli (AFB) smear and Mycobacterium Tuberculosis (MTB) culture of the biopsy specimens were negative. Blood culture was positive for pansensitive MTB.

CT scan of the whole abdomen showed multiple liver nodules at segment II of the liver (2.4 x 4.8 cm and 2.4 x 4.1 cm) and a hypodense nodule in the body of the pancreas

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(0.9 x 0.6 cm). Liver function tests were normal except for hypoalbuminemia. Tumor markers for liver and pancreatic carcinoma, autoimmune panel, and hepatitis profile were negative. She refused to have a biopsy of the liver and pancreatic mass and opted to have them monitored until the completion of TB treatment. She was maintained on anti TB medications for 18 months and gained some weight (10 lbs) after treatment.

She was diagnosed with Type 2 DM in 2012 and was maintained on pioglitazone. A dynamic liver CT scan done after TB treatment showed no significant changes of the liver nodules' size. However, the hypodense nodule in the body of pancreas was not demonstrated on repeat CT scan. CXR after TB treatment revealed regression of the patchy and fibronodular opacities in the left lung.

In 2013, she started to have recurrence of weight loss accompanied with on and off diarrhea. She also developed seborrhoic dermititis-like skin lesions on the centro-facial area and annular rash with crusted borders on the buttocks. The skin lesion was biopsied which was consistent with Necrolytic Migratory Erythema.

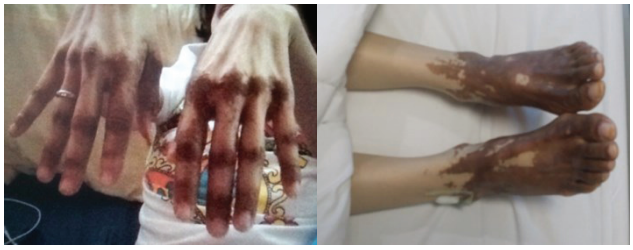

Figure 1. Hyperpigmented plaques with velvety surface on dorsum of both hands and feet (photographs taken before treatment).

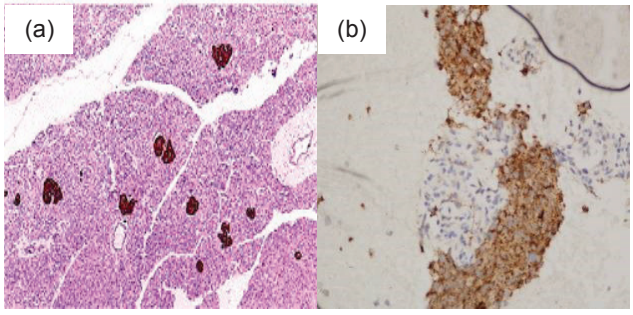

Figure 2. Immunohistochemical stain (Chromogranin, x 100) a. Islands of Langerhans b. Liver Mass

On April 2014, she was admitted for nutritional build up because at this time she was already cachectic with BMI 12.55 kg/m2. There were hyperpigmented plaques with velvety surface on the dorsum of the feet, hands, elbows (Figure 1). A repeat whole abdomen CT scan showed an increase in the size of the enhancing left lobe hepatic mass (6.6 x 6.5 x 5.6 cm). There were also hypodensities in the pancreatic body and tail (0.7 x 1.3 cm and 0.7 x 0.7 cm). Percutaneous FNAB of the pancreatic mass was consistent with pancreatic neuro endocrine neoplasm while the liver mass showed metastatic pancreatic neuro endocrine neoplasm. Immunohistochemical studies were positive for chromogranin, synaptophysin and CEA stain with a Ki67 index of 5% in the pancreas and <5% in the liver (Figure 2a and 2b). Her serum Chromogranin A was elevated at 674.579 ng/mL (NV 6.0-40.0 ng/ml). Glucagon level was also elevated 1243 pg/mL (NV <80 pg/mL). Based on all of these factors, the diagnosis is most likely Glucagonoma. She was given everolimus 5 mg/tab 1 tab once daily and ocreotide LAR 20 mg SQ then monthly thereafter.

After 3 months of medical therapy, she gained 4.5 kg with improvement of the Necrolytic Migratory Erythema (Figure 3). On repeat CT scan, there was a decrease in the size of the inhomogenous mass in the left hepatic lobe (4.4 x 5.8 x 5.2 cm from 7.6 x 7.1 x 6.6 cm) (Figure 4).

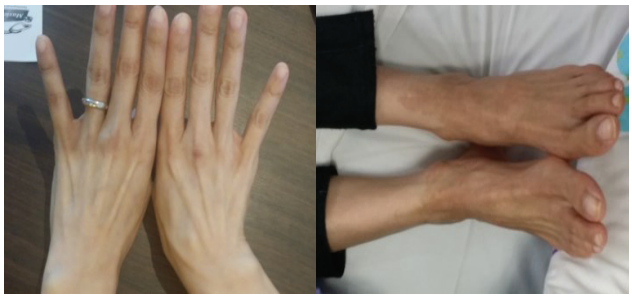

Figure 3. Improvement of Necrolytic Migratory Erythema after treatment compared with Figure 1.

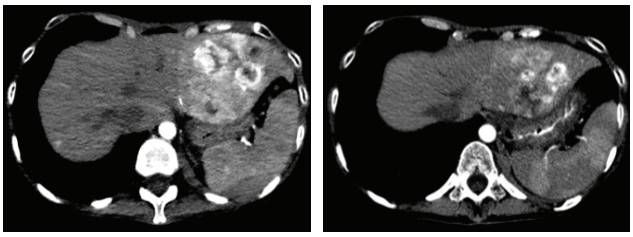

Figure 4. Decreased size of the inhomogenous mass in the left hepatic lobe (left – before treatment; right – after treatment).

DISCUSSION

The clinical findings of weight loss, diarrhea, diabetes, and NME accompanied by elevated glucagon level more than 1000 pg/ml, satisfied the clinical and biochemical parameters for the diagnosis of glucagonoma. Glucagonomas are rare slow-growing tumors arising from the pancreatic alpha-cells.[1] Majority of cases are sporadic, however, between 5 and 17% are associated with Multiple Endocrine Neoplasia Type I (MEN 1) or, rarely, familial adenomatous polyposis. Patients with the sporadic disease present in their fifth decade of life, while those associated with MEN 1 usually have younger disease onset, with a family history of pituitary, pancreatic islet cell, or parathyroid tumors. The characteristic syndrome of glucagonoma is a result of excessive secretion of glucagon and other peptides.[3]

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.13

The tail of the pancreas is the most common site of glucagonoma, seen in 47% to 75% of cases, with an average size of 6 cm.[4] These tumors are generally solid, circumscribed and well vascularized. By the time of diagnosis, 50% to 100% of patients already present with metastatic disease, with the liver as the most common site of metastasis, followed by regional lymph nodes, bone, adrenal gland, kidney, and lung.[5] In this case, the tumors were located at the body and tail of the pancreas with liver metastasis. However, it had a different presentation that made it interesting and difficult to diagnose. In contrast with the large size of the liver metastatic lesion (6.6 x 6.5 x 5.6 cm), the sizes of the pancreatic lesions as the main tumor were very small (0.7 x 1.3 cm and 0.7 x 0.7 cm). Furthermore, the metastatic lesions in the liver appeared before the pancreatic lesion. Despite its unusual presentation, the histopathology and immunohisto-chemical studies of the pancreatic mass proved that it was a pancreatic neuroendocrine neoplasm.

Manifestations associated with glucagonoma include weight loss, NME, diabetes, cheilosis or stomatitis, and diarrhea.[3,6-8] Other findings are anemia, neuropsychiatric symptoms and venous thrombosis. Weight loss, diarrhea, diabetes, and skin lesions consistent with NME were present in this patient. Many of the symptoms of glucagonoma discussed are nonspecific. As a result, glucagonoma is often diagnosed relatively late in the course of the disease. NME is often the clue which leads to the correct diagnosis.[3] Even though it is not pathognomonic for glucagonoma, the presence of NME should prompt further work-up for a pancreatic neuroendocrine tumor.[7] Among all the clinical manifestations, NME is the most prevalent symptoms, occurring in approximately 65 to 80 percent of patients by the time of diagnosis.[3] In a retrospective study by Kindmark et al, records from 340 patients with endocrine pancreatic tumors were reassessed and 23 patients had elevated plasma glucagon levels. This was only 7% of all the endocrine pancreatic tumors in this tertiary center. Only 22% of these patients had developed diabetes prior to the diagnosis of glucagonoma. Necrolytic migratory erythema was diagnosed or clinically suspected in 52% of patients. Seventy eight percent had metastatic disease to the liver at diagnosis.[9]

The diagnosis is based on clinical suspicion and the demonstration of raised glucagon levels in the presence of a pancreatic tumor. Diagnostic plasma glucagon concentrations have not been precisely established but levels in excess of 1000 pg/ml can be considered biochemical evidence for glucagonoma.[3]

The aim of treatment should be curative whenever possible but in the majority of the cases, it is often palliative.[10] Surgery remains the treatment of choice and it is the only approach that can achieve a cure. It may also still be considered even if the tumor is metastatic.[11] However, if the disease is progressive or in patients in whom surgery is contraindicated, symptoms related to specific hormonal production are currently best managed with somatostatin analogues. The only proven hormonal management of NETs is by administration of somatostatin analogues. Somatostatin receptors are present in the vast majority of NETs and somatostatin analogues bind principally to the SSTR subtypes 2 (with high affinity) and 5 (with lower affinity) thus inhibiting the release of various peptide hormones. They also antagonize growth factor effects on tumor cells and at high doses, may induce apoptosis. The two commercially available somatostatin analogues in Philippines are ocretotide and lanreotide.

Two molecularly targeted agents, sunitinib and everolimus, have been approved for treatment for neuroendocrine tumors. Sunitinib is a tyrosine kinase inhibitor that acts downstream from key drivers of tumor angiogenesis, including vascular endothelial growth factor types 2 and 3, platelet-derived growth factor and stem cell factor. It showed a response rate of 72.3%.[11] The mammalian target of rapamycin (mTOR) is a serine–threonine kinase, which is a major regulator of protein synthesis and stimulates cell growth, proliferation, and angiogenesis. Everolimus is an mTOR inhibitor that blocks the mTOR signaling pathway that is activated in many tumors. It showed a response rate of 77.4%.[11] For this patient, surgery was not done because of poor nutritional status and the presence of liver metastasis. Hence, ocreotide LAR 20 mg SQ monthly and everolimus 5 mg daily were given.

Majority of patients with glucagonoma also suffer from a prolonged catabolic state, hence, nutritional support is an important component of therapy. Necrolytic migratory erythema may respond to somatostatin infusion that may suggest a direct effect of ocreotide.[3] However, resolution usually occurs after resection of tumor.

Response to therapy includes symptomatic, hormonal and tumor responses. Tumor responses based on WHO criteria may be classified as: 1) Complete response with complete regression of all clinical, hormonal and radiological evidence of tumor; 2) Partial response with a 50% or greater reduction of all measurable tumor with hormonal and symptomatic improvement; 3) Stable disease wherein there is less than 50% reduction, or no greater than 25% increase of tumor size; 4) Progression of disease wherein there is appearance of new lesions, or an increase of 25% or more of tumor size, and hormonal and symptomatic deterioration.[3]

Follow-up comprises clinical, biochemical and radiological evaluation. The role of follow-up imaging and frequency depends on clinical circumstances and tumor grade. Initially, follow-up imaging may be taken at 3-6 months intervals. If the disease is relatively slow

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.13

growing, the interval can be increased to 9-12 months.[11] In terms of biochemical assessment, serum glucagon may be measured three and six months post-resection. Chromogranin A may be used but it should be interpreted with caution in patients on somatostatin analogues because the reduction in the chromogranin A levels may be a reflection of the effect of the somatostatin analogues rather than a reduction in the tumor size.[10] For this patient, glucagon level was not repeated post therapy. However, the Chromogranin A level one-year post treatment was significantly decreased (from 674.579 ng/mL to 59.261 ng/mL).

Length of survival is directly related to both the extent of the disease at the time of diagnosis and the degree of differentiation of the tumor. Those with metastases have a 5-year and 10-year survival of 32% and 15% respectively. Age at diagnosis and stage are strongly associated with survival. Higher grade also predicted worse survival.[12] Furthermore, Ki-67 is a cell proliferation marker that has some utility in predicting prognosis in neuroendocrine tumors. Five-year disease survival for low, moderate and high risk Ki-67 staining is 92%, 75%, 52% by AJCC stratification with a 10 year disease survival of 80%, 70% and 52%.[13] For this patient, the Ki67 index was 5% (moderate risk) thus predicting a 5 and 10 year disease survival of 75% and 70% respectively.

SUMMARY AND CONCLUSION

In summary, we have reported a rare case of metastatic glucagonoma, with weight loss accompanied by NME as the main clinical presentations. Skin manifestations as NME are essential for early diagnosis of glucagonoma and may prevent metastatic disease.

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JAFES Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

Primary Hyperparathyroidism from Parathyroid Carcinoma Presenting with Multiple Skeletal Fractures and Brown Cell Tumors

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Abstract

We report the case of a 19-year old Filipino woman who presented with hard masses on the left upper arm and leg with multiple fractures on all extremities. Her serum calcium and intact parathyroid hormone (iPTH) levels were elevated, while serum phosphorus was low. Ultrasonography of the neck revealed a left inferior parathyroid mass. Ultrasound-guided fine needle aspiration of the mass revealed findings consistent with parathyroid carcinoma. After hydration and administration of diuretic and bisphosphonate to control the severe hypercalcemia, she subsequently underwent 3½ gland parathyroidectomy with en-bloc left thyroid lobectomy. There was immediate normalization of biochemical indices after surgery. Three months later, the fractures on all extremities were fully resolved.

Key words: hypercalcemia, hyperparathyroidism, parathyroid carcinoma

CASE

A 19-year old Filipino female was admitted due to multiple fractures on all extremities. About 7 months prior to admission, she noted onset of bone pain, initially at the pelvic and lumbosacral areas, progressing to include the arms and thighs. This was associated with fatigue, anorexia, muscle weakness and progressive weight loss about of 30%. She took analgesics and tolerated her condition.

About 3 months prior to admission, she could no longer ambulate due to severe bone pains. She also noted multiple fixed hard masses on the left upper arm and leg. She was brought to a general physician for consultation following spontaneous fracture of her left humerus and left femur. She was referred to an orthopedic surgeon who worked her up as case of primary bone malignancy to rule out multiple myeloma. Bone biopsy revealed brown cell tumor/multifocal polyostotic giant cell tumor consistent with skeletal changes associated with hyperparathyroidism (Figure 1). She was subsequently transferred to our institution for further workup of the etiology of hyperparathyroidism.

On examination, her vital signs were stable. Pertinent physical examination findings were deformities on both arms and the left thigh. These were consistent with radiologic findings of closed complete fractures on the middle third of the humerus on both arms, and the middle third of the right femur (Figures 2 and 3). She experienced severe pain even on minimal movement. She was admitted with the diagnosis of brown cell tumor with multiple lytic bone lesions secondary to primary hyperparathyroidism from a parathyroid adenoma or carcinoma.

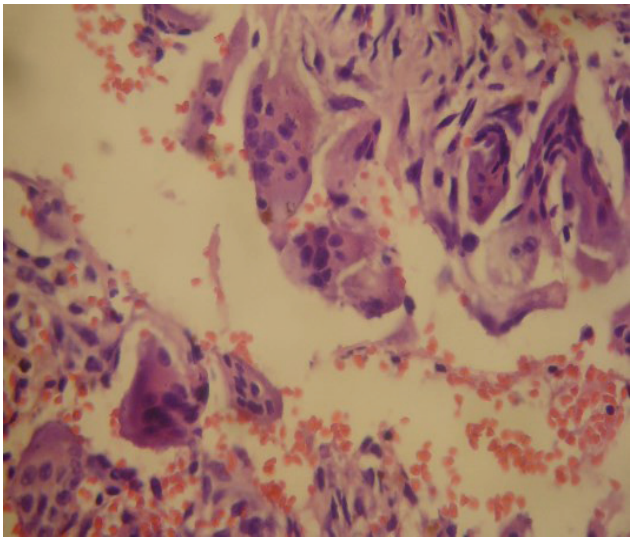

Figure 1. Bone biopsy showing brown cell tumor/ multifocal polyostotic giant cell tumor, with no findings suggestive of malignancy (H&E, X 400).

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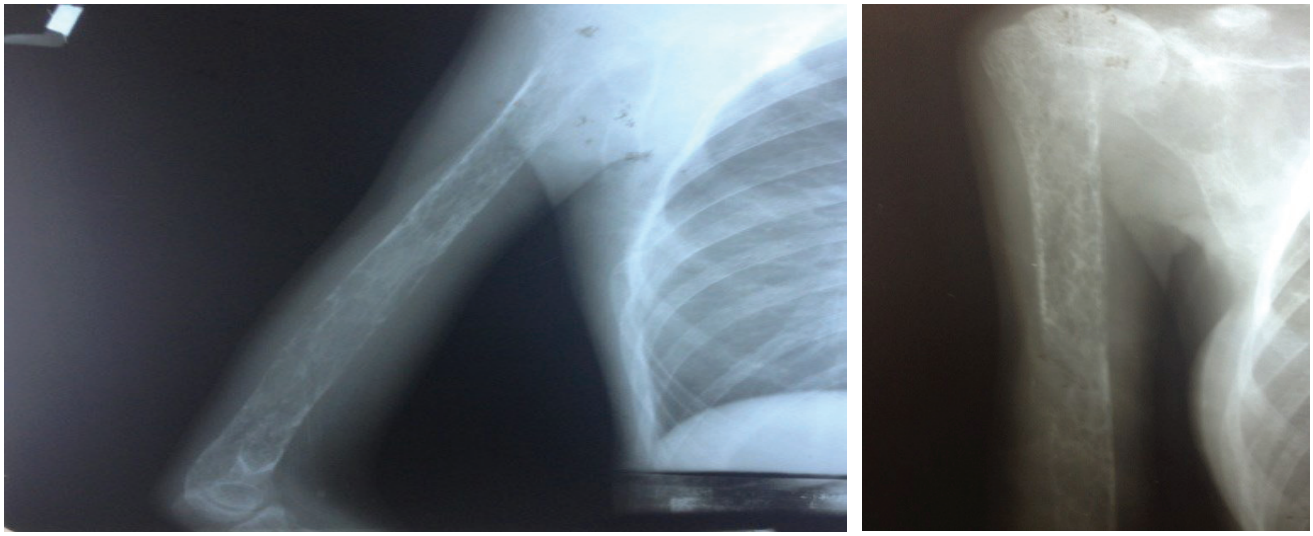

Figure 2. X-ray of the right humerus showed generalized decrease in bone density and subperiosteal and intracortical resorptive changes. Most of the humeral shaft demonstrated a mottled multicystic appearance with prominent trabeculations. A fracture was seen on the middle third of the humerus.

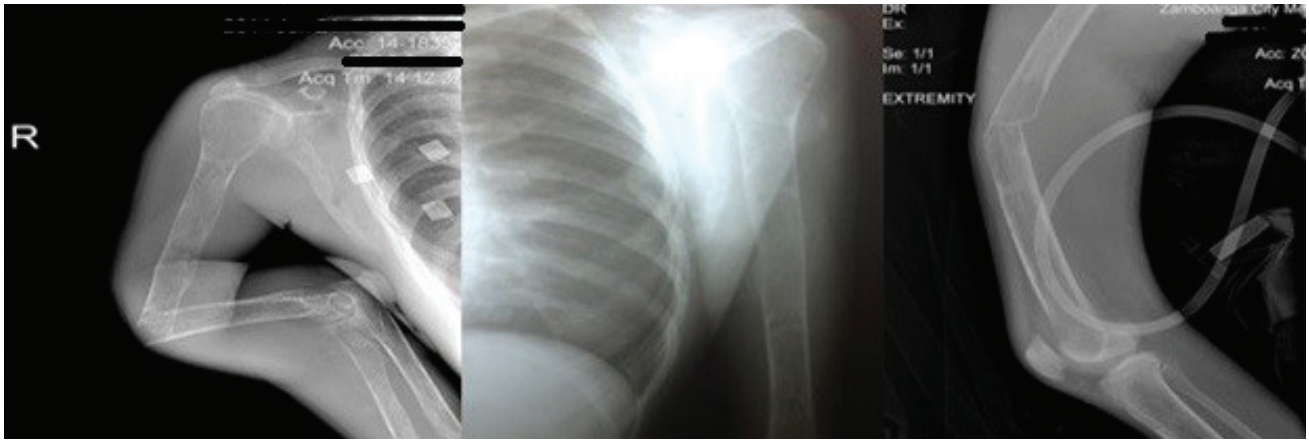

Figure 3. Pathologic fractures bilateral middle 3rd humerus and right femur with angulation of distal fracture segment. Significantly generalized severe osteopenia and subperiosteal reactions.

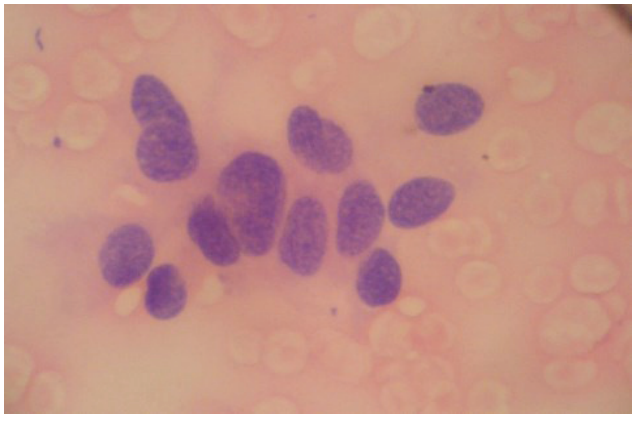

Figure 4. Fine needle aspiration biopsy of left parathyroid. Cytologic findings were suspicious for carcinoma (H&E, x 400).

Laboratory Work-up

Her corrected calcium was elevated at 1361 umol/L [normal value (NV) 760 to 884 umol/L], while serum phosphorus was decreased at 221 umol/L (NV 221 to 396 umol/L). iPTH was extremely high at 2001 pg/mL (NV 8.5 to 72.5 pg/mL). X-ray of the extremities showed osteopenia, endosteal resorptive changes and multiple pathologic fractures. Ultrasonography of the neck revealed a parathyroid mass probably an adenoma at the inferior pole of left thyroid gland measuring 2.3 cm x 1.1 cm x 1.0 cm. Sestamibi scan of the parathyroid gland was not done as this was not available in our region. An ultrasound-guided fine needle biopsy was done instead, which revealed histologic findings consistent with parathyroid carcinoma (Figure 4). Ultrasonography of the kidneys revealed bilateral nephrolithiases. Free thyroxine, triiodothyronine and thyroid-stimulating hormone levels were within normal limits.

Management

Intravenous hydration, furosemide and alendronate were given for the severe hypercalcemia. Conservative treatment with plaster reduction was done by the

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.14

Orthopedics Department for the management of her multiple fractures. After 2 weeks of medical management, she underwent 3½ gland parathyroidectomy with en bloc left thyroid lobectomy. Intraoperative findings revealed a left parathyroid gland mass with poorly circumscribed borders invading the capsule and local tissues, and a well-circumscribed right parathyroid mass. Serum calcium and iPTH immediately decreased (1131 umol/L from 1255 umol/L and 211.8 pg/mL from 2001 pg/mlL, respectively) one hour after the surgery. Further reduction was noted 24 hours (corrected calcium 9.2 mg/dL, iPTH 48 pg/mL) and 72 hours (serum calcium 795 umol/L, phosphorus 232 umol/L) post-surgery. Histopathologic examination of the left parathyroid gland showed cytomorphologic features suspicious for neoplasm, described as areas with monotonous nuclear atypia, fibrosis and focal trabecular growth with prominent nuclear pleomorphism and scant to ample amount of granular cytoplasm (Figure 5a and 5b). The right parathyroid gland showed mild hypercellularity with benign epithelial cells and cystic degeneration consistent with adenoma. Immunohistochemical staining revealed negative results for TTF-1, calcitonin and chromogranin. Ki-67 study also showed low proliferation at less than 6%. These signify the absence of a neuroendocrine tumor and also indicate a slow rate of cell division of the parathyroid malignant cells.

Her postoperative course was unremarkable. She was discharged 7 days after surgery with plaster reduction on all extremities, and home medications of calcium carbonate + cholecalciferol and alendronate sodium.

Outcome and Follow-up

Three months after discharge, the multiple fractures in her extremities resolved completely with no recurrence of fractures or bone pains (Figures 6 and 7). The hard masses in the left femur and tibia also disappeared.

DISCUSSION

While parathyroid adenomas represent a common endocrine problem, parathyroid carcinomas are very rare tumors. With an estimated incidence of 0.015 per 100,000 population and an estimated prevalence of 0.005% in the United States, parathyroid cancer is one of the rarest of all human cancers.[1,2] In Europe, the United States and Japan, parathyroid carcinoma has been estimated to cause hyperparathyroidism (HPT) in 0.017% to 5.2% of cases. However, many series report this entity to account for less than 1% of patients with primary HPT.[1,3,4] The median age in most series is between 45 and 51 years.[1] The ratio of affected women to men is 1:1, in contrast to primary HPT where there is a significant female predominance of 3 to 4:1.[4]

Mutation of the HRPT2 (also called CDC73) tumor suppressor gene has been recognized to play a central role in the molecular pathogenesis of parathyroid carcinoma. HRPT2 is located on chromosome 1 and encodes parafibromin, a protein whose function remains under investigation but appears to involve regulation of gene expression and inhibition of cell proliferation. Sporadic (nonfamilial) parathyroid carcinomas frequently bear HRPT2 mutations. One study reported HRPT2 mutation in 10 of 15 sporadic parathyroid cancers, while another identified the mutation in 4 of 4 carcinomas.[5,6] Most mutations were somatic, implying a selective advantage that attests to their pathogenetic importance. Furthermore, because mutations outside the coding region are expected to occur but would have escaped detection, it is plausible that HRPT2 inactivation drives virtually all parathyroid cancers. Unsuspected germ-line mutations were also discovered in a substantial minority of patients who presented clinically with sporadic disease, suggesting that some of these individuals may have hyperparathyroidism-jaw tumor syndrome (HPT-JT), or a phenotypic variant.[5] This recognition that family members of some patients with apparently sporadic parathyroid cancer are also at risk for parathyroid malignancy has created a new indication for genetic testing.[5]

The frequency of the various parathyroid lesions underlying hyperfunction is 75 to 80% from adenoma, 10-15% from primary hyperplasia, and less than 5% from parathyroid carcinoma.[7] These tumors secrete parathyroid hormone producing hyperparathyroidism, which is usually severe. Parathyroid carcinoma may be suspected but it usually cannot be confirmed prior to operation.[8,9] Parathyroid carcinoma tends to be localized in the inferior parathyroid glands. One study reported that the primary tumor originating in the inferior parathyroid glands was found in 15 of 19 cases involving local invasion.[4]

Certain clinical features may help to distinguish parathyroid carcinoma from adenoma. Parathyroid carcinoma should be suspected clinically if any of the following are present: (1) hypercalcemia greater than 14 mg/dL and serum PTH levels more than twice that of normal, (2) hypercalcemia with a palpable neck mass (3) hypercalcemia associated with unilateral vocal cord paralysis, and (4) markedly elevated serum PTH accompanying renal and skeletal disease.[10,14] Our patient presented with multiple fractures on all extremities, nephrolithiasis, severe hypercalcemia and a markedly elevated serum PTH. Ultrasonographic findings also revealed a parathyroid mass at the inferior pole of the left thyroid lobe, which was later confirmed to be a carcinoma.

No effective medical therapy for parathyroid carcinoma is known. Trials of chemotherapeutic agents have been generally disappointing, with only anecdotal reports of success. This tumor is sufficiently rare that controlled trials are impossible.[9] Medical therapy is primarily geared toward management of the hypercalcemia that is often quite severe. Treatment is similar to hypercalcemia due to

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other causes. At initial presentation and for rapid treatment of severe hypercalcemia, volume loading and diuresis with a calcium-wasting loop diuretic is the treatment of choice. The next line of therapy, used for chronic treatment, is the bisphosphonates. Hypercalcemia due to parathyroid cancer is often resistant to long-term medical management and is usually the cause of death in patients with metastatic disease.[9]

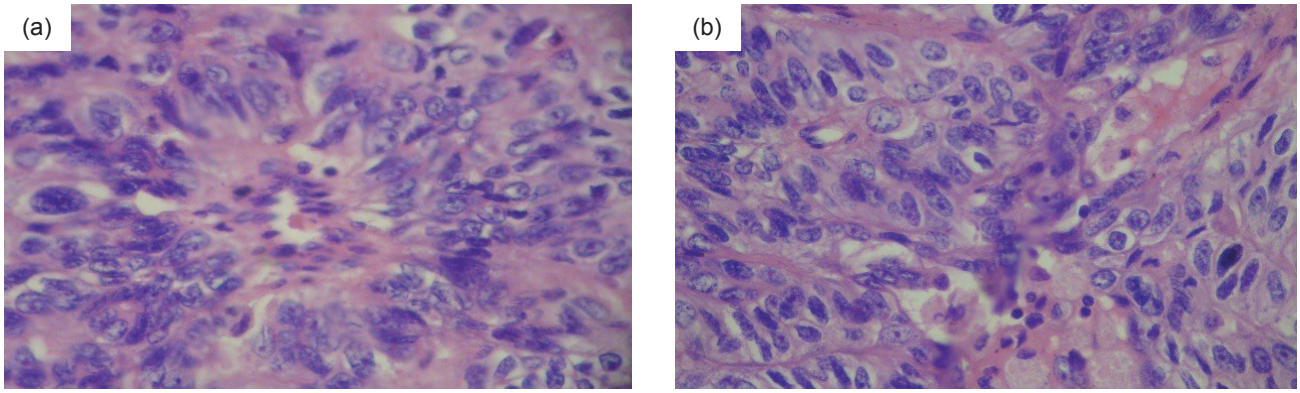

Figure 5a and 5b. Left parathyroid gland showing hypercellularity with fibrosis, trabecular growth, and areas with monotonous nuclear atypia. Capsular, vascular, perineural and thyroid gland invasion were not seen (H&E, x 400).

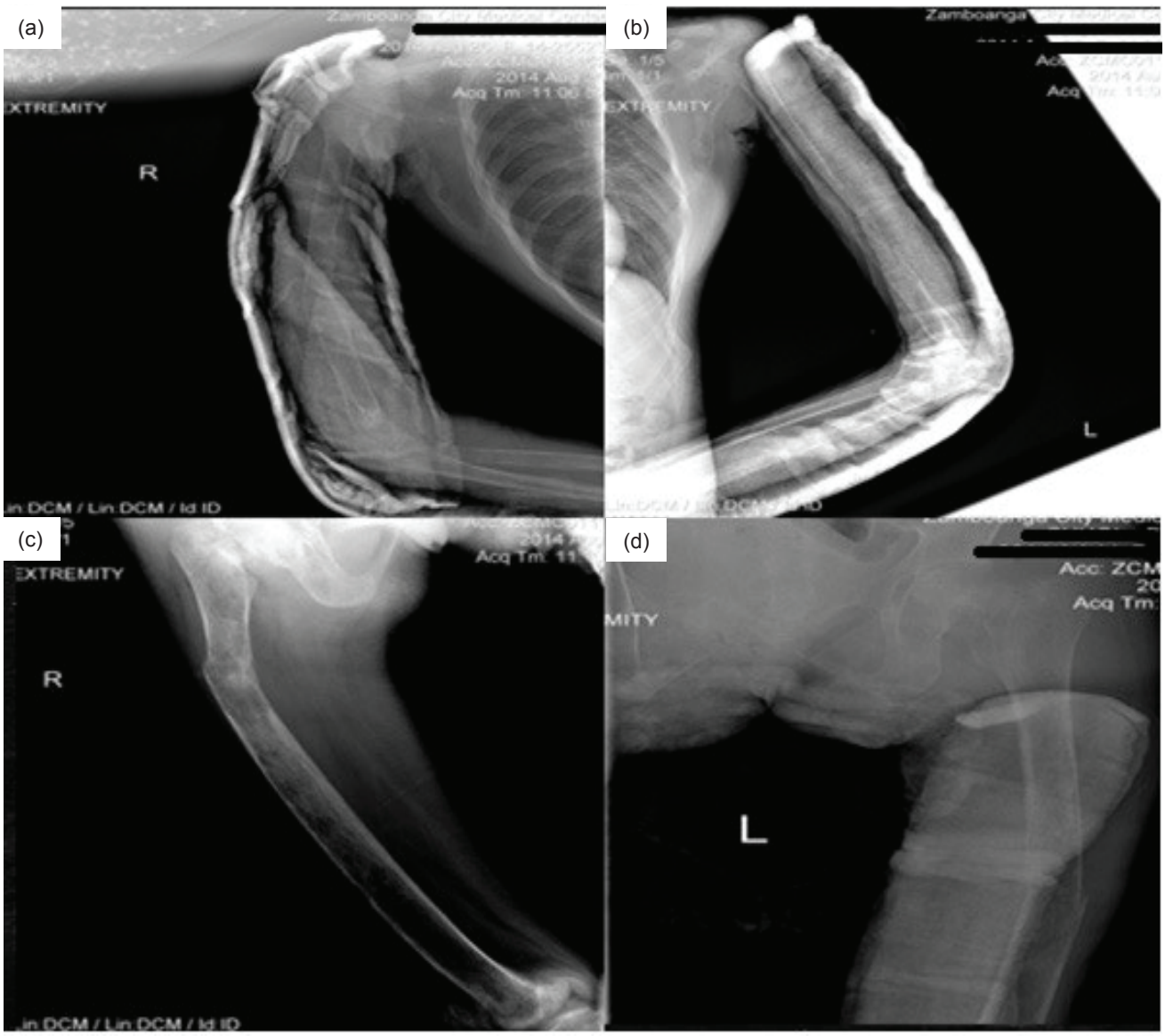

Figure 6. X-rays of the right humerus (a), left humerus (b), right femur (c) and left femur (d) done 3 weeks after surgery. Callus formation was seen at the fractured segments with moderate to severe osteopenia.

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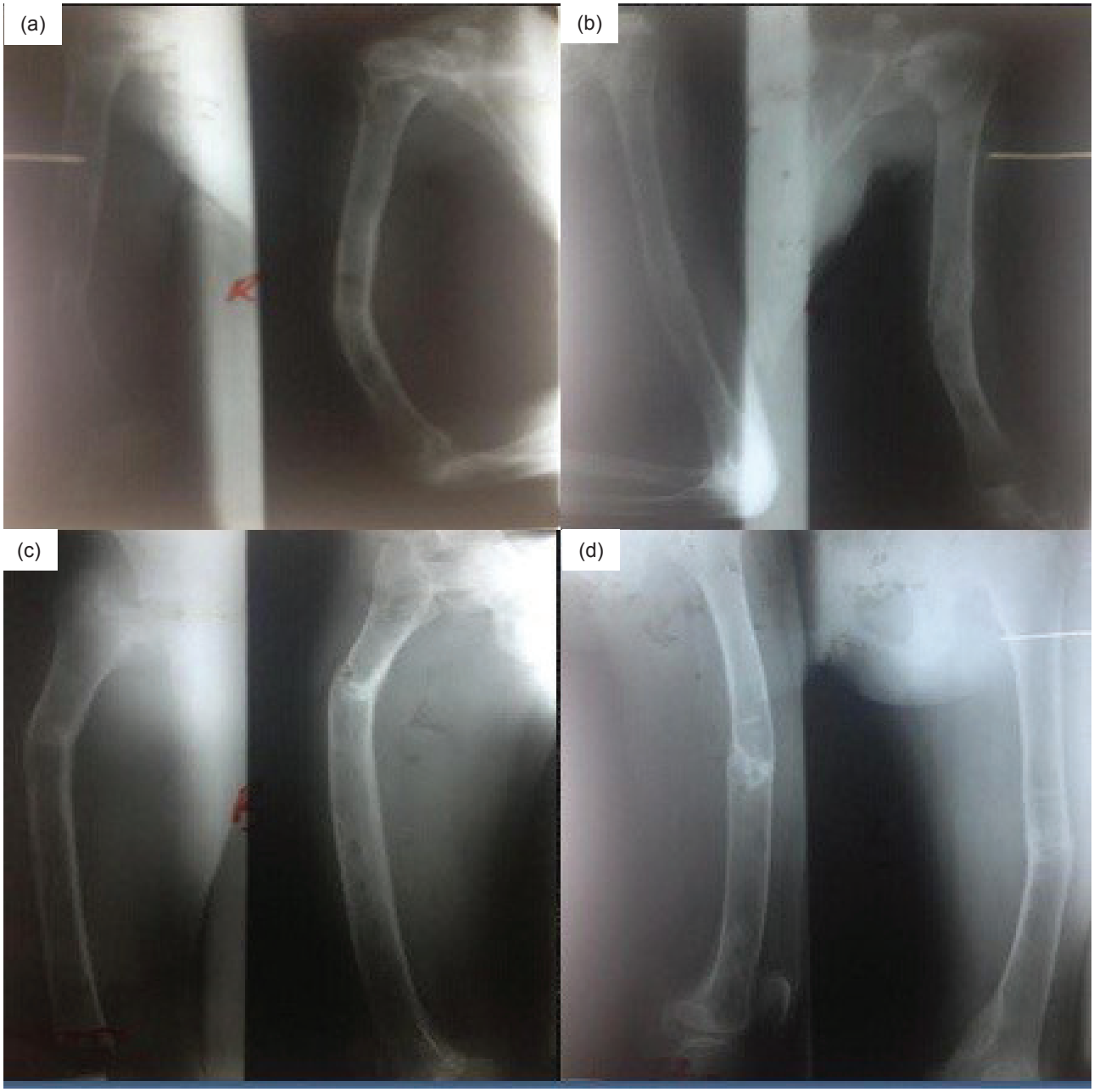

Figure 7. X-rays of the right humerus (a), left humerus (b), right femur (c) and left femur (d) done 3 months after surgery. Callus formation was still seen at the fractured segments, with mild osteopenia. Anterolateral bowing was also observed in the right humerus, right femur and left femur. Anteromedial bowing was seen in the left humerus.

Surgery is the mainstay of therapy. The approach to initial surgery has evolved from an extremely aggressive procedure with ipsilateral thyroidectomy, isthmusectomy, excision of nearby strap muscles and removal of the recurrent laryngeal nerve, to a less aggressive one, involving parathyroidectomy or en-bloc resection of the parathyroid mass and any adjacent tissues that have been invaded by tumor.[14]

In a study of Anderson, Samaan and Vassilopoulou, the disease typically follows one of 3 courses: (1) a third of patients are cured at initial or follow-up surgery, (2) another third recur after a prolonged disease-free survival but may be cured with reoperation, and (3) the remainder experience a short and aggressive course with a high recurrence rate, even after a seemingly successful surgery. The combined 5- and 10-year survival rates varied from 50 to 70% and 13 to 35%, respectively.[14]

In some cases it may not be possible to differentiate parathyroid adenoma or carcinoma at the time of diagnosis or initial surgery. Local recurrence or occurrence of distant metastases at subsequent follow-up ultimately determines the correct pathological diagnosis.[12] Approximately 40% to 60% of patients experience a post-surgical recurrence, typically in the range of 2 to 5 years after the initial resection.[15]

ONLINE FIRST | November 30, 2015 | http://dx.doi.org/10.15605/jafes.030.02.14

CONCLUSION

Severe hypercalcemia in the presence of multiple pathologic fractures, nephrolithiasis, elevated iPTH and constitutional signs and symptoms including bone pain, fatigue, anorexia, nausea, vomiting, weight loss and dehydration strongly point to a diagnosis of primary hyperparathyroidism from parathyroid carcinoma. Complete history, physical examination, a high index of suspicion and histopathologic confirmation is necessary for the diagnosis.

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CASE REPORT

Graves' Disease and Periodic Paralysis

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Abstract

Thyrotoxic periodic paralysis represents a rare neurological emergency of an endocrine disorder. It poses a diagnostic challenge to the clinicians, as it is an uncommon disorder and its clinical presentation is similar to the more common hypokalemic paralysis. Adding to the diagnostic dilemma is that most patients do not have prior history of thyroid disorder and only have subtle features of hyperthyroidism. Hence, the diagnosis can be easily missed without a high clinical index of suspicion. These patients usually present to the emergency department with acute flaccid paralysis and all physicians should be aware of this clinical entity. The disease can be life-threatening if early diagnosis and prompt therapy is not initiated. We report three interesting cases in which periodic paralysis was the initial manifestation of underlying Graves' disease in two and occurred in the third case who was previously diagnosed with thyrotoxicosis due to non-adherence to drug therapy.

Key words: Thyrotoxic periodic paralysis, hypokalemia, Graves' disease, beta blockers, rebound hyperkalemia, paralysis

INTRODUCTION

Periodic paralysis is one of the dramatic and life-threatening complications of Graves' disease (GD). Muscular weakness in GD can be due to thyrotoxic myopathy, periodic paralysis and associated myasthenia. Thyrotoxic periodic paralysis (TPP) is characterized by the acute onset of severe hypokalemia and profound proximal muscle weakness in patients with thyrotoxicosis.[1] The neuromuscular symptoms of TPP are quite similar to that of hypokalemic periodic paralysis except for the presence of signs and symptoms of thyrotoxicosis. Early clinical recognition is pivotal as management strategies of both conditions are different. Antithyroid drugs (ATD) and beta blockers are cornerstones of therapy. Potassium replacement has a risk of rebound hyperkalemia, potassium correction should precede with caution and frequent monitoring. Achieving and maintaining a euthyroid state is key, as it avoids the recurrence of paralytic attack.

CASE 1

A 35-year-old man presented to the emergency department with complaint of generalized weakness of all four limbs. No precipitating factors could be identified on enquiry. There was history of similar attacks, occuring thrice in the past six months but it resolved on its own within a few hours and he was never hospitalized. The weakness appeared at night time. The patient had no history of fever, diarrheal episode, palpitation, nervousness or weight loss. There was no history of similar attack in his family members. On examination, the patient was conscious, oriented and afebrile. The pulse rate was 104/minute and blood pressure was 130/80 mm Hg. Neck examination revealed a small, diffuse, non-tender, grade 1 goiter without any bruit. He had no cranial nerve deficit. The motor power was grade 2/5 in all four limbs and deep tendon reflexes (DTRs) were slightly depressed. There was no sensory or bladder involvement. No thyroid-associated ophthalmopathy or dermopathy was detected. Electrocardiogram (ECG) revealed sinus tachycardia and presence of U waves in leads v2 to v4. Important biochemical investigations and thyroid function tests are summarized in Table 1. Renal function tests, liver function tests and glycemic status were normal. Based on above findings, a diagnosis of TPP was made. He was given intravenous potassium solution (potassium chloride), beta blockers (propranolol) and ATD (methimazole) (Table 2). He made an uneventful recovery from paralysis within six hours. Subsequently, nerve conduction study (NCS) and electromyography (EMG) were

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Table 1. Clinical and biochemical characteristics of patients diagnosed with thyrotoxic periodic paralysis

Case number	Case 1	Case 2	Case 3
Age at onset (years)	35	24	28
Sex	Male	Female	Male
FT3 (NV: 3.1-6.8 pmol/L)	11.26	26.32	9.10
FT4 (NV: 12-22 pmol/L)	45.23	86.7	29.78
TSH (NV: 0.27-4.3 mIU/mL)	0.048	0.027	0.084
Serum K+(NV: 3.5-5.0 mEq/L)	2.3	2.5	2.6
HCO3-(NV: 22-26.0 mEq/L)	23	24	23

FT4- Free thyroxine, FT3- Free triiodothyronine, TSH-Thyroid stimulating hormone, Serum K+-serum potassium at presentation, HCO3--Bicarbonate level

Table 2. Summary of treatment received and time taken for recovery from paralysis among patients

Case number	Case 1	Case 2	Case 3
Initial dose of ATD (mg/day)	20	30	20
Initial dose of propranolol (mg/day in divided doses)	120	120	80
Route of potassium replacement	Intravenous	Intravenous	Intravenous
Dose of potassium replacement received (mEq)	60	120	80
Average time of recovery (in hours)	6	24	12
Serum K+ at recovery (NV: 3.5-5.0 mEq/L)	3.9	4.8	5.8

ATD –Anti-thyroid drugs (methimazole), Serum K+-serum potassium at recovery.

done which revealed no abnormality. Ultrasonography (USG) of the thyroid gland revealed diffuse enlarged thyroid gland with increased vascularity. Technetium 99m scan (Tc 99 m scan) was done later on and it showed a hyperfunctioning gland with increased diffuse tracer uptake. During a nine-month follow-up period, the patient was euthyroid with anti-thyroid medications and was free from any paralytic attack.

CASE 2

A 24-year-old female presented with sudden onset of weakness of both lower limbs for four hours. There was no history of a similar attack in the past or in any family members. The patient was diagnosed with thyrotoxicosis two years prior and was prescribed ATD. In her last clinical follow up she was prescribed 15 mg of methimazole. However, she was non-compliant to medications. Prior to presentation, she has had symptoms of thyrotoxicosis for one year. She was conscious and afebrile. She had a pulse rate of 120/minute and blood pressure was 140/76 mm Hg. Neck examination revealed a diffuse, non-tender goiter without any bruit. She had normal cortical functions and there was no cranial nerve deficit. Motor strength was grade 3/5 in both lower limbs with grade 4/5 in upper limbs. DTRs were diminished. There was no sensory or bladder involvement. There was no associated ophthalmopathy or dermopathy. Biochemical evaluation confirmed presence of thyrotoxicosis and hypokalemia (Table 1). The rest of the parameters were normal. An USG (including color doppler) of the thyroid showed diffusely enlarged goiter with marked increase in intraparenchymal blood flow. In view of frank signs of hyperthyroidism, the diagnosis of TPP was straightforward. This case elucidates the need to explore the possibility of TPP in females even though it is much more common in males. She was managed successfully with potassium supplementation, ATD and beta blockers (Table 2). However, recovery from weakness and hypokalemia took a longer time than the previous case (24 hours). She was counseled regarding compliance to ATD and need for Iodine 131 ablation in case of failure to achieve remission with ATD. She was well till last follow up with the medication and without report of any recurrence.

CASE 3

A 28-year-old man presented with quadriparesis for the last three hours. There was no history of a previous attack. The patient gave a history of strenuous exercise earlier in the day. He also complained of generalized muscle pain prior to paralysis. The patient had no history of fever, diarrheal episode, palpitations, nervousness or weight loss. There was no history of similar attack in any family member. On evaluation, the pulse rate was 96/minute and blood pressure was 126/84 mm Hg. Neck examination revealed a small goiter without any bruit. He had normal cortical functions with no cranial nerve deficit. The power was grade 2/5 in all four limbs and DTRs were depressed. There was no sensory or bladder involvement. There was no associated ophthalmopathy or dermopathy. ECG revealed presence of U waves in leads v2 to v5. Biochemical investigation revealed hypokalemia (Table 1). Renal function tests, liver function tests and glycemic status were normal. Routine thyroid function tests (TFT) revealed elevated thyroid hormone levels (Table 1). Thyrotoxicosis was solely detected due to routine screening (to rule out possible association of hyperthyroidism in such cases of hypokalemic periodic paralysis). This illustrates that TPP should be regarded a strong differential for periodic paralysis especially in males, despite the absence of overt signs of thyrotoxicosis. Basing on above findings, a diagnosis of TPP was made. After receiving treatment (Table 2) he made an uneventful recovery. During his replacement (started with 10 meq/hr), his serum potassium reached 5.8 mEq/L with no untoward clinical sequelae. Hence, caution should be exerted during potassium replacement to prevent the phenomenon of rebound hyperkalemia and its dangerous side effects. Subsequent nerve conduction study (NCS) and electromyography (EMG) revealed no abnormality. Technetium 99 m scan (Tc 99 m scan) revealed a hyperfunctioning gland with diffuse tracer uptake compatible with diagnosis of GD. The patient was maintained well with ATD without any attack of TPP.

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DISCUSSION

The association of periodic paralysis and thyrotoxicosis had been recognized as early as 1902 by Rosenfeld.[2] The first description of the entity in English literature was made by Dunlap and Kepler in 1931, who described four such patients.[3] In Asian populations (where the incidence of TPP is highest), it usually appears between the ages of 20 and 40 years of life, coinciding with the peak age for hyperthyroidism.[4] The male to female ratio ranges from 17:1 to 70:1 despite the fact that hyperthyroidism is more common in females (female-to-male ratio of 9:1).[5] The attack is characterized by recurrent, transient episodes of muscle weakness that range from mild weakness to complete flaccid paralysis. Neurologic examination during an attack demonstrates weakness, usually affecting proximal more than distal muscles and the legs more than the arms. Sensory system and bladder involvement are never seen.[6] Diminished DTRs are typical of TPP in contrast to hyperreflexia seen in the thyrotoxic state. Most patients with TPP have only mildly elevated serum thyroid hormone levels and only about 10% of patients may have mild thyrotoxic symptoms.[5] Rare, life-threatening complications of TPP include bulbar palsy requiring mechanical ventilation and fatal arrhythmias including ventricular fibrillation and ventricular tachycardia.[6]

Although the majority of cases of thyrotoxicosis associated with TPP are due to Graves' disease, TPP can appear with thyrotoxicosis of any origin. Patients with TPP have been reported with thyroiditis, toxic adenoma or toxic nodular goiter.[6] The precipitating factors of TPP reported in the literature include high carbohydrate ingestion, strenuous exercise, trauma, acute upper respiratory tract infection, high-salt diet, emotional stress, exposure to cold, alcohol ingestion, menstruation and use of drugs.[6-8] TPP may be preceded by prodromal symptoms such as muscle pain, cramps or stiffness of muscles of the affected limbs.[6] TPP does not usually recur once the patient is euthyroid. Achieving proper control of hyperthyroidism is essential. Hsieh et al reported that before achieving the euthyroid status, the rate of recurrent attacks was as high as 62.2%, peaking in the first 3 months after TPP diagnosis.[8]

Hypokalemia occurs due to a massive shift of potassium into the cells rather than net loss from the body. Excess thyroid hormone may predispose to paralytic episodes by increasing the susceptibility to epinephrine or insulin, and therefore increasing Na^+/K^+-ATPase activity in the beta-adrenergic receptors in skeletal muscles, which leads to potassium shift into the cells.[9] The hypokalemia observed in these cases is due to the increased K^+ influx into a cell secondary to the increase in the activity of the Na^+/K^+-ATPase pump and by the hyperinsulinemic response to carbohydrate intake in patients susceptible to TPP.[10,11] Androgens can also increase the activity of the Na^+/K^+-ATPase pump, which explains the higher incidence of the disease in young males.[11] Recent studies have shown that susceptibility to TPP can be conferred by loss-of-function mutations in the skeletal muscle specific Kir channel, Kir2.6 and loci on 17q involved in Kir2.1 gene expression.[12-17] These findings also suggest that reduced basal muscular Kir current may also be an important mechanism of TPP.[9,11] The dual effects of increased intracellular K^+ influx from activated Na^+/K^+-ATPase and decreased K^+ efflux from defective Kir channels potentiate the serum hypokalemia that upsets membrane polarization and muscle excitability in TPP.[9-11]

Studies exploring the genetic susceptibility for TPP indicate that defects of the skeletal muscle-specific inward rectifying K^+ (Kir) channel, Kir2.6, encoded by the KCNJ18 gene, is associated with a proportion of TPP patients mainly from the United States, Brazil, France and Singapore.[12] Other important developments are that gene polymorphisms (rs623011 and rs312691) at 17q24.3 may affect the expression of KCNJ2 gene (encoding Kir2.1) in Hong Kong and Thai populations.[14,15] The presence of different HLA antigen subtypes such as DRw8, A2, Bw22, Aw19, B17, B5, and Bw46 in certain ethnic populations (Singaporean, Chinese and Japanese) may make them more susceptible to TPP.[6,7] Hence, TPP is considered as an endocrine channelopathy with genetic background.[11]

In a recently published, large study by Li et al, the authors have explored the genetic susceptibility of Chinese patients with TPP. They concluded that KCNJ18 gene mutations occurred in a small proportion (3.1%) of these patients with TPP.[18] The patients with KCNJ18 mutation had significant clinical difference than patients without KCNJ18 mutation. The former group had shorter attack duration, higher prevalence of muscle soreness and weakness recurrence than the latter. The loci polymorphisms (rs623011 and rs312691) at 17q24.3 are significant risk factors for TPP.[18]

Laboratory findings include hypokalemia, normal bicarbonate level, hypophosphatemia, mild hypomagnesemia and normal blood pH. Urinary findings include low potassium excretion rate (low urinary potassium/creatinine ratio), hypercalciuria and hypophosphaturia. Abnormal thyroid function tests (low TSH; elevated free and total T4 and T3) are hallmarks of the disease. Electrocardiographic findings may be characteristic of hypokalemia, with increased P-wave amplitude, prolonged PR interval, widened QRS complexes, decreased T-wave amplitude, and U waves. Unlike hypokalemia from other causes, sinus tachycardia predominates in patients with TPP. Other electrocardiographic abnormalities include atrioventricular block, atrial fibrillation, ventricular fibrillation and asystole.[19,20] Differential diagnoses of TPP include the causes of periodic hypokalemia, e.g., familial hypokalemic periodic paralysis, sporadic periodic paralysis and other causes of potassium wasting disorders (diuretics use, primary hyperaldosteronism, Bartter's syndrome, Gitelman's syndrome, renal tubular

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acidosis) causing marked hypokalemia. Hence, urinary potassium excretion measurement and arterial blood gas analysis are essential requisites to rule out such disorders.

Management

TPP is managed by correction of hypokalemia and treatment of the underlying hyperthyroid state. It is achieved by intravenous or oral potassium replacement to hasten muscle recovery and prevent cardiopulmonary complications. It has been shown that adequate control of hyperthyroidism by any one of the following modalities, that is, use of antithyroid drugs and non-selective beta blockers, radioactive iodine or surgical thyroidectomy are successful in preventing TPP. Nonspecific beta-adrenergic blockers like propranolol have also been proposed as an alternative treatment to ameliorate the paralysis without rebound hyperkalemia and raise the serum levels of potassium and phosphate. High-dose oral propranolol (3-4mg/kg orally) alone has been reported to rapidly abort the paralysis.[21]

Propranolol, but not the selective beta1-blocker metoprolol, also effectively prevented recurrence of paralytic attacks or inhibited paralysis induced by a carbohydrate load. At a dose of 40 mg four times a day, propranolol prevented paralysis in carbohydrate-induced TPP in about two thirds of cases by inhibiting the activity of Na^+/K^+-ATPase.[6,22]

In a retrospective case series, patients who received intravenous potassium recovered more quickly than those who received oral supplementation.[23] There may be a delayed response of a few hours following potassium administration.[24] Rebound hyperkalemia occurred in approximately 40% of patients with TPP, especially if they received more than 90 mEq of potassium chloride within the first 24 hours.[6] There is a positive correlation between the dose of potassium chloride administered and the degree of rebound hyperkalemia.[4,6,25] This is because hypokalemia in TPP is due to redistribution of potassium rather than net loss from body. Lower doses of potassium chloride may be effective while lowering the patient's risk of hyperkalemia.[25] Required doses of potassium supplementation are variable and range from 10 to 200 mEq.[6] Lower doses of potassium chloride may be effective while lowering the patient's risk of hyperkalemia. Thus potassium supplementation should be given at a slow rate unless there are cardiopulmonary complications.[6] There is no definite role of potassium supplementation for prophylaxis against further paralytic attacks and should be avoided.[6] Therefore, monitoring the serum potassium levels during the treatment and suspending the infusion at the first sign of the muscular force recovery is recommended.[13]

In a recent study by Chang et al, the authors evaluated the efficacy of various treatment modalities for managing patients of GD complicated by TPP. They found out that patients with GD who had TPP appeared to have a greater chance of thyrotoxic and paralysis relapse when managed by ATD alone.[26] A more definitive treatment modality such as surgery or radioiodine therapy is more prudent for patients with GD with TPP. When radioiodine is chosen over surgery, a higher dose (>550 MBq) should be employed in order to cure hyperthyroidism.[26] In two recent studies, the TPP relapse rate during withdrawal or tapering of ATD stood at 29.6% and 50% respectively.[17,26] The discrepancy in relapse rates in these studies may be due to difference in study population and follow-up period.

CONCLUSION

The possibility of TPP should always be borne in mind while dealing with a case of periodic paralysis. Though the prevalence of TPP is highest among Asians, due to migration of population, several cases have been also reported from western countries. As signs of hyperthyroidism are often subtle, it is advisable to routinely measure thyroid hormone levels in high risk population presenting with hypokalemic paralysis. It helps to secure the diagnosis and initiate proper therapy. The patients should be promptly treated with potassium supplements and nonselective beta-blockers to prevent life-threatening complications of hypokalemia. The correction of hypokalemia in TPP is a tricky clinical situation as potassium replacement carries a risk of rebound hyperkalemia. Achieving euthyroidism is the key in preventing recurrence of disease. Physicians should be aware of this life threatening and atypical presentation of Graves' disease.

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BRIEF COMMUNICATIONS

Effect of Cholecalciferol on GLUT4 Expression in Adipocyte of Diabetic Rats

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Abstract

This research was conducted to examine the effect of cholecalciferol on fasting blood glucose (FBG), adipocyte diameter and glucose transporter (GLUT) 4 expression in adipocytes of diabetic rats. Nineteen male Wistar strain diabetic rats were divided into 4 groups (K, X_1, X_2 and X_3). Cholecalciferol was administered in the amount of 6.25 µg/kg in X_1, 12.5 µg/kg in X_2 and 25 µg/kg in X_3 per orem, once daily for 14 days. Group K received the placebo. There were no significant differences in FBG (p=0.199) and adipocyte diameter (p=0.218) between groups but there were significant differences in the expression of GLUT4 between control and treatment groups. Thus, cholecalciferol can increase GLUT4 expression in adipocyte without altering FBG and adipocyte diameter of diabetic rats.

Key words: cholecalciferol, GLUT4, adipocyte, diabetes

INTRODUCTION

Recent evidence from animal and human studies suggests that vitamin D, both cholecalciferol and calcitriol, may play a role in modifying the risk of diabetes.[1] Some authors have reported that vitamin D stimulated the expression of insulin receptor, thereby enhancing insulin responsiveness in glucose transport, improving glycaemic control, insulin secretion and insulin resistance.[1-3]

However, studies on the mechanism and appropriate doses of vitamin D are still unclear and requires further investigation.[4,5] Further in vivo studies are needed to address the effect and the effective dosages of vitamin D in human adipose tissue as well as its relevance in associated diseases.[6]

GLUT4 has a main role in glucose metabolism and the maintenance of glucose homeostasis in the body; its activation has become a therapeutic target in pharmacological intervention strategies to control diabetes.[7] Adipose tissue is a major site of glucose metabolism and has a critical role in the maintenance of glucose homeostasis.[8]

This study reports the effects of cholecalciferol in the histopathology of adipose tissue in diabetic rats, particularly related to its diameter and expression of GLUT4. This study is expected to reinforce the role of vitamin D as adjunctive therapy in diabetes mellitus.

METHODOLOGY

Twenty eight Wistar strain adult male rats (*Rattus norvegicus*) matching the inclusion criteria were acclimatized for 7 days. Combination of high fat diet (lard 22.8%) and intraperitoneal injection of 35 mg/kg streptozotocin (STZ) on day 14 were used to induce diabetes.[9,10] Furthermore, seven days after STZ injection, the FBG from all the rats' tail vein blood were evaluated. They were defined as diabetic rats when the FBG >135 mg/dl.[11,12]

All diabetic rats (nineteen) were divided into one control (K) group and three treatment groups (X_1, X_2, X_3). Control group was a group of diabetic rats given propylene glycol in volume of 1 ml/100 gram/body weight (bw). Treatment groups were groups of diabetic rats given cholecalciferol with a dose of 6.25 µg/kg bw (concentration 0.625 µg/ml) in X_1 group, 12.5 µg/kg bw (concentration 1.25 µg/ml) in X_2 group, and 25 mg µg/kg bw (concentration 2.5 µg/ml) in X_3 group. Cholecalciferol was given in propylene glycol in volume of 1 ml/100 g bw per orem, every day for 14 days, starting on the 21st day. Twenty-four hours after the last treatment, the rats were then fasted for 12 hours and anesthetized with intramuscular injection of ketamine HCl in a dose of 44-60 mg/kg bw, then the FBG was measured from intracardiac blood. The rats were sacrificed by decapitation.[13] Subcutaneous adipose tissue was taken through a 1 x 1 cm incision on the abdominal wall up to

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the subcutaneous layer. The tissue was fixed in neutral buffered formalin solution to be processed into histological preparations by Haematoxylin Eosin (H&E) and immunohistochemistry staining. FBG, adipocyte diameter and GLUT4 expression were analyzed by one-way ANOVA test (α = 0.05) and Least Significant Difference (LSD) for Multiple Comparison Procedure (MCP).

RESULTS AND DISCUSSIONS

There was no significant difference in fasting blood glucose and adipocyte diameter between groups (p> 0.05). However, adipocyte diameter was increased in a dose dependent manner after administration of cholecalciferol.

There was significant difference in the expression of GLUT4 between groups (p <0.05). There was an increasing trend of GLUT4 expression along with the increased dose of cholecalciferol (Table 1).

Our findings have shown that cholecalciferol administration could not improve blood glucose homeostasis nor increase adipocyte diameter in diabetic rats. These results were consistent with Calle et al, (2008) who reported that the administration of calcitriol (1,25 dihydroxyvitamin D3) 3.75 µg/kg bw intraperitoneally for 15 days did not correct hyperglycemia, glycosuria and could not increase adipocyte diameter in STZ-induced diabetic rats, but could normalize the number of insulin receptors in adipocytes.[14] Another study by Anwar et al, (2013) reported that the subcutaneous administration of 10 µg/100g (0.1 µg/kg bw) cholecalciferol for 6 days can reduce FBG by 26.31% in diabetic rats.[2] These findings suggest that the route of administration may affect the effects of vitamin D in improving blood glucose levels and adipocyte diameter in diabetic rats.

Orwoll et al, (1994) reported that vitamin D has no effect on glucose homeostasis in uncontrolled diabetic patients.[15] Another study reported that the administration of high dose cholecalciferol in type 2 diabetic patients was not related to improvement in glucose homeostasis but rather to improvement in plasma adiponectin levels.[16] Recently, in vitro studies report that vitamin D may increase the surface area of inflammation-induced adipocyte, which is analogous to the diabetic condition.[17] Thus, it can be concluded that vitamin D has more influences in inflammatory process mediated by adipokines produced by adipose tissue in diabetes.

The GLUT4 expressions increased dependently along with the increasing dose of cholecalciferol. However, this finding was not statistically significant. In line with the study by Manna and Jain (2012), vitamin D may increase the GLUT4 translocation and glucose utilization in adipocytes through activation of cystathionine-γ-lyase (CSE) and the formation of hydrogen disulfide (H2S).[8]

Table 1. Fasting blood glucose, adipocyte diameter and GLUT4 expression in adipocyte

	Diabetic control, n=4	Cholecalciferol 6.25 µg/kg bw, n=5	Cholecalciferol 12.5 µg/kg bw, n=5	Cholecalciferol 25 µg/kg bw, n=5	p value
Fasting blood glucose (mg/dl)	172.00 ± 6,38	155.40 ± 35,97	203.60 ± 58,96	153.40 ± 31,03	0.199
Adipocyte diameter (µm)	40.66 ± 9,10	48.23 ± 16,39	50.57 ± 16,29	62.40 ± 15,65	0.218
GLUT4 expression in adipocyte (Σ cell)	7.45 ± 1,18	10.98 ± 2,14[a]	12.12 ± 2,75[b]	12.50 ± 3,08[c]	0.035

a. Significant difference with Diabetic control group (p= 0.049)
b. Significant difference with Diabetic control group (p= 0.013)
c. Significant difference with Diabetic control group (p= 0.008)

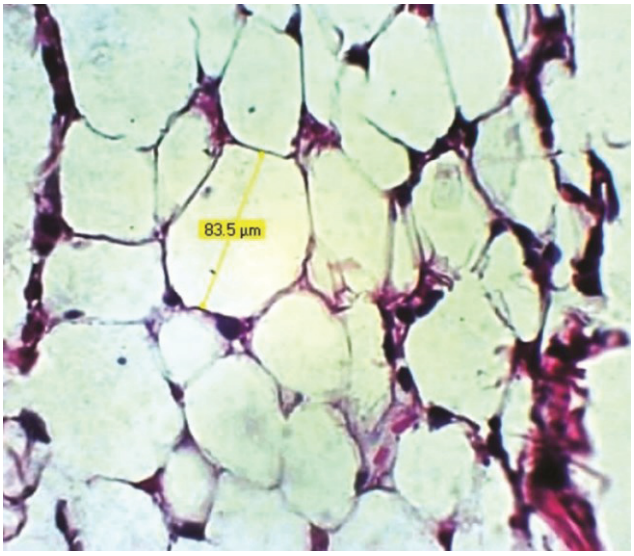

Figure 1. Photomicrograph of adipocyte diameter (H&E, x 400).

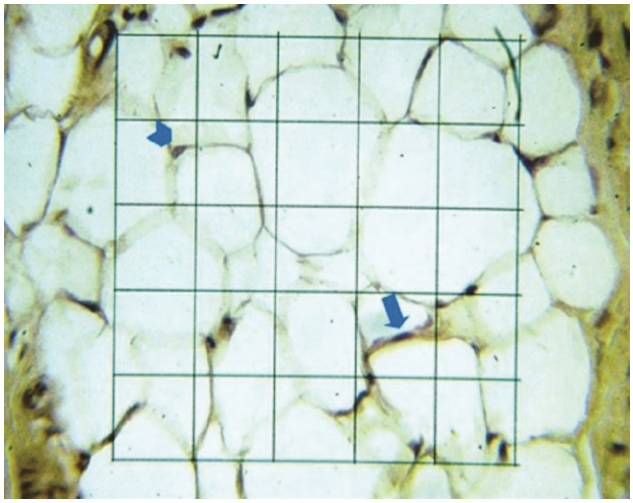

Figure 2. Photomicrograph of GLUT4 expression in adipocyte, immunohistochemistry, graticulae (H&E, x 400). Arrow head: Adipocyte which did not express GLUT4, Arrow: Adipocyte which expressed GLUT4.

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Cholecalciferol can increase the expression of GLUT4 in adipocyte without altering adipocyte diameter and FBG. It might be due to differences in tissue response to insulin. It has been understood that the response of GLUT4 to insulin in adipose tissue is higher than muscle tissue and the rate of fatty acid synthesis in adipocytes is strongly influenced by the plasma insulin concentration.[18,19] However, in adipocytes of rats on a high fat diet, the fatty acid synthesis is highly unresponsive to insulin in which all lipogenic enzyme activities were decreased. A decreased intracellular capacity to utilize glucose for lipogenesis led to the decreased response of glucose metabolism to insulin in adipocytes of rats on high fat diet.[20] In this study, although administration of cholecalciferol can increase adipocyte glucose uptake, it could not restore the intracellular capacity reduction in utilizing glucose for lipogenesis, which has been proven by non-significant increment in adipocyte diameter. Unfortunately, it has not been supported by the plasma insulin level as well as the rate of lipogenesis and lipolysis.

Adipose tissues only take up a small fraction of total body glucose uptake, but it increases along with the elevation of insulin level.[21]

In addition, administration of cholecalciferol in this study might be unable to inhibit glucose production in the liver and increase glycogen storages both in the liver and muscle tissue. There have been studies reporting that vitamin D administration can improve metabolic disorders in STZ-induced diabetic rats and provide therapeutic or protective effects for the liver, pancreas and kidneys of diabetic mice induced by alloxan.[22,23] However, no study has reported the effects of vitamin D on metabolic disorders improvement in the liver of diabetic animals induced by a combination of high-fat diet and STZ. Although one study reported that vitamin D can increase GLUT4 translocation in the muscle tissue of STZ-induced diabetic mice, there is no study reporting the same finding in diabetic animal induced by combination method.[24]

Tannenbaum et al (1997) reported that a high fat diet can lower glucose uptake in skeletal muscle and adipose tissue, decrease the number of insulin receptors in the liver, skeletal muscle and adipose tissue, decrease glycolysis and glycogen synthesis in the liver. High fat diet alters the activity of the hypothalamus-pituitary-adrenal in rats, thus increases the production of adrenal glucocorticoid. Increased adrenal glucocorticoid has antagonistic effects on insulin, leading to insulin insensitivity and decreased glucose uptake in insulin target tissues.[25] Therefore, in this study, cholecalciferol could not significantly reduce FBG level, although the expression of GLUT4 in adipocyte was increased.

CONCLUSION

Cholecalciferol administration can increase adipocyte GLUT4 expression without altering fasting blood glucose level and adipocyte diameter in diabetic rats. Increasing the number of experimental animals, dose variations, duration of administration, and caloric restriction, may obtain a better outcome. Other methods, such as GLUT4 quantification in membrane fraction by Western blot may produce a more accurate result.

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CONSORT 2010 Checklist of Information to include when Reporting a Randomised Trial*

Section / Topic	Item no.	Checklist item	Reported on page no.
TITLE AND ABSTRACT			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
INTRODUCTION			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
METHODS			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
RESULTS			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
DISCUSSION			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
OTHER INFORMATION			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

** We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.*

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CARE Checklist (2013) of Information to include when Writing a Case Report

Topic	Item no.	Checklist item description	Reported on page no.
Title	1	The words "case report" should be in the title along with the area of focus	_____
Key Words	2	2 to 5 key words that identify areas covered in this case report	_____
Abstract	3a	Introduction—What is unique about this case? What does it add to the medical literature?	_____
	3b	The main symptoms of the patient and the important clinical findings	_____
	3c	The main diagnoses, therapeutics interventions, and outcomes	_____
	3d	Conclusion—What are the main "take-away" lessons from this case?	_____
Introduction	4	One or two paragraphs summarizing why this case is unique with references	_____
Patient Information	5a	De-identified demographic information and other patient specific information	_____
	5b	Main concerns and symptoms of the patient	_____
	5c	Medical, family, and psychosocial history including relevant genetic information (also see timeline)	_____
	5d	Relevant past interventions and their outcomes	_____
Clinical Findings	6	Describe the relevant physical examination (PE) and other significant clinical findings	_____
Timeline	7	Important information from the patient's history organized as a timeline	_____
Diagnostic Assessment	8a	Diagnostic methods (such as PE, laboratory testing, imaging, surveys)	_____
	8b	Diagnostic challenges (such as access, financial, or cultural)	_____
	8c	Diagnostic reasoning including other diagnoses considered	_____
	8d	Prognostic characteristics (such as staging in oncology) where applicable	_____
Therapeutic Intervention	9a	Types of intervention (such as pharmacologic, surgical, preventive, self-care)	_____
	9b	Administration of intervention (such as dosage, strength, duration)	_____
	9c	Changes in intervention (with rationale)	_____
Follow-up and Outcomes	10a	Clinician and patient-assessed outcomes (when appropriate)	_____
	10b	Important follow-up diagnostic and other test results	_____
	10c	Intervention adherence and tolerability (How was this assessed?)	_____
	10d	Adverse and unanticipated events .	_____
Discussion	11a	Discussion of the strengths and limitations in your approach to this case	_____
	11b	Discussion of the relevant medical literature	_____
	11c	The rationale for conclusions (including assessment of possible causes)	_____
	11d	The primary "take-away" lessons of this case report	_____
Patient Perspective	12	When appropriate the patient should share their perspective on the treatments they received	_____
Informed Consent	13	Did the patient give informed consent? Please provide if requested	☐ Yes ☐ No

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PRISMA 2009 Checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Section / Topic	Item no.	Checklist item	Reported on page no.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	_____
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	_____
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	_____
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	_____
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	_____
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	_____
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	_____
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	_____
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	_____
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	_____
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	_____
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	_____
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	_____
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	_____
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	_____
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	_____
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	_____
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	_____
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	_____
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	_____
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	_____
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	_____
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	_____
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	_____
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	_____
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	_____
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	_____

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

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STROBE Statement - Checklist of Items that should be included in Reports of Observational Studies

Section / Topic	Item no.	Recommendation
TITLE		
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
INTRODUCTION		
Background / rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
METHODS		
Study Design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants (b) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data Sources / measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study Size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Case-control study*—Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—Report numbers of outcome events or summary measures
Main Results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
DISCUSSION		
Key Results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
OTHER INFORMATION		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

** Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

"The **EQUATOR** (Enhancing the QUAlity and Transparency Of health Research) Network is an international initiative that seeks to improve the reliability and value of published health research literature by promoting transparent and accurate reporting and wider use of robust reporting guidelines. It is the first coordinated attempt to tackle the problems of inadequate reporting systematically and on a global scale; it advances the work done by individual groups over the last 15 years..." lifted from the EQUATOR Network website.

For this issue of JAFES, selected checklists from the EQUATOR Network are featured for the main study types. The updated JAFES Instructions to Authors stipulate that manuscripts should ensure compliance with the appropriate EQUATOR Network Guideline to be considered for acceptance. The complete checklists and full guidelines are available at http://equator-network.org.

equator network

STARD 2015 Checklist of Essential Items for Reporting Diagnostic Accuracy Studies

Section and Topic	No.	Item
TITLE OR ABSTRACT		
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)
ABSTRACT		
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)
INTRODUCTION		
	3	Scientific and clinical background, including the intended use and clinical role of the index test
	4	Study objectives and hypotheses
METHODS		
Study design	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)
Participants	6	Eligibility criteria
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)
	8	Where and when potentially eligible participants were identified (setting, location and dates)
	9	Whether participants formed a consecutive, random or convenience series
Test Methods	10a	Index test, in sufficient detail to allow replication
	10b	Reference standard, in sufficient detail to allow replication
	11	Rationale for choosing the reference standard (if alternatives exist)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test
	13b	Whether clinical information and index test results were available to the assessors of the reference standard
Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy
	15	How indeterminate index test or reference standard results were handled
	16	How missing data on the index test and reference standard were handled
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory
	18	Intended sample size and how it was determined
RESULTS		
Participants	19	Flow of participants, using a diagram
	20	Baseline demographic and clinical characteristics of participants
	21a	Distribution of severity of disease in those with the target condition
	21b	Distribution of alternative diagnoses in those without the target condition
	22	Time interval and any clinical interventions between index test and reference standard
Test Results	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)
	25	Any adverse events from performing the index test or the reference standard
DISCUSSION		
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability
	27	Implications for practice, including the intended use and clinical role of the index test
OTHER INFORMATION		
	28	Registration number and name of registry
	29	Where the full study protocol can be accessed
	30	Sources of funding and other support; role of funders

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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For this issue of JAFES, selected checklists from the EQUATOR Network are featured for the main study types. The updated JAFES Instructions to Authors stipulate that manuscripts should ensure compliance with the appropriate EQUATOR Network Guideline to be considered for acceptance. The complete checklists and full guidelines are available at http://equator-network.org.

JAFES Journal of the ASEAN Federation of Endocrine Societies

CHEERS Checklist - Items to include when Reporting Economic Evaluations of Health Interventions

Section / Item	Item no.	Recommendation	Reported on page no. / line no.
TITLE AND ABSTRACT			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
INTRODUCTION			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	
METHODS			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study Perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
RESULTS			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 3 of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or costeffectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	
DISCUSSION			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
OTHER INFORMATION			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

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Instructions to Authors

The **Journal of the ASEAN Federation of Endocrine Societies (JAFES)** is an open-access, peer-reviewed, English language, medical and health science journal that is published two times a year by the ASEAN Federation of Endocrine Societies (AFES). **Authors may include members and non-members of the AFES.**

Manuscripts, correspondences and other editorial matters should be sent via electronic mail to JAFES@Asia.com or JAFES.editor@gmail.com.

Manuscripts are received with the understanding that they are not under simultaneous consideration by another publisher. Accepted manuscripts become the permanent property of the JAFES and are licensed with an Attribution-Non-Commercial Creative Commons License. Articles may be shared and adapted for non-commercial purposes as long as they are properly cited. Articles and any other material published in the JAFES represent the work of the author(s) and should not be construed to reflect the opinions of the Editors or the Publisher. **Articles that do not subscribe to the Instructions to Authors shall be promptly returned.**

ARTICLE TYPES

JAFES welcomes manuscripts on all aspects of endocrinology and metabolism in the form of original articles, review articles, case reports, feature articles (clinical practice guidelines, clinical case seminars, clinical practice guidelines, book reviews, et cetera), editorials, letters to the Editor, brief communications and special announcements. See Inset Box for descriptions and specific requirements per article type.

COVER LETTER

A cover letter must accompany each manuscript which should cite the title of the manuscript, the list of authors (complete names and affiliations), with one (1) author clearly designated as correspondent, providing his/her complete postal/mailing address, telephone number, e-mail address and fax number.

DECLARATION AND DISCLOSURE

In order for a manuscript to be considered, reviewed or edited, all the authors will be required to accomplish, sign and submit scanned copies of the JAFES "Declaration," "Authorship Certification," and "Disclosure Statement" forms.

ADHERENCE TO EQUATOR NETWORK GUIDELINES

To improve and standardize reporting of findings depending on the study type, authors should ensure compliance with the following EQUATOR (Enhancing the QUAlity and Transparency of Research) Network Guidelines. These guidelines are freely available at: http://equator-network.org.

1. CONSORT (2010) Checklist for Reporting Clinical Trials
2. CARE (2013) Checklist for Reporting Case Reports
3. COREQ (2007) Checklist for Reporting Qualitative Research
4. PRISMA (2009) Checklist for Reporting Systematic Reviews and Meta-Analyses
5. STROBE (2007) Checklist for Reporting Observational Studies
6. STARD (2015) Checklist for Reporting Diagnostic Accuracy Studies
7. CHEERS (2013) Checklist for Reporting Economic Evaluation of Health Interventions
8. SQUIRE (2015) Checklist for Quality Improvement Reporting in Healthcare
9. ARRIVE (2013) Guidelines for Reporting Animal Research

INFORMED CONSENT

Whenever applicable, there should also be a written declaration that the article had written/informed consent for publication from the involved subject/s ("Patient Consent Form"), had conformed to ethical standards, and/or had been reviewed by the appropriate ethics committee. In case the involved subject/s can no longer be contacted (e.g., retrospective studies, et cetera) after all means have been undertaken by the author, the author should state so in his declaration.

GENERAL GUIDELINES

1. The manuscript should be encoded using Microsoft Word, double-spaced throughout with 1¼ cm (½ inch) paragraph indentation, with 3-cm margins (1¼ inch) all around on A4 size paper. The preferred font style and size is Times New Roman 12.
2. The manuscript should be arranged in sequence as follows: (1) Title Page, (2) Abstract, (3) Text, (4) References, (5) Tables, and (6) Figures & Illustrations.
3. References should pertain directly to the work being reported.
4. All the sheets of the manuscript should be labelled with the family name of the main author (all in capital letters) and page number (in Arabic Numerals) printed on the upper right corner.
5. All manuscripts not complying with the above shall be promptly returned for correction and resubmission.

Title Page

1. The title should be as concise as possible.
2. Only the full names of the authors directly affiliated with the work should be included (First name, Middle initial and Last name). There are 4 criteria for authorship (IMCJE recommendations):
   - 2.1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
   - 2.2. Drafting the work or revising it critically for important intellectual content; AND
   - 2.3. Final approval of the version to be published; AND
   - 2.4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
3. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate
4. Name and location of no more than one (1) institutional affiliation per author may be included.
5. If the paper has been presented in a scientific forum or convention, a note should be provided indicating the name, location and date of its presentation.

Abstract

For original articles, the abstract should contain no more than 200 words with a structured format consisting of the objective/s, methodology, results and conclusion. For feature articles, case reports, interhospital grand rounds, and brief communications, the abstract should be from 50 to 75 words and need not be structured.

Keywords

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.

Text

1. Generally, the text should be organized consecutively as follows: Introduction, Methodology, Results and Discussion, and Conclusion (IMRAD format).
2. All references, tables, figures and illustrations should be cited in the text, in numerical order.
3. All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the long names.
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. Acknowledgements 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.

References

1. References in the text should be identified by Arabic Numerals in superscript on the same line as the preceding sentence.
2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
3. All references should provide inclusive page numbers.
4. Journal abbreviations should conform to those used in PubMed.
5. A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
6. The style/punctuation approved by JAFES conforms to that recommended by the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org. Follow the format of the examples shown below:

Journal Article

Padua FR, Paspe MG. Antinuclear antibody in the rheumatic and non-rheumatic diseases among Filipinos. Acta Med Philippina. 1990; 26(2):81-85.

One to Six Authors (Commentary, Online)

Krause RM. The origin of plagues: old and new. *Science*. 1992;257:1073-1078.

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.

More than Six Authors

McGlynn EA, M.Asch S, Adams J, et al. The quality of health care delivered to adults in the United States.N Engl J Med. June 26, 2003;348(26):2635-2645.

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

Byrne, DW. Publishing your medical research paper: What they don't teach in medical school. Baltimore: Williams & Wilkins, 1998.

World Wide Web

The key and critical objectives of JAMA. http://jama.ama-assn.org/misc/aboutjama.dtl. Accessed April 4, 2007.

Tables

1. Cite all tables consecutively in the text and number them accordingly.
2. Create tables preferably using Microsoft Excel with one table per worksheet.
3. Tables should not be saved as image files.
4. The content of tables should include a table number (Arabic) and title in capital letters above the table, and explanatory notes and legends as well as definitions of abbreviations used below.
5. Font should be Arial Narrow size 8.
6. Each table must be self-explanatory, being a supplement rather than a duplicate of information in the text.
5. Up to a maximum of five (5) tables are allowed.

Figures and Graphs

1. Figures or graphs should be identified by Arabic Numeral/s with titles and explanations underneath.
2. The numbers should correspond to the order in which the figures/graphs occur in the text. It is recommended that figures/graphs also be submitted as image files (preferably as .jpeg or .gif files) of high resolution.
3. Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
4. All identifying data of the subject/s or patient/s under study such as name or case numbers, should be removed.
5. Up to a maximum of five (5) figures and graphs are allowed.

Illustrations and Photographs

1. Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as .jpeg or .gif files).
2. For photomicrographs, the stain used (e.g. H&E) and magnification (e.g. x 400) should be included in the description.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn or printed on good quality laser printers. Photocopies are not acceptable.
4. All letterings for illustration should be done professionally and should be of adequate size to retain even after size reduction.
5. Figure legends should be numbered sequentially, typed double-spaced on a separate sheet of paper. Give the meaning of all symbols and abbreviations used in the figure.
6. Up to a maximum of five (5) illustrations/photographs are allowed.

N.B.: For tables, figures, graphs, illustrations and photographs that have been previously published in another journal or book, a note must be placed under the specific item stating that such has been adapted or lifted from the original publication. This should also be referenced in the **References** portion.

PROCESS

1. Upon receipt of the manuscript, the Editor shall review the submission, check if it has met aforementioned criteria and consult with members of the Editorial Board to decide whether it shall be considered for publication or not.

2. Within one (1) week of submission, authors shall be notified through e-mail that their manuscript either (a) has been sent to referees for peer-review or (b) has been declined without review.
3. The JAFES implements a strict double blind peer review policy. For manuscripts that are reviewed, authors can expect an initial decision within forty five (45) days after submission. There may be instances when decisions can take longer than 45 days, in such cases, the editorial assistant shall inform the authors. The editorial decision for such manuscripts shall be one of the following: (a) acceptance without further revision, (b) acceptance with minor revisions, or (c) major manuscript revision and resubmission.
4. Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal.

EDITORIAL OFFICE CONTACT INFORMATION:

Journal of the ASEAN Federation of Endocrine Societies
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E-mail: JAFES@Asia.com
Website: http://www.asean-endocrinejournal.org

ARTICLE TYPES

Original articles
The abstract should contain no more than 200 words with a structured format consisting of the objective/s, methodology, results and conclusion. A manuscript for original articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Reviews
Review articles provide information on the "state of the art." JAFES encourages that reviews not only summarize current understanding of a particular topic but also describe significant gaps in the research, and current debates. The abstract should be from 50 to 75 words and should not be structured. A manuscript for reviews should not exceed 15 typewritten pages (including tables, figures, illustrations and references) or 4000 words.

Case Reports
The abstract should be from 50 to 75 words and should not be structured. A manuscript for case reports should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words.

Feature articles
JAFES may feature articles, either as part of an issue theme, such as Summary Clinical Practice Guidelines on endocrinology from each AFES country society, or a special topic on endocrinology by an international expert or authority. The abstract should be from 50 to 75 words and should not be structured. A manuscript for feature articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Interhospital Grand Rounds
JAFES encourages submission of special articles that summarize and document the proceedings of endocrinology grand rounds, which includes presentation of medical problems of a particular patient, evaluation and work-up, treatment and clinical course, discussion of key diagnostic and management points, and commentaries by specialty experts. JAFES recognizes the importance of this type of article as an educational tool for physicians and health practitioners. The abstract should be from 50 to 75 words and should not be structured. A manuscript for grand rounds should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Brief Communications
Brief Communications are short reports intended to either extend or expound on previously published research OR present new and significant findings which may have a major impact in current practice. If the former, authors must acknowledge and cite the research which they are building upon. The abstract should be from 50 to 75 words and should not be structured. A manuscript for brief communications should not exceed 5 typewritten pages (including tables, figures, illustrations and references) or 1500 words.

Editorials
Articles that represent the scientific opinion and views of an author. Every issue of JAFES includes an Editorial by the Editor-in-Chief and may include one or two additional editorials from experts from the scientific community commenting on a particular field or issue on endocrinology. No abstract or keywords necessary.

Letters to the Editor
JAFES welcomes feedback and comments on previously published articles in the form of Letters to the Editor.
No abstract or keywords necessary. A Letter to the Editor must not exceed 2 typewritten pages or 500 words.

Special Announcements
Special announcements may include upcoming conventions, seminars or conferences relevant to endocrinology and metabolism. The Editors shall deliberate and decide on acceptance and publication of special announcements. Please coordinate with the Editorial Coordinator for any request for special announcements.

Checklist Guide for Submission of Manuscripts to JAFES	
Instructions to Authors	☐ Review manuscript submission guidelines
Cover Letter	☐ Include cover letter as an attachment ☐ Indicate in the letter the title of the work ☐ Indicate all the authors (complete names and affiliations) ☐ Indicate in the letter the corresponding author and provide complete contact information (post address, telephone, fax number, e-mail address)
EQUATOR Network Guidelines	☐ Review manuscript if compliant with appropriate EQUATOR Network Guidelines (e.g., CONSORT for clinical trials, CARE for case reports, et cetera)
Declaration Form	☐ Ensure all authors have read and agreed to the Declaration ☐ Submit a scanned copy of the fully accomplished form
Authorship Certification	☐ Ensure all authors have read and agreed to the Certification ☐ Submit a scanned copy of the fully accomplished form
Disclosure Form	☐ Ensure all authors have read and agreed to the Disclosure ☐ Submit a scanned copy of the fully accomplished form
Patient Consent Form (if applicable)	☐ Submit a scanned copy of the fully accomplished form ☐ If all attempts have been made and consent form is not signed, state so in the Cover Letter
Title Page	☐ Full names of the authors directly affiliated with the work (First name and Last name), highest educational attainment ☐ Name and location of 1 institutional affiliation per author ☐ If presented in a scientific forum or conference, provide a footnote should be provided indicating the name, location and date of presentation
Abstract	☐ Provide an abstract conforming with the format ☐ Structured for Original Articles: Objective/s, Methodology, Results, Conclusion ☐ Unstructured for Case Reports and Feature Articles
Keywords	☐ Provide 3-5 keywords (listed in MeSH)
Content	☐ Provide text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion) ☐ Make sure all abbreviations are spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses; the same abbreviation may then be used subsequently ☐ Make sure all measurements and weights are in SI units ☐ If appropriate, provide information on institutional review board/ethics review committee approval ☐ Acknowledgements 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
References	☐ All references should be cited in the text, in numerical order. Use Arabic numerals ☐ Ensure all references follow the prescribed format.
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