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Milestones

Ancient Romans erected stone pillars or obelisks along roadsides. Set a mile apart, those "milestones" bore numerals and served as markers or reference points to guide travelers. This year, JAFES takes a moment to pause and acknowledge the milestones of its journey, as the Philippines hosts the 20th ASEAN Federation of Endocrine Societies (AFES) Congress in Manila. JAFES has been granted a full symposium at the Congress that is entirely dedicated to matters about publication, with topics on ensuring publication success, peer review, and use of social media for improving the dissemination of scientific outputs. It will be an opportunity to recognize our outstanding authors and reviewers, and also to launch an audiovisual presentation to celebrate our 10th year and renew our commitment to both authors and readers.

We are thankful that our purposeful investments, in incorporating international best practices of ethical and scholarly research, are paying off.

The JAFES improved year by year by bringing home and adapting new guidelines, resources, and tools through our attendance in local and international medical journal editors' conferences. We learned much from online discussions on various ethical and operational publication issues through the World Association of Medical Editors. Our own varied and sometimes *colorful* encounters and experiences with authors, reviewers, and editors, also served to enrich and refine our editorial processes. These milestones are all documented as part of knowledge management, to ensure continuity for the next generation of JAFES editors, peer reviewers, editorial staff members, and authors.

The journey of JAFES is a collective and continual effort that starts with the regular annual support of AFES societies for journal operations and arrives at semi-annual issues bringing readers scholarly contents that have been produced by endocrinologist researchers from the region. We are doing this one step, one innovation, one enhancement, one mile at a time. (Figure 1).

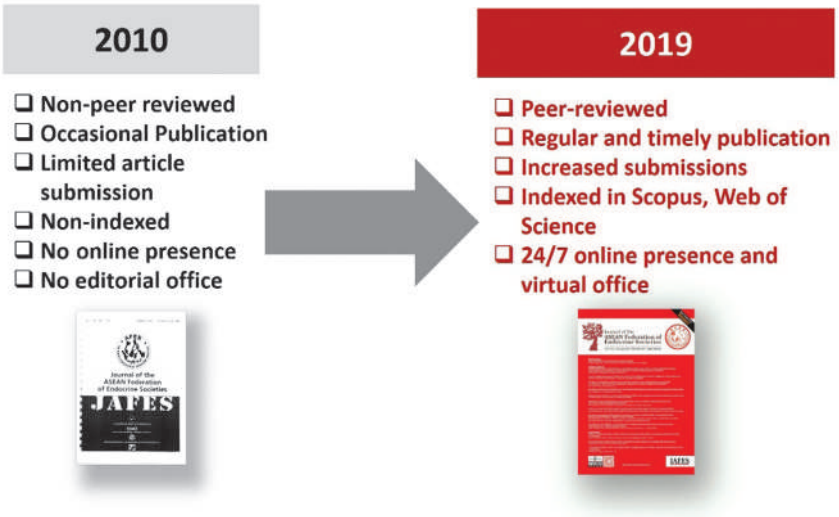

Figure 1. The journey of JAFES 2010-2019.

Among three indexing services that we set out to achieve nine years ago, we reached inclusion in Scopus® under Elsevier in 2016, and more recently in 2019, acceptance to the Emerging Sources Citation Index (ESCI) under Clarivate Analytics™ (formerly Thomson Reuters). Launched in 2017 to cover high-quality, peer-reviewed publications of regional importance and in emerging scientific fields, ESCI effectively places JAFES in the Web of Science Core Collection, further improving the searchability of published articles. Indexing is a testament to the quality of JAFES, a validation of all the international best practices that we have incorporated along the way. Moreover, through measurable citation performance, Scopus and ESCI shall provide us with important insights as to how JAFES content is being used and incorporated into global knowledge.

Where we are, where we have been, and where we are heading, is a fitting reminder of our commitment to ethical publication, for the benefit of endocrinologists in the region, medical practitioners, researchers, readers, and ultimately, our patients.

Elizabeth Paz-Pacheco
Editor-in-Chief

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Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

Engaging the ASEAN Diaspora: Type 2 Diabetes Prevalence, Pathophysiology, and Unique Risk Factors among Filipino Migrants in the United States

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Abstract

Type 2 diabetes prevalence is rising rapidly in Southeast Asia (SEA) where urbanization and adoption of 'western' behavioral lifestyles are attributed as predominant risk factors. The Southeast Asian diaspora to the United States has resulted in a sizable portion of migrant and US born SEAs, with approximately 4 million Filipino Americans, 2 million Vietnamese-Americans, Cambodians (330,000), and Thai (300,000) as the most populous. Their longer exposure to a western lifestyle and participation in clinical studies with other racial/ethnic groups, provide opportunities to evaluate etiologic factors which might inform trends and intervention opportunities among residents of Southeast Asia.

Epidemiologic studies in the US have identified higher T2D prevalence among Filipinos (16.1%) compared to groups perceived to be at highest risk for T2D, namely Latinos (14.0%), Black (13.7%), and Native Americans (13.4%), while SEAs (including Burmese, Cambodian, Indonesian, Laotian, Malaysian, and Thai, 10.5%) and Vietnamese (9.9%) had higher T2D risk compared to Whites (7.7%), despite their absence of general obesity. Asian-Americans, including SEAs, East and South Asians, collectively have higher rates of undiagnosed T2D compared to other racial/ethnic groups in the US. Almost half (44%) of Filipinos with newly diagnosed T2D have isolated post-challenge hyperglycemia and will remain undiagnosed if current screening practices remain limited to measures of glycosylated hemoglobin and fasting plasma glucose.

The University of California San Diego Filipino Health Study found excess visceral adipose tissue accumulation, low ratio of muscle to total abdominal mass area, low adiponectin concentration, multiparity (≥ 6 live births), and sleep insufficiency (<7 hours) to be unique T2D risk factors among Filipino-American women, even after adjusting for established T2D risk factors including hypertension and parental history of T2D. Social determinants such as low educational attainment (less than college completion), and sustained social disadvantage during childhood and adulthood were independently associated with T2D risk. Gestational diabetes is a known risk factor for future T2DM among women; Northern California data shows that following Asian Indians, gestational diabetes was highest among Filipina and SEA parturients, who had twice the GDM prevalence as Black, Hispanic, and White women. Identification of novel T2D risk factors among SEAs may guide early diagnosis, inform pathophysiology, and identify unique opportunities for T2D prevention and management.

Key words: type 2 diabetes, immigration, adiposity, Southeast Asia

Type 2 Diabetes, a global epidemic

Type 2 diabetes (T2D) is an urgent, global public health problem, including in Southeast Asia. The International Diabetes Federation reported that in 2015, over half (56%) of all people with diabetes were living in the South-East Asia Region or the Western Pacific Region. Further, in the next 15 years, by 2035, T2D prevalence is projected to increase by 92% in Vietnam, by 85% in the Philippines, by 73% in Myanmar, by 72% in Malaysia, by 65% in Indonesia, and by 36% in Thailand,[1] compared to lower incremental increases in the United States (by 22%), and in neighboring Taiwan (by 34%), and Korea (by 36%), and a projected 7% decrease in Japan.[1]

T2D prevalence in Malaysia is projected to increase to 12.2% in 2035, exceeding the projected prevalence in the United States (11.6%).[1] The projected T2D prevalence in 2035 in Thailand (8.3%), Vietnam (8.2%), Myanmar (8.0%), the Philippines (7.1%), and Indonesia (6.7%) will exacerbate the burden on medical, fiscal, personnel, and personal resources. Urgent measures to prevent T2D in Southeast Asia, and specifically to further elucidate the unique pathophysiology of T2D in SEAs can inform strategies to prevent, delay, and manage T2D in the ASEAN region.

The colonial relationship between the United States and selected SEA nations, followed by immigration policies

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for family reunification programs, education, and employment to fill selected labor shortages in the US, has resulted in a sizeable SEA diaspora to the United States. US Census data estimates that there are approximately 4 million Filipino Americans, 2.1 million Vietnamese-Americans, 331,733 Cambodian Americans, 319,794 Thai Americans, 309,564 Hmong, 265,138 Lao, 193,056 Burmese, 126,935 Indonesian, and 29,431 Malaysian Americans (www.census.gov).[2] Their long exposure to a western lifestyle and participation in clinical studies with other racial/ethnic groups, provide opportunities to evaluate etiologic factors which might inform etiology and intervention opportunities among residents of Southeast Asia.

The objective of this review paper is to summarize published research on the prevalence and unique T2D risk factors and diagnostic limitations among Filipinos in the United States, which might influence screening, prevention, and management initiatives in the Philippines and the ASEAN region.

Filipino migration to the United States

Asian Americans have emerged as the fastest growing racial group in the US, and Asian migrants have surpassed Latinos as the largest group of new immigrants in the United States (US), with Filipinos comprising the 4th largest immigrant group, behind Mexicans, Chinese, and Indians.[3] Filipino migration to the US began as early as 1587 when states such as California and Louisiana belonged to Spain and Mexico. The earliest permanent settle of Filipinos was established in 1763 in Louisiana. Larger cohorts of Filipino migration to the US occurred in three waves, starting with agricultural workers from 1906 to 1935 in Hawaii and California, followed by a second wave of Filipino migrants who joined the US military during and after World War II. The 3rd wave followed in 1965 through family reunification policies, and recruitment of selected professions, including nurses, physicians, and teachers to address labor shortages in the US. The unique historical, military, commercial, educational, and cultural US-Philippine relationship resulted in 4 million Filipino Americans. Approximately half are immigrants, and 40% reside in California. Selected cities, including Daly City, California and Honolulu, Hawaii have populations where >25% of their residents self-report as Filipino.

DM prevalence among Filipino Americans

The first recorded measures of diabetes among Filipinos in Hawaii was based on a study among 38,103 gainfully employed residents in Oahu, Hawaii during 1958 to 1959. Diabetes was ascertained by serum glucose levels 2 to 2.5 hours after a meal containing at least 50 grams of carbohydrates Diabetes prevalence was already three times higher among Filipinos (2.0%), Japanese (2.2%), and Koreans (2.0%) compared to Whites (0.7%) 60 years ago.[4]

Forty years later, between 1997 and 2000, the North Kohala Study in the big island of Hawaii showed T2D prevalence (by 2 hour oral glucose tolerance test) was significantly higher among Filipinos (19.4%) compared to Whites (4.4%), despite their similar body mass index (mean BMI: Filipino: 26.1 kg/m^2 vs White: 25.5 kg/m^2). Although Native Hawaiians had larger BMI (31.3 kg/m^2) compared to Filipinos (26.1 kg/m^2), T2D prevalence was similar among Native Hawaiians (19.0%) and Filipinos (19.4%).[5]

Recent data from 18,200 participants of the Hawaii Behavioral Risk Factor Surveillance showed age-adjusted diabetes trends between 2011 and 2015 were highest among Native Hawaiians and other Pacific Islanders (NHOPI), followed by Filipinos compared to Japanese Americans and Whites. However, in 2016, Filipinos surpassed NHOPI as having the highest age adjusted diabetes prevalence (13.7%) compared to NHOPI (12.9%), Japanese (9.5%) and Whites (5.5%), although obesity prevalence remained higher among NHOPI (45.6%) compared to Filipinos (21.2%).[6] When stratified by age group, Filipinos had the highest T2D prevalence compared to all other ethnic groups in the following age groups: 55-64 years: 21%, 65 to 74 years: 31%, and 75+ years: 29%.[6]

Data from the US NHANES (National Health and Nutrition Examination Survey) shows that Asian Americans (AA) have the highest prevalence of undiagnosed T2D compared to all other ethnic groups, where 51% of Asian Americans with T2D were undiagnosed.[7] Further, Asian-Americans had similar T2D prevalence (20.6%) compared to Blacks (20.8%) and Latinos (23.1%), and significantly higher T2D prevalence compared to Whites (11,5%); when Asians were stratified by regional origin, T2D prevalence among South Asians (24.8%) and Southeast Asians (23.3%) were highest compared to all other ethnic groups, including compared to East Asians (16.0%).[8]

In California, among 2.2 million members of a large integrated health care system, including 82,781 Filipino patients, T2D prevalence was highest among Pacific Islanders (18.3%, Native Hawaiians, Samoans, Guamanians), followed by Filipinos (16.1%) and South Asians (15.9% Indian, Pakistani, Bangladeshi), exceeding rates among ethnic groups traditionally perceived to be at highest risk for T2D, including Latinos (14.0%), Blacks (13.7%) and Native Americans (13.4%).[9] Moreover, the 1,876 Southeast Asians (10.5%, including Burmese, Cambodian, Indonesian, Laotian, Malaysian, and Thai) and 1,671 Vietnamese Americans (9.9%) had higher T2D prevalence compared to Whites (7.3%) despite the absence of general obesity.[9] Other Asian subgroups also had higher T2D prevalence compared to Whites, including Japanese Americans (10.3%), Korean (9.9%), and Chinese Americans (8.3%).[9]

The UCSD Filipino health study

The Rancho Bernardo Study (RBS), a longitudinal study of myriad health outcomes, including T2D, began in 1972, and has been instrumental in informing the natural history of several disease outcomes. In 1995, the RBS enrolled two ethnic comparison cohorts, including African-American and Filipino women. Filipinos were selected because they comprise the second largest ethnic group in San Diego, California, following Mexican-Americans, and because of observations of an excess of Filipino dialysis patients at a nearby teaching hospital for military veterans. The observed excess of retired Filipino veterans of the United States Navy with access to health care, and a history of

frequent exercise and maintenance of normal body mass index (BMI) as required through their military service, precipitated interest regarding the pathophysiology of T2D in non-obese Filipinos, diabetes sequelae, and underdiagnosed T2D. Enrollment was initially limited to women since our existing grant was interested in ethnic differences in osteoporosis. Filipina women, ages 40 years and older were recruited from community venues to a longitudinal study of osteoporosis, type 2 diabetes, cardiovascular disease and regional obesity.[10] Recruitment materials emphasized general health and included bone density testing for osteoporosis and other conditions, to reduce self-selection bias for participants with known diabetes. A total of 453 Filipino women participated in the baseline clinic visit between 1995 to 1999, followed by subsequent clinic visits 5 years later in 2001-2002, and 10 years later (in 2006 to 2007). Between 2006 to 2007, self-identified Filipino husbands (n=114) of female participants were invited to a baseline visit using the same research protocol, clinic and staff. To our knowledge, the UCSD Filipino Health Study is the oldest, longitudinal study of myriad metabolic conditions among Filipinos in the United States.[10-31]

Filipina immigrants in San Diego had almost three times the T2D prevalence (by oral glucose tolerance test, OGTT) compared to Blacks (32% vs 12%), despite having significantly smaller waist circumference and BMI.[12]

Obesity trends

Studies among migrant populations show increased T2D risk with long duration in the US and increased acculturation to a western lifestyle. Our transnational study showed no difference in T2D prevalence, by fasting hyperglycemia, among Filipino migrants in the San Diego (14.1%), long term and US-born Filipinos in Hawaii (14.7%) compared to residents in the Philippines (11.8%) from the same provinces as the San Diego migrants.[13] The similarities in fasting hyperglycemia was observed despite higher obesity prevalence among US born and longer term immigrant Filipinos in Hawaii (20% with BMI >30 kg/m^2) compared to Filipino immigrants in San Diego (9.3% with obesity), and Philippine residents from the same provinces as the San Diego migrants (5.2%).[13] Further, T2D prevalence (by OGTT) did not differ between Filipino immigrants in San Diego (32%), long term migrants and US born Filipinos in Hawaii (25%),[13] and a Philippine cohort in Luzon (25% among adults aged <50 years).[32]

Duration of migration in San Diego included recent and long term migrants, ranging from six months to 47 years. Percent life years (PLY) in the US was computed to account for both age at and years since immigration. Unlike other immigrant groups where obesity increases with longer duration in the United States, no differences in BMI, percent body fat (by dual x-ray energy absorptiometry), truncal fat, nor T2D prevalence (by OGTT) were observed among recent immigrants who spent <16% PLY compared to long term migrants who spent almost half of their lives (>42.3% PLY) in the US.[33]

Regional fat distribution

Visceral, subcutaneous, pericardial, and muscle to total abdominal mass area were measured by electron beam computed tomography among White, Black, and Filipino women in San Diego, California. Filipinas had significantly more pericardial fat and visceral adipose tissue (VAT) compared to Black and White women despite having significantly smaller waist and BMI compared to Blacks.[12,21] As shown in Figure 1, VAT volume in a Filipina with BMI=20 kg/m^2 and waist circumference and waist circumference of 26 inches, was triple that of an overweight Black woman (VAT: 84 vs 25.4 cm^3). Even when limited to normal weight women, (BMI <23 kg/m^2 cut point for Asians), Filipinas had significantly more VAT at every level of waist girth and percent body fat compared to normal weight (BMI <25 kg/m^2) Black and White women.[12]

Figure 2 shows T2D prevalence was significantly higher among Filipinas at every VAT tertile. However, even among women with the least VAT (<46 cm^3), T2D prevalence was just 1.7% among Caucasians, 7.4% among Blacks but 23% among Filipinas.[12] This suggests that excess VAT explains some, but not all of the attributable risk for T2D among Filipinos. Further, CT measures of VAT are neither convenient nor economical. When limited to women with normal waist girth (<80 cms for Asians and <88 cms for Black and White women), Filipinas with normal waist

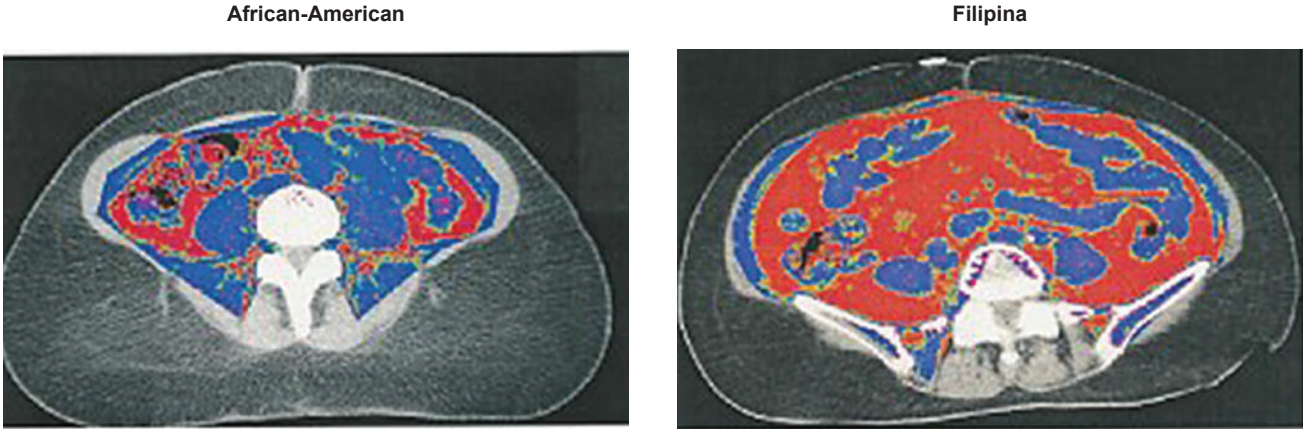
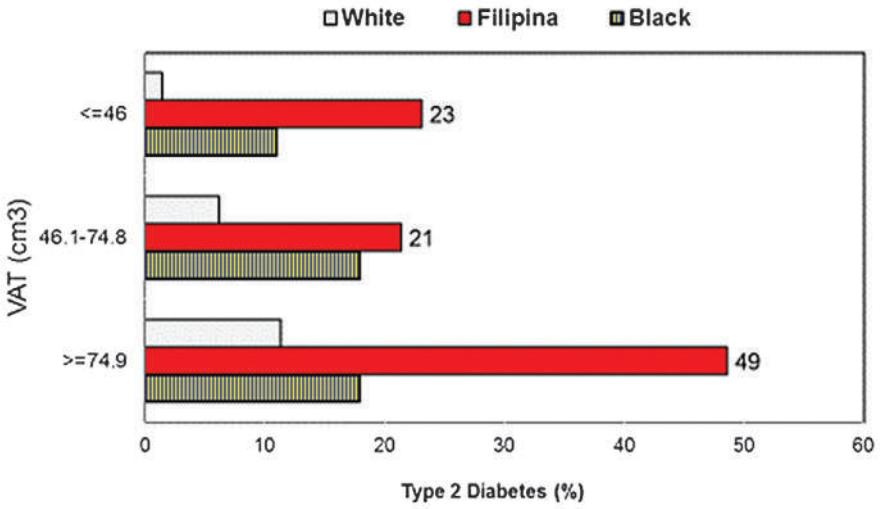


Figure 1. CT-defined Visceral Adipose Tissue (VAT) African-American vs Filipino-American women.[12]



*T2D by OGTT. VAT by computed tomography.

Figure 2. Age-adjusted Type 2 Diabetes* prevalence, by Visceral Adipose Tissue (VAT) tertiles and race, 55-80 year old women.[12]

girth continued to have significantly more VAT (54.8 cm^3) compared to White (50.9 cm^3) and Black women (43.8 cm^3), and significantly higher T2D prevalence despite normal waist circumference (Filipina T2D: 23.3%, White, 3.3%, Black: 10.4%).[12]

Other unique T2D risks among Filipino migrants include low ratio of muscle to total abdominal mass area. Filipinas had significantly more pericardial fat (191 cm^2) compared to White (144 $cm^{2)}$ and Black (123 cm^2) women, and significantly more percent fat in the rectus abdominus muscle (35.4%) compared to White (24.6%) and Black women (26.7%).[21] Neither intermuscular nor intrathoracic far, nor fat in the oblique muscles differed by ethnicity, although White women had significantly more fat in the paraspinal and psoas muscles.[21,23] In the combined cohort of White, Black and Filipino women in San Diego, postmenopausal women with diabetes had significantly less total abdominal muscle and significantly more visceral adipose tissue than non-diabetics.[23,25] Increased VAT and decreased muscle mass are independent risk factors for diabetes. In women with BMI <25 kg/m^2, low muscle to abdominal area was significantly associated with a higher risk for T2D.[25] Low muscle was associated with normal weight metabolic obesity. Interventions that emphasize increasing muscle, rather than weight loss, could increase glucose storage and consumption, enhancing glucose disposal. Further, increasing muscle mass might improve insulin sensitivity and prevent insulin resistance in low BMI ASEAN populations.

Adiponectin

Low levels of adiponectin, a cytokine with insulin sensitizing properties, is predictive of T2D;[34] Filipina-Americans with normal glucose levels had half the adiponectin concentration of normoglycemic Caucasians.[15] Mean adiponectin levels among normoglycemic White women were 16 ug/ml compared to 8 ug/ml among Filipinas in San Diego, California and 10 ug/ml in Black Women. Adiponectin levels are down regulated in the presence of excess visceral adipose tissue,[34] however, these trends persisted even after adjusting for waist, waist-to-hip ratio, BMI, fasting insulin, and insulin resistance (based on homeostatic model assessment, HOMA-IR).

Among Filipinas, T2D prevalence increased with decreasing adiponectin concentration. Among Filpinas with the lowest adiponectin concentration (<5.4 ug/ml) over half (51%) had T2D compared to 29% among those with adiponectin levels ranging from 5.4 to 9.2 ug/ml. Filipinas with the highest adiponectin concentration (≥9.3 ug/ml) had the lowest T2D prevalence at 17%.[35]

The etiology behind low adiponectin levels among Filipinos might have genetic origins. The Cebu Longitudinal Health and Nutrition Survey conducted a genome wide association study to investigate the genetic loci associated with plasma adiponectin. Among their 1776 unrelated Filipina participants, an uncommon haplotype of rs11924390 (KNG1) and rs864265 (ADIPOQ) was strongly associated with lower adiponectin levels.[36]

Nutrition

Behavioral factors, specifically, dietary interventions to increase adiponectin concentration have suggested that higher fiber intake can increase adiponectin concentration. A 24-hour food recall questionnaire was administered among the UCSD Filipino Health Study participants, and data were analyzed at the Willett laboratory at Harvard.[20] Neither intake of protein, carbohydrates, saturated fat, monounsaturated fat nor polyunsaturated fat differed among Filipinas with high versus low adiponectin concentration.[20]

When stratified by OGTT defined diabetes status, neither protein, carbohydrate, nor fat (vegetable, animal, saturated, polyunsaturated, monounsaturated) intake differed among Filipinas with versus without diabetes. Interestingly, Filipinas with T2D had significantly lower calcium intake (736 milligrams) compared to those without diabetes (936 milligrams), and higher caffeine intake (109 vs 61 milligrams).[37]

Other metabolic abnormalities

Other metabolic abnormalities among Filipino migrants include elevated prevalence of the Metabolic Syndrome (MetSyn), hypertension (HTN), dyslipidemia, probable non-alcoholic fatty liver disease (NAFLD, based on hepatic enzymes), hyperuricemia, and inflammation (based on tumor necrosis factor alpha (TNF-α) levels).[10,12,17,22,26] For the previous 33 years, HTN prevalence was remained highest among Black and Filipino men and women in California, compared to other ethnic groups.[36,37] Among Filipino-American women, NAFLD prevalence by hepatic enzymes was similar to that of Hispanic women (17% and 15%, respectively) and twice that of White and African American women.[17] Furthermore, NAFLD was independently associated with T2D (adjusted Odds Ratio: 6.3) among Filipinas, after adjusting for visceral adiposity, adiponectin, and other T2D risk factors.[17]

Reproductive risk factors: Gestational diabetes and grand multiparity

A growing body of evidence indicates that T2D risk begins in-utero, with prenatal exposures, gestational age, low birth weight, and birth complications associated with an increased risk for T2D in adulthood.[40] Intrauterine exposures including gestational diabetes mellitus (GDM), obesity, maternal stress, poor diet/nutrition, low physical activity, and genetic propensity can lead to childhood metabolic dysregulation, including early onset T2DM. Possible mechanisms include fetal nutrition, altered organ growth and maturation, increased glucocorticoid exposure, and genetic and epigenetic links.[40]

Gestational, childhood, and adulthood genetic, epigenetic and environmental exposures are important and often synergistic determinants of T2D.[40] Intrauterine growth restriction (IUGR), preterm birth, low-birth weight, chronic undernutrition, and childhood undernutrition followed by overnutrition later in life are associated with adult T2D risk.[41-42] The 2011 Philippine Food and Nutrition Research Institute (FNRI) survey showed that 16% of newborns had low birthweight (<2500 g) and 38% of infants ages 0-5 months were malnourished. These include 12.4% who were underweight, and 14% of infants with stunting, reflecting poor maternal nutrition, while 11.1% of these babies were wasting, indicative of acute significant food shortage and/or disease.[43]

While the contribution of the fetal environment to T2D susceptibility is well recognized, the mechanisms linking fetal nutrient environment and susceptibility to T2D, are not clear. Adiponectin is an adipocyte and placental secreted protein involved in a variety of metabolic processes including insulin and mTOR signaling sensitivity;[44-45] changes in adiponectin levels in the developing fetus could affect programming of T2D in adulthood. Adiponectin levels are lower in normoglycemic Filipino compared to Black and White women[15] and could be explained, in part, by expression of single nucleotide polymorphisms in an uncommon haplotype at *KNG1–ADIPOQ*.[35] Sub-optimal levels of maternal and fetal adiponectin could alter placental insulin/mTOR signaling and pancreatic beta-cell function in the offspring. Infants with IUGR show reduced circulating insulin levels and impaired beta cell function, however, adiponectin concentration in Filipino IUGR infants and their mothers is unknown. Mechanisms that explain how maternal and fetal undernutrition influences metabolic abnormalities may provide crucial information on the pathophysiology of T2D in the Philippines, which can guide modifiable interventions to improve clinical outcomes.

Gestational, childhood, and adulthood genetic, epigenetic and environmental exposures are important and often synergistic determinants of T2D.[40-41] Preterm birth, low-birth weight, IUGR, chronic undernutrition and childhood undernutrition followed by overnutrition later in life are associated with adult T2D risk. California data from the Northern California Kaiser Permanente Hospitals including 230,000 births, showed Asian Indian and Filipino-American parturients had the highest GDM prevalence in Northern California. Filipina-Americans had significantly higher GDM prevalence (10.9%) compared to Black, White, and Latina (4.4% to 6.8%) mothers despite the absence of preconceptional obesity.[46] Further, GDM risk was higher among Philippine born migrants in California compared to US born Filipinas.[46] Additionally, low prepregnancy adiponectin concentrations six years prior to pregnancy were associated with a five-fold higher risk of gestational diabetes in this cohort of racially diverse women.[47]

Multiparity has been associated with T2D, primarily through post-partum weight retention. To determine whether multiparity is associated with T2D, independent of visceral adipose tissue (VAT) and adipokines, data from the UCSD Filipina Health Study showed that mean parity was 4.3 (range 1-12 births), and T2D prevalence increased with increasing parity. T2D prevalence was 25% in the low parity group (1-2 births), 30.3% in women who had 3 to 5 live births, and was 50% among women with grand multiparity: 6-12 births.[19] Family history of diabetes, exercise, insulin resistance, and leptin and ghrelin levels did not differ by parity group. Compared with women who had 1-2 live births, women with 6 or more births were significantly older (62 vs. 57 years), had lower college completion (22 vs. 58%, p=0.006), more hypertension (72 vs. 55%), higher VAT (74.9 vs. 58.4 cm^3), and lower adiponectin concentration (5.79 vs. 7.61 mcg/ml). In multivariate analysis adjusting for adiponectin, VAT, family history of diabetes, age, education, hypertension, and estrogen use, grand multiparous women had a threefold higher odds of T2D (adjusted odds ratio 3.40 [95% CI 1.13-10.2]) compared with low parity women. No differences were observed in the odds of diabetes between women in the medium and low parity groups.

Multiparity is associated with elevated T2D risk among Filipina migrants in the US,[19] but deciphering the complex etiology of T2D, including in-utero exposures, is essential to curtail the emerging T2D epidemic in cultures where large families are valued, and countries where women have limited contraceptive options.

Lifecourse exposures: War, displacement, and food insecurity

Lifecourse exposures, beginning with adverse fetal exposures such as maternal malnutrition, preterm birth, and childhood stunting exacerbate T2D risk. Malnutrition

is pervasive in the Philippines, where two-thirds (69.3%) are food insecure households, and over one-third (38%) of infants, ages 0-5 months were malnourished.[43] Chronic malnutrition persisted through early childhood, and stunting rates were 41.5% among 3-year-old toddlers.[43] Stunting in toddlers is often irreversible, affecting brain development, physical growth, metabolic function, and increasing their future risk for T2D and cardiovascular disease (CVD) as adults.[48]

Food shortages and malnutrition were widespread during World War II, including the Netherlands where official rations were as low as 500 kcal per day.[49] The Dutch Winter Families Study and other cohorts experiencing famine showed that infants who experienced prenatal malnutrition had glucose abnormalities later in life, including impaired glucose tolerance and hyperglycemia.[49-52] Similarly, during the Japanese occupation of 1941-45, food shortages and malnutrition were ubiquitous in the Philippines, and infant mortality rates were reportedly among the highest in the world. To assess the potential influence of wartime fetal and infant malnutrition (up to age 2), data from the UCSD Filipino Health Study were stratified into birth cohorts: born a) before 1938, b) 2 years prior to the Japanese occupation (1938-40), c) during up to two years after the occupation (1941-1947) or d) more than 2 years post occupation (>1947). Participants born prior to the Japanese occupation were significantly taller than those born during or after World War II, however, T2D risk did not differ by birth cohort.[14]

The impact of war and political instability among war-exposed populations in Vietnam, Cambodia, Laos, displaced communities such as the Hmong and Rohingya, refugees and asylum seekers, and communities displaced by political insurgencies or destructive natural disasters require urgent evaluation and intervention.

Poverty: Leg length, childhood and adult socio-economic disadvantage

Childhood socioeconomic disadvantage influences early growth and adult health in myriad forms, including, but not restricted to poor early diet. Poor growth, particularly of the tibia and fibula in the first years of life, has been associated with insulin resistance and coronary heart disease (CHD) and may contribute to an increased risk of T2D and CHD. Leg length among UCSD Filipino Health Study participants was quantified as the difference between standing and sitting heights, and was used as an estimate of childhood growth and nutrition. Diabetes risk did not differ by leg length, however, coronary heart disease was significantly higher among women with the shortest leg length (<68.6 cm) compared to women with the longest leg length (>84.5).[14]

Filipinas reporting poor childhood family income had a mean height of 1.52 meters and were significantly shorter than women who reported being 'well off' during childhood.[14] Women with sustained childhood and adulthood socioeconomic disadvantage had a fivefold higher odds of T2D in later adulthood compared to those with higher childhood and adulthood incomes.[14] The odds of diabetes were significantly lower in women with better childhood financial conditions, higher education, and higher adult income in analyses that adjusted for BMI, waist circumference, family history of diabetes, smoking, exercise, employment status and household size.

Poverty, income inequality, poor nutrition, and limited social mobility are urgent and modifiable social determinants that exacerbate T2D risk, which require structural changes to eliminate these disparities.

Behavioral factors: Insufficient sleep

Sleep deprivation has been associated with obesity, insulin and T2D, so the UCSD Filipino Health Study evaluated ethnic differences in the associations of nighttime sleep and daytime napping durations with type 2 diabetes. Filipinas had the shortest average sleep durations (6.3 hours) compared to White (7.3 hours) and Black women (6.6 hours), and had the longest napping durations (31.7 minutes among Filipinas) compared to 16.8 minutes among Whites, and 25.9 minutes among Black women.[28] T2D prevalence among those with sleep data was 10.9% among White women, 37.8% among Filipinas, and 17.8% among Black women. Sleep duration showed a significant (p<0.01) nonlinear association with T2D in Filipina women, with increased odds of diabetes at both low (<6 hours) and high (>9 hours) sleep durations independent of age, BMI, triglyceride to high-density lipoprotein (HDL) ratio, hypertension, and daytime napping duration.[28] Daytime napping duration was associated with type 2 diabetes only among White women. Although approximately one-third of Filipina participants in San Diego were nurses, we did not ask about night shift work, nor the reasons for their shorter sleep duration.

Business Process Outsourcing is a thriving industry in the Philippines, where Filipino call center employees work during the graveyard shift in Manila and Cebu, to accommodate business hours in the United States. Anecdotal data have reported sleep deficiency and increasing obesity prevalence among such workers, and exacerbates their risk for T2D and other metabolic abnormalities.

Future directions

Public health efforts to reduce obesity and physical inactivity are necessary interventions to curtail the emerging diabetes epidemic in Southeast Asia; however, efforts to further elucidate the unique pathophysiology of T2D in populations with 'metabolically abnormal but normal weight phenotype' are urgently needed. The mechanisms of excess visceral adipose tissue accumulation despite normal BMI and waist circumference among Filipinos and other Asians are poorly understood. Non-invasive methods to diagnose and eliminate such excess VAT among normal weight individuals require development and implementation, including increasing muscle mass.

While over nutrition has manifested into a global epidemic of obesity and T2D, social inequities, including poverty, sustained childhood and adulthood fiscal disadvantage, lower education, food insecurity, and specifically prenatal malnutrition, threatens generations of resource-limited Southeast Asians with a higher risk of both gestational and type 2 diabetes.

Emerging technology, including genome wide association studies (GWAS) of glycemic traits, obesity, T2D, and other metabolic disorders have allowed identification of T2D susceptibility loci and insights pertaining to pathophysiology. However, the role of these loci among 'metabolically abnormal but normal weight' phenotypes common among Filipinos and other Southeast Asians have not been fully characterized. GWAS studies are in progress in China and Japan to identify such loci, but their environmental and behavioral exposures differ from Asians-Americans, and may differ from Southeast Asians.

Metabolite profiling represents a valuable tool to measure and assess unmeasured environmental factors. Several metabolites have been consistently associated with T2D, including selected branch chain and aromatic amino-acids, and low glutamine-to-glutamate ratio. Moreover, recent work suggests metabolite and genetic risk loci provide complementary and independent information for the T2D prediction. However, the role of these metabolites on disease susceptibility in populations of non-European descent has not been fully interrogated.

Other T2D risk factors include known risk factors including diet, exercise, social disadvantage, and selected comorbidities. Genomic and metabolomics measures are associated with some of these factors and could advance knowledge regarding the intersection of biological and sociocultural risk factors with T2D. Studies need to address these gaps in knowledge of the genetics and biology of diabetes in Southeast Asians, including assessment of genetic variation and profile the metabolome of subjects from ASEAN countries, and the ASEAN diaspora.

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ORIGINAL ARTICLE

Factors associated with the Severity of Findings on Hepatic Transient Elastography among Persons with Type 2 Diabetes and Fatty Liver*

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Abstract

Objective. This study aims to determine the relationship between the different factors associated with the severity of *Fibroscan with CAP* findings among patients with Type 2 diabetes and fatty liver.

Methodology. This is a cross-sectional study. Seven hundred four *Fibroscan with Controlled Attenuation Parameter (CAP)* results were electronically retrieved from a diagnostic center. 285 charts of diabetic patients with fatty liver on ultrasound were reviewed. 164 patients with fatty liver on ultrasound and *Fibroscan with CAP* were included in the study. Several factors were analysed in relation to the severity of *Fibroscan with CAP* findings in the study group.

Results. Fifty five point five percent (55.5%) (91/164) had significant fibrosis and cirrhosis. Hepatic steatosis prevalence was 96% (158/164). Diabetes >5 years (OR 1.75), HbA1c >7% (OR 2.25) and high SGPT levels (OR 2.39) were associated with liver fibrosis and cirrhosis. BMI >25 kg/m^2 (OR 1.45), triglyceride levels >150 mg/dl (OR 1.31) and HbA1c >7% (OR 1.74) were associated with hepatic steatosis.

Conclusion. Factors associated with the severity of hepatic fibrosis, cirrhosis and steatosis included above normal BMI, disease duration of >5 years, poor glycemic control and elevated levels of ALT, and serum triglycerides.

Key words: type 2 diabetes, NAFLD, transient elastography

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as the liver disease component of metabolic syndrome.[1] NAFLD is present when >5% of hepatocytes are steatotic in patients who do not consume excessive alcohol (i.e. <20 g/day for women and <30 g/day for men) and ranges in severity from simple steatosis (fat without significant hepatic inflammation or hepatocellular injury, to steatohepatitis (fat with hepatocellular injury and hepatic inflammation), to advanced fibrosis and cirrhosis.[2]

The definition of NAFLD by the American Association for the Study of Liver Disease (AASLD) requires that (a) there is evidence of hepatic steatosis, either by imaging or histology and (b) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medications, or hereditary disorders. In the majority of patients, NAFLD is associated with metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia.[1]

Up to 90% of patients with NAFLD have simple steatosis, which carries a relatively benign prognosis,[3] with no overall increase in mortality.[4,5,6] However, approximately 10-30% have the potentially progressive form of NAFLD, non-alcoholic steatohepatitis (NASH), which is associated with hepatocellular injury and inflammation.[4,7,8] Approximately 25-40% of patients with NASH develop progressive liver fibrosis, ultimately resulting in cirrhosis in 20-30%.[4,6,9-11]

NAFLD and Type 2 diabetes mellitus frequently coexist because they share the risk factors of excess adiposity and insulin resistance. The prevalence of Type 2 diabetes or impaired fasting glucose ranges from 18–33% in patients with NAFLD, whereas, NAFLD ranges from 49–62% in type 2 diabetes patients. NASH is present in 12.2% of patients with Type 2 diabetes, as compared to 4.7% in those without Type 2 diabetes. Moreover, Type 2 diabetes increases the risk of liver-related death by up to 22-fold as well as overall death by 2.6–3.3-fold in patients with NAFLD.[12]

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The reported prevalence of NAFLD when defined by liver ultrasound ranged between 17% and 46% depending on the population studied. In a study consisting of nearly 400 middle-aged individuals, the prevalence of NAFLD defined by ultrasonography was 46% and the prevalence of histologically confirmed NASH was 12.2%. Estimates of the worldwide prevalence of NAFLD ranges from 6.3% to 33% with a median of 20% in the general population based on a variety of assessment methods.[13]

An ultrasonographic study of patients with Type 2 diabetes showed a 69% prevalence of NAFLD.[14] In another study, 127 of 204 patients with diabetes displayed fatty infiltration on ultrasound, and 87% of the patients with fatty infiltration who consented to biopsy had histologic confirmation of NAFLD.[15]

Ultrasonography is recommended as first-line diagnostic screening test for NAFLD by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO). In their recent recommendations, biomarkers, fibrosis scores and transient elastography are considered acceptable non-invasive procedures for the identification of cases with low risk of advanced fibrosis/cirrhosis.[16]

Current guideline postulates that liver biopsy is the most reliable approach for identifying the presence of steatohepatitis and fibrosis in patients with NAFLD, but it is generally acknowledged that biopsy is limited by cost, sampling error, and procedure-related morbidity and mortality.[1]

Current guidelines state that a liver biopsy is the only way to diagnose NASH, and non-invasive techniques have not been fully validated for diagnosing this condition. However, empiric therapy is included as an option for patients unwilling or unable to undergo a liver biopsy. The American Diabetes Association has made an algorithm for the diagnosis of NAFLD and NASH in patients with pre-diabetes or Type 2 diabetes mellitus in clinical practice (See Appendix A).[17]

Transient elastography (Fibroscan, Echosens, Paris, France) is a non-invasive method of assessing liver fibrosis which can be performed at the bedside or in an outpatient clinic. It uses ultrasound-based technology to measure liver stiffness. Although Fibroscan is less well validated in NAFLD, in a study of 97 NAFLD patients, Area under the receiver operating characteristics (AUROCs) for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis were reported to be 0.88, 0.91, and 0.99, respectively. Another study including 246 NAFLD patients showed AUROCs for the diagnosis of moderate fibrosis, bridging fibrosis, and cirrhosis of 0.84, 0.93, and 0.95, respectively.[18]

Reproducibility of transient elastography is important for its widespread application. The reproducibility of liver stiffness measurement (LSM) was excellent for both interobserver and intra-observer agreement, with intra-class correlation coefficients (ICC) of 0.98.[19] For NASH with advanced fibrosis, pooled AUROC, sensitivity and specificity of Fibroscan are 0.94 (0.90-0.99), 0.94 (0.88-0.99) and 0.95 (0.89-0.99).[20]

A novel non-invasive tool based on ultrasound attenuation has been developed for use with the Fibroscan to assess liver steatosis. Measuring ultrasound attenuation in biological tissues is of great interest because it is related to the composition of tissues and, thus, reflects their pathological state. Transient elastography with Controlled Attenuation Parameter (CAP) is non-invasive and allows measurement of hepatic fat content in numerical scores (See Appendix B). CAP is evaluated using the same radio-frequency data and the same region of interest, as the region used to assess the LSM. CAP is guided by vibration-controlled transient elastography (VCTETM), which ensures the operator automatically obtains an ultrasonic attenuation value of the liver. CAP was shown to be significantly correlated with steatosis grade (Spearman=0.81, P<10−16). CAP was shown to be independent of fibrosis stage, and satisfactorily detected steatosis, with AUROCs for the diagnosis of S1, S2 and S3 of 0.91 (0.86~0.97), 0.95 (0.9~1) and 0.89 (0.75~1), respectively.[21]

Compared with patients without diabetes, people with Type 2 diabetes have an increased risk of developing NAFLD. The presence of NAFLD in patients with Type 2 diabetes is linked to increased cardiovascular disease risk independently from the components of the metabolic syndrome.

As a result of the increasing incidence of NAFLD in Type 2 diabetes and metabolic syndrome, with its associated morbidity and mortality, screening for NAFLD in all patients with one or more metabolic syndrome components by a non-invasive method, such as Transient Elastography with CAP, appears reasonable. Hence, the diagnosis and evaluation of fatty liver is an important part of the management of diabetes. When diabetes patients are diagnosed with NAFLD, more intensive monitoring and therapeutic intervention are necessary to avoid complications of liver fibrosis and cirrhosis, especially hepatocellular carcinoma.

General objective

This study aims to determine the relationship between the different factors associated with the severity of *Fibroscan with CAP* findings among patients with Type 2 diabetes and fatty liver seen at Chinese General Hospital and Medical Center.

Specific objectives

1. To define the metabolic profile of type 2 diabetic patients with fatty liver on ultrasound and *Fibroscan with CAP*.
2. To determine the prevalence of hepatic fibrosis, cirrhosis and steatosis on *Fibroscan with CAP*.
3. To determine the association of the demographic factors (age, gender), clinical factors (weight, BMI, duration of diabetes), biochemical tests (lipid profile, ALT, FBS, HbA1c), and transient elastography findings of patients with Type 2 diabetes with fatty liver on ultrasound.

METHODOLOGY

Study design, setting and participants

We performed a cross-sectional analytic study utilizing chart reviews of qualified patient profiles from January

2017 to June 2018. 704 *Fibroscan with CAP* results were retrieved electronically at a local, independent diagnostic center. This diagnostic test was done as part of routine work-up for patients with fatty liver on ultrasound on an outpatient setting. Complete enumeration of study subjects was done. We identified 285 subjects with Type 2 diabetes mellitus. Applying the inclusion and exclusion criteria, we were able to come up with the total number of 164 subjects eligible for the study. One hundred twenty-one subjects were excluded in the study due to absence of fatty liver on abdominal ultrasound.

A review on the clinical records and laboratory results was done at attending physicians' clinics. Only those patients under the care of physicians from Chinese General Hospital and Medical Center were included in the study. Anthropometric (body mass index, height, weight) and laboratory parameters (fasting blood sugar, ALT, glycosylated hemoglobin (HbA1c), and fasting lipid profile) were recorded in a data collection form. Duration of Type 2 diabetes mellitus was also noted (Figure 1). All pertinent information were gathered and recorded at the period when the *Fibroscan with CAP* was done. Clinic records of patients were checked for history of hepatitis infection thru results of serologic tests, significant alcohol intake (>1 drink per day for adult women, >2 drinks per day for adult men), use of liver supplement medications, or hepatotoxic drug use (See Appendix B). All patients enlisted had undergone abdominal ultrasonography and *Fibroscan with CAP* performed by an experienced operator. To avoid observer variability and to maintain consistency of transient elastography readings, only results read by same authorized trained personnel were accounted for in the study.

Study variables

Multiple independent variables were analyzed in relation to the occurrence of hepatic steatosis, fibrosis and cirrhosis (dependent variable). Age and disease duration categorizations were based on previous epidemiological studies on diabetes and NAFLD.[22,23] BMI was computed by dividing subject's weight (kg) with height (m^2). The Asia-Pacific Asian BMI criteria were used to group patients into underweight, normal, overweight and obese subjects.[24] Glycemic control was defined by the fasting blood sugar and HbA1c levels of the patients. Poorly controlled diabetes is reflected by a fasting blood sugar of >126 mg/dl and HbA1c of >7% as stated in the 2018 American Diabetes Association (ADA) Standards of Medical Care in Diabetes. Blood cholesterol and triglyceride levels categorization into optimal, normal, desired or high levels were based on the National Cholesterol Education Program – Adult Treatment Panel (NCEP-ATP III) 2001 guidelines (See Appendix C). SGPT levels were described to be above 2x or 3x normal based on individual laboratory reference cut-off.

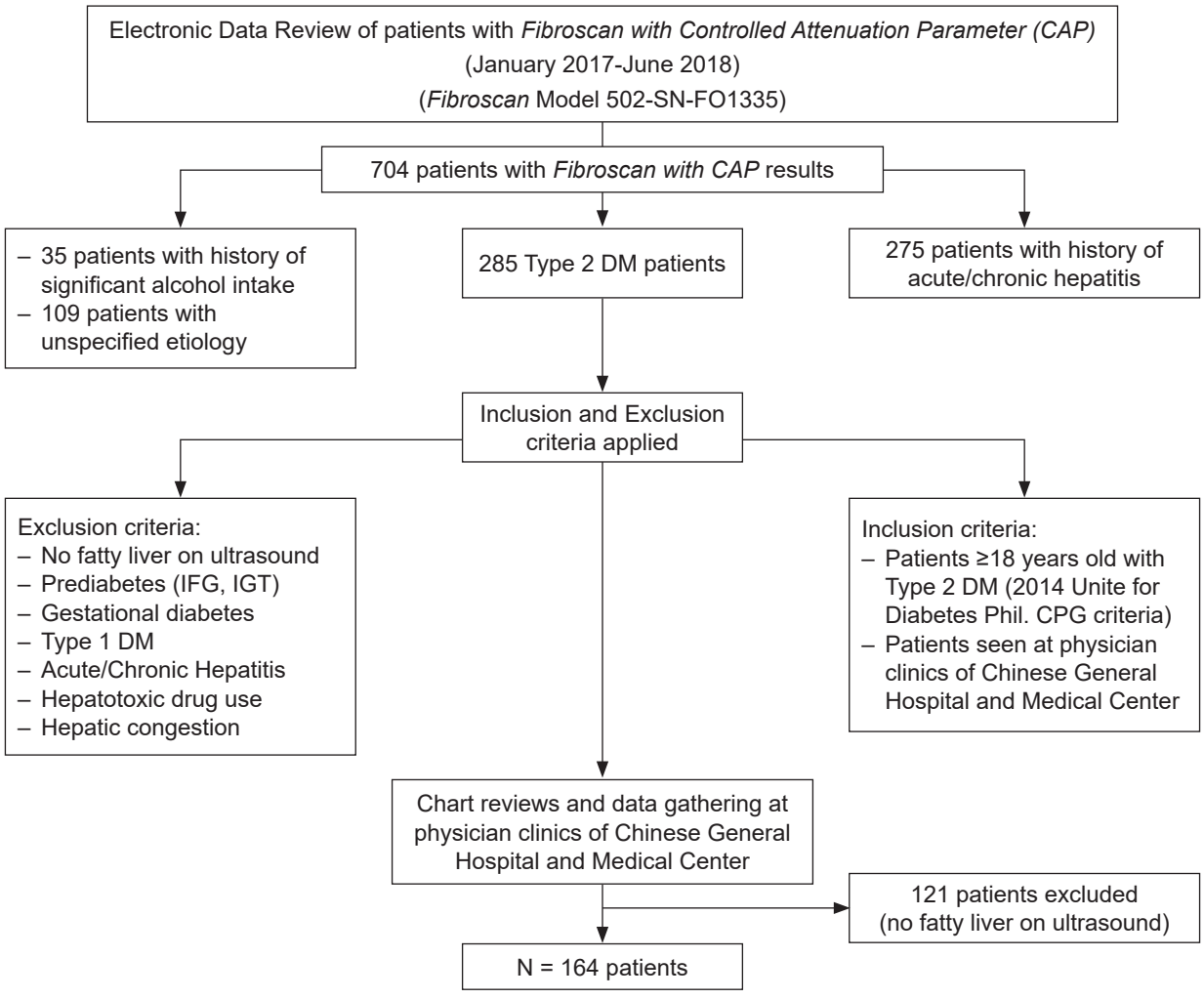

Figure 1. Summary of the study procedure.

Sample size computation

Sample size for this study was computed based on the proportion of patients with fatty liver of 0.58 and the proportion with no fatty liver of 0.42. In a computation for comparison of two proportions carried out at 95% confidence level or z-value at 1.96, a sample of 164 patients with Type 2 diabetes with hepatic steatosis, fibrosis and cirrhosis on *Fibroscan with CAP* was taken from a total of 285 patients from the ideal sample size computation.

Inclusion and exclusion criteria

The study included patients 18 years old and above who were diagnosed with Type 2 diabetes mellitus based on the 2015 Unite for Diabetes Philippines Clinical Practice Guidelines (See Appendix D).[25] Patients with the following attributes were excluded in the study: patients with no fatty liver on ultrasound, impaired fasting glucose, impaired glucose tolerance, gestational diabetes, Type 1 diabetes mellitus; history of liver disease secondary to chronic alcohol intake, acute or chronic viral infections like hepatitis A, B and C; hepatotoxic drug use and intake of liver supplements; cholestasis; hepatic congestion.

Interpretation of transient elastography results

The interpretation of transient elastography results were based on the cut-off parameters laid out by a reliable, independent diagnostic center which utilized the M Probe of Fibroscan device model 502-SN-FO1335 (See Appendix E) handled by a single experienced operator. Interpretation guide for diagnosing non-alcoholic fatty liver disease (NAFLD) were as follows: for liver stiffness measurement (LSM): F0-F1 - minimal or no fibrosis (≥5.8 kPa), F2 – possible intermediate fibrosis (>5.8-<9.6 kPa), F3 - advanced fibrosis (>9.6-11.5 kPa), F4 - Cirrhosis (>11.5 kPa); for controlled attenuation parameter (CAP): Grade S0 - <10% fatty infiltration (<221 dB/m), Grade S1 – 11-33% fatty infiltration (222-232 dB/m), Grade S2 – 34-66% fatty infiltration (233-289 dB/m), Grade S3 – >66% fatty infiltration (≥290 dB/m).

Data analysis

Descriptive analysis of the different sociodemographic and clinical characteristics of the study population was done using means and percentages. Standard deviation was computed as a measure of dispersion for data results with means. The prevalence rate of detecting fatty liver on *Fibroscan with CAP* was determined. Logistic regression analysis of the different variables in the study was done to determine the odds of developing hepatic steatosis, fibrosis and cirrhosis. The estimated or crude odd ratios were then computed. The variables analyzed categorically included age, body mass index, diabetes duration, total cholesterol level, triglyceride level, HDL-C and LDL-C levels, and fasting blood sugar and ALT levels. The Chi square test for independence was used to establish the association between the different factors (age, sex, height, weight, BMI, lipid profile, ALT, FBS, HbA1c, diabetes duration) and transient elastography findings of the diabetic patients with fatty liver on ultrasound that was tested at 0.05 level of significance.

Ethical considerations

Approval from the Institutional Ethics Committee was obtained before initiating the study. Consent from the different attending physicians was pursued concerning collection of vital information from the patients' medical records. Patient identity and information gathered in the data collection forms were coded using letters and numbers to maintain confidentiality. Retrieval of *Fibroscan with CAP* results at an independent diagnostic center was accomplished by a consent letter addressed to the management. To maintain confidentiality, *Fibroscan with CAP* results were also tallied as coded numbers, each code representing a single patient. Privacy and confidentiality of data and results were protected in compliance with the Data Privacy Act.

RESULTS

We retrieved a total of 704 transient *Fibroscan with CAP* results in this study. Two hundred eighty-five patients were identified as having Type 2 diabetes mellitus. We came up with 164 patients eligible for the study after excluding 121 patients with diabetes with no fatty liver findings on ultrasound. Due to the high risk for metabolic and cardiovascular complications in patients with diabetes, as evidenced in several studies,[17,22] we categorized patients in the ages <40 and ≥40 years old. Table 1 described the socio-demographic characteristics of the study population. Mean age was 57 years old. Mean duration of diabetes was 4 years. Mean weight and height were 71.43 kilograms and 1.61 meters, respectively. Majority (89%) of the patients aged at least 40 years old with both males and females equally represented. Most of them were overweight and obese (90%) and had diabetes duration of <5 years (62.8%). Table 2 described the laboratory results of the subjects. Mean FBS and ALT levels were 130 mg/dl and 38.27 IU/L, respectively. 59.76% of the population had high LDL-C levels. However, most had normal fasting blood sugar (58.54%), total cholesterol (60.37%), triglyceride level (60.37%), HDL-C (63.41%), HbA1c (81.1%) and ALT (54.27%).

Around 55.5% of the patients had intermediate to advanced fibrosis and cirrhosis of the liver (Figure 2). Ninety six percent (96%) of the population had minimal to severe

Table 1. Socio-demographic characteristics of the study population

Patient Characteristics (N=164)	N (%)
Mean age ± SD (years)* and (range)	57.27±13.06 (25-84)
a. <40	18 (10.98)
b. ≥40	146 (89.02)
Mean height ± SD (meters) and (range)	1.61±12.50 (1.32-1.83)
Mean weight ± SD (kilograms) and (range)	71.43±8.13 (44-125)
Sex	
a. Male	84 (51.22)
b. Female	80 (48.78)
Body mass index (BMI) (kg/m^2) **	
Mean BMI ± SD	27.58±4.25
a. <18.5 (underweight)	1 (0.61)
b. 18.5-22.9 (normal)	15 (9.15)
c. 23-24.9 (overweight)	28 (17.07)
d. ≥25 (obese)	120 (73.17)
Mean diabetes duration (years) and (range) + SD	4.05±3.63 (0.5-20)
a. <5	103 (62.80)
b. ≥5	61 (37.20)

** Age cut-off as referenced from Unite for Diabetes Philippines CPG 2014[25]
** Asia-Pacific Asian BMI criteria[24]

Table 2. Laboratory data of the study population

Laboratory tests of patients (N=164)	N (%)
Mean Fasting Blood Sugar ± SD (mg/dl) and (range)	130.01±46.39 (72-393)
a. <126	96 (58.54)
b. ≥126	68 (41.46)
HbA1c (%)	
a. ≤7%	133 (81.10)
b. >7%	31(18.90)
Lipid Profile*	
a. Total cholesterol (mg/dl)	
<200 (normal)	99 (60.37)
≥200 (high)	65 (39.63)
b. Triglycerides (mg/dl)	
<150 (normal)	103 (62.80)
≥150 (high)	61(37.20)
c. HDL (mg/dl)	
<40 (low)	37 (22.56)
40-60	104 (63.41)
≥60 (high)	23 (14.02)
d. LDL (mg/dl)	
<100 (normal)	66 (40.24)
>100 (high)	98 (59.76)
Mean ALT level + SD (IU/L)** and (range)	38.27±22.23 (11-118)
a. Normal	89 (54.27)
b. ≥2x normal	50 (30.48)
c. ≥3x normal	25 (15.24)

* National Cholesterol Education Program – Adult Treatment Panel (NCEP-ATP) III Guidelines
** Normal ranges with reference to individual laboratory cut-off values
HbA1c – glycosylated hemoglobin; HDL – high density lipoprotein; LDL – low density lipoprotein; ALT – alanine aminotransferase

hepatic steatosis as documented on transient elastography with CAP (Figure 3). Note that only 44.5% and 3.66% of the subjects presented with minimal to no fibrosis, and no significant steatosis, respectively.

On Tables 3 and 4, the clinical characteristics of patients with fibrosis under LSM, and steatosis under CAP were outlined. 57.5% and 96.57% of the patients aged at least 40 years old had intermediate to advance fibrosis/cirrhosis on liver stiffness measurement, and mild to severe steatosis on controlled attenuation parameter, respectively. Note in the ages ≥40 years, 20 patients presented with cirrhosis (Table 4). There was a higher percentage of males with intermediate to advanced fibrosis and cirrhosis (52.7%) compared to females (47.3%) under LSM.

However, under CAP measurement, there was negligible difference of having steatosis for both sexes (males 49.7% vs females 50.3%). Majority of the population who had higher degrees of fibrosis and steatosis had elevated BMI and LDL-C levels. SGPT levels were also above normal for patients with intermediate to advanced fibrosis/cirrhosis (59.3%) and mild to severe steatosis (55.9%). Majority had normal fasting blood sugar, glycated hemoglobin, total cholesterol and HDL-C levels. For both observations, diabetes duration was less than 5 years in most cases.

Logistic regression analysis was done to determine the association of the different variables in relation to the occurrence of liver fibrosis and cirrhosis in the study population (Table 5). A significant association was seen with duration of diabetes, HbA1c and ALT levels. There is 75% increase in the odds of having liver fibrosis and cirrhosis if diabetes duration was <5 years duration (OR 1.75, 95% CI 1.02-2.99, p=0.041), 125% increase in the odds of having liver fibrosis and cirrhosis if HbA1c levels ≥7% (OR 2.25, 95% CI 1.026-4.90, p=0.043) and 139% increase in the odds if SGPT ≥2-3x elevated from normal value (OR 2.389, 95% CI 1.46-3.93, p=0.001).

Table 6 showed the variables involved in the occurrence of hepatic steatosis of the study group. Significant variables associated with the development of hepatic steatosis included BMI, HbA1c and triglyceride level. There is 31% increase in the odds that the patient will have a CAP score other than S0 if triglyceride levels >150 mg/dl (OR 1.31, 95% CI 0.647-2.59, p=0.0102) compared to those who have triglyceride levels <150 mg/dl. There is 45% increase in the odds that the patient will have a CAP score other than

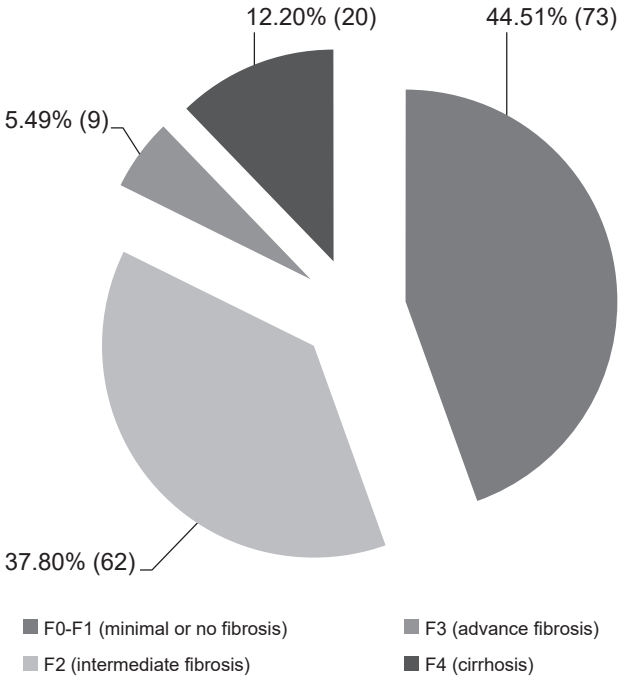

Figure 2. Liver stiffness measurement (LSM) data of patients (N=164).

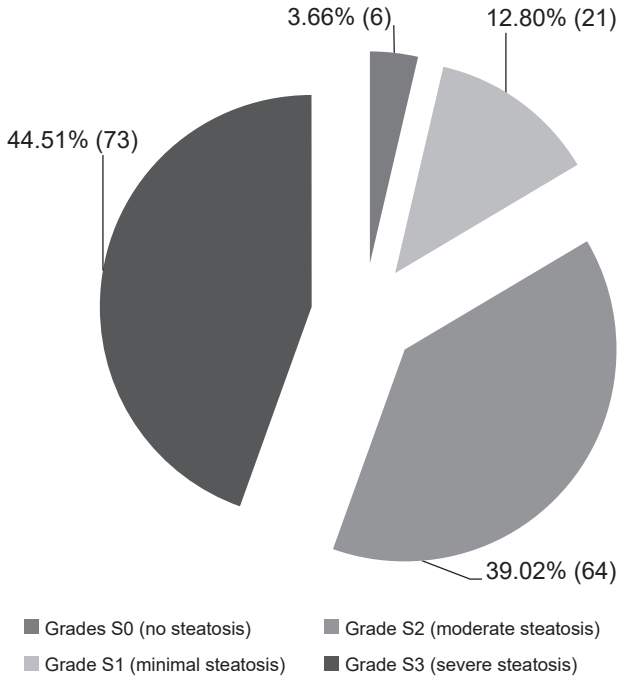

Figure 3. Controlled attenuation parameter (CAP) data of patients (N=164).

Table 3. Liver stiffness measurement (LSM) scores relative to patient characteristics

Patient Characteristics (N=164)	N (%)			
	Minimal to no fibrosis (F0-F1)	Intermediate fibrosis (F2)	Advance fibrosis (F3)	Cirrhosis (F4)
Age (years)*				
<40	11 (15.07)	7 (11.29)	0 (0.00)	0 (0.00)
≥40	62 (84.93)	55 (88.71)	9 (100.00)	20 (100.00)
Sex				
Male	36 (49.32)	37 (59.68)	3 (33.33)	8 (40.00)
Female	17 (50.68)	25 (40.32)	6 (66.67)	12 (60.00)
BMI (kg/m^2)**				
<25	24 (32.88)	9 (38.71)	4 (44.44)	7 (40.00)
≥25	49 (67.12)	53 (61.29)	5 (55.56)	13 (60.00)
FBS (mg/dl)				
<126	44 (60.20)	34 (54.84)	4 (44.44)	14 (30.00)
≥126	29 (39.73)	28 (45.16)	5 (55.56)	6 (70.00)
HbA1c (%)				
<7	63 (86.30)	46 (74.19)	4 (44.44)	16 (80.00)
≥7	10 (13.70)	16 (25.81)	5 (55.56)	4 (20.00)
Total cholesterol (mg/dl)				
<200	44 (60.27)	35 (56.45)	5 (55.56)	15 (75.00)
≥200	29 (39.73)	27 (43.55)	4 (44.44)	5 (25.00)
Triglycerides (mg/dl)				
<150	49 (67.12)	40 (64.52)	4 (44.44)	10 (50.00)
≥150	24 (32.88)	22 (35.48)	5 (55.56)	10 (50.00)
HDL (mg/dl)				
<40	13 (17.81)	15 (24.19)	4 (44.44)	5 (20.00)
40-60	47 (64.38)	41 (66.13)	5 (55.56)	11 (55.00)
>60	13 (17.81)	6 (9.68)	0 (0.00)	14 (25.00)
LDL-C (mg/dl)				
<100	31 (42.47)	22 (35.48)	4 (44.44)	9 (45.00)
≥100	42 (57.53)	40 (64.52)	5 (55.56)	11 (55.00)
ALT (IU/L)***				
Normal	41 (56.16)	24 (38.70)	2 (22.22)	9 (45.00)
≥2x N	20 (27.40)	18 (29.03)	2 (22.22)	4 (20.00)
≥3x N	12 (16.44)	20 (32.26)	5 (55.56)	7 (35.00)
DM duration				
<5 years	49 (67.12)	38 (61.29)	4 (44.44)	12 (60.00)
≥5 years	24 (32.88)	24 (38.71)	5 (55.56)	8 (40.00)

* Age cut-off as referenced from Unite for Diabetes Philippines CPG 2014[25]
** Asia Pacific Asian BMI criteria[24]
*** Normal ranges with reference to individual laboratory cut-off values
BMI – body mass index; FBS – fasting blood sugar; HbA1c – glycosylated hemoglobin; HDL – high density lipoprotein; LDL – low density lipoprotein; ALT – alanine aminotransferase

S0 if BMI >25k/m^2 (OR 1.45, 95% CI 0.578-2.09, p=0.028) compared to those who have BMI <25kg/m^2. There is 74% increase in the odds that the patient will have a CAP score other than S0 if HbA1c is ≥7% (OR 1.775, 95% CI 0.608-4.19, p=0.004) compared to those who have HbA1c <7%.

A Chi square test for independence was done to document the association of the demographic and clinical factors, and biochemical test results with the *Fibroscan* findings. In this study, the fatty liver findings on ultrasound was associated with significant CAP scores since p-value of the chi square test for independence was significant (p *value*=0.033, <*alpha*=0.05).

DISCUSSION

In our study, the prevalence of fatty liver documented on ultrasound among the type 2 diabetes mellitus population was 57.5% (164/285), higher than the results of the study of Prasetya et al.,[22] which was conducted among outpatient persons with Type 2 diabetes in Indonesia. This finding was in congruence with the rising number of patients with metabolic syndrome and/or Type 2 diabetes as reported in several epidemiological studies. Similar to the findings of Lesmana et al.[23] NAFLD was prevalent among age at least 40 years old. There was higher incidence of mild to severe hepatic steatosis (96%) when transient *Fibroscan with CAP* was utilized, a finding consistent with that of Grgurevic et al.,[26] In the study of Roulot et al.,[27] wherein 47 patients with LSM score of ≥8 kPa underwent liver biopsy, 93% had steatosis and 51% had severe fibrosis.

Most of the patients in this study had diabetes mellitus of at least 5 years, indicating that the process of NAFLD might be associated with disease duration. The available literature explained that the process of NAFLD might have occurred long before the diagnosis of Type 2 diabetes mellitus.[28] In our case, the odds of having fatty liver, in relation to diabetes duration, was increased when examined statistically, similar to the findings of Khan et al.[28]

Most of the patients in our study had high BMI. Reviewing the CAP scores of the subjects pointed out that varying degrees of hepatic steatosis (S1-S3) occurred in the overweight to obese population, along with elevated serum triglyceride levels. These findings were consistent with the reports of Trovato et al.[29] In a study by Leite et al.,[14] above normal ALT was associated with hepatic steatosis, however, glycemic control was not associated with the increased risk of NAFLD in patients with diabetes. On the contrary, our findings showed that poor glycemic control was a predictive risk factor for NAFLD. The contradicting results indicate that there are a lot of unidentified factors underlying NAFLD occurrence in patients with diabetes.

Table 4. Controlled attenuation parameter (CAP) scores relative to patient characteristics

Patient Characteristics (N=164)	N (%)			
	Grade 0	Grade S1 (minimal steatosis)	Grade S2 (moderate steatosis)	Grade S3 (severe steatosis)
Age (years)*				
<40	1 (16.67)	0 (0.00)	8 (12.5)	9 (12.33)
≥40	5 (83.33)	21 (100.00)	56 (87.50)	64 (87.67)
Sex				
Male	13 (61.90)	3 (50.00)	36 (56.25)	32 (43.84)
Female	8 (38.10)	3 (50.00)	28 (43.75)	41 (56.16)
BMI (kg/m^2)**				
<25	6 (28.57)	5 (83.33)	17 (26.56)	16 (21.91)
≥25	15 (71.43)	1 (16.67)	47 (73.44)	57 (78.08)
FBS (mg/dl)				
<126	12 (57.14)	4 (66.67)	35 (54.69)	45 (61.64)
≥126	9 (42.86)	2 (33.33)	29 (45.31)	28 (38.36)
HbA1c (%)				
<7	18 (85.71)	5 (83.33)	49 (76.56)	58 (79.45)
≥7	3 (14.29)	1 (16.67)	15 (23.44)	15 (20.55)
Total cholesterol (mg/dl)				
<200	13 (61.90)	3 (50.00)	42 (65.63)	41 (56.16)
≥200	8 (38.10)	3 (50.00)	22 (34.38)	32 (43.84)
Triglycerides (mg/dl)				
<150	12 (57.14)	3 (50.00)	48 (75.00)	48 (54.79)
≥150	9 (42.86)	3 (50.00)	16 (25.00)	16 (45.21)
HDL (mg/dl)				
<40	6 (28.57)	1 (16.67)	14 (21.88)	16 (21.92)
41-59	12 (57.14)	4 (66.67)	39 (60.94)	49 (67.12)
>60	13 (14.29)	1 (16.67)	11 (17.19)	8 (10.96)
LDL-C (mg/dl)				
<100	8 (38.10)	2 (33.33)	29 (45.31)	27 (36.99)
≥100	13 (61.90)	4 (66.67)	35 (54.69)	46 (63.01)
ALT (IU/L)***				
Normal	13 (61.90)	4 (36.36)	28 (43.75)	31 (42.47)
≥2x N	4 (19.05)	4 (36.36)	16 (25.00)	20 (27.40)
≥3x N	4 (19.05)	3 (27.27)	20 (31.25)	22 (30.14)
DM duration				
<5 years	13 (61.90)	5 (83.33)	43 (67.19)	42 (57.53)
≥5 years	8 (38.10)	1 (16.67)	21 (32.81)	31 (42.47)

* Age cut-off as referenced from Unite for Diabetes Philippines CPG 2014[25]
** Asia Pacific Asian BMI criteria[24]
*** Normal ranges with reference to individual laboratory cut-off values
BMI – body mass index; FBS – fasting blood sugar; HbA1c – glycosylated hemoglobin; HDL – high density lipoprotein; LDL – low density lipoprotein; ALT – alanine aminotransferase

Table 5. Analysis of the different variables involved in the occurrence of liver fibrosis

Variable	Odds Ratio	*p* value*	95% CI
Age ≥40 years old	1.285	0.528	0.589-2.801
Male sex	1.182	0.508	0.719-1.943
BMI >25kg/m^2	1.128	0.655	0.664-1.915
Total cholesterol >200 mg/dl	0.757	0.389	0.402-1.425
Triglyceride >150mg/dl	1.205	0.522	0.679-2.139
HDL <40 mg/dl	0.928	0.810	0.506-1.702
LDL >100 mg/dl	1.030	0.922	0.562-1.000
HbA1c ≥7%	**2.254**	**0.043**	**1.026-4.9**
FBS ≥126 mg/dl	0.698	0.242	0.382-1.274
ALT ≥2-3x N	2.389	0.001	1.45-3.93
DM duration >5 years	1.757	0.041	**1.02-2.99**

* *p* value significant at <0.05
BMI – body mass index; HDL – high density lipoprotein; LDL – low density lipoprotein; HbA1c – glycosylated hemoglobin; FBS – fasting blood sugar; ALT – alanine aminotransferase

Table 6. Analysis of the different variables involved in the occurrence of hepatic steatosis

Variable	Odds Ratio	*p* value*	95% CI
Age ≥40 years	0.123	0.404	0.159-0.983
Male sex	0.767	0.414	0.416-1.212
Total cholesterol >200 mg/dl	0.723	0.461	0.310-1.765
Triglyceride >150 mg/dl	1.308	0.010	**0.647-2.591**
HDL <40 mg/dl	0.688	0.383	0.407-1.631
LDL >100 mg/dl	1.666	0.211	0.742-3.039
FBS ≥126 mg/dl	0.713	0.368	0.340-1.453
HbA1c ≥7%	**1.745**	**0.004**	**0.608-4.188**
DM duration >5 years	1.193	0.623	0.569-2.345
BMI >25 kg/m^2	1.448	0.028	**0.578-2.090**

* *p* value significant at <0.05
HDL – high density lipoprotein; LDL – low density lipoprotein; FBS – fasting blood sugar; HbA1c – glycosylated hemoglobin; BMI – body mass index

Our study found the prevalence of significant fibrosis and cirrhosis in 55.5% of patients with NAFLD. The rate was somewhat higher than the results from the study of Prasetya et al.[22] However, studies examining the degree of fibrosis in patients with NAFLD are still limited, probably, due to the mere fact that liver biopsy remains the gold standard for characterizing liver histological alterations in patients with NAFLD as outlined in the 2018 Clinical Practice Guidelines of the American Association for the Study of Liver Disease for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease. Higher ALT levels, HbA1c >7% and disease duration of >5 years were associated with the occurrence of varying degrees of fibrosis in our study.

Strengths and limitations of the study

Our study had a greater number of recruited subjects compared to prior studies published. This is one of a few local studies done on determining the prevalence and incidence of NAFLD in type 2 diabetic patients along with its predisposing risk factors utilizing transient elastography with CAP. However, some limitations included: cross-

sectional retrospective design, it cannot describe the total causality of the disease; single-center study, which may not represent the entire Filipino population. A major limitation was selection bias. The data collection process should have started with the clinic chart reviews of qualified type 2 diabetic subjects, then proceeding to retrieval of ultrasound results, thereafter, the Fibroscan readings. Since we wanted to maintain consistency of *Fibroscan with CAP* readings, we electronically retrieved the results beforehand in a single and independent diagnostic center with the procedure done by a single, well-trained operator. In this way, we were able to avoid inter-observer variability of data which may affect the study results.

Recommendations

Larger studies for longer periods of time are needed to firmly establish the validity of this study results. Multi-center studies are highly recommended. Further studies are also recommended to determine the sensitivity and specificity of *Fibroscan with CAP* as a screening tool for identifying hepatic steatosis and fibrosis among patients with NAFLD.

CONCLUSION

The prevalence of fatty liver among patients with Type 2 diabetes on ultrasound in this study was 57% (164/285). Majority of patients with fatty liver on ultrasound had confirmed hepatic steatosis on *Fibroscan with CAP*, with the prevalence of 96% (158/164). Controlled attenuation parameter scores were associated with the occurrence of varying degrees of steatosis. Factors associated with hepatic steatosis included above normal BMI, HbA1c ≥7% and serum triglycerides.

The prevalence of hepatic fibrosis and cirrhosis, when examined under *Fibroscan with CAP*, among patients with fatty liver on ultrasound, was 55.5% (91/164). Factors associated with the development of liver fibrosis and cirrhosis were elevated ALT, glycosylated hemoglobin ≥7% and ≥5 years duration of diabetes.

Findings in the liver stiffness measurement were independent of the findings of controlled attenuation parameter when using transient elastography with CAP in detecting NAFLD among patients with Type 2 diabetes. Given the above findings, factors associated with the severity of hepatic fibrosis, cirrhosis and steatosis included above normal BMI, disease duration of ≥5 years, poor glycemic control and elevated levels of ALT, and serum triglycerides.

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

Author Disclosure
The authors declare no conflict of interest.

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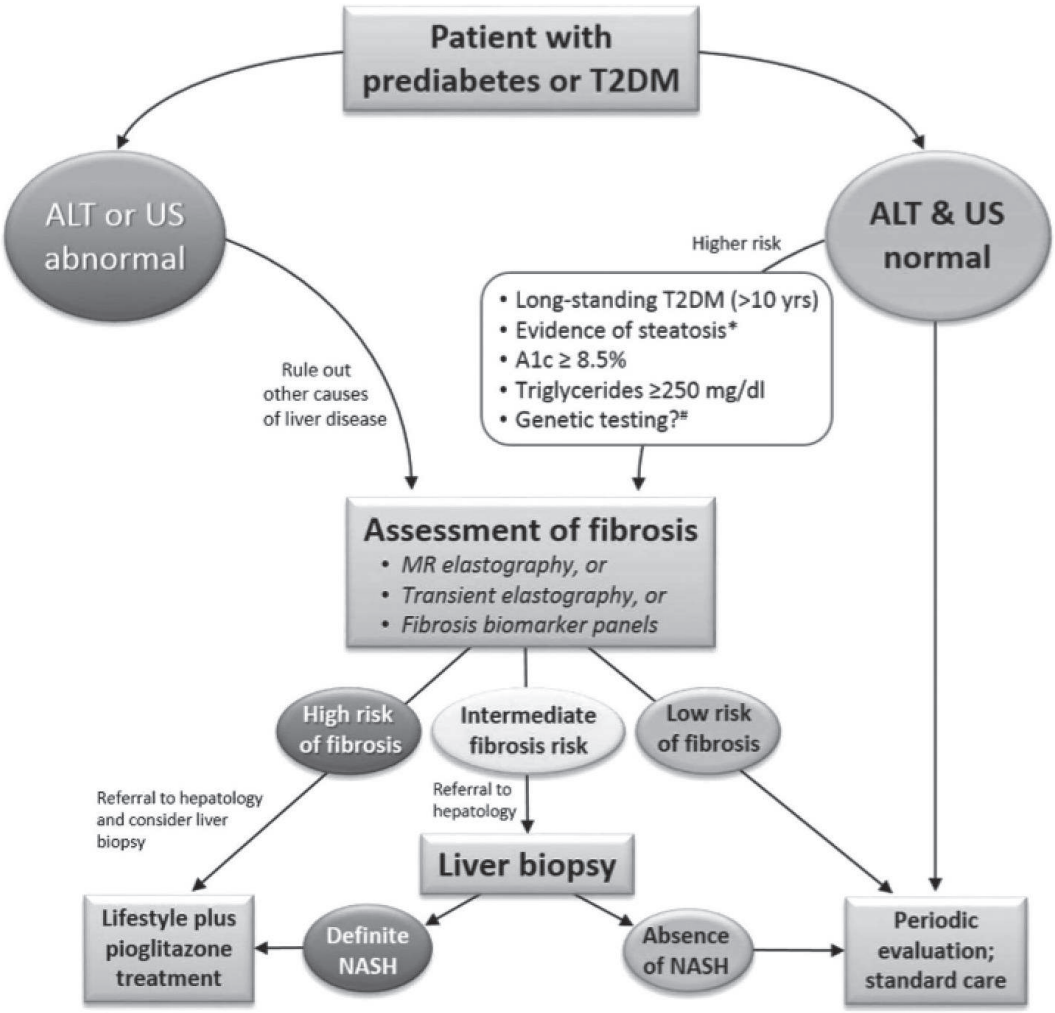
APPENDIX

Appendix A. The algorithm for the diagnosis of NAFLD and NASH in patients with prediabetes and type 2 diabetes mellitus in clinical practice.[17]



Appendix B

Data collection tool form

Code:
Age: Sex: Weight: Height: BMI: Duration of Type 2 Diabetes Mellitus:
Whole Abdomen UTZ Result:
Fibroscan with CAP Result:
Lipid Panel Results: Total Cholesterol Triglycerides HDL-C LDL-C
Glycemic Control: FBS Glycoslyated Hemoglobin (HbA1c)
SGPT
Hepatitis profile: Use of hepatotoxic drugs: History of significant alcohol Intake:

Appendix C

Definition of metabolic syndrome by NCEP ATP III (2005 Revision)

Absolutely required	None
Criteria	Any three of the five criteria below
Obesity	Waist circumference: • 40 inches male • 35 inches female
Hyperglycemia	Fasting glucose ≥100 ng/dl or under treatment
Dyslipidemia	Triglyceride level ≥150 mg/dl or under treatment
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl male, <50 mg/dl female or under treatment
Hypertension	• 130 mm Hg systolic or > 85 mm Hg diastolic or under treatment

Appendix D

Criteria for the diagnosis of type 2 diabetes mellitus (Philippines UNITE for Diabetes Clinical Practice Guideline 2014)[25]

The diagnosis of Type 2 Diabetes Mellitus can be made based on any of the following criteria: (Level 2, Grade B)
1. Plasma glucose ≥126 mg/dl (7.0 mmol/L) after an overnight fast. Fasting is defined as no calorie intake for at least 8 hours up to a maximum of 14 hours
2. Two-hour plasma glucose ≥200 mg/dl (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water after an overnight fast between 8 and 14 hours.
3. A random plasma glucose >/= 200 mg/dl (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia (weight loss, polyuria, polyphagia, polydipsia) or with signs and symptoms of hyperglycemic crisis.

Appendix E

Interpretation of transient elastography results*

Liver Disease	Minimal or No Fibrosis (F0-F1)	Possible Intermediate Fibrosis (F2)	Advance Fibrosis (F3)	Cirrhosis (F4)
Hepatitis B				
Normal ALT	≤6	>6-9	>9-12	>12
Elevated ALT	≤7.5	>7.5-12	>12-13.4	>13.4
HCV-HIV coinfection	<9.2	>9.2-11	>11-12.3	>12.3
Hepatitis C recurrence after liver transplantation	≤6.3-7.9	>7.9-8.5	>8.5-14.5	>14.5
Hepatitis C	≤7	>7-9.5	>9.5-12.5	>12.5
Chronic cholestatic disease	<7.1	>7.1-11.1	>11.1-17.3	>17.3
Alcoholic liver disease	≤7.8	>7.8-11	>11-19.5	>19.5
Nonalcoholic fatty liver disease (NAFLD)	≤5.8	>5.8-9.6	>9.6-11.5	>11.5

*M Probe of *Fibroscan* Model 502-SN-FO1335; Accuserv Diagnostic Center, Quezon City

Controlled attenuation parameter interpretation score*

Steatosis Grading	Amount of Fatty Infiltration	CAP interpretation (dB/m)
S0	<10%	Less than 221
S1 (mild)	11-33%	222-232
S2 (moderate)	34-66%	233-289
S3 (severe)	>66%	290 or more

*M Probe of *Fibroscan* Model 502-SN-FO1335; Accuserv Diagnostic Center, Quezon City

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Effectiveness of Healthy Foodie Nutrition Game Application as Reinforcement Intervention to Previous Standard Nutrition Education of School-Aged Children: A Randomized Controlled Trial*

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Abstract

Objective. Games promoting nutrition education are helpful tools to improve nutrition knowledge. Healthy Foodie is an interactive web-based nutrition game for Filipino children. This study aimed to determine the effectiveness of Healthy Foodie on the nutrition knowledge of children aged 7 to 10 years old.

Methodology. This study had 2 phases. In Phase 1, we developed and validated the Healthy Foodie nutrition game application and Nutrition Knowledge Questionnaire involving 46 participants. The Nutrition Knowledge Questionnaire was divided into 2 15-item questionnaires: Part 1 pertained to Food Group Knowledge and Part 2 on Food Frequency Knowledge. Phase 2 was the implementation of the game and questionnaire. This was a randomized controlled trial conducted in two elementary schools in Manila, involving 360 participants divided equally into control and experimental groups.

Results. For Phase 1, internal consistency of the questionnaire using the Kuder-Richardson Formula 20 was 0.75 for part 1 and 0.70 for Part 2. In Phase 2, comparing the adjusted posttest mean Food Group Knowledge scores, there was statistically higher score (F=111.84, p=0.0001) in the experimental group (11.57±0.20) compared to the control (8.51±0.20). In the adjusted posttest mean Food Frequency Knowledge scores, there was a statistically higher score (F=56.12, p=0.0001) in the experimental group (10.70±0.15) compared to the control (9.07±0.15).

Conclusion. A nutrition game-based intervention such as Healthy Foodie is effective as a reinforcement intervention to previous standard nutrition education of school-aged children.

Key words: nutrition, health education, video games, nutrition questionnaire

INTRODUCTION

Good health and proper nutrition are essential for a child to fully achieve his full potential for growth and development. The double burden of malnutrition includes undernutrition and overnutrition. In a survey conducted by the Food and Nutrition Research Institute, there was a decreasing trend in the number of undernourished individuals, but there was an alarming rise in the trend for obesity among children.[1] The problem with pediatric obesity is that patients are prone to early development of cardiometabolic complications and subsequently, premature death in adulthood.[2] The various cardiometabolic complications associated with overweight and obesity in children are hypertension, vascular dysfunction, early coronary atherosclerosis, left atrial and ventricular dysfunction, insulin resistance, type 2 diabetes mellitus, dyslipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, cirrhosis, arthritis and atopy. It also has a psychosocial impact due to its effect on body image, self-esteem and socialization.[2,3] One way to prevent these untoward complications is to halt its progression with lifestyle modification at the earliest time possible.

The 3 basic food groups are the go, grow and glow foods. Go food pertains to carbohydrate-rich food. Grow food consists of protein-rich food. Glow food are those that are high in vitamins and minerals such as vegetables and fruits. Each food group is essential, with its own role in providing nutrients to make the body healthy. Interventions to promote education on healthy food abound. The American Academy of Pediatrics supports the 5-2-1-0 program, which is an excellent starting point for any nutritional counselling. This consists of 5 or more servings of fruits and vegetables a day, 2 hours or less of recreational screen time per day, one hour or more of daily physical activity and zero consumption of sugar

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* *This study was presented as a poster abstract in the Philippine Society of Endocrinology, Diabetes and Metabolism Annual Convention last March 15, 2019 at the EDSA Shangri-La Hotel, Mandaluyong City, Philippines.*

sweetened drinks.[4] In the Philippines, the Department of Education released DO 13 s. 2017, detailing policies and guidelines on healthy food and drink choices in school canteens nationwide.[5] It categorized food into traffic light food groups of green, yellow and red. The green group includes food and drinks that must be served at all times by school cafeterias. Yellow consists of food and drink items that can be served restricted to the guidelines. The red group lists those that should not be served.[5] This has been implemented in public but not in private schools. Standard nutrition education has also been integrated into the school curriculum. As early as grade 1, healthful and less helpful foods are discussed in class. In grade 2, children are taught about the basic food groups, the Filipino food plate and the food pyramid.[6]

On the other end, malnourished children are at risk of not maximizing their learning abilities and opportunities. While bridging the socioeconomic gap is a Herculean task, innovative methods directed toward the improvement of nutrition status may be implemented. To prevent future complications of malnutrition, proper nutrition education should be emphasized as early as elementary school.

The rapid advancement in technology has modified standard teaching media. Teaching techniques have escalated from the usual blackboard to modern e-learning and slide show modules. Using games as an approach to improve nutrition education have been used worldwide. Depending on the game objective, games are innovative tools to impart important knowledge and concepts.[7-9] Moreover, the advantage of instructional technology is that it can motivate and engage learners in their own learning pace.[10] Video games for health provide innovative, potentially highly effective methods for enriching knowledge by delivering persuasive messages, changing attitudes and behavior, as well as improving health outcomes.[7] Serious games are video games that aim to entertain and promote change in behavior.[11]

Creating a culturally-adapted electronic application on basic nutrition for Filipino children is an innovative concept that will provide them with a window of opportunity to learn basic nutrition food groups and healthy food choices.

This study aims to develop and validate the Nutrition Knowledge Questionnaire and the Healthy Foodie nutrition game application. Furthermore, this study aims to determine the effectiveness of Healthy Foodie nutrition game application using posttest mean nutritional knowledge scores between the control group and the experimental group. Through this investigation, a validated and effective educational tool can be offered to schools to reinforce existing nutrition education among elementary school children.

METHODOLOGY

This study was approved by the University of Santo Tomas Hospital Institutional Review Board. This study's ethical principles were guided by the Ethical Research Involving Children document developed by UNICEF. Parental consent and child verbal assent were secured prior to joining any part of the study.

This study had 2 phases. Phase 1 involved instrument development and validation of the Nutrition Knowledge Questionnaire and the Healthy Foodie nutrition game application. Phase 2 encompassed testing for effectiveness of the Healthy Foodie nutrition game application. The study design was a randomized controlled trial. Figure 1 summarizes the flow of this study.

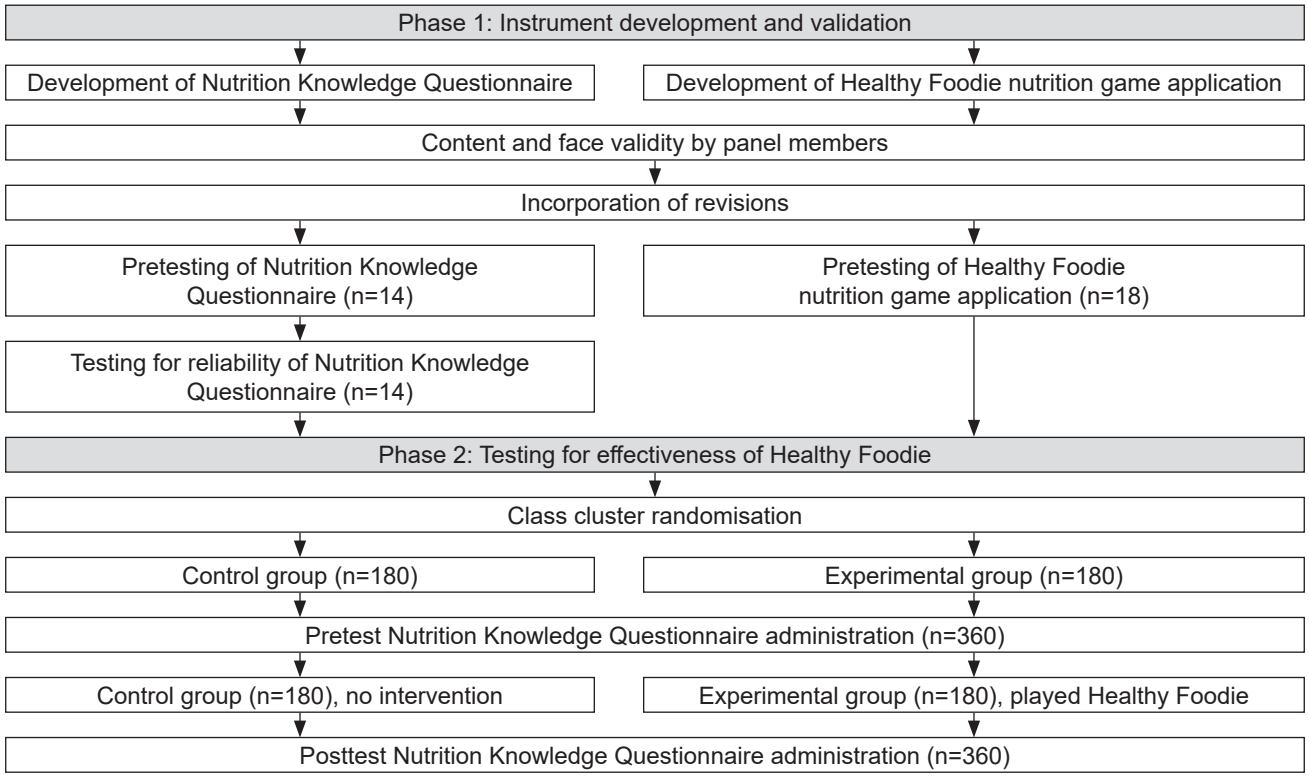

Figure 1. Study flow diagram.

Subjects

This study included grade 2 and grade 3 elementary students from the Cecilio Apostol Elementary School and Saint Jude Catholic School ages 7 to 10 years old. Individuals were excluded if they were blind, deaf, mentally challenged or unable to understand the English language.

Phase 1: Instrument development and validation

A multistep process was followed in the development and evaluation of the Nutrition Knowledge Questionnaire and Healthy Foodie nutrition game application.

Nutrition Knowledge Questionnaire

Literature search for nutrition knowledge questionnaire using the PubMed database yielded no content-specific basic nutrition knowledge questionnaire that matched the needs of the study. A questionnaire was subsequently developed. This was composed of 15 Food Group Knowledge questions and 15 Food Frequency Knowledge questions. The food group classification was based on the recommendations from the Food and Nutrition Research Institute.[12] The food frequency classification of the traffic light food group was based on guidelines from the Department of Education. The panelists had specific training in questionnaire construction and knowledge background on nutrition. The nutrition knowledge questionnaire included food frequently taken by Filipinos. The age group of the audience was taken into account in the construction of the questionnaire. While the average number of test questions in 2016 in grades 2 and 3 were 12 and 13, respectively, standardized assessments tend to choose 15 as the usual number of questions.[13]

The pretest and posttest questionnaires were the same (Appendix A). Close-ended pre-selected multiple choice responses were chosen as the response format. For the scoring system, a point was awarded for each correct answer.[14]

The draft was presented to 3 panel members composed of one physician, one elementary school teacher and one parent, to assess content and face validity. The clarity of the instructions and questions provided was assessed with a score of 1 to 3, with 1 as easily understandable, 2 fairly understandable and 3 difficult to be understood. If 2 or more members perceived an item as fair or difficult to understand, it was replaced and reevaluated. On the other hand, the content of the questionnaire was judged as appropriate or inappropriate. If 2 or more of the panel members perceived an item as inappropriate, it was deleted. A convenience sample of 14 grade 2 and grade 3 students age 7 to 10 years participated in the pretesting of the Nutrition Knowledge Questionnaire. Parental consent and child assent were secured prior to the pretesting. The students judged the clarity of the instructions and questions using a score of 1 to 3, with 1 as easily understandable, 2 fairly understandable and 3 difficult to understand. If more than half of the children perceived an item as fair or difficult to understand, it was replaced and reevaluated. For internal consistency of the questionnaire, a convenience sample of another set of 14 students with the same selection criteria was gathered to answer the pretest and posttest. Using Stata 13.0, the Kuder-Richardson Formula 20 (KR 20) was computed. The KR 20 was used to measure the relationship of the items in the questionnaire as a group. Acceptable consistency was an alpha level ≥0.7.[15]

Healthy Foodie Nutrition Game Application

Literature search for nutrition games in PubMed was done. The game category was games for health to increase knowledge.[7] The game concept development was guided by the principle of social cognitive theory.[16,17] This was developed in cooperation with students from the Institute of Information and Computer Science of the University of Santo Tomas. Screenshots of the game are found in Appendix B. The authors and game developers conducted meetings every 2 weeks for game development updates and finalization.

The game was composed of 2 parts. Part 1 discussed the 3 basic food groups (go, grow and glow) and the Filipino food plate. Part 2 tackled the traffic light food groups (red, yellow and green) and the food pyramid. Prior to each mini-game, a short discussion on the significance and examples of each food group was given. For game instructions in the mini-game of the basic food groups and traffic light food groups, the player had to collect 5 food articles and/or drinks from the specified category within one minute. Once a food item was clicked, the correct answer was displayed. If the player gets 3 incorrect answers or time runs out, the player had to redo the challenge again. The player can only move on to the next food group if he had accomplished the game successfully. The Eberly Center of Testing Excellence recommended that the quiz master should provide thrice his time to accomplish the mini game, so that one minute was deemed sufficient to answer each mini-game.[18]

For the Filipino food plate, the child had to choose one go food, one grow food and two glow foods (one fruit and one vegetable) and drag these food items to the proper place in the plate. Upon clicking next, the background of food placed in the proper category would be highlighted in green, while those highlighted in red were incorrect answers. The player had to get the correct combination to progress to the next part of the game. For the food pyramid, the child had to choose 3 green light food items, 2 yellow light and one red light. These should be dragged and dropped in the correct category inside the pyramid. Upon clicking next, the background of food placed in the proper category would be highlighted in green, while those highlighted in red were incorrect answers. The player would only be able to finish the game if a correct combination was made. If the student felt that the pace was going too fast, the back button takes the participant a step backward to review previous concepts. The game could be completed in 25 to 40 minutes. Content and face validity was assessed by 3 members composed of one physician, one elementary school teacher and one parent. The clarity of each sentence was assessed with a score of 1 to 3, with 1 as easily understandable, 2 as fairly understandable and 3 as difficult to understand. If 2 or more of the members perceived an item as fair or difficult to understand, it was replaced and reevaluated. Each illustration was graded 1 to 3, with 1 as easy to identify, 2 fairly identifiable and 3 difficult to identify. If two or more of the panel members perceived an illustration to be fair or hard to identify, it was replaced and reevaluated by the panel members. The content was assessed as appropriate

or inappropriate. If 2 or more of the members perceived an item as inappropriate, it was deleted. The Healthy Foodie nutrition game application was pretested to 18 students for content and face validity. The clarity of each sentence was judged with a score of 1 to 3, with 1 as easily understandable, 2 fairly understandable and 3 difficult to understand. If more than half of the children perceived an item as fair or difficult to understand, it was replaced and reevaluated. The illustrations were reviewed. Each illustration was graded 1 to 3, with 1 as easy to identify, 2 fairly identifiable and 3 difficult to identify. If more than half of the children perceived an illustration to be fair or difficult, it was replaced and reevaluated.

Phase 2: Testing for effectiveness of Healthy Foodie

Procedure and intervention

Parental consent and child assent were secured by the process discussed above. Students were grouped by class and subsequently randomized to either control or experimental groups by drawing lots conducted by the school coordinator. A pretest Nutrition Knowledge Questionnaire was administered to all students. This served as baseline knowledge scores of participants from both the control and experimental groups. Thereafter, the experimental group played Healthy Foodie in the school's computer laboratory. Each student was provided with his own computer terminal and personal headset while playing the game. The primary investigator and class teacher supervised the students during the administration of the program. The duration was 30 minutes. Both the control and the experimental groups took the posttest Nutrition Knowledge Questionnaire one week after completion of the pretest Nutrition Knowledge Questionnaire and/or Healthy Foodie Nutrition Game Application. All gathered data were kept safely in an envelope stored inside the office locker of the investigator. Dropouts defined as subjects who did not finish the pretest and posttest Nutrition Knowledge Questionnaires and/or Healthy Foodie Game Application were not included in the study.

Sample size computation using G*Power version 3.1.7 showed that a minimum sample size of 67 was necessary to achieve a power of at least 80% and a medium effect size of 0.35 at a significance level of 0.05 (two-tailed). A total of 360 grade 2 and grade 3 students were included in the study. The total population for both schools was 735, including second and third graders age 7 to 10 years old, two-thirds of whom were female.

Statistical analysis

The difference between ages of the students was compared using the independent T-test. Differences between gender, grade level and school category of students were compared using the Chi-square test. One-way multivariate analysis of variance (MANOVA) was used to compare the pretest scores between the control and the experimental groups. A significant result was a p value <0.05. One-way multivariate analysis of covariance (MANCOVA) was used to compare the mean posttest examination scores between the control and experimental groups. A significant result was a p value <0.05.

Debriefing through verbal feedback from children was noted by asking open-ended questions, such as "What can you say about the game?" and "What did you learn from the game?".

RESULTS

The participants were recruited on October 1, 2018 and December 7, 2018. A total of 735 students were invited to join the study, but only 360 returned completely filled-out parental and child assent forms. There were no dropouts. All the 360 participants finished the posttest.

Phase 1: Instrument Validation

Validation of Nutrition Knowledge Questionnaire

Content and face validity

The final questionnaire was assessed to have easily understandable instructions and questions with appropriate content by all members of the panel of experts. All 14 recruited students deemed the instructions clear and questions easily understandable.

The reliability of the questionnaire was computed and analyzed using the Kuder-Richardson Formula 20. Internal consistency was 0.75 for Part 1 (Food Group Knowledge Questionnaire) and 0.70 for Part 2 (Food Frequency Knowledge Questionnaire). Both Parts 1 and 2 of the Nutrition Knowledge Questionnaire met the minimum reliability coefficient, and it was then used for data collection in Phase 2.

Validation of Healthy Foodie Nutrition Application

Content and face validity

The sentences in the game were assessed as easily understandable while the content was deemed appropriate by all the panel members. The following illustrations were revised to meet the criterion "easy to identify" by the panel members: bread, *pan de sal*, cereal, coconut, chicken breast, banana *cue* and *kamote* (sweet potato) *cue*. The game was administered to 18 students. The clarity of the instructions provided was judged as easily understandable. The illustrations were generally easy to understand. One student deemed the following as fairly understandable: beans, spaghetti, cabbage and apple. Two students believed that the chicken breast illustration was fairly understandable.

Phase 2: Testing for effectiveness of Healthy Foodie

Table 1 lists the demographic profile of the students. The mean age of the control and the experimental groups were 8.07±0.78 and 7.94±0.79 years, respectively, which were not statistically different (t=1.62, p=0.106). The control group was mostly composed of males (52.22%), in contrast to the predominantly female experimental group (56.11%). Comparative analysis showed that these proportions were not statistically different (χ^2=2.50, p=0.114). The control group was equally composed of Grade 2 and Grade 3 respondents, while majority of the experimental group were from Grade 2 (56.67%). These proportions, nonetheless, were not statistically different (χ^2=1.61, p=0.205). The control (78.33%) and experimental (68.33%) groups were composed of students from a private school, analyzed to be statistically higher based on comparative analysis (χ^2=4.60, p=0.03).

Table 1. Demographic profile of respondents according to group assignment

Characteristic	Control (n=180)	Experimental (n=180)	Total (n=360)	Statistic	*p*-value (two-tailed)
Mean age, years (SD[a])	8.07 (0.78)	7.94 (0.79)	8.01 (0.78)	1.62	0.106
Sex (%)				2.50	0.114
Male	94 (52.22)	79 (43.89)	173 (48.06)		
Female	86 (47.78)	101 (56.11)	187 (51.94)		
Grade level (%)				1.61	0.205
Grade 2	90 (50.00)	102 (56.67)	192 (53.33)		
Grade 3	90 (50.00)	78 (43.33)	168 (46.67)		
School category (%)				4.60	0.032
Private	141 (78.33)	123 (68.33)	264 (73.33)		
Public	39 (21.67)	57 (31.67)	96 (26.67)		

[a] SD, standard deviation

Table 2. Between-group comparison[a] of the mean pretest Food Group and Food Frequency Knowledge scores

Pretest Score	Control (n=180)	Experimental (n=180)	F-statistic	*p*-value (two-tailed)
Mean Food Group Knowledge score (SD[b])	9.55 (3.72)	9.08 (3.48)	1.55	0.214
Mean Food Frequency Knowledge score (SD[b])	9.67 (2.79)	9.16 (2.55)	3.28	0.071

[a] Multivariate test: Pillai's Test=0.01, F=2.10, p=0.124
[b] SD, standard deviation

Table 3. Within-group comparisons[a] of the mean pretest and posttest Food Group and Food Frequency Knowledge scores

Test Score	Pretest	Posttest	F-statistic[b]	*p*-value (two-tailed)	Partial η^2
Mean Food Group Knowledge score (SD)					
Control	9.55 (3.72)	8.66 (3.82)	18.19[d]	0.001	0.092
Experimental	9.08 (3.48)	11.42 (3.25)	92.50[d]	0.001	0.341
Mean Food Frequency Knowledge score (SD)					
Control	9.67 (2.79)	9.22 (2.75)	6.25[c]	0.013	0.034
Experimental	9.16 (2.55)	10.55 (2.28)	61.00[d]	0.001	0.254

[a] Multivariate test: Pillai's Test=0.30, F=75.14, p=0.0001
[b] Adjusted for the effects of significant confounders: pretest Food Group Knowledge score for posttest Food Group Knowledge score, and both pretest Food Group Knowledge and Food Frequency Knowledge scores for the posttest Food Group Knowledge score
[c] Significant at 0.05
[d] Significant at 0.01

Table 4. Between-Group comparisons[a] of the mean posttest Food Group and Food Frequency Knowledge scores

	Control Group (n = 180)		Experimental Group (n = 180)			*p*-value	
Test Score	Crude Mean (SD)	Adjusted Mean[b] (SE)	Crude Mean (SD)	Adjusted Mean[b] (SE)	F-Statistic	(two-tailed)	Partial η^2
Posttest Food Group Knowledge Score	8.66 (3.82)	8.51 (0.20)	11.42 (3.25)	11.57 (0.20)	111.84[c]	0.0001	0.239
Posttest Food Frequency Knowledge Score	9.22 (2.75)	9.07 (0.15)	10.55 (2.29)	10.70 (0.15)	56.12[c]	0.0001	0.136

[a] Multivariate test: Pillai's Test=0.30, F=75.14, p=0.0001
[b] Adjusted for the effects of significant confounders: pretest Food Group Knowledge score for posttest Food Group Knowledge score, and both pretest Food Group Knowledge and Food Frequency Knowledge scores for the posttest Food Group Knowledge score
[c] Significant at 0.01

Table 2 shows the comparison of the pretest Food Group and Food Frequency Knowledge scores. The mean Food Group Knowledge scores of the control (9.55±3.72) and the experimental groups (9.08±3.48) were not statistically different (F=1.55, p=0.214). A similar finding was noted with the comparison of the mean pretest Food Frequency scores (F=3.28, p=0.071) of the control (9.67±2.79) and the experimental groups (9.16±2.55).

Table 3 illustrates within-group comparisons between the pretest and posttest scores. For the Food Group Knowledge score of the control group, there was a significant (F=18.19, p=0.001) decline from the pretest (9.55±3.72) to the posttest score (8.66±3.82). This finding was also noted in the comparison of the Food Frequency Knowledge scores, with a statistically significant decrease (F=6.25, p=0.013) from pretest (9.67±2.79) to posttest (9.22±2.75). For the experimental group, the Food Group Knowledge scores statistically increased (F=92.50, p=0.001) from pretest (9.08±3.48) to posttest (11.42±3.25). Moreover, 34.10% of the change in Food Group Knowledge score was attributed to the intervention. There was a statistically significant improvement (F=61.00, p=0.001) in the Food Frequency Knowledge scores from pretest (9.16±2.55) to posttest (10.55±2.28). The computed partial η^2 was 0.254, indicating that 25.40% of the improvement in the score was attributed to the intervention.

The between-group comparison of the posttest Food Group and Food Frequency Knowledge scores is presented in Table 4. The adjusted posttest mean Food Group Knowledge scores was statistically higher (F=111.84, p=0.0001) in the experimental (11.57±0.20) compared to the control group (8.51±0.20), after controlling for significant confounders. The 23.90% difference in scores between the control and the experimental groups was attributed to the intervention. The significant confounder was Pretest Food Group Knowledge Score for Posttest Food Group Knowledge Score.

After adjusting for statistically significant confounders, the adjusted posttest Food Frequency Knowledge scores in the control (9.07±0.15) and in the experimental group (10.70±0.15). were statistically significant (F=56.12, p=0.0001) using MANCOVA. The 13.60% difference between the adjusted mean scores was due to the study intervention. Both Pretest Food Group Knowledge and Food Frequency Knowledge Scores were significant confounders for the Posttest Food Group Knowledge Score.

Feedback

The game received positive verbal feedback from the students. Responses included: "*Marami akong natutunan* (I learned a lot)," "*Madali lang* (Easy)," "*Masaya* (Fun)," "I want to play again," and "Fun and easy."

DISCUSSION

The study had developed and validated culturally–adapted, helpful and innovative educational nutrition tools for second and third grade students, namely the Nutrition Knowledge Questionnaire and the Healthy Foodie nutrition game application.

Nutrition Knowledge Questionnaire

Most validated nutrition questionnaires for children addressed food and nutrition literacy in various aspects, such as nutrition knowledge, dietary patterns, behavior, attitudes, food preparation, cooking skills and food labeling.[19-25] These validated questionnaires were long and contained topics not related to this study's nutrition topics. This study's Nutrition Knowledge Questionnaire addressed nutrition knowledge with special interest to common food taken by Filipino children. It was concise, simple and easily administered. Since the content of the questionnaire encompassed topics in the Healthy Foodie game, the change in nutrition knowledge scores after playing Healthy Foodie can be reliably reflected.

Healthy Foodie Nutrition Game Application

Healthy Foodie was developed for Filipino children, with the clear intention to include foods common to Filipinos. Examples were rice, *pan de sal*, *puto* (rice cake), *kamote* (sweet potato), mango, coconut, *banana cue*, *kamote cue* and fish ball. Food seen in fast food chains, such as burger, fries, pancake and donut were also chosen to be included. Inasmuch as the authors wanted to include more examples, the game screen would appear overcrowded. As such, only 9 examples per food group were chosen.

Sensory immersion pertains to the audiovisual effects of the game that engages the player to be "hooked" to the game.[26,27] Healthy Foodie came with audio properties wherein all the sentences and food items were read out loud and background music was available. Sound volume was also adjustable. This key audio feature made players more immersed in the game.[26]

Behavioral concepts present in a game were the central themes that guided the development of this game. First, knowledge as foundation for change was included in the basic concepts prior to each game play.[11] Second, mastery learning is a key concept in this game. Mastery of the concept was demonstrated by achieving the minimum criterion of collecting 5 correct food items with less than 3 mistakes prior to advancement to the next concept.[11,17] Traditional classroom teaching is effective, but due to limited time and need for individualization, mastery of technique cannot be fully implemented.[17] In this regard, the children played Healthy Foodie at their own computer station and at their own pace to achieve mastery of concepts. Furthermore, the "back" button in the game anticipates the learning pace for players. The option to go back can also be used to master previous concepts presented. Third, video games are expected to be fun and entertaining without sacrificing the educational content. Fun is considered an intrinsic motivator to learn.[28] Similarly, Healthy Foodie was a balance of education and fun as evidenced by the feedback of the students.[11] The feedback provided relevant and critical links to the learning process not only for the children, but also to the authors and game developers.[17,29,30]

Second and third graders were chosen to reinforce previous nutrition topics discussed in grades one and two. Positive reinforcement resulted to increased behavior through presentation of a stimulus leading to operant conditioning. Operant behavior results from exposure to the environment. Healthy Foodie served as a positive reinforcer to the previous nutrition lectures in school.[31,32] The concepts were simple, appealing and easy to understand with the use of game play and colorful illustrations.

Effectiveness of Healthy Foodie

There was a statistically significant difference in the number of students from private and public schools. However, there was no statistically significant difference in the pretest scores of the participants. This showed that school category was not a factor in the difference in scores.

In the control arm, within group analysis showed that nutrition knowledge may decline through time. With reinforcement from Healthy Foodie in the experimental arm, the posttest scores of the students improved.

There was a statistically significant improvement in the posttest scores of the children who played Healthy Foodie. There was no immediate nutrition review prior to the pretest, but the tutorials in the game may have contributed to the significant improvement in the posttest scores of the experimental group.

Similar to Healthy Foodie, other nutrition games developed to promote nutrition education showed a positive association of nutrition games and nutrition knowledge improvement.

Pizza Please was a two-part program consisting of an interactive game board and a questionnaire focused on dietary behavior and nutrition knowledge. The topics included dairy consumption, fruit and vegetable consumption, food guide pyramid knowledge, nutrient-food association knowledge and nutrient-job association knowledge. On top of the intervention, nutrition educators provided curriculum-based modules in between assessments. Pizza Please showed that nutrition programs

improved dietary behavior and increased nutrition knowledge in children.[8] Compared to Healthy Foodie, this game incorporated tutorials conducted in a self-directed mastery learning process with minimal intervention from health educators.

Two nutrition education games, Alien Health and Super Shopper, were compared in another study. Alien Health was an interactive game focused on nutritional food profiles as well as the five macronutrients. Super Shopper was a web-based Flash application focused on the nutritional values of products. The study showed that children playing Alien Health outperformed children playing Super Shopper. Alien Health provided a short-term nutrition knowledge improvement as reflected in the immediate postgame play nutrition test scores, but not in long-term nutrition knowledge as reflected in the two-week follow-up test scores.[9] In our study, an immediate postgame nutrition test was not given. However, a one-week follow-up posttest revealed higher scores in the experimental group. The time of follow-up may have contributed in the difference in outcomes. While the pretest and posttest contained the same questions, a time interval of one to 3 weeks made it unlikely for the children to remember their initial responses to the pretest.[33] The posttest results of the Nutrition Knowledge Questionnaire reflected not only learnings from the game, but also knowledge retention after playing Healthy Foodie.

Nutrition games that increase knowledge are effective, but data on behavior correlation are contradicting. In a Japanese study, the relationship between nutrition knowledge and dietary intake of children was analyzed. A higher knowledge level was significantly associated with higher vegetable intake.[23] On the other hand, some studies showed that increased knowledge alone might not influence subsequent health behaviors.[7,16]

One limitation of this study is the measurement of improvement of nutrition knowledge. A follow-through that gauges real world nutrition choices may be done to assess the effect on nutrition behavior after playing Healthy Foodie. A repeat posttest with a longer follow-up may also be done to assess the long-term nutrition knowledge retention after playing Healthy Foodie. Future studies involving more students from different grade levels and different provinces can be considered. A Filipino translation of Healthy Foodie may also be developed to give children an option to choose a language that they are more accustomed to.

CONCLUSION

The Healthy Foodie nutrition game application, together with Nutrition Knowledge Questionnaire, are validated and effective tools for reinforcement intervention to standard nutrition education of second and third grade children. This co-curricular strategy will positively impact nutrition knowledge of school age children.

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APPENDICES

Appendix A. Pretest and Posttest Nutrition Knowledge Questionnaire

Student ID: _____ Age: _____
Grade Level: _____ Gender: _____

PART 1. Food Group Knowledge Questionnaire

INSTRUCTION. Identify the food group where this food belongs. Check the appropriate box on the right that corresponds to your answer.

Food		Go	Grow	Glow
1). Banana				
2). Rice				
3). Carrot				
4). Milk				
5). Fish				
6). Egg				
7). Bread				
8). Eggplant				
9). Chicken				
10). Apple				
11). Pandesal				
12). Cheese				
13). Beef				
14). Noodles				
15). Tomato				

PART 2. Food Frequency Knowledge Questionnaire

INSTRUCTION. I know that some of these food items are your favorites, but how much can you eat these to stay healthy? Check the appropriate box on the right that corresponds to your answer.

Food		Eat More	Eat Some	Eat A little
1). Ice cream				
2). Mango				
3). Potato chips				
4). Rice				
5). Pancake				
6). Donut				
7). French fries				
8). Tomato				
9). Hamburger				
10). Hotdog				
11). Watermelon				
12). Banana cue				
13). Pizza				
14). Candy				
Drink		**Drink More**	**Drink Some**	**Drink A little**
15) Water				

Appendix B. Screenshots of Healthy Foodie

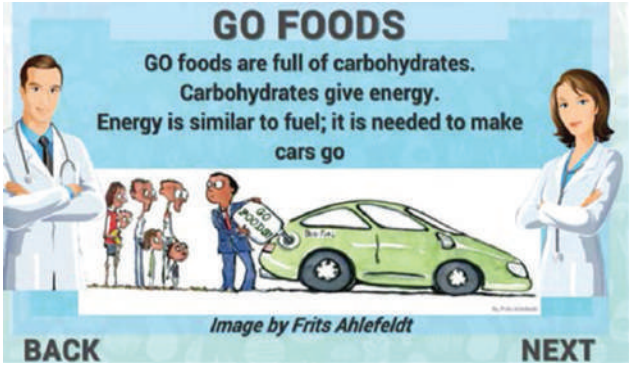

Figure 1. Information regarding Go Foods.

Figure 2. Examples of Glow Foods.

Figure 3. Gameplay of the Filipino Food Plate.

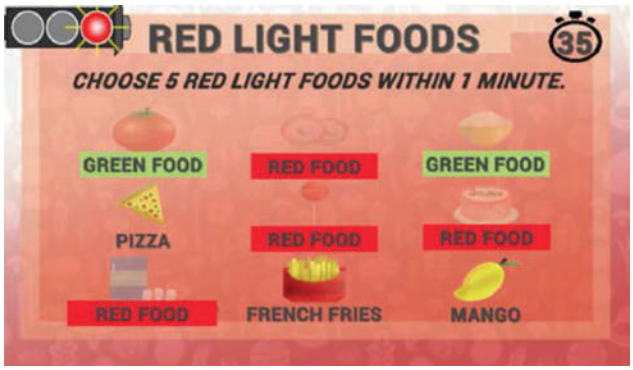

Figure 4. Gameplay of Red Light Foods. After clicking the food, the correct food group classification is displayed.

Figure 5. Gameplay of Food Pyramid. The boxes of food highlighted in green are correct while those in red are incorrect answers.

ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Concurrence of Myasthenia Gravis and Thyroid Disorders: A Retrospective Database Study

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Abstract

Introduction. Both myasthenia gravis (MG) and autoimmune thyroid diseases (AITDs) are autoimmune diseases. Graves'disease (GD) is the most common AITD reported to be associated with MG. Currently, there is limited data on prevalence and clinical features/outcomes of MG in various thyroid diseases in a large database report.

Methodology. A total of 872 patients with MG and 97,251 patients with thyroid disorders had been recorded by the tertiary hospital database. The study period was between 1997 and 2017. Patients with a thyroid disorder and MG were identified by the ICD-10-CM code. Clinical courses of MG accompanied by thyroid disorders were studied.

Results. During the 20-year study period, there were 872 patients with MG and 97,251 patients with thyroid disorders. In the group with thyroid disorders, 28,886 patients (29.70%) had GD, 1,612 patients (1.66%) had Hashimoto's thyroiditis (HT), 13,172 patients (13.54%) had toxic goiter and 53,581 patients (55.10%) had nontoxic goiter. Ninety-seven patients had been diagnosed with both MG and thyroid disorders. Among the four types of thyroid disorders, the rate of MG was highest in HT group (9.92/1,000 HT patients). There were four significant factors among four groups of thyroid disorders including age of onset of thyroid disease (p 0.004), MG classification (p<0.001), MG treatment (p<0.001), and thymic pathology (p 0.034). Among the four groups of thyroid disorders, patients with MG and HT were diagnosed with thyroid disease at the youngest age (27 years) compared with other thyroid diseases. Additionally, the MG patients with HT also had the highest proportion of MG class 4-5 a/b (7 patients, 43.75%), received prednisolone treatment (15 patients, 93.75%), received immunosuppressants (9 patients, 56.25%), received IVIG or PLEX (5 patients, 31.30%), and had thymoma (6 patients, 46.15%).

Conclusion. MG is most prevalent in patients with HT. Patients with both MG and HT had more severe MG status and had higher rate of thymoma.

Key words: autoimmune thyroid diseases, prevalence, treatment

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease that results from the binding of autoantibodies to proteins involved in signaling at the neuromuscular junction (NMJ) causing the failure of neuromuscular transmission. These proteins are called the nicotinic acetylcholine receptors (AChR) or, less frequently, a muscle-specific tyrosine kinase (MuSK) receptor involved in AChR clustering. Much is known about the mechanisms that maintain self-tolerance and modulate anti-AChR Ab synthesis, AChR clustering, and AChR function. As a result, nerve impulses cannot trigger muscle contractions.[1,2] The hallmark of myasthenia gravis is muscle weakness that worsens after use of affected muscles and improves after periods of rest. About two-thirds of patients present with extrinsic ocular muscle weakness that usually progresses to other muscles, resulting in generalized MG. In about 10%, however, symptoms remain limited to the ocular muscle and this condition is termed ocular MG.[3]

The incidence of MG is about 1 to 2 per 100,000 each year while the prevalence is estimated to be as high as 20 to over 50 per 100,000 in the population.[4] The incidence of MG is increasing over time due to either improvements in diagnosis or modern treatments so patients live longer with the disease.[4] The distribution is affected by both gender and age in a bimodal fashion. It is more prevalent

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in women than men in the second and third decades, while in the sixth and seventh decades it affects more men. It is rare in children less than ten years of age.[5] The idea that MG is an autoimmune disease has been applied to other autoimmune disorders of the neuromuscular junction.[6] Patients with MG may have coexisting autoimmune thyroid diseases (AITDs) as well as other autoimmune disorders such as type 1 diabetes mellitus, primary hypogonadism, pernicious anemia, and adrenal insufficiency, known as the polyglandular syndrome.

The thyroid gland is essential for normal human development and maintenance. Rennie described the coexistence of Graves' disease (GD) with MG for the first time in 1908.[7] These coexisting diseases have been reported more frequently afterward.[8] Although the pathogenic link between these two autoimmune diseases remains unclear, an immunological cross-reactivity between the neuromuscular junction and thyroid components was found in overlapping GD and MG.[9] A report found that various thyroid disorders can be seen with MG including hyperthyroidism, hypothyroidism, nontoxic goiter, Hashimoto's thyroiditis and the thyroid antibody-positive euthyroid state.[10] Epidemiological studies showed that thyroid disorders occur in approximately 5–10% of MG patients,[11,12] a fairly low incidence of MG (0.2 %) has been reported in patients with GD. Currently, there are limited data on prevalence and clinical features/outcomes of MG in various thyroid diseases in a large database report.

METHODOLOGY

Population

The data here were used from the ICD-10 diagnostic coding system at Srinagarind Hospital, which is a referral university hospital for the Northeast of Thailand from June 1, 1997 to June 1, 2017. Patients with MG were identified by code G700. Thyroid disorders were divided into diffuse toxic goiter (GD) (code E05.0), toxic nodular/multinodular goiter (codes E05.10 E05.11 E05.20 E05.21), Hashimoto's thyroiditis (HT) (code E06.3), non-functional thyroid nodule/goiter which included simple goiter, nontoxic nodular/multinodular goiter and thyroid cancer (codes E04.9 E04.0; E04.1 E04.2, C73). The inclusion criteria were adult patients with age of 18 years or over and had diagnosis of MG with any thyroid disorders mentioned earlier.

Medical records of eligible patients were reviewed. The studied variables included gender, age, geographic area, employment status, comorbid diseases, age at diagnosis of thyroid disease/MG, clinical course, treatments and thymic pathology. Both neurological and thyroid evaluation in eligible patients were based on data obtained from medical records as follows:

Neurological evaluation

MG was diagnosed by patient clinical characteristics, pharmacological, serological, and electrodiagnostic data. The diagnosis was confirmed by amelioration of muscle weakness during chronic treatment with pyridostigmine. A mediastinal CT or MRI was performed and patients with thymic abnormalities underwent thymectomy. The diagnosis of thymic hyperplasia or thymoma was based on histological findings. The severity of MG was classified using the Osserman criteria and was divided into the following groups:

Class 1: Ocular MG (OMG).
Class 2A: Mild generalized MG (GMG) with no bulbar involvement;
Class 2B: Mild GMG with bulbar involvement.
Class 3A: Moderate GMG with no bulbar involvement;
Class 3B: Moderate GMG with bulbar involvement.
Class 4A: Severe GMG with no bulbar involvement;
Class 4B: Severe GMG with bulbar involvement.
Class 5: Defined by intubation with or without mechanical ventilation, except when employed during routine postoperative management.

The patients were categorized as OMG when the symptoms were restricted to the ocular system for two years or more. Treatment of MG included acetylcholinesterase inhibitors (AChEI), immunosuppressants such as corticosteroids, azathioprine, methotrexate, as well as mycophenolate mofetil (MMF), intravenous immunoglobulin (IVIG) and plasma exchange (PLEX).

Thyroid evaluation

Thyroid dysfunction was evaluated, which included physical examinations, thyroid ultrasonography, and thyroid function tests; free thyroid hormones (free T4 and free T3), TSH. The following tests were also carried out when necessary: anti-thyroglobulin autoantibodies (TgAb), anti-thyroid peroxidase autoantibodies (TPOAb), anti-TSH receptor autoantibodies (TRAb), thyroid scans, and thyroid fine needle aspirations. Thyroid diseases were categorized into four groups as follows: GD, HT, toxic goiter, and non-toxic goiter. Diagnosis of thyroid diseases in this cohort was classified based on primary diagnosis of thyroid diseases prior to thyroidectomy or I-131 therapy.

The diagnosis of GD was based on the presence of hyperthyroidism and/or Graves' ophthalmopathy associated with diffuse goiters and circulating TRAb. All patients with primary hypothyroidism associated with positive TgAb/TPOAb and patients with positive TgAb/TPOAb associated with a firm goiter and a hypoechogenic pattern on ultrasound examination of the gland and/or had lymphocytic infiltration on fine needle aspiration were considered to have HT. Toxic nodular/multinodular goiters have a spectrum of different clinical entities, ranging from a single hyperfunctioning nodule within an enlarged thyroid gland, to multiple hyperfunctioning areas scattered throughout the gland barely distinguishable from nonfunctioning nodules and extranodular parenchyma. Nonfunctioning thyroid nodules or non-toxic goiters were diagnosed in patients with a nodule or goiter associated with normal levels of thyroid hormones including thyroid cancer.

Statistical analysis

The frequency rates per 1,000 population of MG in each thyroid disorder were calculated using incident cases of MG with thyroid disorders as the numerator and incident case of each thyroid disorder as the denominator and frequency rate of thyroid disorders in MG was calculated using the same numerator but the incident case of MG as

the denominator. Confidence interval (CI) estimates were based on the Poisson distribution.

MG-related clinical factors were studied and categorized by various types of thyroid disorders. Data were presented as numbers (percentage) or mean (SD) in each type of thyroid disorders. Among the four types of thyroid disorders, differences of studied variables were compared by Fisher Exact test or Krukal-Wallis test for proportions or numerical variables, respectively. Both statistical tests were used due to small sample size or non-normally distributed data for comparing more than two groups. Statistical analyses were performed by the SPSS software package, version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Frequency

During the 20-year study period, there were 872 MG patients and 97,251 patients with thyroid disorders. Female sex was predominant in both diseases (613/872 or 70.30% in MG and 76,840/97,251 or 79.01% in thyroid disorders). In the group with thyroid disorders, 28,886 patients (29.70%) had GD, 1,612 patients (1.66%) had HT, 13,172 patients (13.54%) had toxic goiter and 53,581 patients (55.10%) had nontoxic goiters. 97 patients had both MG and thyroid disorders; 86 patients (88.66%) were female giving a female: male ratio of 7.8:1. Among the four types of thyroid disorders, the highest number of patient with MG was found in GD (52/97 or 53.61%), but the rate of MG in each thyroid disorder was highest in HT group (9.92/1,000 HT patients) as shown in Table 1.

Clinical characteristics

Table 2 summarizes MG clinical characteristics by various thyroid disorders. There were four significant factors among four groups of thyroid disorders including age of onset of thyroid disease (p 0.004), MG classification (p<0.001), MG treatment (p<0.001), and thymic pathology (p 0.034). Among the four groups of thyroid disorders, MG patients with HT had been diagnosed with thyroid disease at the youngest age (27 years) compared with other thyroid diseases. Additionally, the MG patients with HT also had highest proportions of MG class 4-5 a/b (7 patients, 43.75%), received prednisolone treatment (15 patients, 93.75%), received immunosuppressants (9 patients, 56.25%), received IVIG or PLEX (5 patients, 31.30%), and had thymoma (6 patients, 46.15%). Out of 54 patients who underwent thymectomy, HT group had the highest rate of thymectomy (13/16 patients, 81.25%).

DISCUSSION

MG is an autoimmune neuromuscular disorder due to a defective transmission of the nerve impulse to muscles, causing muscle weakness and abnormal fatigability. The coexistence of other autoimmune diseases in MG is well recognized,[7,10,13,14] including AITD[7,12,13,15-20] which is

Table 1. Frequency of myasthenia gravis detected in 97251 cases of thyroid disorders

Thyroid types	Number	Number of MG	Rate / 1,000	95% confidence interval
Graves' disease	28886	52	1.80018	1.37% to 2.36%
Hashimoto's thyroiditis	1612	16	9.9255583	6.09% to 16.16%
Toxic goiter	13172	12	0.9110234	0.52% to 1.60%
Non-toxic goiter	53581	17	0.3172766	0.19% to 0.51%
Total thyroid disorders	97251	97	0.997419	1.72% to 2.56%

Table 2. Clinical characteristics of myasthenia gravis (MG) patients stratified by coexistent thyroid diseases

	Graves' disease (n=52)	Hashimoto's thyroiditis (n=16)	Toxic goiter (n=12)	Non-toxic goiter (n=17)	*p*-values
Sex (female)	46 (88.46)	14 (87.5)	11 (91.67)	15 (88.24)	0.987
Age at MG diagnosis (Mean±SD,years)	33±11	29±10	34±9	40±14	0.063
Age at thyroid disorder diagnosis (Mean±SD,years)	32±12	27±7	41±14	48±9	0.004
MG classification					<0.001
1	21 (40.38)	2 (12.50)	3 (25.00)	4 (23.53)	
2a/2b	21 (40.38)	1 (6.25)	1 (8.33)	4 (23.53)	
3a/3b	7 (13.46)	6 (37.50)	6 (50.00)	8 (47.06)	
4-5a/b	3 (5.77)	7 (43.75)	2 (16.67)	1 (5.88)	
Treatment					<0.001
AChEI	52 (100)	16 (100)	12 (100)	17 (100)	
Prednisolone	39 (75.00)	15 (93.75)	9 (75.00)	15 (88.20)	
Immunosuppressants	5 (9.61)	9 (56.25)	3 (25.00)	2 (11.76)	
IVIG/PLEX	1 (1.92)	5 (31.30)	1 (8.33)	0 (0)	
Thymectomy					0.118
Yes	28 (53.85)	13 (81.25)	5 (41.67)	8 (47.06)	
No	24 (46.15)	3 (18.75)	7 (58.33)	9 (52.94)	
Thymic pathology					0.034
Normal	3 (10.71)	0 (0)	1 (20)	2 (25)	
Hyperplasia	23 (82.14)	7 (53.85)	4 (80)	5 (62.50)	
Thymoma	2 (7.24)	6 (46.15)	0 (0)	1 (12.5)	

Note: Data presented as number (percentage) unless indicated otherwise; Osserman's classes: Class 1, ocular MG; Class 2A, mild generalized MG with no bulbar involvement; class 2B, generalized MG with bulbar involvement; Class 3, moderate generalized MG; Class 4, severe generalized MG; Class 5, defined by intubation with or without mechanical ventilation, except when employed during routine postoperative management; MG, myasthenia gravis; AChEI, acetylcholinesterase inhibitors; IVIG, intravenous immunoglobulin; PLEX, plasma exchange; azathioprine, methotrexate and mycophenolate mofetil are second-line immunosuppressants used alone or in combination with prednisolone; percentages are given in parentheses.

an endocrine disease characterized by the development of autoimmunity against thyroid antigens. The two main AITDs are Graves' disease (GD) and Hashimoto's thyroiditis (HT) which are the most common diseases coexisting with MG, with a frequency of 7% and 3%.[17] In the present study, the rate of MG patients with thyroid disorders were 0.99/1,000 which was comparable with the general population (0.01%).[4,21] The rate of MG was higher in those with AITD (1.80 and 9.92/1,000 in GD and HT, respectively). Unlike the previous studies, we found that the rate of MG in HT was higher than GD (Table 1). Not surprising, female sex accounted for almost 90% of patients with MG in all types of thyroid diseases (Table 2).[11,12] Note that MG coexisting with HT also had younger age at diagnosis of HT than other groups of thyroid disorders.

We also found that MG coexisting with HT was quite severe, required more aggressive treatments, and was more related with thymoma (Table 2) than other types of thyroid disorders including GD. Over 80% of MG patients have thymic abnormalities, including hyperplasia and thymoma.[22,23] Several previous studies have analyzed the incidence of thymoma in MG with AITDs, but the estimates vary widely across studies because of differences in study populations and diagnostic criteria. A Japanese study demonstrated a greater frequency of thymic hyperplasia in MG patients with AITDs,[24] but not in the Chinese or Italian study.[8,25] Thymic status was available for about 56% (54/97) of patients in this current study; mostly in GD group. The study showed a greater number with thymic hyperplasia in MG patients with GD and a greater number of thymomas in MG patients with HT. Since thymectomy in MG patients usually tends to be performed in those patients with thymoma or a more severe status, this would result in selection bias. The reason why MG with HT in this study was more severe and more common than the GD group may be due to different circulating thyroid antibodies in HT and GD.[20,26-28] The TPOAb and TgAb are primary thyroid antibodies in HT, while the TRAb is primarily seen in GD.[28] The differences in thyroid antibodies may lead to different clinical manifestation of MG. GD with MG had more patients with ocular MG (40.38%) than other thyroid disorders (Table 2).

From the results of this study, there are two clinical implications. First, patients with ocular MG or mild generalized MG have high prevalence of Graves' diseases (40.38%). For those with class 3-5 MG or moderate to severe MG, the prevalence of HT or toxic goiter was between 37.50%-50% (Table 2). These patients should be evaluated for thyroid function tests, thyroid antibodies or thyroid scan when appropriate. Second, MG patients with HT may need more aggressive treatment such as immunosuppressive treatment (56.25%) or prednisolone (93.75%) and relate to thymoma (46.15%).

The main limitation of this study is that it is retrospective and not a case–control study. The data were acquired from existing medical records such as summary charts of admitted patients and OPD cards of outpatients. Therefore, some specific details of each patient such as disease severity, treatment outcome or patient compliance might not have been available for analysis. Secondly, the small sample size of the cases studied remains an important factor limiting the interpretation of the results, although attempts were made to minimize these limitations by reviewing all cases in the study period. Finally, HT in this study was diagnosed only in hypothyroidism which resulted in markedly low prevalence than the GD group.

CONCLUSION

MG is most prevalent in patients with HT. Patients with both MG and HT had more severe MG status and had higher rate of thymoma.

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ORIGINAL ARTICLE

Comparison of the Efficacy of Levothyroxine Suppression Dose Computed Based on Actual Body Weight vs. Lean Body Mass among Differentiated Thyroid Cancer Patients: A Randomized Controlled Trial

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Abstract

Background. The dose of levothyroxine (LT4) after total thyroidectomy is usually computed based on actual body weight. However, metabolism through deiodination of thyroid hormones usually occur in the lean body compartment. An optimal dose to reduce delay in achieving target levels is essential to improve quality of life, reduce risk factors and cost.

Objectives. Comparison of the efficacy of two methods of computation for the initial levothyroxine dose in patients with differentiated thyroid cancer based on actual body weight vs. lean body mass in achieving thyroid-stimulating hormone (TSH) goals.

Methodology. Randomized, single-center, 12-week open label controlled trial among adult patients with differentiated thyroid cancer post total thyroidectomy who underwent radioactive therapy at St. Luke's Medical Center Quezon City from July-December 2018. Participants were divided into 2 groups - Actual Body Weight (ABW) and Lean Body Mass (LBM). Levothyroxine dose was computed based on ABW vs. LBM and TSH determined at 6th and 12th weeks after.

Results. 52 participants (ABW n=26; LBM n=26) were included. ABW group had significantly higher mean LT4 dosage (2.2 mcg/kg) compared to the LBM group (1.4 mcg/kg) (*p-value*<0.001). ABW group had lower TSH levels at 6th week (5.7 uIU/mL) than LBM group (18.4 uIU/mL) but the difference was not significant. (*p-value*=0.064). A significantly lower TSH level was observed at week 12 in the ABW group (1.6 uIU/mL) compared to the LBM group (3.8 uIU/mL) (*p-value*=0.010). However, both methods were not associated with achievement of TSH goal at 6th and 12th week (*p-value*=0.512 and 0.780, respectively).

Conclusion. Among patients with differentiated thyroid cancer who underwent 1st time RAI therapy, ABW method of computation for LT4 dosage is better compared to the LBM method due to the lower TSH trend seen at 6th week and statistically significantly lower mean TSH at week 12, although, both method of computations did not achieve target TSH levels at the 6th nor 12th week.

Key words: lean body mass, differentiated thyroid cancer, TSH suppression

INTRODUCTION

Surgical removal of the thyroid gland requires replacement with exogenous thyroid hormone medication. Patients with differentiated thyroid cancer should be treated with thyroid hormone after total thyroidectomy. The purpose of the replacement is to correct surgery-induced hypothyroidism and to suppress the pituitary secretion of TSH which retards the growth and spread of the neoplastic disease.[1] This concept of tumor growth accelerated by TSH is well established in the clinical and experimental literature.[2]

According to surgical literature, the time to achieve euthyroidism following thyroidectomy ranges from 2 weeks to 2.5 years, with a median of 3.6 months and is dependent on the magnitude of change in dose from baseline.[3]

Based on body weight, hypothyroid patients with minimal endogenous thyroid function require LT4 doses of 1.6 to 1.8 mcg/kg of ABW while LT4 doses in thyroid cancer patients requiring TSH suppression are generally higher ranging from 2.1 to 2.7 mcg/kg of ABW.[4] Evidence shows that ABW, TSH goal, ideal body weight, etiology of hypothyroidism, degree of serum TSH elevation, pregnancy, and age can influence dose requirement.[4] While some studies regarding primary hypothyroidism have shown that the LT4 requirement is more closely related to LBM than ABW, the drawback is that accurate assessment of LBM requires complex techniques and instrumentation such as body impedance measurements and dual energy X-ray absorptiometry (DEXA) which are not routinely available in clinical practice, and may be tedious and not cost-effective.[5] Still, for newly diagnosed patients with hypothyroidism, it is difficult to predict the final dose each

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patient will require. Often, in other countries, the dose is started empirically and adjustments are made based on the TSH results.

Many reviews report a period of 4 to 6 months before normalization of TSH levels is attained.[4] In line with this, as the number of patients requiring thyroid hormone replacement increases, a more rapid normalization could be beneficial to this group in reducing cardiac risk factors, improvement of quality of life, reducing overall cost, and limiting the difficulty of repeated testing, which compels multiple visits to the hospital for repeated TSH testing.

A few studies[1-4] have reported that LBM and body mass index (BMI) are better predictors of LT4 dose than ABW in achieving TSH goals among hypothyroid patients, but their results have been conflicting. Although the guidelines recommended a range for starting LT4 replacement in thyroid cancer, it did not recommend what dose to start in low, intermediate, or high risk differentiated thyroid cancer. In this study, we aim to compare the efficacy of two different methods of computation for the initial levothyroxine dose in patients diagnosed with differentiated thyroid cancer based on ABW vs. LBM in achieving target TSH suppression goals.

METHODOLOGY

Study design

We performed a randomized, 12-week open label controlled trial among adult patients diagnosed with differentiated thyroid cancer who underwent first time Radioactive (RAI) therapy at St. Luke's Medical Center, Quezon City from July- December 2018.

Inclusion criteria

Adult (18 to 65 years old) patients diagnosed with differentiated thyroid cancer who underwent 1st time RAI therapy after total thyroidectomy were included in the study.

Exclusion criteria

Patients taking medications known to interfere with levothyroxine absorption or alter levothyroxine binding proteins (e.g., estrogen and testosterone, iodine, propranolol, amiodarone, lithium, dopamine agonists or antagonists, somatostatin analogues, steroids, phenytoin, carbamazepine, sertraline, rifampin, bile acid sequestrants, antacids, kayexalate, cholestyramine, colestipol, and raloxifene), pregnant or lactating patients, patients with chronic, serious diseases such as cardiac, pulmonary, gastro-intestinal, renal, and pituitary diseases were excluded in the study.

Study procedure

Adult patients diagnosed with differentiated thyroid cancer admitted for first dose of RAI therapy at the St. Luke's Medical Center Quezon City Social Service as well as those seen privately by participating endocrinologists were recruited in the study. Informed consent was obtained prior to enrollment. A total of 62 patients met the criteria and were included in this study. Five participants were excluded due to poor compliance and 5 participants were lost to follow up. The remaining 52 participants were included in the study and were randomized to ABW and LBM groups via a web based generated random numbers assigned by the primary investigator. Risk stratification for disease recurrence and or persistence was done based on the 2015 ATA Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thirteen patients were stratified under intermediate risk and 39 patients were classified low risk. Baseline demographics which included age, weight and height, BMI, medications taken, year diagnosed with thyroid cancer, date of surgery and current medical conditions were obtained from the participants. Weight and height were taken upon admission using calibrated weighing scale at the nurses' station. Standard protocol in measuring height and weight was followed. LBM was computed based on validated anthropometric prediction equations for estimation of lean body mass in Indian men and women[6] as follows:

For Men: LBM= -15.605 – (0.032 x A) + (0.192 x H) + (0.502 x W)
For Women: LBM=-13.034–(0.018xA)+(0.165xH)+(0.409xW)
(where A is age in years, W is body weight in kg and H is body height in cm)

Dose of levothyroxine was computed based on the formula:
Actual Body Weight: Levothyroxine dose = ABW in kg x 2.2
Lean Body Weight: Levothyroxine dose = LBM in kg x 2.2

The participants were instructed to take LT4 on an empty stomach, to wait one hour prior to eating, to separate thyroid hormone from other medications by four hours and to take LT4 if possible, about the same time every day. The participants were called every week to remind them about compliance. All participants were prescribed with the same name brand thyroid hormone and were maintained on the same LT4 preparation. The computed dose of LT4 was then rounded off to the nearest available preparation (25 mcg, 50 mcg, 100 mcg, 150 mcg).

Participants in both groups were asked to follow up with their attending physician at 6th and 12th weeks wherein TSH values were obtained (2 determinations). Among participants who did not achieve TSH suppression goals at the initial determination, a repeat TSH was obtained after 6 weeks and LT4 dose was adjusted with increments or decrements of 25 mcg.

The primary outcome was mean TSH levels between ABW and LBM groups at 6th and 12th weeks post RAI while the secondary outcome was achievement of TSH suppression goal defined as proportion of patients achieving adequate suppression (TSH of 0.5 to 2 uIU/mL for low risk and TSH 0.1 to 0.5 uIU/mL for Intermediate Risk) at 6th and 12th weeks post RAI.

Sample size was calculated based on the comparison between mean TSH level 6 weeks after treatment between patients given LT4 calculated using ABW versus LBM. Assuming that mean TSH level for dose given LT4 using ABW is 2.25±0.91 SD, and those given LT4 using LBM, 3.27±1.097,[7] with an alpha error of 5 percent power of 95% and a two tailed alternative hypothesis, sample size required was 26 per group or 52 per 2 groups.

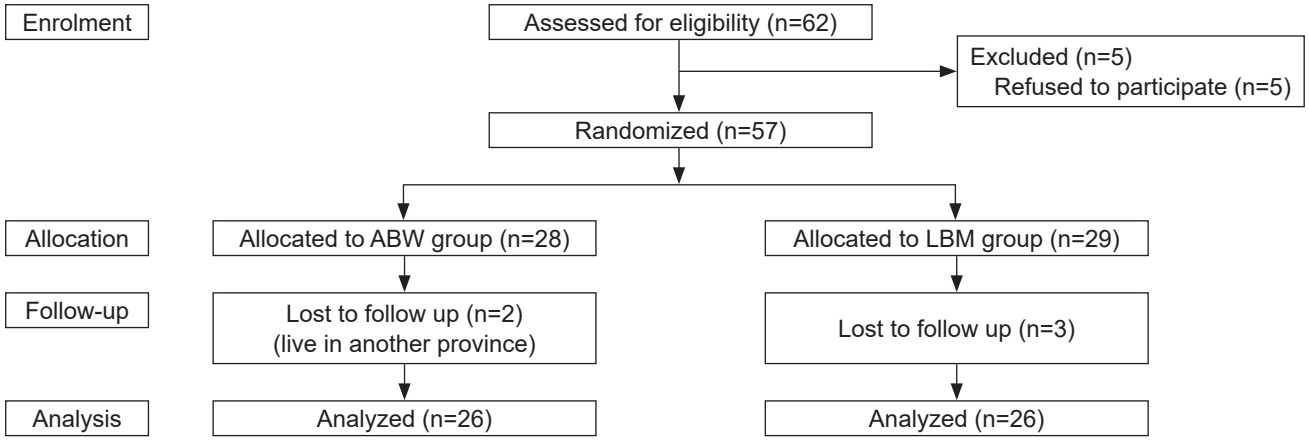

Figure 1. Study participants: Enrollment, allocation, follow-up and analysis.

Data analysis

Descriptive analysis of the demographic and clinical profile of patients with differentiated thyroid cancer was done. Continuous variables were described using mean and standard deviation. Categorical variables were described using frequency and percentage. Wilcoxon rank-sum test was used to compare non-normal continuous variables (age, BMI, lean body mass, LT4 dose, TSH levels) between ABW and LBM groups. Chi-square test was done to compare categorical variables (sex and achievement of TSH targets). The association between method of calculation and TSH levels during 6th and 12th weeks was assessed using simple linear regression. The odds ratio and the corresponding 95% confidence interval for the achievement of the suppression goal was also calculated using simple logistic regression. A p-value of less than 0.05 is statistically significant. STATA 14 SE version was used in all statistical analysis.

Ethical considerations

This study was conducted in accordance with the ethical principles (Declaration of Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee) of the Philippines. The clinical protocol and all relevant documents was reviewed and approved by the St. Luke's Medical Center Quezon City Institutional Ethics Review Committee (IERC). Patient confidentiality was respected by ensuring anonymity of patient.

Patient information and records of the procedure were kept strictly confidential by the primary investigator. The source documents were coded and did not contain identifying information in order to ensure confidentiality.

The source documents are kept by the primary investigator in a secure location in the research library of the section and after 5 years of the study, hard copy of the data will be shredded.

Written documentation of informed consent was provided during recruitment of patients by the primary investigator prior to obtaining data. Participation in the study was purely voluntary and without financial compensation. Recruitment of the participants was conducted once admitted for 1st dose of RAI after thyroidectomy by the primary investigator. Informed consent with explanation of the risks and benefits as well as answering of other questions or concerns was done by the primary investigator in the respective rooms prior to RAI treatment.

RESULTS

A total of 52 participants were included in the study (Figure 1). Table 1 describes the baseline characteristics of the participants included in this study. The baseline characteristics between the two groups were similar. The median age of the participants in the ABW group (48.0) did not differ with those in the LBM group (48.0). Majority of participants were female (n=49). The median BMI and LBM of the participants in the ABW group (26.0 kg/m^2 for BMI and 38.6 kg for LBM) did not differ with those in the LBM group (26.4 kg/m^2 for BMI and 39.1 kg for LBM) (Table 1).

Table 1. Baseline characteristics of the study population

Characteristics	ABW (n =26)	LBM (n=26)	*p-value*
Age (years)*	47.6±9.5 (48.0)	45.4±11.0 (48.0)	0.420
Sex			
Male	3 (11.5)	0 (0.0)	0.235
Female	23 (88.5)	26 (100.0)	
BMI (kg/m^2)*	25.5±3.7 (26.0)	27.6±5.4 (26.4)	0.207
Underweight	1 (3.8)	0 (0.0)	0.761
Normal	6 (23.1)	5 (19.2)	
At risk for obesity	3 (11.5)	4 (15.4)	
Obese I	13 (50.0)	11 (42.3)	
Obese II	3 (11.5)	6 (23.1)	
Lean Body Mass*	39.7±7.3 (38.6)	39.9±4.7 (39.1)	0.522

Participants in the ABW group had significantly higher LT4 dosage (2.2 mcg/kg) compared to the LBM group (1.4 mcg/kg) (*p-value*<0.001) (Table 2). Participants in the ABW group had lower TSH levels at 6th week (5.7 uIU/mL) compared to the LBM group (18.4 uIU/mL) but this difference was not significant (*p-value*=0.064). A significantly lower TSH level was observed at 12th week in the ABW group (1.6 uIU/mL) compared to the LBM group (3.8 uIU/mL) (*p-value*= 0.010) (Table 2).

Participants were divided based on risk stratification as low or intermediate risk for recurrence and or persistence of disease. Among the 52 participants, 25% were intermediate risk and 75% were categorized low risk.

Table 2. Comparison of LT4 dosage and TSH levels between the two study groups

	ABW (n =26) Mean±SD (median)	LBM (n=26) Mean±SD (median)	*p-value*
LT4 dosage (mcg/kg)	2.2±0.1 (2.2)	1.4±0.1 (1.4)	<0.001
TSH 6th week (uIU/mL)	5.7±9.3 (1.4)	18.4±28.5 (4.5)	0.064
TSH 12th week (uIU/mL)	1.6±2.5 (0.4)	3.8±5.5 (2.2)	0.010

Table 3 shows the proportion of participants who achieved TSH suppression goal at 6th and 12th week. Nineteen percent of the participants (5 Low Risk, 0 Intermediate Risk) from ABW group reached TSH target at 6th week while 26.9% (5 Low risk, 2 Intermediate Risk) from LBM group achieved TSH suppression goal. Forty-six percent (10 Low risk, 2 Intermediate risk) from ABW group and 50% (10 Low risk, 3 Intermediate risk) from the LBM group achieved TSH target at 12th week (*p-value*= 0.781).

Table 3. Comparison of participants who reached TSH target at 6th and 12th weeks

	ABW (n=26)	LBM (n=26)	*p-value*
6th week	5 (19.2)	7 (26.9)	0.510
12th week	12 (46.2)	13 (50.0)	0.781

Table 4 shows the result of linear regression to determine the association between method of computation for LT4 dosage and the TSH levels at 6th week (β= -0.48, 95% CI= - 1.60 to 0.63, *p-value*=0.382 for ABW and β= -0.17, 95% CI= - 0.38 to 0.03, *p-value*=0.088 for LBM) and 12th week (β= 1.03, 95% CI= - 3.77 to 5.82, *p-value*=0.659 for ABW and β= -0.71, 95% CI= - 1.76 to 0.33, *p-value*=0.171 for LBM).

Table 4. Association of LT4 dosage computed based on lean body mass and actual body weight with TSH level at 6th and 12th weeks

	Unadjusted β-coefficient	95% CI	*p-value*
6th week			
ABW	-0.48	-1.60 to 0.63	0.382
LBM	-0.17	-0.38 to 0.03	0.088
12th week			
ABW	1.03	-3.77 to 5.82	0.659
LBM	-0.71	-1.76 to 0.33	0.171

Table 5 shows the result of logistic regression to determine the association between method of computation for LT4 dosage and the achievement of TSH suppression goal at 6th and 12th weeks; (OR=0.65, 95% CI=0.17 to 2.38, *p-value*=0.512 and OR=0.86, 95% CI=0.29 to 2.54, *p-value*=0.780, respectively).

Table 5. Association of lean body mass versus actual body weight computation with achievement of TSH suppression goal at 6th and 12th weeks

	Unadjusted Odds Ratio	95% CI	*p-value*
6th week			
ABW:LBM	0.65	0.17 to 2.38	0.512
12th week			
ABW:LBM	0.86	0.29 to 2.54	0.781

DISCUSSION

Different studies[8,9] have suggested that LBM has been shown to be superior to other measures of body size for dosage of many drugs.[8,9] LBM equals the total weight of a person's bone and muscles minus their fat weight.[10] Pharmacokinetic parameters are mostly dependent on LBM and most metabolic processes occur within this body compartment.

Thyroid hormones are metabolized by different pathways (glucuronidation, sulfation and deiodination). Type 2 deiodinase enzyme which converts T4 to T3, has been detected in skeletal muscle, making this tissue an important site for T4 metabolism and degradation.[8] Due to the importance of deiodination in the metabolism of thyroid hormones, studies have shown that LBM appears as the best correlate of LT4 daily requirements while fat mass has little or no effect.[8] The observation of this study suggests that T4 metabolism mainly occurs within the lean compartment.[8]

To further understand the effect that body composition may exert on LT4, we studied a group of hypothyroid patients who underwent total thyroidectomy, received RAI ablation due to thyroid cancer and was placed on TSH suppressive doses. These patients were admitted for isolation and received RAI therapy at least 6 weeks after total thyroidectomy with RAI dose ranging from 50 to 150 mci. None of them were given recombinant TSH. The advantage of studying these group of patients[8] were the following: no functioning thyroid tissue remnants, narrow TSH goals, and good compliance to drug prescriptions which is usually obtained for patients with cancer under strict follow up.

In this study, LBM was computed based on validated anthropometric prediction equations for estimation of LBM in Indian men and women[6] in contrast to a few studies[7-9] where LBM was measured by dual energy X-ray absorptiometry (DEXA). The use of this prediction equation was simple, reproducible, noninvasive, and inexpensive compared to the estimation of LBM by MRI or DEXA. The mean differences between the LBM measured by DEXA and prediction equation based on age, height, and weight in the case of men and women were ~0.28 kg and ~0.02 kg, respectively with a standard error of estimate of 1.92 kg.[6]

Among patients diagnosed with thyroid cancer, it is well established in literature that TSH levels must be suppressed to prevent recurrence or persistence of cancer. According to the 2014 ATA Guidelines for the Treatment of Hypothyroidism, ABW, TSH goal, ideal body weight, etiology of hypothyroidism, degree of serum TSH elevation, pregnancy, and age are factors that can influence dose requirement in patients with hypothyroidism.[4] The current standard of care in the local setting, based on these guidelines, is to compute the initial LT4 dose based on ABW. In hypothyroid patients with minimal endogenous thyroid function, LT4 dose is computed at 1.6 to 1.8 mcg/kg ABW per day while in patients with thyroid cancer for suppression, the estimated doses are higher computed at 2 to 2.7 mcg/kg ABW per day.[4] Similar to the study of Olubowale and Chadwick,[11] since the participants were all differentiated thyroid cancer patients, we computed both ABW and LBM at 2.2 mcg/kg/day.

Our study revealed that the final LT4 dose was higher in the ABW group than in the LBM group likely because of the higher ABW than the computed LBM. LBM is made of body cell mass and the non-fatty intercellular connective tissue which would account for the significant difference in weight. From the analysis, we found that computation based on ABW required a mean LT4 dose of 2.2 mcg/kg/day compared with the LBM based computation which required a lesser dose of 1.4 mcg/kg/day. With the anthropometric equation, the LT4 dose of LBM group was nearly 30 kg BW less than that of the ABW group. Hence, there was nearly one third less dose of LT4 in the LBM group.

Between the two groups, ABW was better than LBM in lowering the TSH near target levels. The TSH level of ABW at 6th week was 5.7 uIU/mL compared to the LBM group 18.4 uIU/mL (*p-value*=0.064) and this trend was consistent with the significant lower TSH level observed at 12th week in the ABW group (1.6 uIU/mL) compared to the LBM group (3.8 uIU/mL) (*p-value*= 0.010) (Table 2). This finding was similar to the study done by Sukumar et al.,[7] wherein mean TSH after 6 months revealed a lower TSH value seen using ABW than LBM (2.25 uIU/L vs 3.27 uIU/L). In their study, they reported an increased requirement of LT4 with increasing weight as reported in literature.[11] In addition, mean per kg body weight requirement of LT4 was higher in Asians compared to their western counterparts.

In this study, majority of the participants did not achieve TSH suppression goal by 6th and 12th weeks (Table 3). This is likely since according to literature, normalization of TSH following thyroidectomy can range from 4 to 6 months and dependent on the magnitude of change in dose from baseline.[3]

Our study results emphasize that the initial LT4 dose is more important in the achievement of desired TSH in the first weeks post RAI, before the first follow up and titration. In addition, statistical analysis suggests that LT4 dosage computed based on ABW or LBM was not significantly associated with TSH levels at 6th and 12th weeks. Furthermore, the odds of achieving TSH suppression goals at 6th and 12th weeks in patients who underwent total thyroidectomy and RAI ablation for differentiated thyroid cancer, were not significantly different between LT4 dosage computed using ABW and LBM (*p-value* 0.512 and 0.781, respectively) (Table 5). Hence, there is no significant difference between the two groups in terms of the effectiveness in achieving TSH suppression goal. This finding was in agreement to a previous study[11] which showed that estimates of LBM based on routine anthropometric measurements were no better in predicting LT4 requirement in achieving TSH goals after total thyroidectomy than body weight. Moreover, another study even states that although total daily requirements of LT4 are related to LBM, there are unexplained differences such as ethnicity[9] which occur among individuals of the same age and body size even in the absence of functioning thyroid tissue.

CONCLUSION AND RECOMMENDATION

Among patients with differentiated thyroid cancer who underwent 1st time RAI therapy, ABW method of computation for LT4 dosage is better than LBM method due to the lower TSH trend seen at 6th week and statistically significantly lower mean TSH at 12th week, although, both method of computations did not achieve target TSH levels at 6th nor 12th week.

Since achievement of TSH target is not yet expected at 6th nor 12th week, we recommend a longer study duration to monitor TSH levels at 12 to 24 months after RAI ablation therapy with more patients of different weight categories and different target levels.

Limitations

A number of factors limited this analysis. For practicability, simplicity, convenience and desire to avoid cost, we employed a validated anthropometric prediction equation for estimation of LBM similar to the body composition of the study population which has a standard error of estimate of 1.92 kg. Another limitation of this study was that baseline TSH prior to starting LT4 dosage was not documented. Although the participants were called every week to remind them about compliance and the same name brand of LT4 was prescribed to the participants, no pill count was done to confirm that they indeed took the medication with the same brand. Additionally, majority of thyroidectomy patients in our institution were prescribed with calcium supplements raising the concern regarding interference with LT4 absorption. Although participants have been educated to take them separately, compliance cannot be proven. Still, another limitation is the low achieved power of the logistic regression analysis computed at 14.4%.

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All authors certified fulfillment of ICMJE authorship criteria.

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ORIGINAL ARTICLE

Insulin Resistance and β-Cell Function of Lean versus Overweight or Obese Filipino Patients with Newly Diagnosed Type 2 Diabetes Mellitus*

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Abstract

Objectives. To compare the level of insulin resistance and β-cell function between lean and overweight/obese Filipino patients with newly diagnosed type 2 diabetes mellitus (T2DM).

Methodology. This was a cross-sectional analytical study including newly diagnosed T2DM Filipino patients from St. Luke's Medical Center - Quezon City. The patients were classified as either lean or overweight/obese. Age, sex, smoking history, anthropometric measures and blood pressure were obtained. Insulin resistance and β-cell function were determined using the homeostasis model assessment (HOMA). The original model (HOMA1) and the updated model (HOMA2) were used.

Results. A total of 80 subjects were included. There were 40 subjects in each group. The overweight/obese subjects had significantly higher mean insulin resistance (HOMA1-IR 9.8±11.7, HOMA2-IR 3.0±2.0) compared to the lean group (HOMA1-IR 2.9±1.5, HOMA2-IR 1.3±0.5). This was consistent in both HOMA1 and HOMA2 (*p-values*=0.001 and <0.001, respectively). The mean β-cell function of the overweight/obese patients was significantly higher than the lean subjects when using HOMA1 (lean=57.8±35.5, overweight/obese=93.6±66.4, *p-value*=0.003), but not in HOMA2 (lean=57.6±30.5, overweight/obese=74.8±45.7, *p-value*=0.051). Overweight/obesity increased HOMA1-IR by 4.0 and HOMA1-B by 46.1 (*p-values*= 0.002 and <0.001, respectively). Through the use of HOMA2, overweight/obesity increased HOMA2-IR by 1.4 and HOMA2-B by 29.1 (*p-values*<0.001). Being overweight/obese was also associated with significantly higher odds for developing greater insulin resistance (HOMA1-IR adjOR = 5.6, 95%CI= 1.7-19.2, *p-value*=0.005; HOMA2-IR adjOR=10.9, 95%CI=3.4-34.9, *p-value*<0.001) and lower odds for a decreased β-cell function (HOMA1-B adjOR = 0.2, 95%CI = 0.05-0.9, *p-value*=0.033; HOMA2-B adjOR=0.2, 95%CI=0.04-0.9, *p-value*=0.043) compared to being lean.

Conclusion. Newly diagnosed overweight/obese T2DM had higher mean insulin resistance and β-cell function compared to lean T2DM. Overweight/obesity was also associated with higher odds of developing insulin resistance and lower odds for a decreased β-cell function compared to being lean. The overweight/obese T2DM group also had worse metabolic profile manifested by higher FPG, HbA1c, SGPT and blood pressures compared to the lean T2DM group.

Key words: type 2 diabetes mellitus, insulin resistance, beta-cell function, lean, overweight, obese

INTRODUCTION

Type 2 diabetes mellitus (T2DM) exerts a major impact in developing countries, particularly in the Philippines.[1] In 2009, a cohort study derived from a larger population-based investigation demonstrated a 9-year incidence rate of T2DM in the Philippines to be around 16.3%.[2] T2DM is a chronic metabolic disorder which has been attributed to insulin resistance since the 1930s. Recent studies, however, support the view that T2DM is a heterogeneous disorder where decreased β-cell function is the main genetic factor and insulin resistance is the main acquired factor.[3]

Obesity has been considered as a fundamental aspect behind the worldwide epidemic of T2DM particularly in the western world. In many Asian countries, however, a significant proportion of T2DM patients are considered to be lean.[4] The clinical profile and complications of T2DM differ among lean and obese patients. Lean T2DM has a younger age of onset with male predominance. They are mostly smokers with early failure to oral anti-diabetic drugs.[5] Microvascular complications, particularly retinopathy, are highly prevalent among the lean while macrovascular complications are noteworthy among the overweight and obese T2DM patients.[6, 7]

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Newer studies have further clustered T2DM into whether they are insulin resistant or deficient. Overweight and obese patients are classified under insulin resistant while lean persons with diabetes are noted to be insulin deficient.[7-9] In Koreans, regardless of BMI, the development of T2DM was attributed to a defect in insulin secretion.[10] In Hong Kong, the insulin resistance index of newly diagnosed T2DM patients were similar in lean and overweight patients.[11] In a study done in Malaysia with predominantly overweight and obese T2DM patients, diabetes was primarily attributed to insulin resistance.[12]

Insulin resistance on top of β-cells that are incapable of compensating will lead to impaired glycemic control.[13] Similarly, lifestyle modification will be necessary in the management of both lean and overweight or obese T2DM patients. A logical approach in treating T2DM would be to address both the defect in insulin secretion and insulin resistance. However, if lean persons with diabetes are clustered under deficiency in insulin secretion, they will most likely benefit the use of sulfonylureas as an early intervention provided they still have preserved β-cell function.[13,14]

In the Philippines, there are still limited data on the characteristics of lean and overweight or obese T2DM patients. Understanding their differences will guide us in providing the appropriate cost-effective management that will best suit the patients' different metabolic profile. The current treatment guidelines are unable to predict which patients will need intensified treatment in either reducing insulin resistance or intensifying β-cell function. Hence, this study aims to compare the insulin resistance (HOMA-IR) and β-cell function (HOMA-B) between lean and overweight/obese T2DM patients.

METHODOLOGY

This was a cross-sectional analytical study conducted at St. Luke's Medical Center – Quezon City (SLMC-QC), a tertiary hospital in the Philippines, from January to December 2018. This study included all adult Filipino patients ≥18 years old, both from the social service and private divisions, who were newly diagnosed with T2DM, defined as diagnosis within one year prior to study enrollment. The exclusion criteria included the following: those who had other medical conditions including malignancy, cardiac failure, cirrhosis, end stage renal disease, chronic obstructive pulmonary disease and trauma requiring hospitalization or surgical intervention; those who used anti-diabetic medications, including both insulin and oral agents, within the past two weeks prior to study enrollment; those who took medications that altered insulin sensitivity like prazosin, diuretics, steroids and oral contraceptive pills within the past three months prior to study enrollment; those who had intentional or unintentional weight loss, either a decrease of ≥5% of baseline body weight or a change in BMI category within one year prior to inclusion in the study. Pregnant women with gestational diabetes mellitus (GDM); history of GDM per se, however, was not part of the exclusion criteria. Subjects who had other endocrinopathies including thyrotoxicosis, acromegaly, prolactinoma, hypopituitarism, adrenal insufficiency, Cushing's disease or any other syndrome where T2DM was part of the presentation. Lastly, vulnerable populations such as those with mental retardation or psychological disorders were not included.

All newly diagnosed T2DM patients based on the American Diabetes Association (ADA) 2018 criteria (FBS ≥126 mg/dL, HbA1c ≥6.5% or classic symptoms of hyperglycemia with a random plasma glucose ≥200 mg/dL) were recruited for inclusion in the study. This included all patients consulting in both the social service out patient department (SS-OPD) and in the private clinics. Patients who were admitted solely for executive/ diagnostic check up but otherwise asymptomatic were included. An informed consent form (ICF) was subsequently obtained from all the patients who met the inclusion criteria. The ICF was taken at the clinic after fully explaining the study. After the patient consented, he was given a copy of the ICF. The demographics and clinical profile of the study participants were taken through a detailed history and physical examination. Data included age, sex, hypertension, and smoking history in pack years. The patient's anthropometric measures including height, weight, waist and hip circumference were attained. Height and weight were measured using a similar type of stadiometer and weighing scale in all patients. Waist and hip circumference were measured by the use of the same tape measure as well. Blood pressure was taken through a calibrated sphygmomanometer. Compliance to the intake of anti-hypertensive medications was asked. They were then classified according to their body mass index (BMI). Subjects who had BMI in the underweight to normal range were classified as lean while those in the overweight and obese range were classified together. The World Health Organization's classification of BMI in adult Asians was used. Categorization was as follows: underweight (<18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2), obese I (25-29.9 kg/m^2) and obese II (≥30 kg/m^2). Subsequently, patients were advised to have a 12-hour overnight fasting. Blood extraction was done at the laboratory using two yellow tops containing 3.5 mL of blood each. After which, the following biochemical parameters were obtained: fasting plasma glucose, fasting insulin, HbA1c, serum creatinine, estimated glomerular filtration rate, SGPT and lipid profile. Insulin resistance and β-cell function were compared between the two groups using the Homeostatic Model Assessment (HOMA). Both the original model (HOMA1) and the updated model containing physiological modifications in a computer version (HOMA2) were used. HOMA1 computation were as follows: HOMA-IR=fasting insulin concentration (mIU/L) x fasting blood glucose concentration (mmol/L) divided by 22.5; HOMA-B=20 x fasting insulin concentration (mIU/L) divided by [fasting blood glucose concentration (mmol/L) –3.5].[15] The HOMA2 calculator was downloaded from the University of Oxford, Center for Diabetes, Endocrinology and Metabolism, Diabetes Trial Unit (http://www.dtu.ox.ac.uk/homacalculator). The cut-off values for the definition of insulin resistance were HOMA1-IR ≥2.9 and HOMA2-IR ≥1.7.[16, 17] Insulin deficiency, on the other hand, was defined as HOMA1-B ≤48.9% and HOMA2-B ≤54.2%.[18]

A total of 80 newly diagnosed T2DM subjects (40 subjects from the lean group and 40 subjects from the overweight/obese group) were recruited in this study. Power analysis performed showed that the linear and logistic regression models fitted in this study (i.e. HOMA1-IR, HOMA2-IR, HOMA1-B, and HOMA2-B models) had at least 90% with this sample size. Power analysis was conducted using G*Power 3.0.10 software.

Statistical analysis

Statistical analysis was done using STATA14. Quantitative variables were summarized using mean and standard deviation. The qualitative variables were summarized using frequencies and percentages. Comparison of the HOMA-IR, HOMA-B, and other continuous variables between lean and overweight/obese T2DM was done using student's t-test. Multiple linear regression was done to assess the association between overweight/obesity and HOMA-IR/HOMA-B values. Multiple logistic regression was done to assess the association between overweight/obesity and HOMA-IR/HOMA-B. Potential confounders (age, sex, SGPT, HBA1C) identified through related literature were controlled in the multiple linear and logistic regression models.

Ethical consideration

The clinical protocol and all relevant documents were reviewed and approved by the SLMC-QC Institutional Ethics Review Committee. Confidentiality and anonymity were ensured with the use of data generated code. The main investigator was responsible for the integrity of the data including accuracy, completeness and legibility. The manner of disseminating and communicating the study results guaranteed the protection of the patient's confidentiality. The principal investigator shouldered the laboratory tests needed where the funds came from the SLMC-QC Research and Biotechnology Division and the PSEDM-Servier research grant.

RESULTS

A total of 80 subjects were included in the study. There were 40 subjects in each group. The clinical and demographic characteristics of the study population are shown in Table 1. The mean age of lean T2DM patients was 55.5±12.1 years old while the overweight/obese patients had a mean age of 46.5±12.0 years old. In terms of sex, most of the subjects were females (lean=72.5%, overweight/obese=52.4%). The mean systolic and diastolic blood pressures were 110.5±14.1/70.5±9.3 mmHg among the lean T2DM and 128.8±11.7/ 81.4±7.2 mmHg among the overweight/obese T2DM. The proportion of smokers were as follows, lean=10% and overweight/obese=11.9%.

Table 1. Demographic characteristics and anthropometric measurements of the subjects (N=80)

Characteristics	Lean (N=40)	Overweight/Obese (N =40)
	Mean±SD or Percent (n/N)	
Age (years)	55.5±12.1	46.5±12.0
Sex		
Male (%)	11 (27.5)	20 (47.6)
Female (%)	29 (72.5)	22 (52.4)
Weight (kg)	55.0±8.6	87.1±26.4
Height (m)	153.7±26.6	163.7±8.1
BMI (kg/m^2)	21.9±1.3	32.6±8.6
Waist circumference (cm)	84.2±9.0	106.7±16.6
Hip circumference (cm)	89.8±7.8	108.2±15.5
Systolic blood pressure (mmHg)	110.5±14.1	128.8±11.7
Diastolic blood pressure (mmHg)	70.5±9.3	81.4±7.2
Smoker		
No (%)	36 (90.0)	37 (88.1)
Yes (%)	4 (10.0)	5 (11.9)

The biochemical parameters of the subjects included in the study are shown in Table 2. There was a significant difference in the mean fasting plasma glucose between the two groups (lean=142.0±64.9 mg/dL, overweight/obese=174.9±73.5 mg/dL, *p-value*=0.035). There was significantly higher mean fasting insulin (*p-value*=<0.001), HbA1c (*p-value*=0.043) and SGPT (*p-value*=0.027) among overweight/obese patients compared to lean patients. In contrast, no significant differences were observed in terms of lipid profile (total cholesterol, *p-value*=0.901; triglycerides, *p-value*=0.492; LDL, *p-value*=0.637; HDL, *p-value*=0.267) and creatinine level (*p-value*=0.509) between the two groups.

The differences in insulin resistance and β-cell function between the two groups are shown in Table 3. In both HOMA1 and HOMA2, overweight/obese patients (HOMA1-IR 9.8±11.7, HOMA2-IR 3.0±2.0) had significantly higher mean HOMA-IR values (HOMA1-IR *p-value*=0.001, HOMA2-IR *p-value*<0.001) compared to lean patients (HOMA1-IR 2.9±1.5, HOMA2-IR 1.3±0.5). In terms of HOMA-B levels, overweight/obese subjects had significantly higher values compared to lean subjects when using HOMA1 (lean=57.8±35.5, overweight/obese = 93.6±66.4, *p-value*=0.003). This difference in HOMA-B levels was not observed when using HOMA2 (lean=57.6±30.5, overweight/obese=74.8±45.7, *p-value*=0.051).

Being overweight/obese was significantly associated with increased insulin resistance and β-cell function (Table 4). Using HOMA1, being overweight/obese significantly increased HOMA-IR value by 4.0 (95%CI=1.5-6.5, *p-value*=0.002) and HOMA-B value by 46.1 (95%CI=26.0-66.1, *p-value*<0.001) compared to being lean. Using HOMA2, being overweight/obese significantly increased HOMA-IR value by 1.4 (95%CI=0.6-2.1, *p-value*<0.001) and HOMA-B value by 29.1 (95%CI=15.6-42.7, *p-value*<0.001) compared to being lean. Age, sex, SGPT and HBA1C were adjusted as potential confounders in the regression models.

Table 2. Biochemical parameters of the study subjects

	Lean (N=40) Mean±SD	Overweight/ Obese (N =40) Mean±SD	*p-value*
Fasting plasma glucose (mg/dL)	142.0±64.9	174.9±73.5	0.035
Fasting insulin (uU/mL)	8.8±3.6	21.4±18.7	<0.001
HbA1c (%)	7.3±6.5	8.4±2.5	0.043
SGPT (U/L)	42.6±23.6	58.8±39.3	0.027
Lipid Profile			
Total Cholesterol (mg/dL)	198.6±51.4	200.1±58.0	0.901
Triglycerides (mg/dL)	191.1±270.8	232.9±277.4	0.492
LDL (mg/dL)	121.3±41.8	116.9±41.0	0.637
HDL (mg/dL)	48.8±15.2	44.2±21.2	0.267
Creatinine (mg/dL)	1.01±0.69	0.93±0.35	0.509
eGFR (mL/min/1.73m^2)	79.6±26.5	89.7±25.9	0.094

Table 3. Mean insulin resistance and β-cell function

	Lean (N=40) Mean±SD	Overweight/ Obese (N =40) Mean±SD	*p-value*
HOMA1-IR	2.9±1.5	9.8±11.7	0.001
HOMA1-B	57.8±35.5	93.6±66.4	0.003
HOMA2-IR	1.3±0.5	3.0±2.0	<0.001
HOMA2-B	57.6±30.5	74.8±45.7	0.051

Table 4. Association of overweight/obesity with insulin resistance and β-cell function using HOMA as continuous variable

	B-coefficient (95% CI)	*p-value*	AdjB-coefficient[1] (95% CI)	*p-value*
HOMA1-IR	5.5 (3.2-7.9)	<0.001	4.0 (1.5-6.5)	0.002
HOMA1-B	34.8 (12.0-57.5)	0.003	46.1 (26.0-66.1)	<0.001
HOMA2-IR	1.7 (1.04-2.4)	<0.001	1.4 (0.6-2.1)	<0.001
HOMA2-B	17.2 (-0.1-34.5)	0.051	29.1 (15.6-42.7)	<0.001

[1] Age, Sex, SGPT, HBA1C were adjusted as potential confounders

As shown in Table 5, being overweight/obese was significantly associated with elevated HOMA values (insulin resistance and β-cell function). Through the use of HOMA1, overweight/obese T2DM subjects had significantly higher odds in having an increased HOMA-IR (adjOR=5.6, 95%CI=1.7-19.2, *p-value*=0.005) and significantly lower odds in developing a decreased HOMA-B (adjOR=0.2, 95%CI=0.05-0.9, *p-value*=0.033) compared to lean T2DM subjects. Upon the use of HOMA2, similar trend was observed. Overweight/obese T2DM patients had significantly higher odds for an elevated HOMA-IR (adjOR=10.9, 95%CI=3.4-34.9, *p-value*<0.001) and significantly lower odds for a decreased HOMA-B (adjOR=0.2, 95%CI=0.04-0.9, *p-value*=0.043) compared to lean T2DM patients. Age, sex, SGPT and HBA1C were also adjusted as potential confounders in the regression models.

DISCUSSION

The levels of insulin resistance and β-cell function differed between the lean and overweight/obese newly diagnosed T2DM. The measurement of insulin resistance and β-cell function was done through the use of HOMA. HOMA1 is the original model consisting of mathematical computation widely used in epidemiological and clinical studies while HOMA2 is the updated computer model. The updated version accounts for variations in hepatic and peripheral glucose resistance providing a more accurate index.[15, 17] Wallace et al.,[15] further emphasized that HOMA allocates the basal state of insulin and glucose in terms of resistance and β-cell function. Hence, if the β-cell function data will be reported in isolation, a mistaken assumption can be made that the subject has failing β-cells contrary to an appropriately low secretion due to high insulin sensitivity of the body. Insulin resistance was defined as HOMA1-IR ≥2.9 and HOMA2-IR ≥1.7 while β-cell dysfunction was labeled as HOMA1-B ≤48.9% and HOMA2-B ≤54.2%.[16-18]

In our study, both HOMA1 and HOMA2 showed that overweight/obese T2DM subjects had significantly higher mean HOMA-IR values compared to the lean T2DM group (*p-values*=0.001 and <0.001, respectively). Overweight/obesity was also associated with higher odds of having increased insulin resistance consistent to both HOMA1-IR and HOMA2-IR (*p-values*=0.005 and <0.001, respectively) compared to lean T2DM subjects. This supported previous data that insulin resistance was significantly increased in overweight/obese T2DM patients.[19-21] Chung et al.,[20] indicated that BMI had a positive relationship with indices of insulin resistance. The mechanism of insulin resistance in overweight/obese subjects had been attributed to chronic inflammation, mitochondrial dysfunction, hyperinsulinemia, lipotoxicity or energy surplus mediated by adenosine triphosphate (ATP).[21] In terms of HOMA-B, the overweight/obese T2DM group had statistically significant higher mean values when using HOMA1 (*p-value*=0.003) but the difference was not statistically significant when using HOMA2 (*p-value*=0.051). The HOMA2-B trend, however, was still observed to be higher in the overweight/obese patients. Overweight/obesity was also associated with significantly lower odds in having decreased β-cell function compared to the lean group. This trend was consistent in both HOMA1-B and HOMA2-B (*p-value*=0.033 and 0.043, respectively). It is noteworthy that the HOMA1 model was calibrated to an insulin assay used in the 1970s, hence, may fluctuate in the assessment of β-cell function when compared with the newer assays.[15, 22] Thus, in assessing β-cell function, the computer model (HOMA2) is preferably used as this has been recalibrated in line with current insulin assays.

In our study, the difference in the mean HOMA2-B values between the two groups might not be statistically significant (*p-value*=0.051), but this could still be of marked clinical value when interpreted in relation to the HOMA-IR. Therefore, with a higher HOMA-IR and HOMA-B values in the overweight/obese newly diagnosed T2DM subjects, it could be deduced that they still had preserved β-cell function that was able compensate with the higher insulin resistance. Ferrannini[23] noted that as insulin resistance increased, β-cells compensated by increasing insulin secretion leading to hyperinsulinemia. In another study, it was also observed that obesity was associated with an increase in β-cell mass where the upsurge in BMI was correlated with a rise in β-cell function. They further noted that obesity could be a form of primary insulin hypersecretion.[24] The lean group, on the other hand, were more insulin sensitive as evidenced by a lesser percentage of insulin resistant individuals along with lower mean HOMA-IR and HOMA-B levels.

Table 5. Association of overweight/obesity with insulin resistance and β-cell function using HOMA cut-off values

	Lean (N =40)	Overweight/Obese (N =40)	Odds Ratio (95% CI)	*p-value*	Adj Odds Ratio[1] (95% CI)	*p-value*
HOMA1-IR						
Normal (<2.9)	23 (57.5)	6 (15.0)	Reference		Reference	
Increased (≥2.9)	17 (42.5)	34 (85.0)	7.7 (2.6-22.4)	<0.001	5.6 (1.7-19.2)	0.005
HOMA1-B						
Normal (>48.9%)	22 (55.0)	25 (62.5)	Reference		Reference	
Decreased (≤48.9%)	18 (45.0)	15 (37.5)	0.7 (0.3-1.8)	0.496	0.2 (0.05-0.9)	0.033
HOMA2-IR						
Normal (<1.7)	33 (82.5)	11 (27.5)	Reference		Reference	
Increased (≥1.7)	7 (15.5)	29 (72.5)	12.4 (4.2-36.3)	<0.001	10.9 (3.4-34.9)	<0.001
HOMA2-B						
Normal (>54.2%)	22 (55.0)	23 (57.5)	Reference		Reference	
Decreased (≤54.2%)	18 (45.0)	17 (42.5)	0.9 (0.4-2.2)	0.822	0.2 (0.04-0.9)	0.043

[1] Age, Sex, SGPT, HBA1C were adjusted as potential confounders

Between the two groups, the newly diagnosed lean T2DM were clinically better compared to the overweight/obese group, taking into consideration the lower mean FPG, HbA1c, fasting insulin and SGPT. The β-cells of the lean T2DM subjects did not have to compensate to produce more insulin to maintain normal glucose tolerance.

With these findings, it is reasonable to conclude that an individualized cost-effective treatment should be established for every T2DM patient. It is necessary to understand their residual β-cell function and corresponding insulin resistance. The outcome of our study was dissimilar to the data of Ahlqvist et al.,[7] and Hartmann et al.,[25] which clustered lean persons with diabetes under insulin deficiency, having shortest time to second oral diabetic drugs, with less benefit to metformin and more often treated with insulin. Our findings were congruent to the data of Das[9] and Barma et al.,[26] that lean T2DM could achieve good glycemic control with oral diabetic agents. In particular, since the lean T2DM subjects of our study were more insulin sensitive, (likely with preserved β-cell function) and weight loss was not key in its management, these patients could benefit the most from insulin secretagogues like sulfonylureas. Newly diagnosed overweight/obese T2DM, on the other hand, having higher insulin resistance would have a favorable response to an insulin sensitizer like metformin. This would not only enhance insulin sensitivity but would also preserve β-cell function. Therapeutic interventions should have an emphasis on the reduction of insulin resistance and preservation of β-cell function.

Lean and overweight/obese T2DM also had differences in their demographic and biochemical parameters. Decrease in insulin sensitivity and β-cell function had been correlated to aging. This was attributed to the changes in body composition, decrease in skeletal muscle mitochondrial function and age-related impairment of pancreatic endocrine function.[27-29] Karakelides et al.,[30] however, noted that age had no independent effect on insulin resistance. Scheen[31] and Imbeault et al.,[32] further noted that increasing age *per se* did not influence glucose homeostasis and was not a cause of insulin resistance. Hence, the role of age in decreasing insulin sensitivity and β-cell function in the older population has to be further evaluated.

In the present study, lean T2DM group were older compared to the overweight/obese group. Despite being older though, they were noted to have better insulin sensitivity than the overweight/obese group. The association of age to insulin resistance and β-cell function, however, could not be well established in this study due to the method of sampling. As regards to sex, majority of the subjects were females. Geer and Shen[33] indicated that there is an elevated visceral and hepatic adiposity reported in males. Along with lower adiponectin levels and absence of estrogen, males are noted to have higher insulin resistance compared to females.[33] Similar to age, the relationship of sex to insulin resistance and β-cell function could not be generalized in this study due to the sampling method used.

The mean systolic and diastolic blood pressures of the overweight/obese group were also higher compared to the lean group. This was congruent to the study of Shikha et al.,[34] that daytime, nocturnal and 24-hour mean systolic blood pressure were significantly higher in obese subjects. Obesity is known as a major risk for hypertension because it surges tubular reabsorption impairing pressure natriuresis resulting to volume expansion thru the activation of the renin-angiotensin system.[35]

The proportion of smokers between the two groups was comparable in this study. This was similar to the study of Mohan et al.,[6] indicating that there was no significant difference in the smoking habits of the two groups. Keith et al.,[36] further noted that there was no consistent association between tobacco use and insulin resistance regardless of whether the subject was a persistent smoker or a quitter. This was in contrast to other previous studies, which noted that lean T2DM were mostly smokers.[5, 25] Nagaya et al.,[37] on the other hand, noted that heavy smoking moderately increased the risk of diabetes in obese men while light smoking reduced the risk in lean men. The association of smoking in T2DM, whether in the lean or overweight/obese group may require more extensive studies.

In the analysis of the biochemical parameters, mean fasting plasma glucose (FPG) and HbA1c were significantly higher in the overweight/obese group compared to the lean (*p-values*=0.035 and 0.043, respectively). This was consistent to previous studies, which explained that obesity was associated to chronic systemic inflammation because adipose tissues release pro-inflammatory substances and non-esterified fatty acids (NEFA). Apart from inflammatory state having a fundamental role in the development of insulin resistance, NEFA secreted from adipose tissues also lead to insulin resistance and β-cell dysfunction, thereby resulting to poor glycemic control.[38-40] Other studies, however, showed that lean T2DM had more severe hyperglycemia attributed to early β-cell failure or more severe β-cell dysfunction.[6, 41] In both groups, there was no significant derangement in liver function represented by SGPT in this study. It can be observed though, that the SGPT level in the overweight/obese group was higher compared to the lean T2DM subjects (*p-value*=0.027). Being overweight or obese had been associated with expanded adipose tissue that resulted to chronic inflammation. This lead to a problem in the normal storage and endocrine functions of adipose tissues that also altered the metabolic state of the liver.[42]

In terms of lipid profile, there was no significant differences observed between the two groups. This was contrary to the data of Das[9] that BMI had a positive relationship with LDL and that lean persons with diabetes had lower incidence of dyslipidemia with a generally favorable lipid profile. Both lean and overweight/obese T2DM subjects in our study probably had preserved β-cell function that was able to compensate the presence of insulin resistance in the peripheral bed leading to better hepatic handling of lipids. Renal function did not also differ between the two study groups (*p-value*=0.094). This was mainly attributed to the fact that subjects enrolled in this study were newly diagnosed with T2DM, hence, complications of diabetes might not yet be present.

CONCLUSION

The overweight/obese newly diagnosed T2DM patients had higher mean insulin resistance and β-cell function compared to lean T2DM patients. Overweight/obesity

was also associated with higher odds of having increased insulin resistance and lower odds of developing decreased β-cell function compared to the lean group. The overweight/obese T2DM had worse metabolic profile manifested by higher FPG, HbA1c, SGPT and blood pressures compared to lean T2DM.

Limitation and recommendation

Due to the nature of the research design, the level of β-cell function (HOMA-B) cannot be interpreted in isolation and may not reflect the true β-cell reserve. A cohort design may be better to determine the rate of β-cell deterioration.

The population included in this study also represented the highly urbanized patients from Metro Manila only and may not represent the T2DM Filipinos from the rural areas. The subject's levels of physical activity, which may influence insulin resistance, were not assessed in detail as well. Further studies can be done in the future which should take the aforementioned issues into consideration.

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

Author Disclosure
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ORIGINAL ARTICLE

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Prevalence of Metabolic Syndrome and Cardiovascular Risk Factors among Community Health Workers in Selected Villages in the Philippines

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Abstract

Objective. This study aimed to estimate the prevalence of cardiovascular risk factors and metabolic syndrome among community health workers (CHWs) in selected villages in the Philippines. It also determined the association of urbanization and socio-demographic characteristics with hypertension, diabetes mellitus and metabolic syndrome among CHWs.

Methodology. A cross-sectional study was conducted among CHWs who were actively rendering service from selected communities at the time of the study. Standardized interviews were conducted and clinical measurements were collected.

Results. Of the total of 457 CHWs who participated, 96% were females with a median age of 50 years. The prevalence of hypertension in this population was 32.4%. Hypertension was found to be associated with older age [adjusted odds ratio (aOR) 5.3, 95% CI: 3.2 to 8.8, p<0.001], obesity (aOR 2.4, 95% CI: 1.4 to 4.0, p=0.002) and alcohol consumption (aOR 1.7, 95% CI: 1.0 to 3.0, p<0.040). The prevalence of diabetes mellitus (DM) was 13.6%. It was found to be more prevalent among CHWs who were at least 50 years old (aOR 2.7, 95% CI: 1.4 to 5.1, p=0.002), and those who spent at least 5 hours a day in sedentary activities (aOR 3.8, 95% CI: 1.1 to 12.7, p<0.033). Borderline to high total cholesterol, low density lipoprotein cholesterol (LDL-c) and triglycerides (TG) were seen in 41%, 37% and 20%, respectively. Sixty percent had low high density lipoprotein cholesterol (LDL-c). The overall prevalence of metabolic syndrome was 52.3%.

Conclusion. Metabolic syndrome is prevalent among CHW participants, with obesity, hypertension and low LDL-c as the most common components present. The prevalence of cardiovascular risk factors in this population was not found to be significantly different between rural and urban areas after adjusting for other factors.

Key words: community health workers, hypertension, diabetes mellitus, metabolic syndrome, cardiovascular diseases

INTRODUCTION

Community health workers, as in many other countries, are the front liners in the delivery of primary health care at the grassroots level, both in urban and rural communities in the Philippines. The term CHWs embraces a variety of community health aides who are selected, trained and are working in the communities from which they come. According to the World Health Organization (WHO), CHWs should be: (1) members of the communities where they work, (2) selected by the communities, (3) answerable to the communities for their activities, (4) supported by the health system but not necessarily as part of its organization, and (5) should have shorter training than professional workers.[1]

In the Philippines, CHWs refer mainly to *Barangay* Health Workers (BHWs) although CHWs can also include *Barangay* Nutrition Scholars (BNSs), Rural Health Midwives (RHMs) and Mother Leaders (MLs). In some areas of the country, there are MLs who perform the same roles as BHWs. Mostly females, BHWs are volunteers who are supposed to be accredited by the Local Health Board (LHB) and who have been trained to provide primary health care services in the community in accordance with the guidelines promulgated by the Department of Health (DOH).[2] The number of health workers in the community is set by the DOH. It is determined by the ideal ratio of BHWs relative to the number of households, provided that the total number of BHWs nationwide shall not exceed one percent (1%) of the total population.[2]

BHWs, usually of age 20 to 45 years, play significant roles in providing primary health care in the communities they serve.[1] A study conducted in Camarines Sur in the Luzon island in the Philippines reported that majority of BHWs

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were women, age 45 and above. BHWs are considered competent as community organizers, health educators, and healthcare service providers, although continuing education may be warranted so that they will be more adept in their knowledge and skills.[3] Given that the BHWs are aging, it can be surmised that they also have medical conditions such as hypertension, diabetes and other cardiovascular diseases (CVD). A large body of epidemiologic studies likewise demonstrated associations between CVD and common lifestyle determinants including tobacco use, alcohol, physical inactivity, obesity, and diet. Urbanization was also believed as one of the key drivers of non-communicable diseases especially in low- and middle-income countries.[4]

The limited literature about CHWs were mainly about the definition of CHWs, their general functions, level of competence and existing CHW programs. CHWs are expected to take care of the health of their community members. Ironically, there is no existing program that has been cited in the literature that paid attention to the health of the aging CHWs. In the Philippines, to the best of our knowledge, the cardiovascular risk profile of CHWs has not been studied. Paradoxically, the CHWs are advocates for promoting health through education and dissemination of information. The CHWs must be in good health condition in order to perform better in the delivery of health services in the communities.

CHWs have been identified as one strategy in addressing the growing shortage of health workers, particularly in low-income countries.[1] On average, each health worker is expected to work with approximately 20 families in their communities.[5] In the Philippines, BHWs are considered as volunteers under Republic Act (R.A.) No. 7833, known as The Barangay Health Workers' Benefits and Incentives Act of 1995. Only a few BHWs in the *barangay* (village) receive a modest allowance from the Local Government Unit (LGU). Availability of allowance depends on factors such as LGU income and political considerations. Various bills have been proposed to improve the benefits and incentives of BHWs. The latest is the one filed by Senator Grace Poe, Senate Bill No. 2219, an act to improve and promote quality delivery of health services in *barangays*, enacting the BHWs and services reform act of 2014. This Senate Bill states that: (1) the entry pay level of a BHW shall be the prevailing rate equivalent to Salary Grade One (SG 1), (2) BHWs shall be entitled to the same incentives and benefits provided under the Magna Carta for Public Health workers, and (3) BHWs shall be covered by the existing statutory benefits from the Government Service Insurance System (GSIS), the Philippine Health Insurance Corporation (PhilHealth) and the affordable shelter financing program, *Pagtutulungan sa Kinabukasan: Ikaw, Bangko, Industriya at Gobyerno* (Pag-IBIG).[6]

CHWs, in general, perform a wide range of tasks including home visits, environmental sanitation, first aid and treatment of simple and common ailments, health education, nutrition and surveillance, maternal and child health and family planning activities, TB and HIV/AIDS care (i.e. counselling, peer and treatment support, and palliative care), malaria control, treatment of acute respiratory infections, communicable disease control, community development activities, referrals, record keeping, and collection of data on vital events. These tasks are performed in many different combinations and with varied degrees of breadth and depth in diverse countries.[7]

OBJECTIVES

This study aimed to estimate the prevalence of cardiovascular risk factors and metabolic syndrome among CHWs in selected areas in the Philippines. It also determined the association of urbanization and other socio-demographic characteristics with hypertension, diabetes mellitus, and metabolic syndrome among CHWs.

METHODOLOGY

Study design and setting

This study was conducted in conjunction with the main **LIFE**course study in **CAR**diovascular disease **E**pidemiology (LIFECARE). The LIFECARE study is a community-based prospective cohort of apparently healthy individuals aged 20 to 50 years old that examined the effects of socioeconomic factors, psychosocial stress and lifestyle factors in the development of cardiovascular disease risk factors and CVD.[8] Unlike the main LIFECARE study, this sub-study on CHWs was cross-sectional in design with just one data collection point and no specific age range for enrolment in the study. This sub-study was conducted in 2 selected urban *barangays* in Metro Manila, and in 54 urban and rural *barangays* in Central and Southern Luzon (provinces of Batangas, Bulacan, Rizal, and Quezon). Participants were CHWs who were actively rendering service from the selected communities at the time of the study. Standardized interviews were conducted and clinical measurements were done. Informed written consent was obtained from participants prior to the interview. The study was approved by the University of the Philippines Manila Research Ethics Board (UPMREB 2008-027-01).

Trained research assistants interviewed and conducted clinical measurements. The clinical evaluation and collection of samples were carried out at screening centers set up at the *barangay* health centers of the selected *barangays*. The participants' anthropometric data such as height, weight, waist and hip circumferences were taken. The weight was measured using the standardized bathroom scale (10 kg weight was used). The height was measured with a stadiometer. The waist circumference was determined at midway between the sub-costal margin and the iliac crest while the hip circumference was taken at the widest diameter. The blood pressure measurements were taken in the seated position 3 times in the upper arm using an Omron digital sphygmomanometer with appropriate cuff sizes and validated by the Philippine Society of Hypertension. One to 2 tablespoons (10 mL) of fasting blood was taken from each participant and transferred into a plain vial for blood chemistry. Analysis of fasting blood glucose was done in a central laboratory using Roche Cobas Mira blood analyzer. All samples were analyzed at the Department of Medicine's Lipid Research Laboratory in the Philippine General Hospital. The total cholesterol and triglycerides were measured by enzymatic colorimetric method and high-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol by

differential precipitation enzymatic colorimetric using semi-autoanalyser Mitra Photometer. All parameters were expressed as mmol/L.

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or both, and/or concomitant use of antihypertensive medications according to the WHO/International Society of Hypertension (ISH) guidelines.[9]

The current WHO diagnostic criteria for diabetes was used, which included a fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL) or a 2-hour plasma glucose ≥11.1 mmol/L (200 mg/dL), and/or concomitant use of antidiabetic medications.[10]

Cut-off values for lipid profile were adopted from the National Cholesterol Education Program Adult Treatment Panel 3 (NCEP ATP III) report. Dyslipidemia was defined as having one of the following: high TC (≥6.2 mmol/L), high TG (≥2.26 mmol/L), high LDL-c (≥4.1 mmol/L) and/or low LDL-c (<1.03 mmol/L for male and <1.29 for female).[11]

The diagnosis of metabolic syndrome was based on the interim statement of the International Diabetes Federation (IDF) Task Force composed of several major organizations. Three abnormal findings out of 5 would qualify a person for the metabolic syndrome, and that abdominal obesity will not be a prerequisite for diagnosis but will continue to be a useful tool for screening.[12] The harmonized criteria defined the following component risk factors: (1) elevated BP with SBP ≥130 mmHg or DBP ≥85 mmHg or on drug treatment, (2) elevated TG ≥1.7 mmol/L or on drug treatment, (3) elevated FBG ≥5.5 mmol/L or on drug treatment, (4) low HDL-c <1.0 mmol/L for men and <1.3 mmol/L for women or on drug treatment, and (5) abdominal obesity or increased waist circumference of ≥90 cm for men and ≥80 cm for women for Asians.

Rural and urban classification or geographic location of *barangays* was based on the Philippine Statistics Authority definition. This was determined in terms of population size, number of establishments and employees, and available facilities (e.g. town hall or provincial capitol, church, public plaza, market place, public buildings, etc.).

Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m^2). The current WHO BMI cut-off points were as follows: <18.5 kg/m^2 (underweight), 18.5 to 24.9 (normal), 25 to 29.9 (overweight), and ≥30 (obese). For adult Asians, the proposed BMI categories were as follows: <18.5 kg/m^2 (underweight), 18.5 to 22.9 (normal), 23 to 24.9 (overweight), and ≥25 (obese).[13]

Participants were also classified as current smoker if they answered "Yes" to the question, "Do you presently smoke cigarettes, cigars, pipes or any other tobacco products?"

Alcohol consumption was based on the question, "In your entire life, have you ever consumed one or more drinks of any type of alcoholic beverage?" Another question on the frequency of alcohol consumption in the past 12 months was also included.

Physical activity includes exercise as well as other activities which involve bodily movement and are done as part of playing, working, active transportation, house chores and recreational activities.[14] In adults aged 18 to 64, physical activity includes leisure time physical activity (e.g. walking, dancing, gardening, hiking, swimming), transportation (e.g. walking or cycling), occupational (i.e. work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities. For this study, recreation-related activities such as sports and fitness that cause large increases in breathing or heart rate for at least 10 minutes continuously were estimated for each participant (both moderate and vigorous-intensity recreation-related). Moreover, average amount of hours per day spent for sedentary activities such as sitting or reclining were also calculated.

Statistical analysis

A total of 449 CHWs from the selected communities was required to estimate the prevalence of low HDL-c in this population within the interval (64±5%) with a 95% confidence level, adjusted to a 20% non-response. This was considered the final sample size and was deemed sufficient to cover estimation of prevalence of all other cardiovascular risk factors. Descriptive statistics such as mean, standard deviation, median and range were calculated for continuous variables while frequency and percentages were presented for categorical variables. Differences in demographic and clinical characteristics by geographical location and health status were analyzed using independent t-test, Mann-Whitney U test, and Chi-square test, where appropriate. Bivariate analysis and multivariate logistic regression determined the association of urbanization and other selected demographic and anthropometric measures with hypertension, diabetes and metabolic syndrome. Crude and adjusted odds ratios with 95% confidence intervals, and p values were derived. A p value of less than 0.05 was considered significant. All statistical analyses were performed using Stata© version 14.[15]

Ethical considerations

The study was approved by the institutional review board of the University of the Philippines Manila (UPMREB 2008-027-01). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Written informed consent was obtained from all individual participants included in the study.

RESULTS

A total of 457 CHWs were interviewed in this study: 96% were females with a median age of 50 years and age range of 20 to 78 years (Table 1). Sixty percent of the CHWs were from urban *barangays*. Majority of the participants were married, and more than half reached at least high school level of education. Six out of 10 participants were BHWs,

Table 1. Demographic characteristics of community health workers in selected areas in the Philippines

Characteristic	Total (n=457)	Rural (n=181)	Urban (n=276)	*p* value
Sex (%)				
Male	18 (3.9)	7 (3.9)	11 (4.0)	
Female	439 (96.1)	174 (96.1)	265 (96.0)	
Age, yr				
n	452	180	272	
Mean (SD)	49.3 (10.8)	50.1 (11.0)	48.7 (10.6)	0.189
Median	50	50.5	49	
Range	20 - 78	20 - 78	21 - 76	
Civil status (%)				
Single never married	24 (5.3)	8 (4.4)	16 (5.8)	0.038
Married	316 (69.2)	134 (74.0)	182 (65.9)	
Widow/widower	59 (12.91)	28 (15.5)	31 (11.2)	
Separated/annulled	23 (5.0)	6 (3.3)	17 (6.2)	
Live-in	21 (4.6)	3 (1.7)	18 (6.5)	
No answer	14 (3.1)	2 (1.1)	12 (4.4)	
Education[a] (%)				
Elementary	79 (17.3)	31 (17.1)	48 (17.4)	0.318
High school	238 (52.1)	102 (56.4)	136 (49.3)	
Vocational/college	124 (27.1)	43 (23.8)	81 (29.4)	
Missing	16 (3.5)	5 (2.8)	11 (4.0)	
Barangay designation[b] (%)				-
Barangay health worker	280 (61.0)	152 (84.0)	128 (46.4)	
Barangay nutrition scholar	28 (6.1)	10 (5.5)	18 (6.5)	
Mother leader	93 (20.4)	0	93 (33.7)	
Nutritionist	2 (0.4)	1 (0.6)	1 (0.4)	
Midwife	18 (3.9)	9 (5.0)	9 (3.3)	
Councilor for health	22 (4.8)	10 (5.5)	12 (4.4)	
Lingkod lingap sa nayon	15 (3.3)	0	15 (5.4)	
Municipal Health Officer	1 (0.2)	0	1 (0.4)	
Ethnicity (%)				-
Tagalog	385 (84.2)	156 (86.2)	229 (83.0)	
Bisaya/Binisaya	18 (3.9)	5 (2.8)	13 (4.7)	
Bikol/Bicol	19 (4.2)	7 (3.9)	12 (4.4)	
Ilocano	2 (0.4)	0	2 (0.7)	
Kapampangan	2 (0.4)	0	2 (0.7)	
Pangasinan/Panggalatok	3 (0.7)	0	3 (1.1)	
Others	3 (0.7)	1 (0.6)	2 (0.7)	
No answer	25 (5.5)	12 (6.6)	13 (4.7)	
Ever consumed ≥1 drink of any type of alcoholic beverage in the past 12 months (%)	117 (25.6)	51 (28.2)	66 (23.9)	0.407
Daily	2 (1.7)	1 (2.0)	1 (1.5)	
5-6 days / week	1 (0.8)	1 (2.0)	0	
1-4 days / week	12 (10.3)	5 (9.8)	7 (10.6)	
1-3 days / month	17 (14.5)	9 (17.7)	8 (12.1)	
Less than once a month	79 (67.5)	32 (62.7)	47 (71.2)	
Current smoker (%)	28 (6.1)	16 (8.8)	12 (4.4)	0.061
Physical activity (%)				
With recreation activity[c]	226 (49.4)	94 (52.2)	132 (47.6)	0.340
Median time spent for recreation-related activity per day (minutes)	30.0	25.7	30.0	0.044
Average amount of sedentary activity (hours)[d]	8.0	7.5	8.3	0.012

[a] Includes those with some level and those who graduated for each specific category (e.g. elementary, includes those with some level and those who graduated elementary education)
[b] Multiple response; some community health workers with multiple roles in the barangay
[c] Did any moderate- to vigorous-intensity sports, fitness or recreational (leisure) activities that cause large increases in breathing or heart rate (e.g. running or football) for at least 10 minutes continuously
[d] Sitting or reclining (at work, at home, getting to and from places) but does not include time spent sleeping

and another 20% were Mother Leaders who performed similar functions as BHWs. There were 3 CHWs who reported that they performed multiple roles in their *barangay* (e.g. serving as BHW and BNS at the same time). Twenty six percent said that they had ever consumed at least one drink of any type of alcoholic beverage in the past 12 months, and majority consumed alcoholic beverage less than once a month. There were 2 female CHWs who reported daily consumption of any type of alcoholic beverage in the past 12 months. No significant differences found in lifestyle activities between CHWs in rural and urban areas except for physical inactivity. Six percent of the participants were current smokers and the proportion of current smokers was higher among those in rural areas (9%) compared to those in urban areas (4%) although not statistically significant. In terms of physical activity, almost half of the CHWs reported to have done any recreation-related activity (moderate to vigorous-intensity sports, fitness and recreation activities) averaging to about 30 minutes per day. CHWs from urban areas had higher time spent for recreation activities than CHWs from rural areas (p=0.044). Moreover, the average amount of time spent for sedentary activities (sitting or reclining) reported by CHWs was estimated to be about 8 hours per day. This was higher among CHWs from urban areas compared to those from rural areas (p=0.012).

Table 2 shows the prevalence of cardiovascular risk factors by geographical location. The overall prevalence of overweight was 33% by WHO and 21% by Asia Pacific classification. Meanwhile, the overall prevalence of obesity was 11.2% by WHO and 43.8% by the Asia Pacific classification. There were more CHWs who were obese in urban areas using either criterion. The overall prevalence of hypertension was 32.4%, almost two-thirds of which were at stage 1. Three out of 10 CHWs were in the pre-

Table 2. Prevalence of cardiovascular risk factors among community health workers by geographical location

Risk Factor	Total (n=457)	Rural (n=181)	Urban (n=276)	*p* value
BMI[a] (WHO[b]), kg/m^2 (%)				
Underweight (<18.5)	19 (4.2)	6 (3.3)	13 (4.7)	0.208
Ideal (18.5-24.9)	228 (49.9)	100 (55.2)	128 (46.4)	
Overweight (25-29.9)	149 (32.6)	57 (31.5)	92 (33.3)	
Obese (≥30)	51 (11.2)	15 (8.3)	36 (13.0)	
No data	10 (2.2)	3 (1.7)	7 (2.5)	
BMI[a] (Asia Pacific), kg/m^2 (%)				
Underweight (<18.5)	19 (4.2)	6 (3.3)	13 (4.7)	0.106
Ideal (18.5-22.9)	132 (28.9)	64 (35.4)	68 (24.6)	
Overweight (23-24.9)	96 (21.0)	36 (19.9)	60 (21.7)	
Obese (≥25)	200 (43.8)	72 (39.8)	128 (46.4)	
No data	10 (2.2)	3 (1.7)	7 (2.5)	
Android obesity[c] (%)				
≥0.85 (Female) (n=439)	323 (73.6)	127 (73.0)	196 (74.0)	0.529
≥1.0 (Male) (n=18)	2 (11.1)	0	2 (18.2)	0.476
Blood pressure[d] (%)				
Normotensive	162 (35.4)	70 (38.7)	92 (33.3)	0.762
Pre-hypertensive	136 (29.8)	52 (28.7)	84 (30.4)	
Stage 1 hypertension	93 (20.4)	35 (19.3)	58 (21.0)	
Stage 2 hypertension	55 (12.0)	21 (11.6)	34 (12.3)	
No data	11 (2.4)	3 (1.7)	8 (2.9)	
Total cholesterol, mmol/L (%)				
<5.2 (Desirable)	250 (54.7)	110 (60.8)	140 (50.7)	0.143
5.2-6.1 (Borderline high)	114 (25.0)	42 (23.2)	72 (26.1)	
≥6.2 (High)	74 (16.2)	24 (13.3)	50 (18.1)	
No data	19 (4.2)	5 (2.8)	14 (5.1)	
LDL[e]-cholesterol, mmol/L (%)				
<2.6 (Optimal)	111 (24.3)	53 (29.3)	58 (21.0)	0.073
2.6-3.3 (Near/above optimal)	160 (35.0)	65 (35.9)	95 (34.4)	
3.4-4.0 (Borderline high)	90 (19.7)	36 (19.9)	54 (19.6)	
≥4.1 (High)	77 (16.8)	22 (12.2)	55 (19.9)	
No data	19 (4.2)	5 (2.8)	14 (5.1)	
HDL[f]-cholesterol, mmol/L (%)				
Low[g]	275 (60.2)	124 (68.5)	151 (54.7)	0.006
Triglycerides, mmol/L (%)				
<1.7 (Normal)	347 (75.9)	142 (78.4)	205 (74.3)	0.791
1.7-2.25 (Borderline high)	49 (10.7)	19 (10.5)	30 (10.9)	
≥2.26 (High)	42 (9.2)	15 (8.3)	27 (9.8)	
Fasting blood glucose, mmol/L (%)				
<5.5	151 (33.0)	63 (34.8)	88 (31.9)	0.082
5.5-6.9 (Pre-diabetes)	224 (49.0)	96 (53.0)	128 (46.4)	
≥7.0 (Diabetes)	62 (13.6)	17 (9.4)	45 (16.3)	
Resting heart rate, beats/minute (%)				
<70	196 (42.9)	101 (55.8)	95 (34.4)	<0.001
≥70	241 (52.7)	76 (42.0)	165 (59.8)	

[a] BMI, body mass index
[b] WHO, World Health Organization
[c] High waist-hip ratio
[d] Stage I, SBP≥140 to ≤159 mmHg, or DBP≥90 to ≤99 mmHg; stage II, SBP ≥160 mmHg or DBP ≥100 mmHg
[e] LDL, low density lipoprotein
[f] HDL, high density lipoprotein
[g] Low HDL-cholesterol, <1.03 mmol/L for males and <1.29 mmol/L for females

hypertensive level. Furthermore, the overall prevalence of diabetes mellitus was at 13.6%, more commonly in CHWs in urban compared to rural areas. The percentage of CHWs with low HDL-c was higher in rural compared to those from urban areas (p=0.006). On the other hand, the percentage of CHWs with heart rate of at least 70 bpm was higher in urban compared to those in rural areas (*<0.001*).

Table 3 presents the prevalence of hypertension and diabetes mellitus among CHWs by urbanization and other selected demographic and anthropometric characteristics. By bivariate analysis, hypertension was not found to be significantly different between rural and urban locations. Conversely, significant factors found to be associated with hypertension were age (at least 50 years old), civil status (without domestic partner), educational attainment (elementary level of education), and BMI (overweight/obese). Multivariate logistic regression analysis showed that age (aOR 5.3, 95% CI: 3.2 to 8.8, p<0.001), obesity (aOR 2.4, 95% CI: 1.4 to 4.0, p=0.002), and alcohol consumption (aOR 1.7, 95% CI: 1.0 to 3.0, p<0.040) were strongly associated with hypertension. On the other hand, diabetes mellitus was found to be associated with geographical location, age and time spent in sedentary activities by bivariate analysis. The prevalence of diabetes was higher among CHWs at least 50 years old (aOR 2.7, 95% CI: 1.4 to 5.1, p=0.002), and those who spent at least 5 hours in sedentary activities (aOR 3.8, 95% CI: 1.1 to 12.7, p<0.033) by multivariate analysis.

Amount of physical activity was compared in those with and without hypertension (Table 4). The amount of time doing recreation-related activities and sedentary activities was not found to be significantly different between CHWs with or without hypertension. On the other hand, the average time doing sedentary activities such as sitting and reclining (excluding sleeping) was higher among CHWs with diabetes compared to those without diabetes (p=0.048).

Table 3. Prevalence of hypertension and diabetes mellitus according to socio-demographic and anthropometric characteristics

Demographic characteristics	n	Hypertension (%)	*p* value	Diabetes mellitus (%)	*p* value
Age, yr					
<50	222	16.2	<0.0001	9.9	0.021
≥50	230	48.7		17.4	
Place or residence					
Rural	181	30.9	0.529	9.4	0.035
Urban	276	33.3		16.3	
Civil status[a]					
No domestic partner	106	41.5	0.027	16.0	0.437
With domestic partner	337	30.3		13.1	
Education					
Elementary	79	49.4	0.001	13.9	0.927
High school/college	362	29.3		13.5	
BMI[b] (WHO[c]), kg/m^2					
Underweight (<18.5)	19	10.5	0.014	0	0.024
Ideal (18.5-24.9)	228	29.4		12.3	
Overweight (25-29.9)	149	36.9		13.4	
Obese (≥30)	51	45.1		25.5	
BMI[b] (Asia Pacific) kg/m^2					
Underweight (<18.5)	19	10.5	0.008	0	0.191
Ideal (18.5-22.9)	132	25.0		12.1	
Overweight (23-24.9)	96	35.4		12.5	
Obese (≥25)	200	39.0		16.5	
Ever consumed ≥1 drink of any type of alcoholic beverage					
Yes	117	34.2	0.658	13.7	0.954
No	324	32.1		13.9	
Current smoker					
Yes	28	25.0	0.329	14.3	1.000
No	413	33.2		13.8	
Time spent in sedentary activities (hrs)					
<5 hours	69	29.0	0.564	4.4	0.012
≥5 hours	362	34.0		15.2	

[a] No domestic partner includes those who were never married, widow/widower, and separated/annulled
[b] BMI, body mass index
[c] WHO, World Health Organization

Table 4. Average amount of physical activity per day according to hypertension status

Physical activity	Hypertension		*p* value
	With	Without	
Amount doing recreation-related activity, minutes			
N	67	154	
Mean (SD)	47.9 (49.2)	60.2 (95.8)	
Median	30.0	27.9	0.739[a]
Mean amount of sedentary activity, hours (SD)	8.00 (3.1)	8.03 (3.3)	0.936[b]

[a] Mann-Whitney U test
[b] t-test

Table 5. Average amount of physical activity per day according to diabetes status

Physical activity	Diabetes mellitus		*p* value
	With	Without	
Amount doing recreation-related activity, minutes			
N	28	198	
Mean (SD)	39.8 (44.4)	59.1 (87.7)	
Median	25.7	30.0	0.622[a]
Mean amount of sedentary activity, hours (SD)	8.7 (3.4)	7.9 (3.2)	0.048[b]

[a] Mann-Whitney U test
[b] t-test

The prevalence of metabolic syndrome and component risk factors in this population are shown in Table 6. The overall prevalence of metabolic syndrome was 52.3%. Among the component risk factors of metabolic syndrome, the prevalence of low HDL-c among CHWs from rural areas was higher compared to those from urban areas (p=0.006). The prevalence of metabolic syndrome was higher with increasing age and among those with lower level of education (Table 7).

DISCUSSION

To the best of our knowledge, this is the first study in the Philippines about cardiovascular risk profile and metabolic syndrome in CHWs. It is significant to note that the prevalence of cardiovascular risk factors was common among CHWs who participated in this study.

The results of the 8th National Nutrition Survey (NNS) done in 2013 by the Food and Nutrition Research Institute of the Department of Science and Technology (FNRI-DOST) showed that more Filipinos have hypertension, high fasting blood sugar (FBS) and high cholesterol and triglyceride levels, which are risk factors for cardiovascular diseases, diabetes and other lifestyle-related diseases.[16] One in every 4 Filipino adults has hypertension or a blood pressure (BP) reading equal to or higher than 140/90. In the Asia-Pacific Region, the prevalence of hypertension ranges from 5 to 47% in men and 7 to 38% in women.[17] In other developing countries like Nigeria, the prevalence of hypertension is even higher at 35.4% in the semi-urban community as against 25.1% in rural community.[18]

The prevalence of high fasting blood sugar, an indicator of diabetes mellitus, is 5 in every 100 Filipinos, based on the 8th NNS. The prevalence of high FBS or hyperglycemia peaks at age 50 to 59 years. The NNS also showed that almost half of Filipino adults had borderline to high TC level. More than one-third of Filipinos have borderline to high TG level. The prevalences of low HDL-c and borderline to high LDL-c levels were 71% and 47%, respectively.[16]

Compared to the health profile of in this study of CHWs, the 8th NNS showed a higher overall prevalence of current

Table 6. Prevalence of metabolic syndrome and component risk factors by geographical location

Component risk factor	Total (n =457)	Rural (n=181)	Urban (n=276)	*p* value
BP[a] ≥130/85 or on treatment, %	46.4	46.4	46.4	0.906
Fasting glucose ≥5.5 mmol/L, %	57.1	58.0	56.5	0.981
Low HDL[b]-cholesterol, %	60.2	68.5	54.7	0.006
Triglycerides ≥1.7 mmol/L, %	19.9	18.8	20.7	0.538
WC[c], %	65.9	61.9	68.5	0.118
Metabolic syndrome by IDF[d], %	47.3	42.5	50.4	0.101
Metabolic syndrome by mNCEP[e], %	52.3	51.4	52.9	0.491

[a] BP, blood pressure
[b] Low HDL, high density lipoprotein <1.0 mmol/L for males, <1.3 mmol/L for females
[c] High WC, waist circumference ≥90 cm for males, ≥80 cm for females
[d] IDF, International Diabetes Federation
[e] mNCEP, modern National Cholesterol Education Program

Table 7. Prevalence of metabolic syndrome according to socio-demographic characteristics of CHWs

Demographic characteristics	n	MetS[a] by IDFb (%)	*p* value	MetS[a] by mNCEPc (%)	*p* value
Age, yr					
<50	222	42.3	0.045	43.7	<0.0001
≥50	230	51.7		60.4	
Civil status					
No domestic partner	106	49.1	0.736	57.6	0.145
With domestic partner	337	47.2		51.3	
Education					
Elementary	79	57.0	0.060	67.1	0.004
High school/college	362	45.3		49.5	
Place of residence					
Rural	181	42.5	0.101	51.4	0.491
Urban	276	50.4		52.9	
Ever consumed ≥1 drink of any type of alcoholic beverage					
Yes	117	44.4	0.422	47.9	0.271
No	324	48.8		54.6	
Current smoker					
Yes	28	21.4	0.004	39.3	0.101
No	413	49.4		53.8	
Time spent in sedentary activities, hours					
<5	69	44.9	0.632	53.6	0.854
≥5	362	48.1		52.8	

[a] MetS, metabolic syndrome
[b] IDF, International Diabetes Federation
[c] mNCEP, modern National Cholesterol Education Program

smokers, borderline to high TC, TG, LDL-c, and low HDL-c. On the other hand, this study showed a higher prevalence of obesity (11.2% by WHO and 43.8% by the Asia Pacific classification), hypertension (32.4%) and diabetes (13.6%) compared to the national data. These two populations may not be comparable since majority of the CHWs in this study were females and older with a median age of 50 years, compared with the NNS adult population which was randomly selected nationwide.

The current policy under R. A. 7833 considers BHWs as merely volunteers. CHWs, in general, were mostly females. One usual explanation for this is the cultural expectations and social norms that men are supposed to be breadwinners while women are homemakers, which includes the role of taking care of the sick. Majority of Filipino males have full-time jobs, and more women are out of the workforce. The 2016 Labor Force Survey showed that 78% of Filipino men are in the labor force compared to just 49% among women.[19] It was also observed by Najafizada in Afghanistan that female CHWs accomplished their tasks vis-à-vis maternal and child health with greater ease compared to their male counterparts. Female CHWs may be more helpful in the realm of maternal health because female patients are more comfortable sharing problems related to reproductive health to a female CHW.[20]

Six percent of the CHWs in the present study were current smokers, lower than the overall national prevalence (25%) in the 8th NNS.[16] It was expected that the prevalence of current smokers among CHWs was lower since 96% of the participants were females, and the national prevalence of current smokers among women was only 7.8%. However, the prevalence of current smokers was higher among rural CHWs compared to their urban counterparts. Rural residency has long been associated with higher rates of smoking. Based on a study in the United States, compared to their urban counterparts, rural communities have higher rates of risky behaviors such as smoking.[21]

Older age, alcohol consumption and higher BMI were independently associated with hypertension in the study population. This finding was consistent with other studies in Malaysia, India, and Kenya.[22-25] Similarly, bivariate analysis showed that civil status was found to be associated with hypertension, as observed in other studies.[26,27] It was hypothesized that social integration, such as marital state and cohabitation, can influence health status, specifically blood pressure level.[27] It can partly be explained that when cohabiting, there may be a social support system which is protective from having hypertension. On the other hand, the economic aspects of living alone may also be considered as a factor contributing to higher blood pressure, since married individuals potentially have higher financial resources that could promote healthy lifestyles.[26] In this study, hypertension was higher among CHWs with lower educational attainment, consistent with other studies in

Malaysia and rural Delhi.[22,25] Many researchers prefer education as an indicator of lifetime socio-economic status and it has been shown to be positively associated with better health.[28]

The prevalence of diabetes was higher among CHWs compared to the national estimate of the 8th NNS among the general adult population. Older age, those living in urban areas and those who spent at least 5 hours a day in sedentary activities were more likely to have diabetes. These findings were similar with previous studies conducted in Vietnam and South Asia.[29,30] The cause of diabetes has been attributed to a variety of social and lifestyle factors that can be modified. Higher rate of obesity in this population may explain the high prevalence of diabetes, as it is a major contributory factor to the current diabetes epidemic.[31] The lifestyle of CHWs living in the rural areas is relatively more active as compared to those in the urban areas as indicated by the higher percentage of physical inactivity. Most people in the rural areas live and work on farms or fisheries which require physical activities such as walking, swimming, gardening, planting or fishing. The higher prevalence of diabetes in urban areas may partly be explained by the sedentary lifestyle observed in urban areas. Sedentary lifestyle is characterized by sitting or lying down while engaged in activities like reading, watching television or using mobile phones, to name a few. Environmental factors associated with cardiovascular risk factors differ widely across populations. This may be due to culture and stage of urbanization. Specific populations in different locations may adopt diverse lifestyles, and one of the most marked societal and environmental changes has been linked with urbanization.[32]

CHWs are the significant link between communities or families and the formal health systems. They are known to be effective community organizers, health educators, and health care providers. With the recent passage of R.A. No. 11223, the Universal Health Care Act, for the DOH to effectively implement their strategic thrust to attain universal health care for all, the contribution of CHWs cannot be overlooked. However, based on the results of this study, CHWs are aging and have higher rates of obesity, hypertension and diabetes compared to the general population. Their credibility as health workers is linked to their health status. Modelling healthy behaviour is a vital function of CHWs, and unhealthy behaviours and conditions among them render their ability to promote health and provide health messages less effective. Full implementation of R.A. 7883 is essential to look into the welfare of the CHWs and provide them due benefits and incentives under the Magna Carta for Public Health workers. CHWs can be considered as among the priority in appropriating budgetary allocation using the "Special Health Fund" of the Universal Health Care Act. The local authorities hiring community health workers must establish well-defined selection criteria and adopt occupational health programs to ensure effectiveness of services given by the health workers. The provision of patient support programs, such as free medicines, laboratory exams and lifestyle advice, would also improve the present health condition of CHWs in the communities. The health status of CHWs must be addressed for them to perform better in the delivery of health services in their respective communities.

The results of this study gave us an overview of the cardiovascular risk profile among CHWs from selected villages in the Philippines. These findings may be validated in a greater scale that would be representative of the CHWs nationwide. This can be made possible once the Universal Health Care law is fully implemented.

CONCLUSION

Metabolic syndrome is prevalent among CHW participants, with obesity, hypertension and low-HDL-c as the most common components of metabolic syndrome present. Older CHWs, those who consumed alcoholic drinks and those with higher BMI were more likely to have hypertension. Moreover, older CHWs and those who spent at least 5 hours of sedentary activities tended to have diabetes. The prevalence of cardiovascular risk factors in this population was not found to be significantly different between rural and urban areas after adjusting for other factors.

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All authors certified fulfillment of ICMJE authorship criteria.

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The authors declared no conflict of interest.

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ORIGINAL ARTICLE

Diabetes-Related Attitudes of Health Care Providers in Rural Health Centers in Aklan, Philippines using the Filipino Version of Diabetes Attitude Scale (DAS-3)

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Abstract

Objectives. To determine the beliefs and attitudes towards diabetes of rural health care providers in Aklan, Philippines using the Diabetes Attitude Scale 3 (DAS-3) and to determine factors associated with it.

Methodology. This is a cross-sectional analytic survey. A total of 339 health care providers were given self-administered DAS-3 questionnaires. Additional data gathered included their age, highest educational attainment, position, municipality class, diabetes as a co-morbidity, attendance to diabetes classes, and family history of diabetes.

Results. Rural health care providers showed an overall mean positive attitude score of 3.5 using the DAS-3 questionnaire. In decreasing order, mean scores of participants according to subscale is as follows: "Need for Special Training in Education" (4.13) >"Autonomy of diabetes for patients" (3.70) >"Psychosocial Impact of Diabetes" (3.60) >"Value of Tight Glucose Control" (3.14) and "Seriousness of Type 2 Diabetes" (3.09). Physicians have the highest mean scores consistently in all subscales compared to other health care providers. Among the different factors considered, educational attainment (p=0.005) and work position (p=<0.001) were found out to affect attitude score of health care providers.

Conclusions. This study has shown that the majority of the rural health care providers believe in the need for special training of healthcare providers, psychosocial impact of diabetes and patient autonomy in diabetes self-care. However, the majority still do not strongly believe in the seriousness of diabetes and the benefits of tight sugar control. Educational attainment and work position are the consistent factors that impact diabetes-related attitude; therefore, the need to strengthen continuous medical education among health care providers.

Key words: DAS-3, type 2 diabetes, attitude, Rural Health Center

INTRODUCTION

Diabetes and its complications impose a heavy burden to the individual, to the individual's family and to the society in general. In the Philippines, it is estimated that there are 3.2 million cases of Type 2 Diabetes Mellitus with a 5.9% prevalence rate among adults between the ages of 20 and 79 years, of which only 20% have good glycemic control (Hba1c <7%).[1,2] The high burden of diabetes and its complications in the country is somehow an indirect reflection of its health care delivery system.

The Philippine health care delivery system is a three-tier system, similar to other countries, composed of both private and public facilities. Data from the 2008 National Demographic and Health Survey (NDHS) showed that about 50% percent of Filipino patients availed health services from public health facilities, 42% from private facilities and 7% from alternative or traditional medicine.[3] Rural Health Units (RHUs) and Barangay Health Centers, which represent the most basic unit, is the most visited public health care delivery facility across the country. This constitutes 33% of all visits mainly because of affordability and easy access.[3]

With the advent of healthcare decentralization from the national government to the local government unit, Rural Health Units (RHU) and Barangay Health Centers became the primary unit for the delivery of basic health services for patients belonging under the municipal and barangay level (local neighborhood).[4] These local facilities are managed by the municipal health officer (local physician) and supported by rural health nurses, midwives, and barangay health workers (BHWs). In relation to diabetes care, healthcare providers from both RHU and BHS are responsible for the basic screening and provision of lifestyle change, diabetes self-managed education (DSME) and provision of low-cost medications to the local community especially the indigent patients.[3,5]

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To ensure the proper delivery of these basic services to the grass root levels, it is imperative that these front liners of basic health units have the proper attitude and beliefs towards diabetes, since an individual's attitude influences on how an individual responds to health promotion information and how an individual would educate his/her patients. It has been reported that poor diabetic care of patients is due to the prevalent and misguided attitudes of both healthcare professionals and patients with diabetes.[6] Barangay Health Workers (BHWs) in particular, being the first line in the barangay level (local neighborhood) and constitute the largest number among rural health care professionals, are particularly vulnerable to having misguided attitudes toward diabetes due to inadequate diabetes education and training. There are currently no published data about that impact of diabetes-related attitudes on rural healthcare professionals, especially the BHWs. Therefore, it is essential to determine the diabetes-related attitudes of healthcare professionals since the improvement of attitude toward diabetes also improves adherence to diabetes care.

The third version of Diabetes Attitude Scale (DAS-3) by Anderson et al. of the University of Michigan is one of the several questionnaires that was developed to measure general diabetes-related attitudes of both people with diabetes and health care professionals.[7]

This validated tool has already been used and adapted in different languages and has shown to be valid and reliable. Studies done on diabetes-related attitudes of healthcare professionals have different attitude patterns across different parts of the world, showing the influence of diverse cultural settings. In the Philippines, Yao et al., in 2004 have developed a validated Filipino version DAS-3 which was used to survey persons with diabetes in the outpatient department of the UP-Philippine General Hospital.[8] This questionnaire was likewise utilized by Ardeña et al., to evaluate the knowledge, attitudes and practices of a person with Type 2 diabetes in a rural community in the Philippines.[9] However, no study yet was conducted evaluating the diabetes-related attitude of healthcare professionals in the local setting, hence the purpose of this study.

Using the Filipino version of Diabetes Attitude Scale (DAS-3) questionnaire, it is the aim of this study to determine the beliefs and attitudes of rural healthcare professionals in Aklan, Philippines towards diabetes and its treatment which include the following aspects: 1) need for special training in education, 2) seriousness of type 2 diabetes, 3) value of tight glucose control, 4) psychosocial impact and 5) patient autonomy. Moreover, this study aims to determine the association of DAS-3 scores with factors such as age, highest educational attainment, health care provider's position, municipality class, diabetes as a co-morbidity, attendance to diabetes classes and family history of diabetes.

The data that would be gathered from this study would be helpful for national policymakers to identify areas in which improvement can be implemented through policies and programs that would provide additional educational and technical support for rural HCPs to provide better diabetes care.

METHODOLOGY

Study design / methodology

This is a cross-sectional analytical, multicenter survey among health care providers of rural health units in Aklan, Philippines.

Study population

This study included health care providers from different rural health centers from all municipalities of the province of Aklan, Philippines. This included the physicians, nurses, midwives, and the barangay health workers (BHW). They were provided with consent form prior to participating in the study.

Sample population size of healthcare providers from each municipality was determined using stratified random sampling, in which representatives of each healthcare provider position were included in the study. The number of subjects was computed based on a master list of employees obtained from each municipal health office of all 17 municipalities from the province of Aklan, Philippines. Computation of sample population size for each group of health care workers was set with the level confidence of 95%, response to distribution of 50% and a margin error of 5% based on previous DAS-3 survey. Because the population size of physicians, rural health nurses and midwives per municipality are small, almost all were included in the sample population (See Appendix 1). The target sample population number of barangay health workers were evenly distributed to every 17 municipalities.

Inclusion criteria

Participants who can read, write and comprehend either Filipino, *Akeanon* (local dialect) and English language.

Exclusion criteria

a) Health care providers who have difficulty reading and understanding questionnaires due to language barrier
b) Healthcare providers who will not consent to answer the questionnaires

Instrument

The diabetes attitude scale was adapted from the Third Version (DAS-3) developed by Anderson et al. and a Filipino version by Yao et al. The Filipino version was validated and translated by the *University of the Philippines Manila Sentro ng Wikang Filipino* which was used in the study of Yao et al in their study at University of the Philippines - Philippine General Hospital. The authors gave formal consent regarding the use of Filipino version of DAS-3 questionnaire in this study. The local version was translated to *Akeanon* dialect and underwent peer-review by the *West Visayas State University Sentro ng Wikang Filipino* (Center of Filipino Language).

The questionnaire contains 33 questions, composed of five subscales, namely:

1. The need for special training in education (Number of Items: 5)
   - Assesses the respondent's attitude about the need for health care providers who care for patients with diabetes to have special training in teaching, counseling and behavior change techniques.
2. Seriousness of Type 2 Diabetes (Number of Items: 7)
   - Assesses the respondent's attitude about the seriousness of Type 2 Diabetes
3. The overall value of tight glucose control in diabetes care (Number of items: 7)
   - Assesses the respondent's attitude about whether the potential benefit of tight glucose control is justified in terms of the cost to the patient
4. Psychosocial impact of diabetes on patients (Number of items: 6)
   - Assesses the respondent's attitude toward the psychosocial impact of diabetes on the lives of the people with the disease
5. Attitude toward patient autonomy (Number of items: 8)
   - Assesses the respondent's attitude about whether patients should be the primary decision-makers regarding the daily self-care of their diabetes

Additional data that were gathered included the age of the participant, gender, healthcare provider position/role, educational attainment, history of diabetes, attendance in diabetes classes, presence of relatives with diabetes and the municipality class to which the participant's rural health center belong. For the classification of municipality class, this is based on the municipality's annual average income set by the Philippine Government's Department of Finance.[10]

The survey proper was conducted under the supervision of the researchers. Clarifications regarding the questions/ items were allowed under the proper supervision of the researchers.

Survey Proper

The study protocol and informed consent forms were submitted to and approved by the Institutional Research Ethics Review Board (IRB). Letter of intention to conduct the study was also sent to each of the department heads of rural health centers involved in the study.

Each subject was given a printed explanation of the study including its purpose, type of information sought and the confidentiality of their response. Participants were given the choice of which version of the DAS-3 questionnaire they will answer in accordance to which language they are more adept with. This is to minimize errors in comprehending questions due to language barrier. They were then requested to complete the self-administered DAS 3 questionnaire. Patients at the onset of the survey are requested to indicate if he/she has difficulty of understanding majority of the questions as to exclude them from the study. No further revisions were made on the translated Filipino version of the questionnaire.

Survey proper and data collection was done from May 2018 to July 2018 in all municipal health office of each municipality included in the study.

One-way Analysis of Variance (ANOVA) and a Tukey HSD post hoc test was used for data analysis to compare score among the healthcare professionals. A univariate and multivariate regression analysis was also used to determine the relationship of attitude scores (both in nominal and ordinal form) and socio-demographic characteristics such as municipality class to which the participant's rural health center belong, age of the participant, gender, healthcare provider position/role, educational attainment, diabetes as co-morbid, attendance in diabetes classes and presence of family history with diabetes. The statistical software package Microtab statistical software and Raosoft sample size calculator was used for this analysis.

RESULTS

Out of 487 participants that were invited in this study, only 339 participants were able to participate with an overall response rate of 69.60%. There were 19 doctors, 27 nurses, 122 midwives, and 171 barangay health workers who participated with response rates of 95%, 84.38%, 129.79%, and 50.15% respectively.

The majority of participants are females (N=287, 84.6%) and have a mean age of 49.66±11.33 years with most respondents coming from the 50-59 years old bracket (N=144, 52.8%).

Majority of the responders are barangay health workers comprising 50.44% of the total population (N=177). Most of the subjects were college graduates (N=186, 54.6%). More than half (N=194, 57.23%) have in any way attended some form of DM class. A third of the respondents have diabetes themselves (N=107,31.56%), and more than half of the respondents have 1 or more relatives who have diabetes (N=192,56.64%) (Table 1).

Table 1. Demographic characteristics of the study sample (n=339)

Characteristics	Mean±SD; frequency count (percentage)
Age	49.66±11.33
Sex	
Male	52 (15.34)
Female	287 (84.66)
Educational Attainment	
Elementary	40 (11.80)
High School	69 (20.35)
Vocational	26 (7.67)
College	186 (54.87)
Doctor of Medicine	18 (5.30)
Attended Diabetes Class	194 (57.23)
Diabetes as co-morbid	107 (31.56)
With Family History of Diabetes	192 (56.64)
Healthcare provider's Position	
Barangay Health Workers	171 (50.44)
Midwives	122 (35.99)
Nurses	27 (7.96)
Doctors	19 (5.60)
Municipality Class of RHU	
1	50 (14.75)
3	89 (26.25)
4	152 (44.84)
5	48 (14.16)

Note: RHU - Rural Health Unit. Municipality Class 1 -55,000,000 average annual income; Class 2 - 45,000,000 - 54,999,999; Class 3 - 35,000,000 - 44,999,999; Class 4 - 25,000,000 - 34,999,999; Class 5 - 15,000 to 24,999,999; Class 6 - less than 15,000,000

The overall Diabetes Awareness Score among all the participants shows a mean positive score of 3.5, or a positive score, according to the DAS-3 questionnaire scoring system. (Table 2) Among the given subscales, "The Need for Special Training in Education" garnered a positive response with a score 4.13 of the total population, while "Seriousness of Type 2 Diabetes" garnered the lowest score of 3.09, which is a neutral response. In decreasing order, the overall response score is as follows: "Need for Special Training in Education">"Autonomy of diabetes for patients">"Psychosocial Impact of Diabetes">"Value of Tight Glucose Control and lastly seriousness of Type 2 Diabetes."

Using one-way analysis of variance (ANOVA), the mean scores for each subscale were compared among the healthcare professionals. In the subscale of 'need for special training,' rural health physicians have greater mean scores statistically compared to nurses, midwives, and barangay health workers, who have comparable mean scores. This is also true in the other subscales such as 'seriousness of diabetes' and 'psychosocial impact of diabetes.'

In the subscale of 'value of tight glucose control,' both medical doctors and rural health nurses have no significant difference in their attitude scores but are significantly higher compared to midwives and barangay health workers (BHWs).

For the subscale of 'autonomy of diabetes for patients' showed that the mean scores of the doctors, nurses and barangay health workers are comparable and are statistically higher than that of the midwives (Table 3).

A univariate and multivariate regression analysis done showed that highest educational attainment and position of health care providers are statistically significant (*p* 0.005, <0.001). The coefficients suggest that education and position are positively related to diabetes attitude scores. These imply that professionals with higher educational attainment and those with higher work position tend to have high scores. However, in the multivariate regression analysis, only position was statistically significant. The coefficient suggests that position is positively associated with diabetes attitude scores (Table 4).

Table 2. Diabetes Attitude Scores of Health Care Professional

Subscales	Mean	SD
Need for Special Training	4.13	0.59
The Seriousness of Diabetes	3.09	0.38
The Value of tight blood glucose	3.14	0.49
The Psychological impact of diabetes	3.6	0.47
Autonomy of diabetes for patients	3.7	0.5
Overall	3.53	0.47

Legend: Very positive 4.21 – 5.00, positive 3.41 – 4.20, neutral 2.61 – 3.40, negative 1.81 – 2.60, very negative 1.00 - 1.80

Table 3. Comparison of Diabetes Attitude Scores among Health Care Professional Groups

Items	Professional Category	Mean (±SD)	F	*P*
Need for Special Training	Medical Doctors	4.7263 (0.2922)	7.3	<0.001
	Nurses	4.1111 (0.3523)		
	Midwives	4.1311 (0.5885)		
	BHW	4.0737 (0.6185)		
The Seriousness of Diabetes	Medical Doctors	3.6095 (0.4026)	15.06	<0.001
	Nurses	3.0056 (0.3422)		
	Midwives	3.0866 (0.3410)		
	BHW	3.0446 (0.3600)		
The value of tight blood glucose	Medical Doctors	3.7300 (0.3433)	16.76	<0.001
	Nurses	3.3815 (0.4926)		
	Midwives	3.1543 (0.4031)		
	BHW	3.0182 (0.5059)		
The psychological impact of diabetes	Medical Doctors	3.8947 (0.2501)	16.17	<0.001
	Nurses	3.0741 (0.5396)		
	Midwives	3.5965 (0.3960)		
	BHW	3.6488 (0.4735)		
Autonomy of diabetes for patients	Medical Doctors	3.9295 (0.1694)	8.45	<0.001
	Nurses	3.7522 (0.3143)		
	Midwives	3.5353 (0.4581)		
	BHW	3.7968 (0.5449)		

Note: **Significant at 0.05 using Analyses of Variance (ANOVA)
Since the *P*-Values are less than 0.05 (the level of significance), then the F-values are statistically significant. This means that there are at least two means that are significant different. BHW – Barangay Health Worker

Table 4. Univariate and multivariate regression analysis of Diabetes Attitudes Score and demographic/medical variables of the Health Care Professionals

Demographic/medical variables	Univariate regression analysis				Multivariate regression analysis			
	Coefficient	SE Coefficient	T	*P*	Coefficient	SE Coefficient	T	*P*
Municipality Class	0.01611	0.01248	1.29	0.197**	0.01581	0.01287	1.23	0.220**
Age	-0.002508	0.001309	-1.92	0.056**	-0.002149	0.001366	-1.57	0.117**
Diabetes	-0.01496	0.03006	-0.5	0.619**	0.05244	0.03281	1.6	0.111**
Educational Attainment	**0.03512**	**0.01229**	**2.86**	**0.005****	0.00683	0.01828	0.37	0.709**
Position	**0.07086**	**0.01722**	**4.11**	**<0.001****	**0.0754**	**0.02583**	**2.92**	**0.004****
Family History	0.02242	0.02999	0.75	0.455**	-0.00857	0.0312	-0.27	0.784**

Note: **Significant at 0.05

Table 5. Univariate and multivariate ordinal analysis of Diabetes Attitudes Score and demographic/medical variables of the Health Care Professionals

Demographic/medical variables	Univariate regression analysis				Multivariate regression analysis			
	Coefficient	SE Coefficient	T	*P*	Coefficient	SE Coefficient	T	*P*
Class (First)								
Third	-1.1915	0.3	-3.2	**0.001****	-1.3112	0.27	-3.29	**0.001****
Fourth	-0.5826	0.56	-1.78	0.076**	-0.6228	0.54	-1.78	0.076**
Fifth	-0.4116	0.66	-1.01	0.311**	-0.4542	0.63	-1.01	0.310**
Age	0.02029	1.02	1.99	**0.046****	0.02292	1.02	2.04	**0.042****
Diabetes (No)								
Yes	0.0824	1.09	0.36	0.716**	0.2118	1.24	0.82	0.412**
Education (College)								
Elementary	0.1603	1.17	0.45	0.649**	0.6075	1.84	1.19	0.234**
High School	-0.099	0.91	-0.34	0.734**	0.2033	1.23	0.44	0.658**
Medical Doctor	-2.5856	0.08	-2.61	**0.009****	0.422	1.52	0.11	0.911**
Vocational	0.1525	1.16	0.36	0.719**	0.6919	2	1.24	0.214**
Position (BHW)								
MHO	-2.5391	0.08	-2.8	**0.005****	-2.943	0.05	-0.79	0.428**
MW	0.0402	1.04	0.17	0.869**	0.2685	1.31	0.61	0.540**
PHN	0.746	2.11	1.78	0.074**	1.2597	3.52	2.25	**0.025****
Family History (No)								
Yes	0.0873	1.09	0.39	0.699**	0.0562	1.06	0.22	0.827**

Note: **Significant at 0.05
BHW – Barangay Health Worker; MHO – Municipal Health Officer; MW – Midwife; PHN – Primary Health Nurse

A univariate and multivariate ordinal regression analysis was also done for attitude scores that were classified as very positive, positive, neutral, very negative, and negative according to the DAS-3 questionnaire scoring system. Results showed that third class municipality, age, medical doctor degree, and municipal health officer position are statistically significant. The coefficients and odds ratios indicate that medical doctor degree, medical health officer position and health care professionals who belong from third class municipalities are more likely to respond "very positive" than other factors that were examined (Table 5).

In the multivariate logistic regression analysis, third class municipality, age, and primary health nurses (PHN) are also statistically significant. The coefficients and odds ratios indicate that the health care professionals from third class municipalities are more likely to respond “very positive” than those from first class municipalities; the older the health care professional is, the more likely he/she is to respond “neutral;" and primary health nurses (PHN) is more likely to respond "neutral” than the BHW.

DISCUSSION

This study shows that rural health center healthcare professionals generally have neutral diabetes-attitude scale. Health care professionals showed the most positive response towards the issue of “Need for Special training in education” and least responsive towards “Seriousness of Type 2 Diabetes,” which is a neutral response. Factors that consistently affect the attitude scores of healthcare professionals include highest educational attainment and the health care professional’s position.

The subscale “Need for Special Training in Education” assesses the respondent’s attitude about the need for health care professionals who care for patients with diabetes to have special training in teaching, counseling, and behavior change techniques. In this study, health care professionals scored positively (4.13) in this subscale, reflecting the importance of training in improving effective communication to patients regarding daily diabetes care. In this subscale, medical doctors scored a very positive attitude score as compared to other health care professionals.

The importance of being adept in proper counseling among health care professionals is that this will allow them to be effective in communicating the basics of diabetes education and care to their patients. This will also enable them to confidently clarify frequently asked questions and correct the patient's misconceptions.[11]

The subscale of 'Psychological Impact of Diabetes’ and 'Autonomy of Diabetes for Patients’ have mean scores that are generally positive. This shows that healthcare professionals, in general, have a positive attitude towards issues concerning on how diabetes affects patient’s daily lives and empowering the role of patients for self-autonomy in management of their problems. Attitude towards these subscales could be further improved with continuous medical education and training of the healthcare professionals.

It is alarming that the majority of the respondents are least responsive towards 'seriousness of type 2 diabetes' and 'value of tight glucose control'. 'Seriousness of type 2 diabetes’ scale assesses the respondents’ attitude towards the belief that type 2 diabetes is a serious disease. On the other hand, the 'overall value of tight glucose control’ scale assesses the respondent’s attitude about whether the potential benefit of tight glucose control is justified in terms of the cost to the patients. The attitude toward both of these subscales is vital because it influences the health care provider's aggressiveness in patient management and prevention of complications. The results show that the majority of the health care providers, except for medical doctors, still take type 2 diabetes and its complications lightly. The measly attitude score reflects the seeming lack of awareness regarding the nature of type 2 diabetes and its chronic complications among health care providers.

This poor awareness is also true regarding the overall benefits of good sugar control in the prevention of long-term complications brought about uncontrolled diabetes. The need to address the prevention of microvascular and macrovascular complications in both Type 1 and Type 2 Diabetes has been emphasized in both Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS).[12,13] Both these landmark studies and their respective follow-up studies, have shown that tight glycemic control significantly lowers the occurrence of both microvascular and macrovascular complications.

The reason in which attitude towards 'value of tight glucose control' might have garnered a low score by health care providers is the misconception that complications brought about by diabetes are inherent to the disease and are not related to glucose control.[8] Another factor is the fear of overtreatment and the risk of hypoglycemia. This fear of hypoglycemia might be attributed to overall poor basic knowledge of diabetes care among healthcare workers, thus the fear of hypoglycemia limit the goal for intensive glucose control. This is seen in the previous study by Nakar et al., in which it showed that the fear of hypoglycemia is the most common reason for not starting insulin therapy on both physicians and patients.[14]

The overall mean scores of this study are comparable to previous studies done in Argentina, Yemen, and United Arab Emirates (UAE) (See Table 6).[6,15,16] It showed a similar trend in which high scores are garnered in 'need for special training in education and autonomy for patients,' while subscales that consistently fared the lowest are the 'seriousness of diabetes' and 'the value of tight glucose control'. Using analysis of variance to compare attitude scores among health care professionals from different countries, it showed that Argentina and United Arab Emirates (UAE) have significantly higher scores in the subscales of 'need special training,' 'seriousness of diabetes' and 'value of tight glucose control' as compared to this local study. This could be explained by the sample population included in the Argentina and UAE studies. Both the Argentina and UAE studies included only professional and licensed health care providers who got certifying exams, while in this local study, more than half of the population are barangay health workers (BHW), of which 50% are only high school graduates and did not undergo certifying exams.

Barangay health workers (BHWs), or known internationally as Community Health Workers (CHW), play a huge and essential role in terms of the scope of the population served, being the first line in the health care delivery system. The Philippine law, by Republic Act 7883, refers to a Barangay Health Worker as a person who voluntarily renders primary health care services in the community after undergoing accredited training under the guidelines set by the Department of Health (DOH). Their primary function is to provide information, education, and motivation services for primary health care, maternal and child health, family planning, and nutrition in the communities they live in. Unfortunately, the majority of the BHWs lack competency and basic training in effectively performing their duties which was seen in a local study by Dagangon et al. The results of that study showed that BHWs lack sufficient knowledge and skills in areas of BHW orientations, safer motherhood, women's health, children's health and interpersonal health.[17] Moreover, their functions go beyond what was mentioned earlier, because, in reality, they are also utilized as an adjunct to physicians and nurses in national programs such vaccination, deworming, tuberculosis program and non-communicative diseases such as diabetes. The imbalance between the BHW's level of training and the programs thrust to them leads to inadequate and ineffective health care delivery. This same pattern of the inadequacy of training is evident in this present study as reflected by their poor diabetes-related attitude scores as compared to other members of the rural health center, who are professionally certified.

In contrast, this local study has the highest score in "autonomy of patients" and garnered second only to UAE in issues concerning 'psychosocial impact of diabetes'. This data showed that each country differs in attitudes toward a particular subscale, possibly because of cultural differences.

In analyzing factors that might be associated with the attitude scores of this local study, results of univariate and multivariate regression analysis and univariate and multivariate ordinal regression analyses showed that degree of educational attainment and work position has consistently shown a positive correlation to mean attitude scores. This association is consistent with an earlier study by Steele et al., in which it showed that the lowest educated individuals have a higher risk of developing Type 2 Diabetes and its complication during the follow-up period as compared to patients who are highly educated.[18] It is expected that the municipal health physicians have superior knowledge as compared to other members of the health unit because of their rigorous training and regular attendance in continuous medical education (CME). Therefore, there is a need to improve the knowledge gap between the physicians and other members of healthcare providers, by supporting them to undergo regular continuous medical education, especially in diabetes care.

Other factors that significantly affect mean attitude score are age and health care professionals coming from the third class municipalities. The coefficients and odds ratios indicate that the health care providers from the third class municipalities are more likely to respond "very

Table 6. Comparison of DAS-3 Mean scores of healthcare professionals in Philippines, Yemen, UAE and Argentina

Subscale	Philippines (Aklan)	Yemen[8]	Argentina[10]	UAE[9]	F-value	*P*-value
Need for special training in education	4.13±0.59	4.2±0.47	4.58±0.35	4.5±0.38	82.29	<0.01
Seriousness of diabetes	3.09±0.38	2.99±0.49	3.64±0.54	3.84±0.48	178.68	<0.01
Value of tight glucose control	3.14±0.49	3.3±0.67	3.5±0.38	3.5±0.43	54.43	<0.01
Psychosocial impact of diabetes	3.6±0.47	3.5±0.49	3.29±0.46	3.85±0.49	99.8	<0.01
Autonomy of diabetes for patient	3.7±0.47	3.3±0.49	2.79±0.38	3.31±0.45	308.71	<0.01

Note: Significant at <0.01

positive" than those from first-class municipalities. The result is counter-intuitive since it is expected that those coming from first class municipalities should have better diabetes-related attitudes since they have easier access to CME and have more well-equipped health facilities. This goes to show that belonging to rural health center of a lower class municipality is not a hindrance in improving diabetes-related attitude through CMEs. The other factor is age, in which older health care providers are more likely to respond with a "neutral" attitude score. This can be explained by the accumulation of training and experience dealing with patients with diabetes through years of service.

Other factors did not show a significant association with mean attitude scores. Factors such as attendance of diabetes classes, presence of diabetes in the family, and diabetes as a co-morbid did not show a positive relationship with the DAS-3 scores. This underscores the need to improve the quality and adequacy of diabetes education given by diabetes educators to health care providers to affect their diabetes-related attitude significantly.

Limitation of the study

The limitation of this study is the small sample size and poor response rate, especially from the barangay health workers. The problem arose because the study covered the whole province of Aklan, Philippines which brings geographic and logistic limitations in reaching all barangay health workers, especially those assigned in far-flung health stations within a specific study time frame.

CONCLUSIONS

Using DAS-3 questionnaires, this study has shown that rural health care professionals garnered an overall positive attitude towards diabetes. Notably, they are most responsive to the need for special training among health care professionals, the psychosocial impact of diabetes and patient autonomy in caring for their condition. However, the majority of HCPs have neutral responses in "value of tight glucose control" and "seriousness of type 2 diabetes" suggesting that most of them do not believe in the benefits of controlling sugar to prevent diabetes complications and the seriousness of the disease. Among the factors considered, educational attainment and work position was found out to be the consistent factors that affect the diabetes-related attitude of HCPs. This suggests that education and training impacts in improving the diabetes-related attitude of HCPs. Therefore, there is a need to strengthen continuous medical education among the first line of health care providers, especially the midwives and the Barangay health care workers.

Recommendations

This study recommends increasing the scope of the population of this study to include rural health centers across the country. In this way, it could provide baseline data which could accurately determine the attitudes towards diabetes of health care providers in the country. A posttest can be done after an intervention is given, such as formal diabetes classes and workshops using DAS-3 used in this study to assess the effectivity of the intervention given. Furthermore, assessment can be done not only to the health care providers of rural health centers but also those belonging to the urban City Health Centers as well.

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APPENDIX

Appendix 1. Study population response rate size according to health care worker group

Respondents	Population size	Minimum sample size	N	Response rate
Physicians	20	20	19	95.00%
Rural Health Nurses	34	32	27	84.38%
Rural Health Midwives	123	94	122	129.79%
Barangay Health Workers	3067	341	171	50.15%
TOTAL	3244	487	339	69.60%

Note: Target sample size computed using the Raosoft sample size calculator. Confidence Interval 95%, response distribution 50% and margin of error 5%.

Appendix 2. Frequency of diabetes attitude scores of health care professionals according to subscale

	Very Positive (5)	Positive (4)	Neutral (3)	Negative (2)	Very Negative (1)
Need for Special Training	157 (46.31%)	130 (38.35%)	47 (13.86%)	5 (1.47%)	0
The Seriousness of Diabetes	4 (1.18%)	65 (19.17%)	244 (71.98%)	26 (7.67%)	0
The Value of tight blood glucose	1 (0.29%)	120 (35.40%)	161 (47.49%)	57 (16.81%)	0
The Psychological impact of diabetes	21 (6.19%)	198 (58.4%)	114 (33.63%)	6 (1.77%)	0
Autonomy of diabetes for patients	56 (16.52%)	180 (53.10%)	102 (30.09%)	1 (0.29%)	0

Notes: Values are listed according to frequency and corresponding percentage

Appendix 3. Post hoc test for one-way ANOVA using Tukey HSD comparing mean scores among healthcare professionals

Items	Pair	Tukey HSD Q Statistic	Tukey HSD P-Value
Need for special training	BHW vs MHO	6.6097	0.0010053**
	BHW vs MW	1.1876	0.8140649
	BHW vs PHN	0.4426	0.8999947
	MHO vs MW	5.9102	0.0010053**
	MHO vs PHN	5.0317	0.0024073**
	MW vs PHN	0.2307	0.8999947
Seriousness of diabetes	BHW vs MHO	9.3237	0.0010053**
	BHW vs MW	1.4144	0.7241862
	BHW vs PHN	0.7518	0.8999947
	MHO vs MW	8.4623	0.0010053**
	MHO vs PHN	8.0494	0.0010053**
	MW vs PHN	1.5201	0.6822831
Value of tight blood glucose	BHW vs MHO	9.0035	0.0010053**
	BHW vs MW	3.5121	0.0644366
	BHW vs PHN	5.366	0.0010053**
	MHO vs MW	7.1404	0.0010053**
	MHO vs PHN	3.56	0.0591311
	MW vs PHN	3.2678	0.0975715
Psychological impact of diabetes	BHW vs MHO	3.2453	0.1012762
	BHW vs MW	1.4099	0.7259577
	BHW vs PHN	8.8575	0.0010053**
	MHO vs MW	3.8594	0.0336748*
	MHO vs PHN	8.7463	0.0010053**
	MW vs PHN	7.8389	0.0010053**
Autonomy of diabetes for patients	BHW vs MHO	1.5977	0.651527
	BHW vs MW	6.4282	0.0010053**
	BHW vs PHN	0.6277	0.8999947
	MHO vs MW	4.6554	0.0060371**
	MHO vs PHN	1.7243	0.6013456
	MW vs PHN	2.9708	0.1550656

Note: ** Significant at 0.01 and * significant at 0.05
MHO – Municipal Health Officer; PHN – Primary Health Nurse; MW – Midwife; BHW – Barangay Health Worker

Appendix 4. Post hoc test for one-way ANOVA using Tukey HSD comparing mean scores among different countries

	Need for special training *p*-value	Seriousness of diabetes p-value	Value of tight glucose control *p*-value	Psychological impact of diabetes *p*-value	Autonomy of diabetes for patients *p*-value
PHL vs YEMEN	0.6059	0.3769	**<0.01**	0.3561	**<0.01**
PHL vs ARG	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
PHL vs UAE	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
YEMEN vs ARG	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
YEMEN vs UAE	**<0.01**	**<0.01**	**<0.01**	<0.01	0.9978
ARG vs UAE	**<0.01**	**<0.01**	1	**<0.01**	**<0.01**

Note: * Significant at 0.01

ORIGINAL ARTICLE

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Association of Diabetes-related Emotional Distress with Diabetes Self-care and Glycemic Control among Adult Filipinos with Type 2 Diabetes Mellitus at a Tertiary Hospital in Manila, Philippines

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Abstract

Objective. The study aims to determine the association of diabetes-related emotional distress with reported diabetes self-care, and glycemic control of adult Filipinos with type 2 diabetes mellitus at The Medical City using 2 psychometric tests.

Methodology. This is a cross-sectional study conducted among 94 Filipinos diagnosed with type 2 diabetes mellitus, who answered 2 validated English questionnaires: Problem areas in diabetes (PAID-20) and Diabetes self-management questionnaire (DSMQ) that screen for diabetes-related emotional distress and diabetes reported self-care, respectively. Data were encoded and analyzed using Stata SE v.13.

Results. 42.6% of Filipinos with type 2 diabetes mellitus had emotional distress showing moderate to severe distress in factor 1 (diabetes-related emotional distress) and factor 3 (food related problems). 51.1% had suboptimal self-care, poorly scoring in areas of health-care use and dietary control. Majority of those who had diabetes-related distress and poor self-care where young, pre-obese and had diabetes duration of ±5 years. There was no significant association between diabetes-related emotional distress with diabetes self-care and emotional distress with glycated hemoglobin, but majority of those who had diabetes distress had higher glycated hemoglobin. There was significant association between diabetes self-care and glycemic outcomes (p=0.006) with relative risk of 1.51 (95% CI 1.10-2.07). There was linear inverse weak correlation between all subdomains of DSMQ with glycated hemoglobin except Dietary Control.

Conclusions. Diabetes-related emotional distress and sub-optimal self-care are prevalent among Filipinos with type 2 diabetes mellitus. Those who had poor self-care were 1.5 times more likely to have poor glycemic outcomes.

Key words: emotional distress, Filipino, self-care, diabetes self-management questionnaire

INTRODUCTION

The global burden of diabetes mellitus is looming. It is estimated by the World Health Organization in 2016 that 422 million adults are living with the disease.[1] Locally, according to the National Nutrition and Health Survey of 2008, one out of every 5 adult Filipinos could potentially have diabetes mellitus or prediabetes.[2] The care of persons with diabetes is lifelong owing to the chronicity of the disease. It involves more than simple adherence to pharmacotherapy but should be patient-centered care, defined as respectful of, and responsive to individual patient preferences, needs and values. It ensures that patient values guide all clinical decisions.[3]

A person with diabetes will require integration of the long-term treatment regimen as well as coping with the fear of the occurrence of diabetic complications. This psychological burden can have a significant impact on many aspects of the quality of life-affecting work, interpersonal relationships, social functioning, physical and emotional well-being.[4] It is well studied that psychological burden can lead to emotional distress and negatively impact a person's motivational behavior over the course of the illness. The psychological aspect of diabetes mellitus however, is often a neglected component in the diabetes care despite the fact that having the disease itself is a risk factor for developing decreased psychological well-being.[5]

Diabetes-related emotional distress or diabetes distress is a unique entity arising from the disease manifesting as a hidden emotional burden or worry. It is often significantly associated with low diabetes self-efficacy and poor quality of life even after management for clinical depression.[6] A number of studies have also shown that patients with diabetes who have high levels of depressive affects do not necessarily fulfill the criteria for clinical depression. Moreover, there is a significant association between diabetes-related emotional distress with diabetes-related behavior and biologic variables than major depressive disorder or depressive state.[7]

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In 2015, the Diabetes Center of The Medical City in its aim to provide a more patient-centered care launched the Lifestyle Assessment and Management Program (LAMP) in partnership with the Psychiatry Department. This program screens for diabetes-related emotional distress, depression, anxiety, as well as diabetes self-management of patients using validated self-administered English questionnaires. The results of the psychometric tests are interpreted and a session with a psychiatrist for life coaching is made. Screening for diabetes-related distress and self-reported diabetes care are crucial not only for assessment of psychological issues but because they may have an impact on clinical parameters such as glycemic control and disease-related complications. Numerous studies have looked into the significant association of diabetes-related emotional distress and self-care with glycemic control, but none were done locally using the aforementioned questionnaires.

The general objective of this study is to determine the association between diabetes-related emotional distress with overall quality of diabetes self-care and glycemic control of adult Filipinos with Type 2 Diabetes Mellitus at The Medical City. The specific objectives are: (1) to determine the prevalence of diabetes-related emotional distress using the Problem Areas in Diabetes Questionnaires-20 and the prevalence of self-reported overall quality of diabetes reported self-care using Diabetes Self-Management Questionnaires (DSMQ); (2) to determine the association between diabetes-related emotional distress with diabetes reported overall quality of self-care; (3) to determine association between diabetes-related emotional distress and glycemic control; and (4) to determine the association between diabetes reported overall quality of self-care and glycemic control.

METHODOLOGY

The Instruments: PAID-20 and DSMQ

Various questionnaires have been developed and validated to aid clinicians in identifying patients who may be experiencing diabetes-related emotional distress and for assessing diabetes self-management care including Problem Areas in Diabetes-20 (PAID) which is the most widely used, and Diabetes Self-Management Questionnaire (DSMQ) which is the preferred.

The PAID scale is an English self-report 20-item measure of emotional adjustment to life with diabetes developed by Polonsky et al., in 1995.[8] Each item represents a unique area of diabetes-related psychosocial distress, and the degree is reported using a six-point Likert scale. It could be used for insulin dependent and non-insulin dependent diabetes mellitus patients.[4] In comparing various diabetes-related emotional distress instruments, one meta-analysis has shown that the Problem Areas in Diabetes-20 (PAID) is the best validated, widely used and recommended among the other instruments.[9] Furthermore, PAID-20 was also the same questionnaire utilized in the DAWN study to screen for diabetes-related emotional distress.[10]

The self-management of diabetes involves multiple domains of care including compliance to pharmacotherapy, health care visits and lifestyle modifications. The DSMQ was introduced by Schmitt et al., in 2013.[11] This an English self-report scale comprising of 16 items which focuses on four domain, namely (1) glucose management; (2) dietary control; (3) physical activity; and (4) health-care use. It recalls the previous 8 weeks of self-care and includes both positively and negatively formulated questions structured in alternating manner, and a four-point Likert scale was used to report the magnitude. The instrument was useful for evaluating problematic behaviors of patients with both type 1 and type 2 diabetes and has been shown to have very good psychometric properties in terms of item characteristics, reliability and validity.[11] In addition, this scale has been evaluated to be the preferred tool when analyzing self-reported behavioral problems in relation to control of blood sugar of patients with diabetes in Caucasian populations.[12]

Questionnaire interpretation

PAID: Each item has 5 possible answers using the Likert scale with values from 0 to 4 with 0 representing "no problem" and 4 representing "a serious problem." The scores were added up and multiplied by 1.25, generating a total score between 0-100. Patients scoring 40 or higher may be at the level of "emotional burnout" and warrant special attention. An extremely low PAID-20 score (0-10) combined with poor glycemic control may be indicative of denial.[4] In the original study on the utilization of PAID-20, the multiple subdomains of the questionnaire was not explored and was only interpreted as one factor,[8] however on multiple studies using the questionnaire in different races, some investigators proposed either a 1-to-4 factor domain in the analysis of PAID-20 with Snoek et al.,[13] proposing a four-factor subscale (Table 1) that includes: (1) diabetes-related emotional problems; (2) treatment-related problems; (3) food-related problems; and (4) social support-related problems.[14] To date however, no consensus has yet been formulated regarding which factor tool structure should be uniformly used in its interpretation.[15] Nevertheless, in the clinical interpretation of the PAID-20, it is recommended that clinicians aside from computing the raw score, should take note of the specific areas where the patients scored 3 to 4 in the Likert scale corresponding to having moderate to severe distress, and using these items as a take-off point in the discussion during consultation.[16]

DSMQ: Each item has 4 possible answers using the Likert scale with value from 0 to 3 with 0 representing "does not apply to me" and 3 representing "applies to me very much". Seven of 16 items were formulated positively and 9 were inversely stated with regard to what is considered effective self-care. Scoring of the questionnaires involved reversing the negatively structured questions such that the higher values are indicative of more effective self-care and they include items 5, 7, 10, 11, 12, 13, 14, and 15. Scale scores were calculated as sums of item scores and then transformed to a scale ranging from 0 to 10 [(raw score/ theoretical maximum score) x 10] (Table 2). A transformed score of 10 thus represented the highest self-rating of the assessed behavior. If "not required as part of my treatment" had been marked in an item, it means that it was not used and the scale score computation should be adapted accordingly by reducing the theoretical maximum score by 3 points.[17]

Table 1. Scoring and subset scales of PAID*

Sub scales	
Diabetes-related Emotional Distress (Items 3, 6, 7, 8,9, 10, 12, 13, 14, 16, 19, 20)	
Treatment-related Problems (Items 1, 2,15)	
Food-related Problems (Items 4, 5,11)	
Social support-related Problems (Items 17,18)	
Sum scale	(Raw score x 1.25)
	Score (Highest score: 100)

* Proposed by Snoek et al.[13]

Table 2. Scoring and subset scales of DSMQ

Sub scales	
Glucose Management (Sum of items 1, 4, 6, 10 and 12)	(Raw score /15) x 10
Dietary Control (Sum of items 2, 5, 9 and 13)	(Raw score/ 12) x 10
Physical Activity (Sum of items 8, 11, and 15)	(Raw score/ 9) x 10
Health-Care use (Sum of items 3, 7, and 14)	(Raw score /9) x 10
Sum scale	(Raw score/ 48) x 10
	Score (Highest score: 10)

A cut off score of ≤6.0 is indicative of suboptimal self-care as proposed by Schmitt using German populations while no cut off score was suggested on the individual subscale domains.[17]

Study design

This is a cross-sectional study done at The Medical City approved by Institutional Review Board and participated by adult Filipinos with Type 2 diabetes mellitus from June 2017 to November 2017. The original authors of PAID-20 and DSMQ expressed their consent to the use of their questionnaires and gave recommendations as to its proper interpretation. Consent forms were first handed and thoroughly explained to each participant including data privacy and the limitation of the study not to include psychiatric consultations. Once they agreed, they were given 2 sets of English validated questionnaires of PAID-20 and DSMQ and they were asked to answer it in 5-15 minutes. Questionnaires were tabulated and interpreted on the same day and patients who had emotional distress or suboptimal self-care, were individually contacted and advised to return to the Diabetes Center for scheduling of initial life coaching with a psychiatrist of choice and to continue consult as advised. Their attending endocrinologists were likewise notified of the results for proper coordination and follow-up.

Glycated hemoglobin was done at The Medical City using high performance liquid chromatography (HPLC) using Bio-RAD D-10 HbA1c with NGSP certification until January 1, 2019. Results were viewed and collected using the Laboratory Information System (LIS) of the Hospital. The Average time lapse from the actual administration of the questionnaires and glycated hemoglobin was 6.6±11 days.

Sample population

A total of 94 health-care diagnosed adult Filipinos with type 2 diabetes mellitus were enrolled in the study. They were either seen at the Diabetes Center, at the clinic of endocrinologists or admitted in the hospital.

Sample size

Using NCSS-PASS 2013, the minimum sample size requirement is at least 84 patients based on the correlation between emotional distress and glycemic control =0.30[6] with alpha level =5% and power =80%. Inclusion criteria: (1) 18 years old and above, (2) type 2 diabetes mellitus diagnosed by health care provider, (3) with HbA1C done within 3 months at The Medical City. Exclusion criteria: (1) the participant was unable to read or understand English, (2) no HbA1C results or results done outside The Medical City, and (3) recent history of blood loss, or blood transfusion.

Analysis

Descriptive statistics were used to summarize the characteristics of the population. Frequency and proportion were used for nominal variables, mean and standard deviation were used for quantitative variables.
Independent T-test was used to compare the means for age, body mass index, diabetes duration, subset scores in PAID-20 and DSMQ and glycated hemoglobin, while Pearson's Chi-square was used to compare gender, and type of anti-diabetes medications as well as the association between diabetes related emotional distress with glycated hemoglobin; self-care with glycated hemoglobin and emotional distress with self-care while relative risk was used to ascertain the likelihood of the association. Pearson's correlation coefficient was used to determine the linear correlation of the subset domains of DSMQ and glycated hemoglobin. All tests were performed using Stata SE version 13 and set at 0.5% level of significance.

RESULTS

General characteristics

A total of 94 adult Filipinos with type 2 diabetes mellitus were analyzed in the study. The overall demographic profile was summarized in Table 3. The mean age was 54.03±11.45 years with majority belonging to the pre-obese category using the Asia-Pacific cut-off. Most of these patients were married and finished college and were currently employed. They had diabetes for 5.6±4.9 years, mostly maintained on oral anti-diabetic medications and had a mean glycated hemoglobin of 8.37±2.16% with 66% uncontrolled.

Diabetes-related emotional distress

The mean PAID score of 94 adult Filipinos with diabetes was 32.18±20.51(Table 3). The prevalence of diabetes-related emotional distress was 42.6% with PAID-20 mean scores of 52.75±10.26 (cut-off of >40) (Table 5). Only 7 patients were classified under "in denial" category (e.g. PAID-20 <10 with glycated hemoglobin ≥7%), with majority of them males (71.4%), had a mean BMI of 31.7±7.7 kg/m^2 with diabetes duration of 4±4.8 years. 62.5% of them were treated with oral anti-diabetic medications with an average glycated hemoglobin of 9.2±2.2%.

Patients who had emotional distress had a cut-off score of ≥40 and showed moderate to severe distress (Likert scale of 3-4) in 16 out of the 20 specific item questions (Table 4). On the other hand, patients who had no emotional distress or who were in denial did not show any moderate or severe

Table 3. Sociodemographic and clinical characteristics of the study population

Characteristics (N=94)	Mean±SD or n (%)
Age (years)	54.0±11.5
Gender	
Male	45 (47.9)
Female	49 (52.1)
BMI (kg/m²)	28.1±5.3
Marital Status	
Single	20 (21.3)
Married	66 (70.2)
Separated/Divorced	3 (3.2)
Widowed	5 (5.3)
Educational Attainment	
Elementary	4 (4.3)
High school	8 (8.5)
College	68 (72.3)
Post Graduate	12 (12.8)
Vocational	2 (2.1)
Employment	
Employed	43 (45.7)
Self-employed	18 (19.2)
Unemployed	13 (13.8)
Retired	20 (21.3)
Diabetes Duration (years)	5.6±4.9
Anti-diabetic Medications	
Oral only	64 (68.1)
Insulin only	8 (8.5)
Combination of both	22 (23.4)
PAID Scores	32.2±20.6
Without Distress (<40)	40 (42.6)
With Distress (≥40)	47 (50)
In denial (<10 with HbA1c ≥7%)	7 (7.5)
DSMQ Scores	6.5±1.4
Suboptimal self-care (<6)	48 (51.1)
Optimal self-care (≥6)	46 (48.9)
HbA1C (%)	8.4±2.2
Good glycemic control (<7%)	32 (34)
Poor glycemic control (≥7%)	62 (66)

distress in any specific item in the questionnaire. Using the 4 subscale factors proposed by Snoek at el[13], all four factors were significantly different between those with emotional distress and those without. Moreover, in those that had emotional distress, the factors that scored the highest were in factor 1, diabetes-related emotional distress and factor 3, food-related problems (Table 5).

When gender, body mass index, diabetes duration and type of anti-diabetic medications were compared between those with emotional distress and those without, no significant differences were seen (Table 5). In terms of age however, majority of those who had emotional distress were younger (p=<0.001) with a mean age of 49.6±10.0 years and their glycated hemoglobin was significantly lower (p=0.004) although still above the <7% cut-off for optimal control. No statistically significant association was noted between the presence of emotional distress and glycemic control (Table 5).

Diabetes reported self-care

The mean DSMQ scores of the sample was 6.46±1.44 (Table 3). The prevalence of suboptimal reported self-care (cut-off score of ≤6) was noted at 51.1% (Table 6) and these patients had a mean age of 50.1±10.86 years and were younger compared to those who had good self-care (p=<0.001). Body Mass Index, duration of diabetes and types of anti-diabetic medications were comparable between the two groups and did not show any statistical difference (Table 6). Comparing the glycated hemoglobin between the two groups, there was a significant difference (p=0.001) between those in the suboptimal and optimal self-care with the latter having lower glycated hemoglobin albeit still not within the ideal glycemic target of <7%. All the scores in the subset domains were statistically different from the two groups (Table 6) with majority of patients in the suboptimal group scoring poorly in Dietary Control followed by Health-Care Use. In comparison, those who had optimal self-care scored highest in areas of Glucose Management followed by Dietary Control (Table 4). Furthermore, there was a statistically significant association between the quality of self-care and glycemic outcomes (p=0.006) (Table 6) with a relative risk of 1.51 (95% CI 1.10-2.07). In terms of the subdomains of DSMQ, only Dietary Control showed no significant linear correlation with glycated hemoglobin, while others showed a weak, inverse linear correlation (Figure 1).

Table 4. Specific items in the PAID-20 questionnaire and their mean scores

Item No.	Abbreviated item content	Percentage of Missing Values	With Emotional Distress⁺ (n=40)	Without Emotional Distress⁺ (n=47)	In Denial⁺ (n=7)
1	Concrete goals	1.1	**2.3±1.1***	0.9±1.1	0.3±0.5
2	Discouraged	0	**2.1±0.9***	0.6±0.9	0
3	Scared	0	**3.0±0.8***	0.8±0.9	0.7±1.5
4	Social Situations	0	**2.5±0.9***	1.0±0.9	0.1±0.4
5	Deprivation	0	**2.6±0.8***	0.7±0.7	0
6	Depressed	0	**2.6±0.8***	1.0±0.8	0
7	Indistinguishable mood	0	**2.6±0.8***	0.9±1.0	0.4±0.5
8	Overwhelmed	0	**2.1±0.9***	0.9±1.0	0
9	Reactions	0	**2.5±0.9***	0.9±0.8	0.1±0.4
10	Angry	0	**2.2±0.8***	0.4±0.6	0.3±0.5
11	Concerned	0	**2.5±0.9***	1.0±0.9	0.1±0.4
12	Worry about the future	0	**3.3±0.6***	1.5±1.2	0.4±0.5
13	Guilty	0	**2.4±1.1***	1.3±0.8	0
14	Accepting	0	**2.0±1.4***	0.6±0.9	0
15	Unsatisfied	1.1	0.7±0.7	0.2±0.5	0
16	Energy	0	**2.2±0.8***	0.4±0.6	0
17	Alone	0	1.4±0.9	0.2±0.5	0
18	Supportive	0	0.9±0.8	0.4±0.7	0
19	Coping	0	1.8±1.0	0.9±1.0	0
20	Burned out	0	**2.1±1.0***	0.7±0.7	0

⁺ Data presented in Mean±SD
* Mean Scores ≥3

Table 5. Summary of PAID scores and HbA1C results

	With Emotional Distress⁺ n=40	Without Emotional Distress⁺ n=47	*p* value
Age	49.6±10.0	57.8±11.2	**<0.001***
Gender			0.866
Male	18 (45%)	22 (46.8%)	
Female	22 (55%)	25 (53.2%)	
BMI	27.9±4.8	27.8±5.2	0.922
Diabetes Duration (years)	5.6±5.2	5.9±4.7	0.815
Anti-diabetic medications			0.615
Oral	26 (29.9%)	33 (37.9%)	
Insulin	3 (3.5%)	5 (5.7%)	
Combination	11 (12.6%)	9 (10.3%)	
PAID Scores			
Sum Score	52.8±10.3	18.8±9.6	**<0.001***
Factor 1 (Diabetes-related emotional distress)‡	2.4±1.0	0.8±0.8	**<0.001***
Factor 2 (Treatment related problems)‡	1.7 ±1.3	0.5±0.9	**<0.001***
Factor 3 (Food related problems)‡	2.5 ±0.8	0.9±0.8	**<0.001***
Factor 4 (Social support related problems)‡	1.2 ±0.8	0.3±0.3	**<0.001***
HbA1C (%)	9.0±2.5	7.7±1.7	**0.004***
Glycemic Control			0.226
Good Glycemic Control (<7%)	12 (13.8%)	20 (23%)	
Poor Glycemic Control (≥7%)	28 (32.2%)	27 (31%)	

⁺ Data presented in Mean±SD or n (%)
‡ proposed by Snoek et al.[13]
* Statistically significant at 5% level

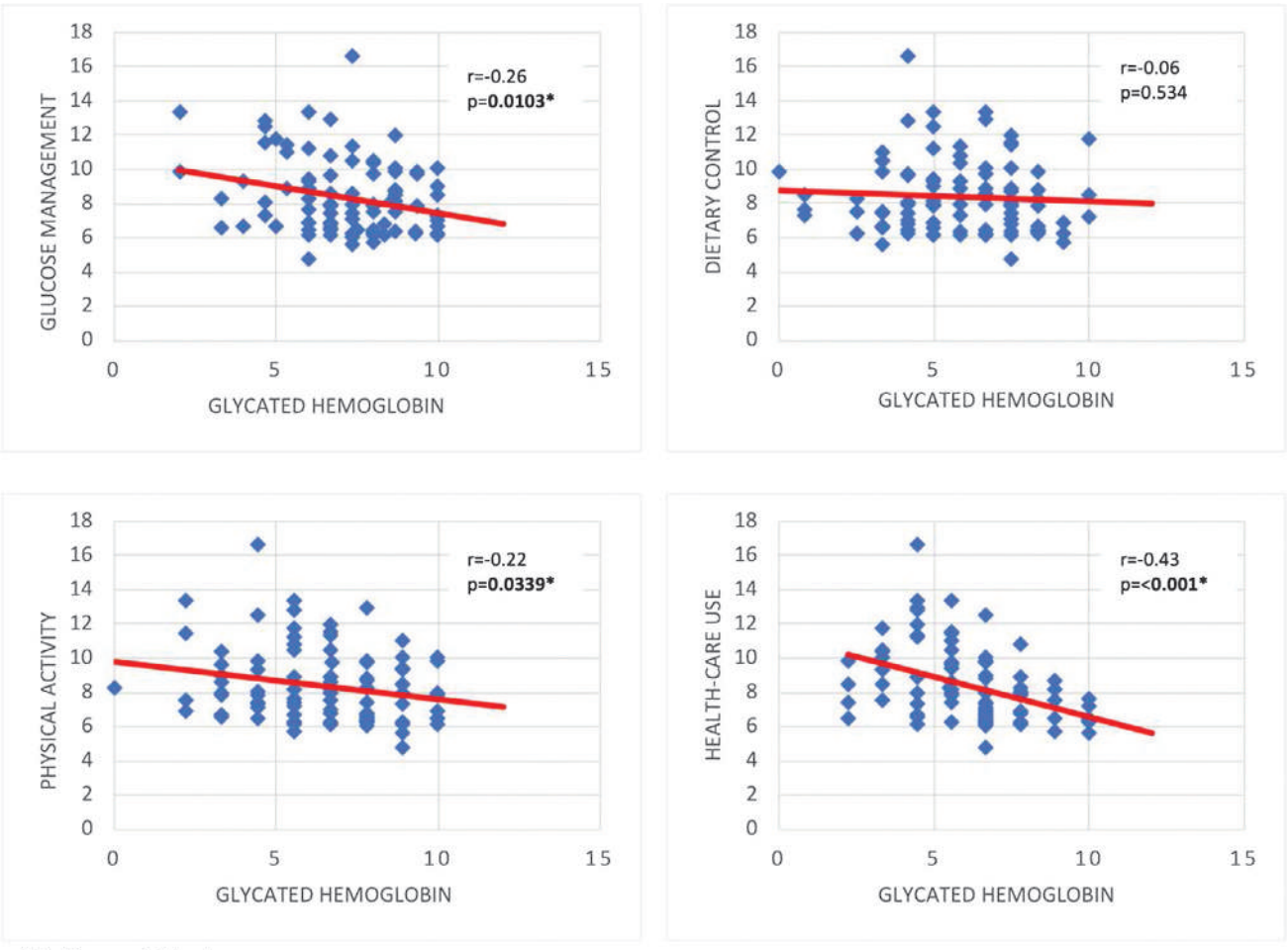

Figure 1. Linear correlation of DSMQ subdomains with glycated hemoglobin.

Table 6. Summary of DSMQ scores and HbA1C results

	Sub-optimal self-care+ n=48	Optimal self-care+ n=46	*p* value
Age	50.1±11.3	58.1±10.1	<0.001*
Gender			0.1507
Male	19 (39.6%)	29 (63%)	
Female	26 (54.2%)	20 (43.5)	
BMI	28.1±4.3	28.2±6.2	0.921
Diabetes Duration (years)	6.2±5.3	5.1±4.5	0.310
Anti-diabetic medications			0.704
Oral	33 (68.8%)	31 (67.4%)	
Insulin	3 (6.3%)	5 (10.9%)	
Combination	12 (25%)	10 (21.7%)	
DSMQ scores			
Sum Score	5.31±0.9	7.80±1.8	**<0.001***
Sub-scale scores			
Glucose Management	6.2±1.7	8.2±1.3	**<0.001***
Dietary Control	4.5±1.8	7.6±1.8	**<0.001***
Physical Activity	5.5±2.1	7.5±1.8	**<0.001***
Health Care Use	5.3±1.6	7.1±1.9	**<0.001***
HbA1C (%)	9.1±2.3	7.6±1.7	**0.001***
Glycemic Control			**0.006***
Good Glycemic Control (<7%)	10 (10.6%)	22 (23.4%)	
Poor Glycemic Control (≥7%)	38 (40.4%)	24 (25.5%)	

+ Data presented in Mean±SD or n (%)
* Statistically significant at 5% level

Table 7. Cross tabulation (PAID and DSMQ)

PAID outcomes	DSMQ outcomes		*p* value
	Sub-optimal Self Care+	Optimal Self-Care+	
Without Emotional Distress	31%	23%	
With Emotional Distress	32.2%	13.8%	
			0.226

+ Data presented in n (%)

Diabetes-related emotional distress and diabetes reported self-care

The presence of emotional distress did not show significant association with the quality of reported diabetes self-care (Table 7).

Emotional distress as measured by the PAID questionnaire was not significantly associated with the quality of reported diabetes self-care.

DISCUSSION

More than a quarter of patients in this study reported diabetes-related emotional distress. This high prevalence of diabetes-emotional distress (42.6%) was similar to that seen in the DAWN2 study (44.6%), which included 17 countries with China and Japan as the only two Asian countries.[18] Compared to the DAWN1 study, the prevalence of diabetes-related emotional distress in the DAWN2 study doubled. Interestingly, the DAWN1 study also reported a high prevalence of emotional distress (85.2%), but this was commonly observed in newly diagnosed patients with diabetes.[19]

In the PAID-20 subscale domains proposed by Snoek et al.,[13] Filipinos with type 2 diabetes mellitus seem to manifest a great deal of distress in factor 1 that is specific to diabetes-related emotional distress and comprised of 12 items, followed by factor 3 that deals with food-related problems and has 3 items. In fact, in the individual questions, the items that scored the highest were those that tackled the feeling of being scared about living with the disease and worrying about its possible complications. Taking into account that majority of the persons enrolled in this study have diabetes in a 5-year period, it is understandable that many show distress in terms of how such a condition will affect their lives. This finding is also similar to the study involving Koreans with type 2 diabetes where majority had a mean age of 58.02±10.88 years old, diabetes duration of 10 years and on combination regimen with insulin. The study reported moderate to severe distress in the item concerning diabetic complications.[15]

In the study done by Lee et al.,[15] as described above, and the original study of Snoek et al.,[13] that looked into Dutch and Americans aged 51±16 years with diabetes duration of 16±12 years, a high incidence of insulin use, whether alone or in combination with an oral anti-diabetic medication was found. In our study however, only 32% of the subjects were on insulin, the rest were solely on oral anti-diabetic medications (68%). This mirrors the findings of Jimeno et al.,[20] in their survey about the glycemic control and status of diabetes care and complications of Filipinos with type 2 diabetes mellitus, where 78.5% of the population were treated exclusively with oral anti-diabetic medications. It may be speculated that unlike those seen in other countries, the distress brought about by using insulin may not be the sole reason why it is infrequently used in the local setting considering that while most of the subjects reported distress, majority of them did not use insulin at all. On the other hand, the possible distress brought about by insulin use cannot be eliminated especially for those participants who reported distress. However, since no focus group discussion was done, the matter was not investigated thoroughly.

As noted earlier, the results of this study share the same moderate to severe distress in factors 1 and 3 of the sub-analysis proposed by Snoek et al.[13] One key difference in this study however is that the items for factor 3 individually scored moderate to severe distress. This may support the colloquial knowledge that Filipinos are passionate eaters and being diagnosed with diabetes where the cornerstone of management entails careful selection and proper control of food intake, will presumably cause distress. The results of these studies support the conclusion that having diabetes may lead to significant physical and psychological burden. However, cultural background continues to influence certain aspects of diabetes distress.

This study did not show significant association between the presence of diabetes-related emotional distress and poor glycemic outcomes. This finding is contrary to the first study conducted at Joslin Diabetes Center Clinic on the assessment of PAID-20 where greater distress was significantly associated with poorer glycemic outcomes with PAID-20 having a predictive glycemic outcome control of up to 12 months.[8] The results of the study done by Stranderg et al., in 2014[21] on Norwegians with type 1 diabetes mellitus similarly showed no significant linear relationship between diabetes-related emotional distress and glycated hemoglobin but after 1 year of follow-up, showed significant correlation.[22] In the meta-analysis on several instruments for assessment of diabetes-related emotional distress by Lee et al.,[9] the generalized conclusion

was a positive but weak pooled correlation between emotional distress and glycated hemoglobin. Although this study failed to show any significant association between the presence of diabetes-related emotional and poor glycemic outcomes, it is still noteworthy to point out that the average glycated hemoglobin of those with emotional distress and without, were statistically significant (p=0.004) with those with emotional distress having higher glycated hemoglobin. This difference in glycated hemoglobin although not reaching the optimal target of <7%, may still be clinically relevant because as pointed out in the landmark results of UKPDS, every percentage point decrease in glycated hemoglobin will have a 35% decrease in the overall risk of developing diabetes complications.[23]

There was no significant association between the presence of diabetes-related emotional distress and quality of diabetes reported self-care. This was in contrast to the study done by Ogbera and Adeyemi-doro[24] on Nigerians with type 2 diabetes mellitus, where PAID-20 had a very weak correlation (r=0.21) with self-care using Self-Care inventory. The suggested reason is that diabetes distress impacts self-care in various levels, affecting multiple domains that ultimately results to poor self-care in general.[24] Patients who have emotional distress may feel powerless over their disease, and this feeling of powerlessness can significantly impact self-care behaviors.[24] In this study, the effect of diabetes-related emotional distress on self-care may have been too weak to show any statistical significance.

Diabetes self-care or self-management includes activities like glucose monitoring, compliance to medications and diet prescription, regular health-care follow up and adherence to physical activities. All of these require adequate knowledge and motivation from the patient. In this study, 52.1% of Filipinos with type 2 diabetes who were young, pre-obese, and had diabetes duration of ±5 years, reported suboptimal self-care, scoring poorly in subset domains for Dietary Control and Health Care Use. These findings were similar to the self-care management behaviors reported in the DAWN1 study were patients who had poor self-care scored lower in area of diet.[19] The probable reasons why younger Filipinos in this study reported poor self-care may be related to their lack of proper education with regards to the disease and their limited experience in their active role in its management. Moreover, there was a significant difference in the glycated hemoglobin of those who reported optimal self-care from those who did not (p=0.001). In the group that reported optimal self-care, it was observed that their mean glycated hemoglobin level was not the targeted optimal level of <7%, reaching an average of 7.63±1.70%. This discrepancy between the patient's perceived and reported self-care behavior and unmet glycemic outcomes should alert physicians to be more vigilant with their advice to patient's self-care behavior; scrutinize health-care practices in order to address deep-seated knowledge gaps and more importantly, provide motivation in the management of their illness. Factors such as coping behaviors to chronic illness that is influenced by ethnic and sociocultural variations should likewise be explored to explain the possible reasons behind this discrepancy. To date however, limited data have been published on the way Filipinos cope with debilitating diseases.

Optimal glycemic control requires an interplay of several factors including adherence to medications, dietary counseling, self-monitoring of blood glucose and education on diabetes.[24] These factors were the very same domains that were evaluated using structured questions in the Diabetes Self-Management Questionnaires (DSMQ). In the initial correlation study done by the author of the DSMQ on both German patients with type 1 and type 2 diabetes, there was an inverse nearly moderate correlation between the two (p=<0.001; r=-0.46) and DSMQ was the better self-management questionnaire compared to others[10]. In another study that looked into the association of DSMQ with the presence of diabetes-related microvascular complications among Iranian patients with diabetes, DSMQ sum scale had a statistically significant association with neuropathy and a weak association with nephropathy.[25] The results of our study showed significant association between diabetes reported self-care and glycemic outcomes (p=0.006) with patients who have poor self-care 1.5 times likely to be uncontrolled. Although a self-care assessment questionnaire does not need to always correlate with glycemic outcome for it to be considered a valid psychometric instrument,[11] DSMQ stands apart because it has consistently proven in various studies, including ours, to correlate with clinically measured endpoints like glycated hemoglobin.

In the individual subset domains of DSMQ, dietary control was one of the subset domains that scored poorly in persons that had suboptimal self-care and was the second highest for those who had good self-care (Table 6). It was however the sole factor that did not show linear relationship when correlated with glycated hemoglobin. Glucose management, physical activity and health-care used, all showed a negative inverse although weak correlation that reached statistical significance (Figure 1). In a study involving Pakistanis with type 2 diabetes mellitus, glucose management and dietary control subscales were the only factors that had linear correlation.[26] This variation may be because of cultural differences.[26]

CONCLUSIONS AND RECOMMENDATIONS

The study found that for Filipinos with type 2 diabetes mellitus at The Medical City, 42.6% had emotional distress showing moderate to severe distress in factor 1 (diabetes-related emotional distress) and factor 3 (food related problems) while 51.1% had suboptimal self-care, poorly scoring in areas of health-care use and dietary control. Majority of patients who had emotional distress and poor self-care were young, pre-obese and had diabetes duration of ±5 years. No significant association was seen between emotional distress and diabetes reported self-care, together with diabetes related emotional distress and glycated hemoglobin. However, majority of those with emotional distress had higher glycated hemoglobin compared to those without. Moreover, those with poor self-care were 1.5 times more likely to have uncontrolled glycemic outcomes.

Further study is recommended to ascertain other cultural factors that influence diabetes-related emotional distress and diabetes reported self-care as well as other compounding variables that can influence glycemic outcomes.

Limitations of the study

Multivariate analysis on other confounding factors that influence glycated hemoglobin was not done because of the small sample size. Moreover, although participants who had emotional distress or poor self-care were encouraged to attend the life coach sessions in order to discuss the results of their test, the scope of the study did not include triangulation using focus group discussion to provide further information on the exact reason for such distress as well as identify other variables that may influence diabetes distress and reported self-care.

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All authors certified fulfillment of ICMJE authorship criteria.

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ORIGINAL ARTICLE

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Prevalence of Depression among Patients with Type 2 Diabetes Mellitus and its associated Clinical Factors

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Abstract

Introduction. Type 2 diabetes mellitus has been linked to depression. However, this has been largely unrecognized and untreated. There are no current data available in the Philippine setting of the prevalence of the disease.

Objective. The objective of the study was to determine the prevalence of depression among adult Filipino patients with type 2 diabetes mellitus and investigate the different clinical factors associated with it.

Methodology. This is a single-center, analytic cross-sectional study conducted at a tertiary hospital, with 476 patients aged above 18 years old diagnosed with type 2 Diabetes Mellitus included. The Physicians Health Questionnaire 9 (PHQ-9) with a score of >5 was used to make a diagnosis of depression.

Results. Prevalence of depression among patients with type 2 diabetes mellitus was 19.9%. Factors associated with increased odds of depression were having a post-graduate degree (*p-value*=0.012), presence of retinopathy (*p-value*=0.018), and higher MMA Score (lower adherence) (*p-value*=0.000).

Conclusion. Depression is prevalent among Filipino patients with type 2 diabetes mellitus. An integrated approach by the attending physicians and psychiatrists is required for the effective management of these patients.

Key words: depression, type 2 diabetes mellitus, Filipino, Philippines

INTRODUCTION

Depression is a common public health issue which affects all aspect of a person's life and has been recognized as an important co-morbid condition in diabetes and diabetes related complications.[1] People with diabetes are almost twice as likely to suffer from depression and anxiety as the general population. But this factor remains unrecognized and thus untreated.[2] Many studies have documented the high rate of depression found among patients with diabetes, compared with non-patient control subjects.[2,3,4] However, minimal data had been gathered of the prevalence of it here in the Philippines.

In China, the prevalence of depression among patients with diabetes was 5.7%. Higher body mass index (BMI) score, high glycosylated hemoglobin (HbA1c) level and low health quality insurance were associated with presence of depression.[5] According to the study of Al et al., there was also increased prevalence of depression among Jordanians with diabetes which was associated with gender (female), socioeconomic status and insulin therapy.[4] In the Mexican American population, 25% presented with minor depression and 9% with lifetime diagnosis of major depressive disorder. Greater incidence of both macro- and microvascular complications and greater incidence of disability in activities of daily living were seen among depressed depressed persons with diabetes.[6] Several factors were correlated with depression in type 2 diabetes, such as low levels of education, physical inactivity, subjective somatic complaints, and physical impairment.[7] However, there has some inconsistencies of the associations between depression and HbA1C.[5,7]

The purpose of this study was to determine the prevalence of depression and its associated clinical factors among patients with type 2 diabetes mellitus seen at a tertiary hospital in the Philippines.

METHODOLOGY

This was an analytic cross- sectional study that was conducted to determine the prevalence of depression and associated factors in patients with type 2 diabetes in St. Luke's Medical Center from May 2018 to December 2018. Inclusion criteria of the study were diagnosed with type 2 Diabetes mellitus fulfilling criteria of American Diabetes Association (FBS >126, HbA1c >6.5, symptoms with RBS>200 mg/dl); age >18 years old; and able to read and understand the English questionnaire.

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The exclusion criteria were patients with type 1 diabetes mellitus, with history of severe hypertension (HTN >160 mmHg); those clinically diagnosed with Bipolar disorders, Schizophrenia, Dementia, Anxiety Disorder, Mental retardation as reported by their attending physician; Drug or Alcohol addicts; Patients who had major life events like death of a loved one and job lost; and having diabetic ketoacidosis.

A letter of invitation to participate was disseminated to endocrinology consultants, endocrinology fellows and internal medicine residents of St. Luke's Medical Center Quezon City. The attending physicians referred their patients to the investigator who passed the inclusion criteria of the study. Informed consent was obtained prior to collection of data.

The 30-minute interview and examination were conducted at a room at the Diabetes, Thyroid and Endocrine Center of St. Luke's Medical Center-Quezon City to ensure privacy. Data on socio-demographic characteristics (age, gender, civil status, education, and occupation), diabetes history (duration, insulin therapy, chronic complications, glycemic control as HbA1c on the past 3 months), number of concomitant medication, BMI (body mass index — kg/m^2), previous episodes of depression, treatment with antidepressant drugs and family history of depression were collected.

The questionnaires were administered by the primary investigator trained by a psychiatrist. The participants were provided 2 questionnaires. Depressive symptoms were assessed with Patient Health Questionnaire-9 (PHQ-9). It is a screening tool which incorporates diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. The tool rates the frequency of the symptoms which factors into the scoring severity index. The total score can range from 0 to 27, with higher scores indicating greater severity of depression. A score of 0-4 is none to minimal depression requiring no treatment. A score of more than or equal to 5 makes a diagnosis of depression. A score of 5-9 is mild, 10-14 is moderate, 15-19 is moderately severe and 20-27 is severe depression, all requiring treatment. PHQ scores of more than 10 had sensitivity of 88% and specificity of 88% for major depression.[8] Compliance to diabetes medications were assessed with the eight-item version of the Morisky Medication Adherence Scale (MMAS).[9] The questionnaires have been validated among Filipinos.[10] These were interpreted by a psychiatrist. The results were then forwarded to the attending physicians and psychiatric consult were discussed.

Description of outcome measures

The primary outcome of the study was the prevalence rate of depression among patients diagnosed with Type 2 Diabetes Mellitus using the PHQ-9.

Secondary outcomes determined the severity of depression, medication adherence and association of BMI, duration of diabetes, compliance with medications, type of medications (OADs versus insulin therapy), number of medications (single or multiple drug therapy) socioeconomic status and other comorbid diseases (hypertension, dyslipidemia, ischemic heart disease) with depression.

Sample size estimation

Minimum needed sample size for logistic regression analysis was computed using G*power 3.0.10 software.[11] Based on expected medium effect size (r^2 =15%), 95% confidence interval, 90% power, and 20 independent variables (sociodemographic and clinical variables) the minimum needed sample size was 191.

Data analysis

The socio-demographic and clinical characteristics were summarized using means and standard deviations for continuous data and frequencies and percentages for categorical data. Pearson chi-square and Fisher's exact tests were used to determine if the distribution of levels of depression significantly differed per category of each variable. Multiple logistic regression analysis was used to evaluate the relationship between different variables and presence of depression among patients with type 2 diabetes mellitus. *P-values* less than 0.05 was used and confidence level was set at 95%. All variables that have *p-value*<0.10 during univariate tests of association were included in the multiple logistic regression analysis. STATA 14 was used for data analysis.

Ethical considerations

The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee. Upon the referral from the attending physicians, the significance of study was explained and an informed consent was sought by the primary investigator. Patient's autonomy and confidentiality were respected. Data were coded and identification anonymized. All data were recorded and investigators were responsible for the integrity of the data i.e., accuracy, completeness, legibility, etc. Results were disseminated to the attending physician with the approval of the patient. The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data. The data will be kept by the investigator until 5 years from the end of the study. Data gathered will be discarded after 5 years.

RESULTS

Table 1 describes the characteristics of the 476 patients included in this study. The mean age was 58.3 (SD=11.8) and majority were female (63.5%). Majority were also married (75.2%) and were college or vocational course graduates (69.1%). Almost half of them were employed (45.6%). The mean BMI of the patients was 26.7 (SD=4.9). More than half of them were also obese (59.7%).

In terms diabetes duration, more than half had the disease for more than 5 years already (59.6%). Their mean HbA1c value was 7.4 (SD=1.6) with almost half having uncontrolled diabetes (56.0%). The most prevalent complication experienced by the patients was neuropathy (42.4%) followed by retinopathy (28.8%) and nephropathy (26.7%). The most commonly used medication was a

Table 1. Characteristics of patients with type 2 diabetes mellitus

Variable	N=476 (%)
Age (Mean±SD)	58.3±11.8
Gender	
Male	174 (36.5)
Female	302 (63.5)
Marital Status	
Never married	73 (15.3)
Married	358 (75.2)
Widowed	45 (9.5)
Educational Status	
Elementary	28 (5.9)
High School	91 (19.1)
College/Vocational	329 (69.1)
Post graduate	28 (5.9)
Occupation/Employment	
Not employed	259 (54.4)
Employed	217 (45.6)
BMI (Mean±SD)	26.7±4.9
BMI category	
Underweight	12 (2.5)
Normal	89 (18.7)
Overweight	91 (19.1)
Obese	284 (59.7)
Duration of Diabetes	
<1 year	37 (7.8)
1-5 years	155 (32.6)
6-10 years	106 (22.3)
>10 years	177 (37.3)
HbA1c (Mean±SD)	7.4±1.6
DM control	
Controlled	187 (44.0)
Uncontrolled	238 (56.0)
Complications	
Retinopathy	137 (28.8)
Nephropathy	127 (26.7)
Neuropathy	202 (42.4)
Stroke	42 (8.8)
CAD	49 (10.3)
PAOD	29 (6.1)
Medications	
Insulin	148 (31.2)
Biguanides	346 (72.7)
Sulfonylureas	122 (25.7)
DPP-IV inhibitors	178 (37.4)
SGLT-2 inhibitors	119 (25.0)
GLP-1 agonist	1 (0.2)
TZD	51 (10.7)
Comorbidities	
Hypertension	296 (62.2)
Dyslipidemia	247 (52.1)
Hyperuricemia	19 (4.0)
Hypothyroidism	20 (4.2)
MMAS	
Low	153 (32.1)
Medium	145 (30.5)
High	178 (37.4)

BMI, Body Mass Index; HbA1c, glycosylated hemoglobin; DM, Diabetes Mellitus; MMAS, Morisky Medication Adherence Scale

biguanide (72.7%), followed by DPP-IV inhibitors (37.4%), and then insulin (31.2%). In terms of their comorbidities, 62.2% had hypertension and 52.1% had dyslipidemia. It was also observed that only 37.4% had good compliance with regards to their medications.

Table 2 describes the prevalence of depression among the patients with type 2 diabetes mellitus included in the study. The mean PHQ score was 2.6 (SD=3.4). More than half of the patients had none to minimal depression (81.1%). A PHQ score of more than five denotes depression. There was a prevalence of depression of 19.9 %, with mild depression at 12.6%. Moderate depression was reported

Table 2. Prevalence of depression and PHQ scores among patients with type 2 diabetes mellitus

Variable	N=476 (%)
PHQ scores (Mean±SD)	2.6±3.4
Depression Severity	
None to Minimal	386 (81.1)
Mild	60 (12.6)
Moderate	24 (5.0)
Moderately Severe	6 (1.3)
Severe	0 (0.0)

PHQ, Patient Health Questionnaire

by 5.0% of the patients and 1.3% had moderately severe depression. None have severe depression.

Table 3 describes the prevalence of depression disaggregated per socioeconomic and clinical characteristics of the patient. Only gender, BMI, DM control, presence of neuropathy as complication, and level of medication adherence, had significant differences in terms of distribution of levels of depression (All *p-values*<0.05). Females had higher prevalence of mild depression (15.9%) and moderate to moderately severe depression (6.9%) compared to males. The prevalence of none/minimal and mild depression was 77.2% and 17.3% among those with neuropathy. In terms of BMI, moderate to moderately severe depression was highest among those with normal BMI (25.0%) and lowest among obese (4.2%). In terms of DM control, the prevalence of none/minimal (85.3%) depression was higher among those with controlled DM and the prevalence of moderate to moderately severe was higher among those with uncontrolled DM (7.5%). In terms of medication adherence, the prevalence of none/minimal (90.4%) depression was highest among those with high adherence and the prevalence of moderate to moderately severe was highest among those with low adherence (10.5%).

Table 4 shows that results of the univariate logistic regression analysis on the association of socioeconomic status and clinical factors with depression among patients with type 2 diabetes mellitus. It can be seen that increasing age (*p-value*=0.001), hypertension (*p-value*=0.015), having diabetes for 6-10 years (*p-value*=0.027) and medium/high medication adherence (*p-value*=0.005 and 0.000, respectively) were significantly associated with decreased odds for depression. On the other hand, being female (*p-value*=0.012), having a post-graduate degree (*p-value*=0.020), being underweight (*p-value*=0.022), higher HbA1c (*p-value*=0.002), uncontrolled diabetes (*p-value*=0.017), presence of retinopathy (*p-value*=0.026), and higher MMA Score (lower adherence) (*p-value*=0.000) were significantly associated with increased odds for depression.

Table 5 shows that results of the multiple logistic regression analysis on the association of socioeconomic status and clinical factors with depression among patients with type 2 diabetes mellitus (R2 value=21.20). It can be seen that increasing age (*p-value*=0.021) and chronic duration of diabetes (6-10 years) (0.033) were significantly associated with decreased odds for depression. On the other hand, having a post-graduate degree (*p-value*=0.012), presence of retinopathy (*p-value*=0.018), and higher MMA Score (lower adherence) (*p-value*=0.000) were significantly associated with increased odds for depression.

Table 3. PHQ score and severity of depression among patients with type 2 diabetes mellitus

Variable	None to Minimal	Mild	Moderate to Moderately Severe	*p*-value
Gender				
Male	153 (87.9)	12 (6.9)	9 (5.2)	0.008*
Female	233 (77.2)	48 (15.9)	21 (6.9)	
Marital Status				
Never married	54 (74.0)	11 (15.0)	8 (11.0)	0.142
Married	298 (83.2)	40 (11.2)	20 (5.6)	
Widowed	34 (75.6)	9 (20.0)	2 (4.4)	
Educational Status				
Elementary	27 (96.4)	1 (3.6)	0 (0.0)	0.072
High School	70 (76.9)	13 (14.3)	8 (8.8)	
College/Vocational	271 (82.4)	39 (11.9)	19 (5.8)	
Post graduate	18 (64.3)	7 (25.0)	3 (10.7)	
Employment				
Not employed	217 (83.8)	29 (11.2)	13 (5.0)	0.236
Employed	169 (77.9)	31 (14.3)	17 (7.8)	
BMI category				
Underweight	76 (85.4)	5 (5.6)	8 (9.0)	0.012*
Normal	7 (58.3)	2 (16.7)	3 (25.0)	
Overweight	69 (75.8)	15 (16.5)	7 (7.7)	
Obese	234 (82.4)	38 (13.4)	12 (4.2)	
Duration of Diabetes				
<1 year	27 (73.0)	7 (18.9)	3 (8.1)	0.509
1-5 years	122 (78.7)	23 (14.8)	10 (6.4)	
6-10 years	92 (86.8)	10 (9.4)	4 (3.8)	
>10 years	144 (81.4)	20 (11.3)	13 (7.3)	
DM control				
Controlled	203 (85.3)	21 (8.8)	14 (5.9)	0.035*
Uncontrolled	142 (75.9)	31 (16.6)	14 (7.5)	
Complications				
Retinopathy	103 (75.2)	25 (18.2)	9 (6.6)	0.058
Nephropathy	98 (77.2)	23 (18.1)	6 (4.7)	0.075
Neuropathy	156 (77.2)	35 (17.3)	11 (5.5)	0.026*
Stroke	34 (80.9)	7 (16.7)	1 (2.4)	0.433
CAD	43 (87.8)	5 (10.2)	1 (2.0)	0.447
PAOD	24 (82.8)	3 (10.3)	2 (6.9)	1.000
Number of Medications				
0	16 (88.9)	2 (11.1)	0 (0.0)	0.678
1-2	246 (81.2)	35 (11.5)	22 (7.3)	
3 or more	124 (80.0)	23 (14.8)	8 (52)	
Comorbidities				
Hypertension	248 (83.8)	34 (11.5)	14 (4.7)	0.103
Dyslipidemia	208 (84.2)	23 (9.3)	16 (6.5)	0.073
Hyperuricemia	18 (94.7)	0 (0.0)	1 (5.3)	0.245
Hypothyroidism	16 (80.0)	2 (10.0)	2 (10.0)	0.673
Morisky Medication Adherence				
Low	102 (66.7)	35 (22.9)	16 (10.5)	0.000*
Medium	123 (84.8)	14 (9.7)	8 (5.5)	
High	161 (90.4)	11 (6.2)	6 (3.4)	

BMI, Body Mass Index; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; PAOD, Peripheral Arterial Occlusive Disease
* Significant at 0.05 level

DISCUSSION

In a survey conducted by Perlas, Tronco et al., in the Philippines, about 5.3 percent of Filipinos with chronic illness were suffering from depression.[12] In the study of Dy Nieva et al., 31% of patients with type 2 diabetes mellitus had depression, with 24% as mild, and 7% had moderate depression.[13] In our study, the prevalence of depression among patients with diabetes mellitus in the Philippines was lower at 18.2%, with mild depression at 13% and moderate depression at 5.2%. Unlike the study of Dy Nieva et al.,[13] our sample size was larger.

The prevalence result of our study was lower than Varma et al. (49.48%),[14] Al Ghamdi (34%),[15] Sweileh et al. (40%),[16] Salinero- Fort et al. (20.03 %),[17] and Rodriguez Calvin (32.7),[18] but higher than the study of Zhang in China (5.7%).[5]

The prevalence of moderate to severe depression in our study was 6.3%. This was lower in comparison with the Mexican American population which 25% presented with minor depression and 9% with lifetime diagnosis of major depressive disorder.[6] In the study of Varma et al., in India, their prevalence of depression in patients with Type 2 diabetes mellitus was 49.5%, with those having severe depression at 7.16%.[14]

Inconsistent with other studies, female gender did not increase the risk of depression.[14,16-17] Being single, including being unmarried, widowed, and divorced, was identified as a risk factor according to the study of Zhang,[5] however, in our study the marital status was not a significant factor. Having higher educational degree, increases depression, which were in contrast with the results of the other studies.[16]

Different from other studies,[5,14] the number of medications and type of medication, whether oral antidiabetic medications or insulin, did not increase the risk of depression. Furthermore, in contrast with the study of

Table 4. Univariate logistic regression analysis on the association of socioeconomic status and clinical factors with depression among patients with type 2 diabetes mellitus

Variable	Odds Ratio	95% CI	p-value
Age (Mean±SD)	0.964	0.944 - 0.984	0.001*
Gender			
Male	Ref		
Female	2.102	1.179-3.749	0.012*
Marital Status			
Never married	Ref		
Married	0.538	0.286-1.015	0.055
Widowed	1.018	0.416-2.491	0.969
Educational Status			
Elementary	Ref		
High School	2.657	0.847-52.312	0.071
College/ Vocational	4.278	0.567-32.267	0.159
Post graduate	12.789	1.493-109.544	0.020*
Employment			
Not employed	Ref		
Employed	1.273	0.773-2.097	0.343
BMI	0.952	0.900-1.007	0.090
BMI category			
Normal	Ref		
Underweight	4.583	1.250-16.799	0.022*
Overweight	1.925	0.883-4.120	0.100
Obese	0.902	0.446-1.823	0.774
Duration of Diabetes			
<1 year	Ref		
1-5 years	0.423	0.179-0.999	0.050*
6-10 years	0.345	0.134-0.884	0.027*
>10 years	0.551	0.241-1.257	0.157
HbA1c (Mean±SD)	1.269	1.093-1.372	0.002*
DM control			
Controlled	Ref		
Uncontrolled	1.928	1.125-3.303	0.017*
Complications			
Retinopathy	1.800	1.027-3.022	0.026*
Nephropathy	1.131	0.651-1.967	0.661
Neuropathy	1.582	0.959-2.610	0.072
Stroke	0.557	0.192-1.610	0.280
CAD	0.333	0.101-1.099	0.071
PAOD	0.876	0.296-2.597	0.812
Number of Medications	1.119	0.900-1.392	0.309
Medications			
Insulin	1.363	0.810-2.294	0.244
Biguanides	0.849	0.491-1.466	0.556
Sulfonylureas	1.021	0.578-1.804	0.942
DPP-IV inhibitors	0.979	0.584-1.641	0.937
SGLT-2 inhibitors	1.471	0.853-2.535	0.165
TZD	1.209	0.561-2.604	0.628
Comorbidities			
Hypertension	0.535	0.324-0.884	0.015*
Dyslipidemia	0.675	0.409-1.116	0.125
Hyperuricemia	0.297	0.039-2.260	0.241
Hypothyroidism	1.402	0.455-4.320	0.556
Morisky Medication Adherence			
Low	Ref		
Medium	0.426	0.233-0.778	0.005*
High	0.241	0.125-0.464	0.000*
Morisky Medication Adherence Score	1.418	1.245-1.614	<0.001*

BMI, Body Mass Index; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; PAOD, Peripheral Arterial Occlusive Disease
* Significant at 0.05 level

Table 5. Multiple logistic regression analysis on the association of socioeconomic status and clinical factors with depression among patients with type 2 diabetes mellitus

Variable	Odds Ratio	95% CI	*p*-value
Age	0.962	0.932-0.994	0.021*
Gender			
Male	Ref		
Female	2.011	0.999-4.051	0.050*
Marital Status			
Never married	Ref		
Married	0.806	0.350	1.854
Widowed	1.906	0.551	6.590
Educational Status			
Elementary	Ref		
High School	4.809	0.534-43.289	0.161
College/Vocational	5.054	0.595-42.909	0.138
Post graduate	19.683	1.938-199.922	0.012*
BMI	0.948	0.885-1.016	0.132
Duration of Diabetes			
<1 year	Ref		
1-5 years	0.428	0.146-1.254	0.122
6-10 years	0.267	0.079-0.899	0.033*
>10 years	0.601	0.200-1.811	0.366
HbA1c	1.130	0.881-1.450	0.336
DM control			
Controlled	Ref		
Uncontrolled	1.444	0.591-3.523	0.420
Retinopathy			
None	Ref		
Yes	2.361	1.158-4.813	0.018*
Neuropathy			
None	Ref		
Yes	1.606	0.836-3.083	0.155
CAD			
None	Ref		
Yes	0.483	0.129-1.814	0.281
Hypertension			
None	Ref		
Yes	0.703	0.355-1.395	0.314
Morisky Medication Adherence Score	1.458	1.240-1.714	0.000*

BMI, Body Mass Index; DM, Diabetes Mellitus; CAD, Coronary Artery Disease
* Significant at 0.05 level

Zhang,[5] Sweileh[16] and Dy Nieva,[13] which revealed higher BMI had association with depression, weight was not a factor for depression in our study.

Diabetic complications were found to be strongly associated with increasing depression.[6,14] Other studies showed depression was associated with neuropathy[17] but in our study, retinopathy was the connected complication. Blurring of vision or visual abnormalities are noticeable symptoms which may add to the stress of the patient and affect their activities of daily living.

As seen with the study of Sweileh et al.,[16] low medication adherence revealed to be associated with depression. Patients with poor glycemic control have greater risk of experiencing depression than those who have good control as seen in our study. Several studies have confirmed this association.[14,18] When T2DM and depression co-exist in an individual, he/she is more prone to develop worse glycemic control due to poorer medication adherence, which could lead to diabetic complications and associated morbidity.

Based from other reviews, there is a biological basis of depression and type 2 diabetes mellitus. Depression is associated with subclinical hypercortisolism secondary to hypothalamic-pituitary adrenal (HPA) axis activation.[19-20] Cortisol also activates lipolysis and release of free fatty acids, which can induce insulin resistance. Repeated stress with the repeated induction of corticosteroids can result in hippocampal damage, causing a failure in the downregulation of corticosteroid production by the feedback mechanism and thus persisting elevated

circulating cortisol levels.[21,22] In the study of Gold et al., individuals with type 2 diabetes have clear deficits in hippocampal-based (recent or declarative) memory and selective MRI-based atrophy of the hippocampus relative to matched control subjects.[23] These may provide an additional explanatory link between depression and type 2 diabetes.

Metabolic disturbances of diabetes also lead to changes in the brain that alter susceptibility to social stressors. It induces changes in neuronal function and structure on areas of the brain that regulate affect and, therefore, increase risk for depression.[24]

It was also noted that inflammation is also present on both diabetes mellitus and depression. A study by Brummett et al.,[25] found depression to be associated with higher inflammatory markers (CRP and IL-6), and interestingly the association was stronger in women compared with men. Both depression and diabetes are associated with enhanced cytokine production and elevation of inflammatory markers which may be another biological mechanism through which these two disorders are related.[19,22] Catecholamines and inflammatory cytokines are known to induce insulin resistance.[19,26] Features of type 2 diabetes, such as fatigue, sleep disturbance, and depression, are likely to be at least partly due to hypercytokinemia and activated innate immunity.[21]

It is beyond the scope of the study to investigate further the biological basis of depression among diabetes mellitus. In this study, the associated clinical risk factors for depression were: being employed, having low medication adherence and poorly controlled diabetes mellitus and, the presence of retinopathy.

Limitations of the study

Our study investigated the prevalence and associated factors of depression in patients with type 2 diabetes mellitus in the Philippines. However, our study has few limitations: (1) Consecutive sampling was done to recruit participants, (2) samples were recruited from 1 hospital only and are not representative of the subsets of patients in the Philippines, (3) complications of diabetes were noted per chart review and as reported by the subjects only, (4) this study is cross-sectional where causal relationship between diabetes and depression cannot be established.

CONCLUSION

Depression is prevalent among Filipino patients with Type 2 Diabetes Mellitus. About two out of five patients (19.9%) with diabetes mellitus have depression. Low medication adherence, having a postgraduate degree and presence of retinopathy as complication, were significantly associated with depression. These findings support a recommendation for routine screening and regular psychosocial assessment for depression among Filipino patients with diabetes. Integrated approach by the attending physicians and psychiatrists may be required for the effective management of these patients.

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All authors certified fulfillment of ICMJE authorship criteria.

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Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

Weathering the Crisis: A Case of Thyroid Crisis with Propranolol-Induced Circulatory Collapse Successfully Treated with Therapeutic Plasma Exchange

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Abstract

Thyroid crisis is a life-threatening form of thyrotoxicosis characterized by multi-system dysfunction. Therapeutic plasma exchange has been reported to be effective in removing excessive circulating thyroid hormones. We present a 46-year-old female with recently diagnosed Graves' disease associated with thyrotoxic cardiomyopathy admitted for thyroid crisis complicated by propranolol-induced circulatory collapse, acute kidney injury and ischemic hepatitis. The tachyarrhythmia was refractory to conventional therapy. Initiation of TPE resulted in rapid clinical and biochemical stabilization.

Key words: thyroid crisis, circulatory collapse, cardiomyopathy, propranolol, therapeutic plasma exchange

INTRODUCTION

Thyroid crisis is a potentially lethal complication of thyrotoxicosis if inadequately treated. It is a state of metabolic crisis characterized by multisystem dysfunction due to excess thyroid hormone release. Patients with thyroid crisis should be managed in a multi-modality approach with anti-thyroid drugs (ATDs), inorganic iodide, glucocorticoids and anti-adrenergic drugs.[1] Propranolol, a non-cardio-selective β-blocker (NCBB) is an anti-adrenergic agent commonly used to control the sympathomimetic symptoms in thyroid crisis patients due to its additional effect of blocking the peripheral conversion of inactive thyroxine (T4) to the active thyroid hormone, tri-iodothyronine (T3)[2]. However, patients with thyroid crisis may have clinical or subclinical thyrotoxic cardiomyopathy that predisposes them to an exaggerated response to β-blocker therapy manifesting as circulatory collapse. Therapeutic plasma exchange (TPE) is an alternative treatment for thyroid crisis when life-threatening symptoms are present or conventional medical therapy has failed or is contraindicated.[2] We report a 46-year-old female with recently diagnosed Graves' disease associated with thyrotoxic cardiomyopathy who presented with thyroid crisis and developed circulatory collapse after administration of β-blocker and was subsequently treated with TPE.

CASE

A 46-year-old female with background history of hypertension and type 2 diabetes with recently diagnosed Graves' disease associated with thyrotoxic cardiomyopathy was admitted for thyroid crisis. She was diagnosed with Graves' disease four months ago. She had presented with heart failure along with a seven-month history of palpitations, diaphoresis, weight loss, and tremors. Her free thyroxine (FT4) level was 68.1 pmol/L (reference range 11.8-23.2) while thyroid stimulating hormone (TSH) level was suppressed. Her anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) were positive while thyroid stimulating hormone receptor antibodies (TRAb) was not sent as it was not available in our centre. She was treated with carbimazole, propranolol and furosemide. Unfortunately, the patient defaulted her medications and follow-up. She presented again with a two-month history of progressive exertional dyspnea, orthopnea and bilateral leg swelling. On examination, she was restless, clinically thyrotoxic and tachypneic with a respiratory rate of 22 cycles per minute, her blood pressure (BP) was 155/117 mmHg, temperature was 37.1^{0}C. Cardiovascular examination revealed a raised jugular venous pressure, bibasal crepitations in the lungs and bipedal edema up to mid-shin. Electrocardiogram showed atrial fibrillation with rapid ventricular rate of 170 beats per minute. Capillary blood glucose was 5.5 mmol/L. Chest radiograph showed cardiomegaly with pulmonary congestion (Figure 1). Her free T4 level was 105.3 pmol/L and TSH was <0.01 mU/L (reference range 0.35- 5.5 mU/L). A diagnosis of thyroid crisis precipitated by non-compliance to medication was made with a Burch-Wartofsky score of 60. A loading dose of oral propylthiouracil 600 mg, intravenous (IV) hydrocortisone 200 mg and oral propranolol 40 mg were administered. Twenty minutes after the administration of propranolol, the patient developed sudden onset of severe respiratory

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distress, hypotension with a BP of 85/40 mmHg leading to emergency intubation. Post-intubation, she progressed into pulseless electrical activity with return of spontaneous circulation after 18 minutes of cardiopulmonary resuscitation. The diagnosis of propranolol-induced circulatory collapse was made and she was admitted to intensive care unit requiring triple inotropic support with IV adrenaline, noradrenaline and dopamine infusions.

A repeat electrocardiogram showed persistent atrial fibrillation with no ST segment changes. Echocardiogram revealed poor heart contractility, global hypokinesia with estimated left ventricular ejection fraction of 30%. She remained in rapid atrial fibrillation with cardiogenic shock despite synchronized cardioversion, digoxin and amiodarone. IV esmolol infusion for control of the tachyarrhythmia had to be discontinued after 3 hours due to worsening hypotension. Her clinical condition continued to deteriorate despite high dose of oral carbimazole 30 mg six hourly, IV hydrocortisone 100 mg eight hourly and Lugol's iodine 10 drops six hourly. She developed ischemic hepatitis, coagulopathy, and anuric acute kidney injury with metabolic acidosis requiring continuous veno-venous hemodialysis (CVVHD). The first cycle of TPE was initiated on the fourth day of hospitalization with two liters of fresh frozen plasma and one liter of human albumin. The patient's hemodynamic status improved significantly within 24 hours allowing tapering of the inotropic support with heart rate reduced to 120-130 beats per minute. Another two cycles of TPE were performed on day five and day seven of hospitalization followed by resolution of pulmonary congestion and successful extubation by day nine of hospitalization (Figure 2). Inotropes were also tapered off by day eight of hospitalization followed by restoration of sinus rhythm at day 15. There was no transfusion reaction or hemodynamic instability throughout the three cycles of TPE. Her free T4 level decreased markedly into the normal range (13.8 pmol/L) after three sessions of TPE and continued to fall to 7.3 pmol/L at day 13 of hospitalization necessitating reduction of carbimazole to maintenance dose of 10 mg daily (Figure 3). Liver and renal dysfunction also resolved by day 16 of hospitalization. The patient's recovery was complicated by critical illness neuropathy post extubation. She was transferred to another rehabilitative facility one month after admission and continued to recover neurologically with intensive physiotherapy. The patient was planned for radioactive iodine therapy in six months as definitive treatment of the Graves' disease.

DISCUSSION

Thyroid crisis carries a mortality rate of up to 30% if not recognized and treated promptly.[1,2] It is characterized by multisystem dysfunction involving mainly cardiovascular, neurological, gastro-intestinal and hepato-biliary systems due to excessive release of thyroid hormone. Hyperthyroidism creates a state of high cardiac output by increasing cardiac contractility, heart rate and decreasing peripheral resistance. It also induces a hyperadrenergic state by amplifying formation and reducing degradation of β-adrenergic receptors.[3] Both mechanisms play a compensatory role in maintaining cardiac output of patients with clinical or subclinical thyroid cardiomyopathy during states of stress. Propranolol is an NCBB commonly used in the treatment of thyroid crisis. The administration of propranolol to patients with pre-existing clinical or subclinical thyrotoxic cardiomyopathy may result in an uncommon but serious adverse outcome. Administration of NCBB may impede the thyrotoxicosis induced hyperadrenergic state, halting the compensatory mechanism causing significant fall in cardiac output in the setting of stress such as thyroid crisis, leading to circulatory collapse.[2] Our patient had evidence of pre-existing thyrotoxic cardiomyopathy when she presented with heart failure four months prior to current hospitalization. She developed a drastic drop in BP followed by cardiac arrest shortly after propranolol administration. The temporal association between propranolol administration

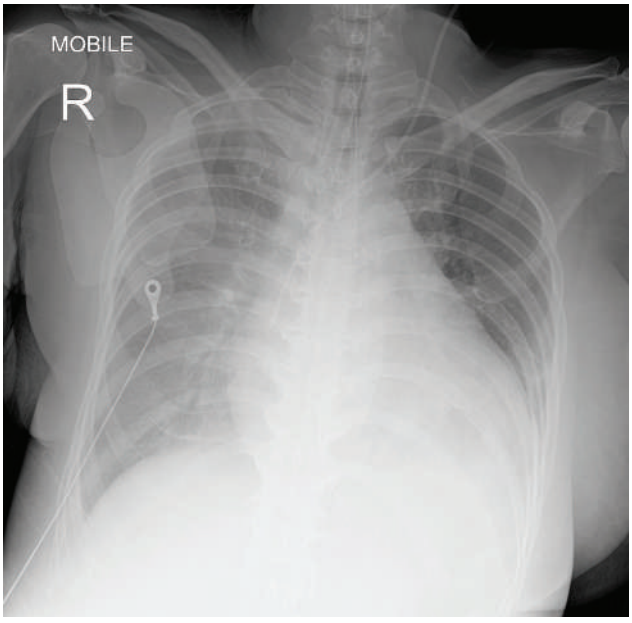

Figure 1. Chest radiograph showing cardiomegaly and pulmonary congestion upon admission.

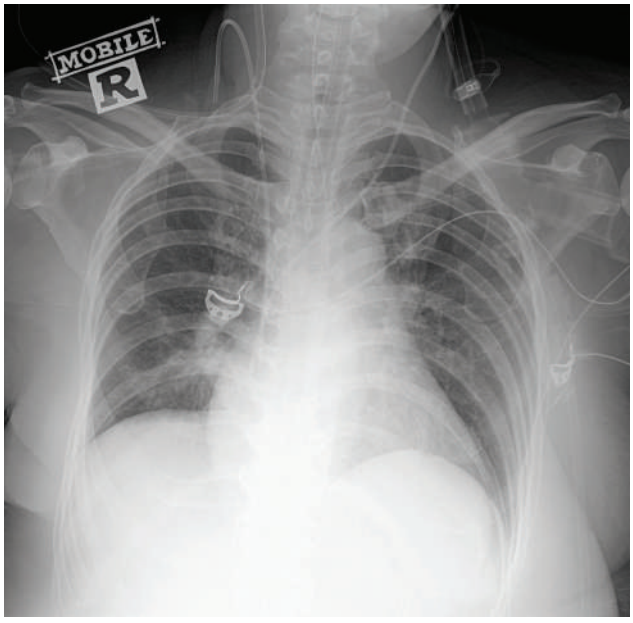

Figure 2. Chest radiograph showing resolution of cardiomegaly with marked improvement of pulmonary congestion by day nine of hospitalization.

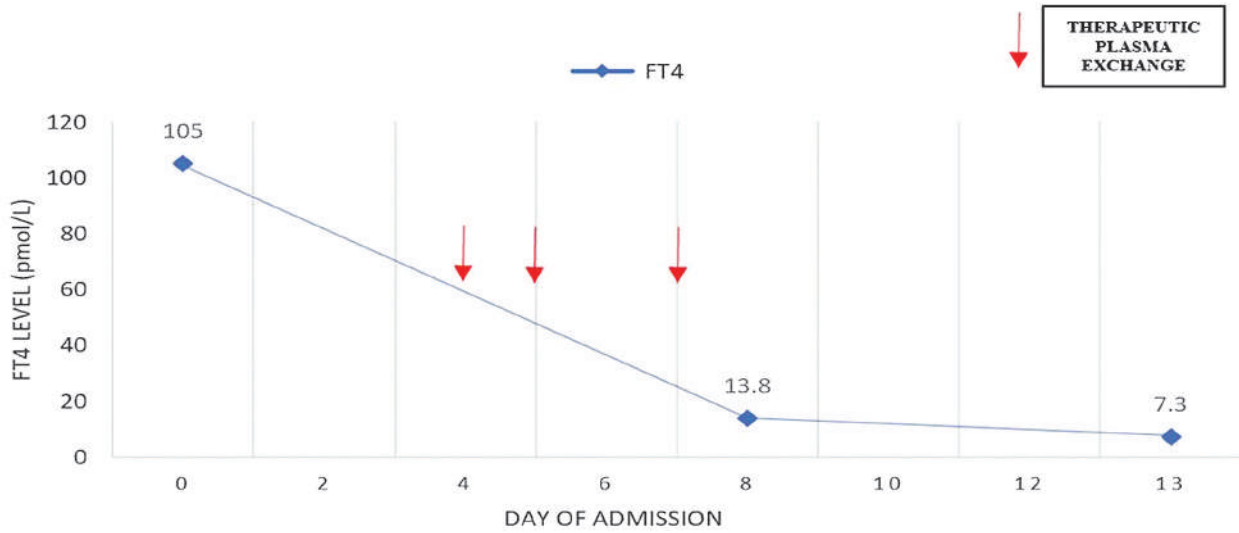

Figure 3. Free thyroxine (FT4) serum concentrations during hospitalization before and after therapeutic plasma exchange (TPE).

and the sudden onset of hemodynamic instability led to the diagnosis of propranolol-induced cardiogenic shock confirmed by the echocardiographic findings of reduced ejection fraction with poor heart contractility. A total of 11 cases of β-blocker induced circulatory collapse in thyroid crisis have been described in the literature.[3] Almost all the patients had evidence of pre-existing thyrotoxic cardiomyopathy with five of them having documented low ejection fraction prior to the adverse event. Six of them had cardiac arrest while the rest had hypotension with three fatalities reported. Propranolol was the most commonly used β-blocker. The presence of thyrotoxic cardiomyopathy especially with low output heart failure may predispose one to an exaggerated response to β-blocker therapy manifesting as circulatory collapse secondary to cardiogenic shock. However complete cessation of β-blocker therapy may not be possible due to uncontrolled tachycardia. IV esmolol infusion was used in our patient to control the refractory tachyarrhythmia but it was not well tolerated due to hypotension most probably related to the concomitant CVVHD for anuric acute kidney injury and metabolic acidosis. In a Japanese nationwide survey that compared the use of β_1-selective and non-selective β-blocker in thyroid crisis, it was found that all deaths among patients with congestive heart failure Killip class three and above were treated with NCCB while those who survived were treated with β_1-selective blocker.[4] Both esmolol and landiolol are ultra-short acting IV β-blockers with high cardio-selectivity and short half-life of four to nine minutes as opposed to 23 hours for propranolol.[4] Due to the ultra-short half-life which allows frequent dose titration and rapid weaning from the β blockade effect upon discontinuation, they may be considered as safer alternatives in patients with underlying thyrotoxic cardiomyopathy compared to propranolol especially during thyroid crisis.[3,5] The Japanese Thyroid Association recommended the use of β_1-selective blocker such as esmolol, landiolol or bisoprolol over NCCB in the treatment of tachycardia in thyroid crisis. IV esmolol or landiolol is preferred over oral bisoprolol if heart rate is more than 150 beats per minute. It can be switched to oral bisoprolol when heart rate is less than 150 beats per minute in Killip class three or below.[4]

The use of TPE in thyroid crisis has been described in the literature as early as 1970s.[6] The benefits of TPE mainly results from plasma removal of thyroid hormones and their bound proteins, putative autoantibodies, cytokines, catecholamines etc. Although its efficacy is yet to be verified in prospective randomized control trial as thyroid crisis is a rare endocrine emergency, many successful cases of TPE use in thyroid crisis have been reported.[6] TPE should be considered early in the presence of life-threatening symptoms in thyroid crisis when rapid removal of excess thyroid hormones and its binding proteins is essential as it is the fastest way to produce clinical and biochemical improvement. In our patient, the decision to initiate TPE was made at day two of hospitalization in view of the refractory tachyarrhythmia in shock with onset of renal and liver dysfunction indicating high risk of mortality if urgent measure to reduce the thyroid hormone level was not performed. However, the risk of hemodynamic compromise and the technical difficulties involved with the ongoing CVVHD only allowed the initiation of TPE at day four of hospitalization. Significant clinical improvement was observed within 24 hours after the first cycle of TPE. The FT4 level dropped by 85% into the normal range after three cycles of TPE over four days. Thyroid function test was not repeated until the end of third cycle of TPE. Clinically, patient continued to improve with each cycle of TPE. The cardiac, liver and renal dysfunction resolved completely 12 days after the initiation of TPE. It was believed that the clinical improvement was predominantly contributed by the TPE as the patient failed to improve within the first 72 hours of presentation when she was on high dose of ATD. Among the reported cases of thyroid crisis successfully treated with TPE, clinical improvement was typically observed within 24 to 72 hours with one to five cycles of TPE.[6] However, its effect was transitory in nature and conventional treatment with ATDs, glucocorticoids, β-blocker and inorganic iodide should be administered concomitantly unless contra-indicated to prevent early relapse. Early biochemical improvement in thyroid hormone levels was also frequently observed but its improvement varied between 15 to 78% depending on baseline thyroid hormone levels. Clinical-biological dissociation is not

uncommon in which clinical improvement often preceded the decrement in thyroid hormone levels. The overall incidence of adverse events associated with TPE such as hemodynamic instability, transfusion reaction, infectious complications etc., is about 5%. Death was rare and was usually due to the underlying disease.[6] The Japan Thyroid Association recommended the use of TPE when there is no clinical improvement with conventional therapy within 24 to 48 hours.[4] The American Society of Apheresis graded the use of TPE in thyroid crisis as category III in which an optimal role is not established and decision should be individualized.[7] It is also recommended to perform every 24 to 72 hours with 40-50 ml/kg of replacement fluids until clinical improvement.[7,8] Both societies recommended the preferential use of fresh frozen plasma which contains T4-binding globulins to albumin as replacement solution.[4,7] The overall incidence of adverse events associated with TPE is about 5%.[6] Notable side effects of TPE include hemodynamic instability, transfusion reaction, infectious complications, citrate-related nausea and vomiting, respiratory distress and seizure.[9] Death is rare and is usually due to the underlying disease. However, none of these adverse events occurred in our patient.

CONCLUSION

This case highlights the importance of awareness of this uncommon but life-threatening adverse event of propranolol-induced circulatory collapse in patients with thyroid crisis associated with pre-existing thyrotoxic cardiomyopathy. Ultra-short acting β-blockers with high cardio-selectivity should be considered over NCBB in a critical care setting with careful titration and close hemodynamic monitoring. TPE should be considered in thyroid crisis associated with life-threatening symptoms especially in the presence of multi-organ dysfunction or rapid clinical deterioration apart from failure to respond to conventional medical therapy. The duration and frequency of TPE should be individualized. It may be discontinued upon significant clinical improvement and resolution of end organ dysfunction.

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

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CASE REPORT

A Trial of Oral Glucocorticoids in the Resolution of Recurrent Granulomatous Hypophysitis: A Case Report

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Abstract

Granulomatous hypophysitis is an extremely rare condition, with no established definitive treatment. An elderly Asian woman was diagnosed to have recurrent granulomatous hypophysitis 5 years after transsphenoidal surgery. No other intervention was done post-operatively. Since another surgery was not advisable due to the high probability of recurrence, she was started on a trial of oral glucocorticoids. After 3 months of steroid therapy, complete resolution of symptoms and sellar mass were achieved.

Key words: granulomatous hypophysitis, autoimmune hypophysitis, glucocorticoids

INTRODUCTION

Granulomatous hyphophysitis is a rare condition that can occur as a primary phenomenon or secondary to tuberculosis, syphilis, sarcoidosis, Wegener's granulomatosis and other inflammatory diseases. Clinical manifestations include hypopituitarism and local mass effects, with sudden onset of headache being the most common symptom. Some cases were initially diagnosed as pituitary adenoma because of their clinical and radiologic similarities, prompting surgery. Definitive management has not yet been established for granulomatous hypophysitis due to the limited number of cases and variable response to therapy.

CASE

A 70-year-old Asian female with good functional capacity and independence in activities of daily living presented in 2012 with frontal headache of sudden onset, characterized as non-radiating, intermittent, with a pain scale of 10/10 and aggravated by movement and sneezing. The pain was temporarily relieved by paracetamol and other non-steroidal anti-inflammatory drugs. There were no associated symptoms of blurring of vision, diplopia, visual field cuts, anosmia, change in shoe size, galactorrhea, nausea and vomiting. Upon consult, cranial magnetic resonance imaging (MRI) showed an enhancing suprasellar mass measuring 1.3 cm x 1.3 cm x 1.4 cm indenting the optic chiasm, consistent with pituitary macroadenoma (Figures 1A and B). Further biochemical evaluation showed decreased LH and a normal baseline perimetry studies (Table 1).

Her other comorbidities were hypertension for more than 10 years, type 2 diabetes mellitus for 10 years and osteoporosis diagnosed one year ago. She had undergone right mastectomy for ductal carcinoma in situ 18 years ago, with no subsequent radiation or chemotherapy. Her menstrual history was unremarkable. She was nulligravid despite normal fertility work up and clomiphene intake for almost 3 years. She had also undergone cataract surgery and laparoscopic cholecystectomy. Her medications were sitagliptin, metformin, amlodipine, losartan, tamoxifen and ibandronic acid. She had no history of steroid use.

Table 1. Preoperative and postoperative hormonal studies during initial presentation

Hormone	Pre-operative result	Post-operative result	Reference value
Cortisol[a], µg/dL	13.4	10.68 7.97	6.2-19.4
Prolactin, ng/mL	11.265	6.409	3.6-18.9
TSH[b], µIU/mL	0.665	1.734	0.27-3.75
FT4[c], pmol/L	12.900	12.773	8.8-33
LH[d], mIU/mL	1.876	–	5-20
FSH[e], mIU/mL	15.144	–	5-20

[a]Taken at 0800H/0900H
[b]TSH, thyroid stimulating hormone
[c]FT4, free thyroxine
[d]LH, luteinizing hormone
[e]FSH, follicle stimulating hormone

The clinical impression in 2012 was pituitary macroadenoma. The patient underwent transsphenoidal surgery with an unremarkable post-operative course. Post-operative cranial MRI showed interval resolution of the previously noted pituitary mass, with normal appearance of the pituitary gland including the optic chiasm and pituitary stalk (Figures 1C and 1D). Post-operative pituitary hormones showed normal results (Table 1).

The histologic features were consistent with chronic granulomatous inflammation with focal necrosis instead of a pituitary adenoma (Figure 2). Acid-fast

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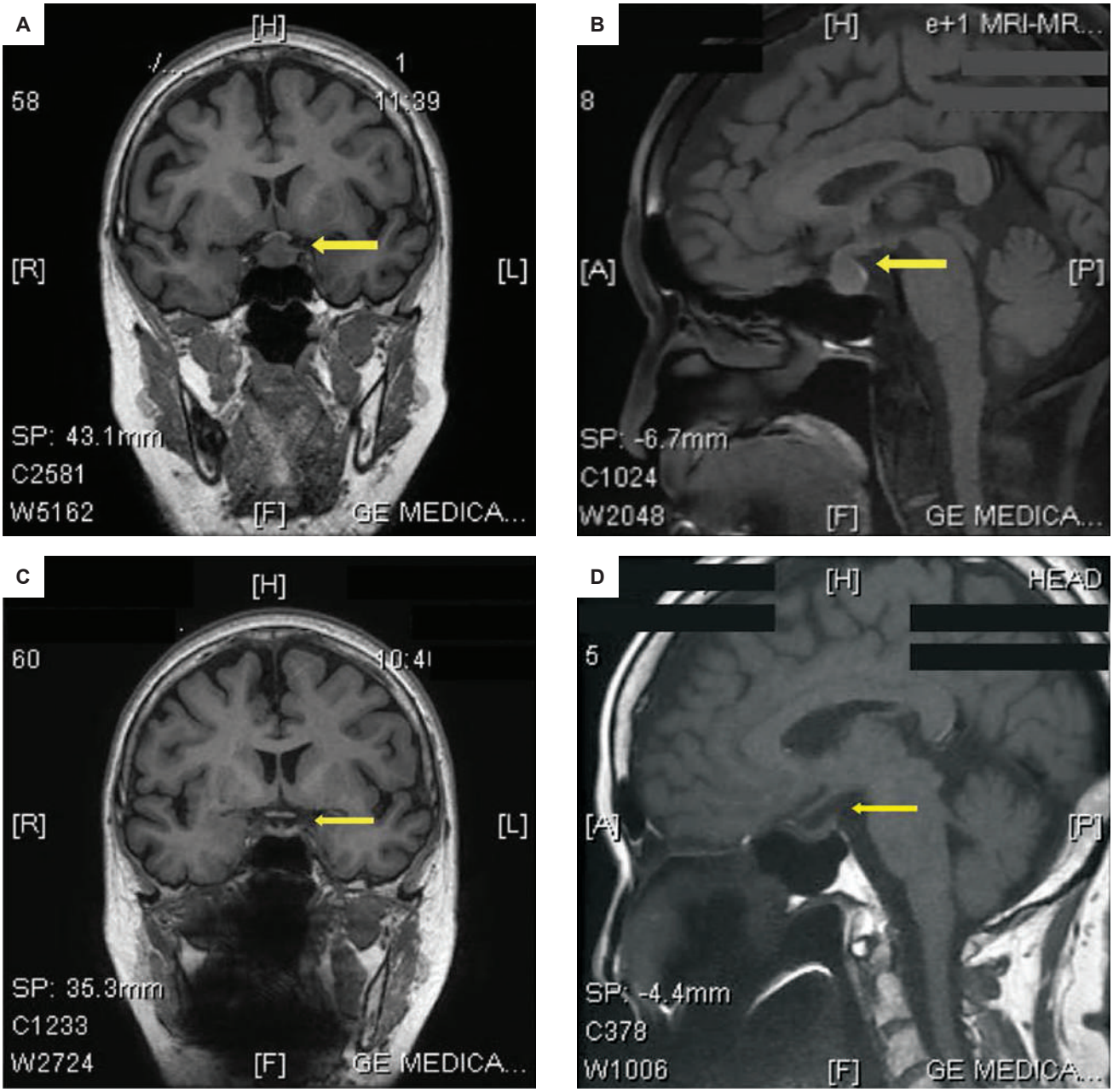

Figure 1. Preoperative cranial magnetic resonance imaging (MRI) in **(A)** coronal and **(B)** sagittal views showed an enlarged pituitary gland, with a 1.3 cm x 1.3 cm x 1.4 cm enhancing suprasellar nodule indenting the optic chiasm. Features of cystic degeneration, calcification and hemorrhage were absent. After transsphenoidal surgery, MRI showed interval resolution of the previously noted pituitary nodule, with normal appearance of the pituitary gland, optic chiasm and pituitary stalk on **(C)** coronal and **(D)** sagittal views.

bacilli and silver sethenamine stains showed negative results. Upon consult with another institution abroad, the diagnosis was non-caseating granulomatous inflammation involving the pituitary gland, with primary considerations of tuberculosis, giant cell granuloma (idiopathic granulomatous hypophysitis) or sarcoidosis. *Mycobacterium tuberculosis* PCR/nucleic acid amplification were also negative. There was no treatment rendered during that time. She was advised to have annual MRI for monitoring but the patient was lost to follow-up.

Interval history was unremarkable until five years after the surgery. The patient began to experience intermittent, non-radiating headache, with a pain scale of 3 to 10/10, temporarily relieved by paracetamol and tramadol. The persistence of her symptoms prompted consult with a Neurologist. Cranial MRI showed a 1.2 cm x 1.3 cm x 1.5 cm enhancing left sellar nodule (Figure 3). No visual field defects were noted on perimetry. Hormonal tests showed central hypothyroidism and hypogonadism (Table 2).

Surgical intervention was not advised at that time due to the high probability of recurrence and eventual impairment of pituitary function. As several case reports have shown that granulomatous hypophysitis may respond to steroid therapy, the patient was started on prednisone at 30 mg per day. Resolution of symptoms were noted after initiation of treatment. Prednisone was eventually tapered by 5 mg

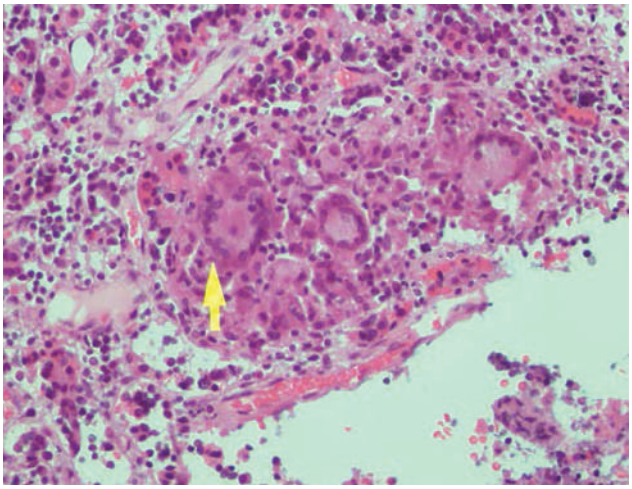

Figure 2. Photomicrograph showing granuloma formation characterized by central epithelioid, foamy macrophages and giant cells (H&E, 200x).

Table 2. Pretreatment and post-treatment hormonal studies on recurrence

Hormone	Pre-treatment	Post-treatment		Reference value
		After 6 months	After 18 months	
Cortisol[a], nmol/L	454.50 312.75	–	359.5	138-690
ACTH[b], pg/mL	1.579	–	17.8	Less than 50
IGF[c], ng/mL	47.125	–	–	72-167
HGH[d], ng/mL	0.076	–	–	0-7
Prolactin, ng/mL	2.976	–	5.64	3-20
TSH[e], µIU/mL	1.001	2.667	3.67	0.27-3.75
FT4[f], pmol/L	6.865	20.196	16.49	8.8-33
LH[g], IU/mL	2.355	–	9.38	9.03-70.6
FSH[h], IU/mL	4.951	–	15.78	24-141

[a]Taken at 0800H/0900H
[b]ACTH, adrenocorticotropic hormone
[c]IGF, insulin-like growth factor
[d]HGH, human growth hormone
[e]TSH, thyroid stimulating hormone
[f]FT4, free thyroxine
[g]LH, luteinizing hormone
[h]FSH, follicle stimulating hormone

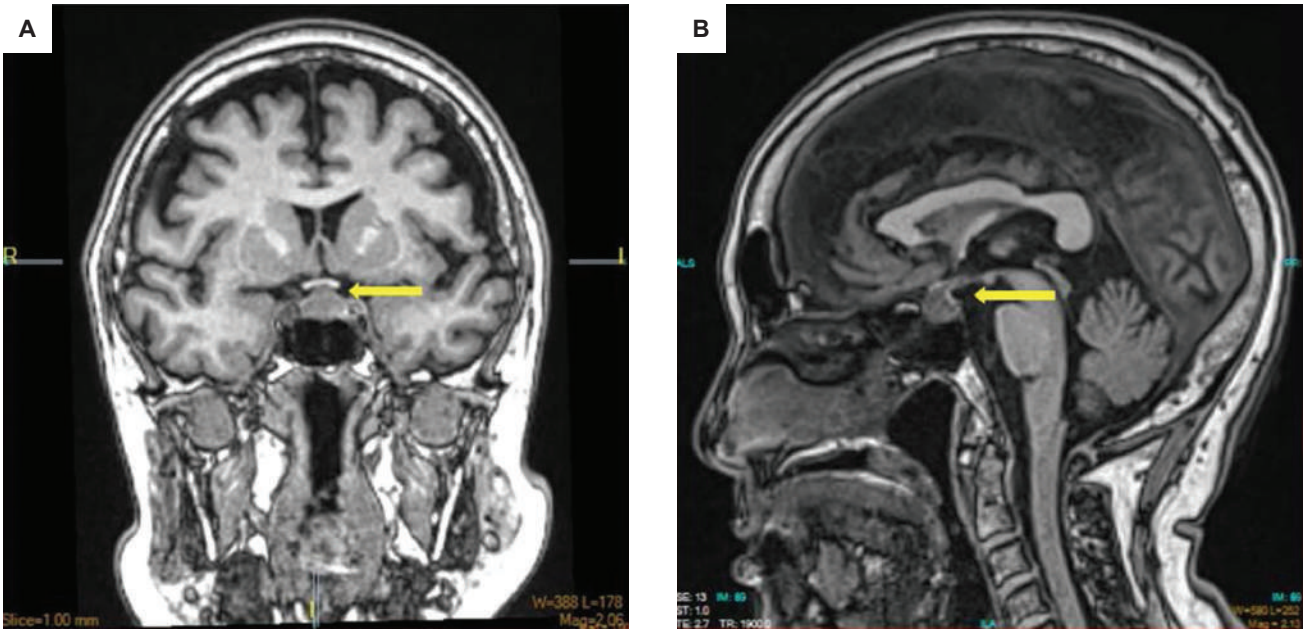

Figure 3. Cranial MRI upon recurrence of symptoms in **(A)** coronal and **(B)** sagittal views showing an enhancing left sellar nodule measuring 1.2 cm x 1.3 cm x 1.5 cm superiorly deviating the pituitary infundibulum to the right and abutting the optic chiasm.

per day every 2 weeks. After attaining a dose of 5 mg per day for two weeks, it was then given at 3 times a week, twice a week, once a week, and then discontinued, with an interval of 2 weeks each. After 3 months of steroid therapy, cranial MRI showed complete resolution of the sellar mass (Figures 4A and 4B). During the course of treatment, the patient was clinically evaluated for the possible side effects of the steroid therapy and symptomatic hypothyroidism. Aside from the weight gain which completely resolved after treatment, there were no other adverse effects noted, particularly hypotension, uncontrolled hypertension, hypoglycemia, uncontrolled hyperglycemia, headache, body weakness, constipation and electrolyte imbalance. Upon reevaluation approximately 6 months post-treatment, cranial MRI showed no enhancing lesion in the pituitary gland (Figures 4C and 4D) and normal thyroid function (Table 2).

The patient remained asymptomatic during periodic monitoring. Biochemical tests done at one and a half years post-treatment showed complete resolution of central hypothyroidism (Table 2). The gonadotrophic hormones also showed improvement as compared to pretreatment results. Cranial MRI still showed absence of the pituitary mass.

DISCUSSION

Hypophysitis is a rare inflammatory disorder of the pituitary gland, which can be classified as lymphocytic, granulomatous, xanthomatous, xanthogranulomatous or necrotizing.[1] Granulomatous hypophysitis, one of its most common types, has an estimated incidence of one case per 9 million people per year.[2] This condition is mostly seen in females especially in older age groups.

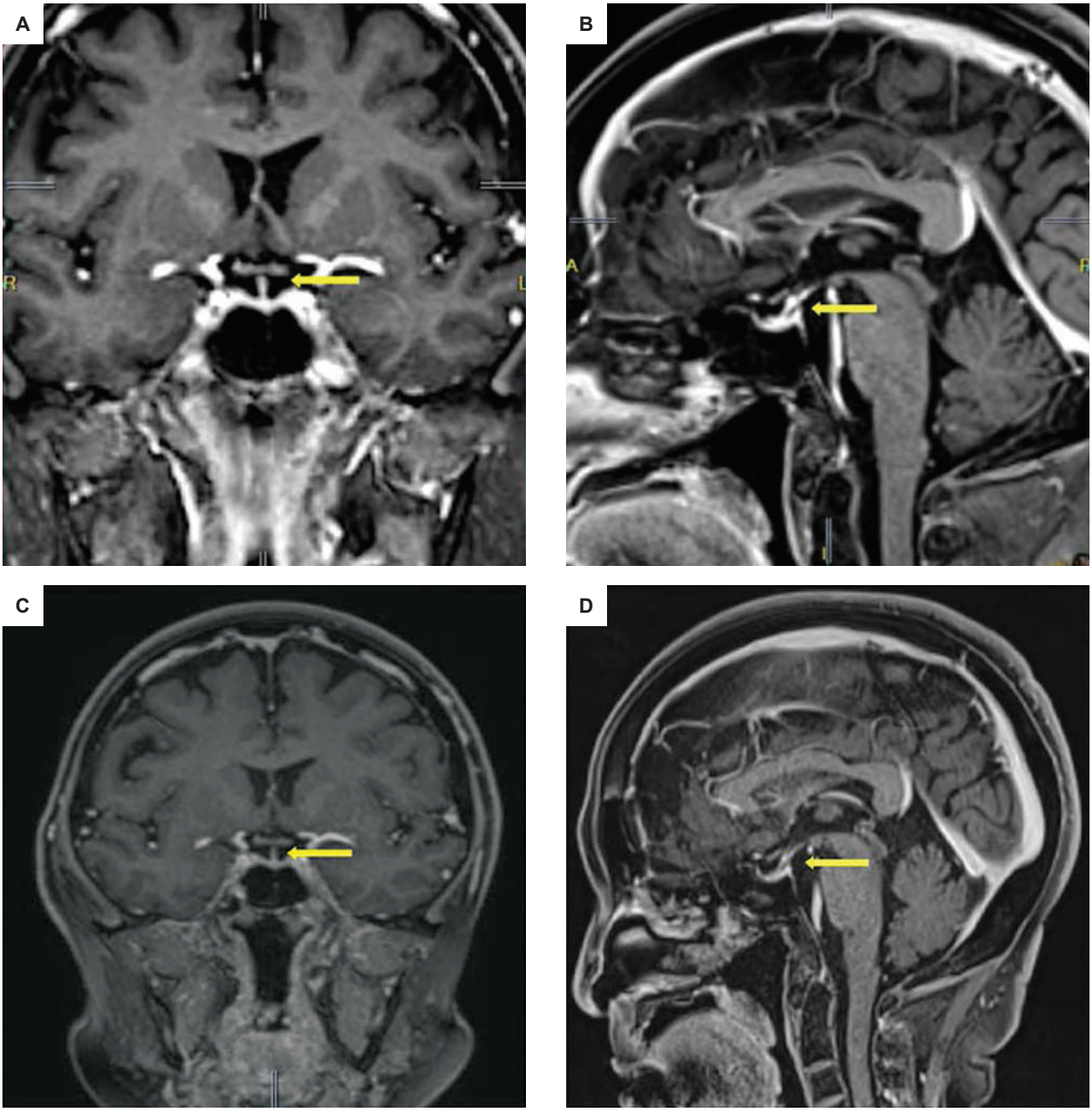

Figure 4. Cranial MRI in **(A)** coronal and **(B)** sagittal views after 3 months of steroid therapy showing complete resolution of the sellar nodule. A normal-sized pituitary gland, midline infundibulum and normal optic chiasm on both views **(C and D)** were seen approximately 6 months after treatment.

Granulomatous hypophysitis can also be caused by systemic diseases characterized by granuloma formation such as sarcoidosis, syphilis and tuberculosis. It is also associated with other intrasellar lesions such as adenomas, mucoceles and Rathke's cleft cysts.[1,2]

Signs and symptoms of granulomatous hypophysitis, particularly visual disturbances, headaches and hypopituitarism, are usually secondary to mass effect. In a systematic review of 82 cases of idiopathic granulomatous hypophysitis, the most common presenting symptoms were headache and visual disturbances.[3]

Biochemical findings appear to be normal in some cases. This may be attributed to a non-functioning pituitary adenoma, as seen in our patient during the first occurrence of the mass. Abnormal results were frequently associated with low adrenocorticotropic hormone and/or cortisol, low growth hormone, central hypothyroidism, and low follicle stimulating hormone (FSH) or luteinizing hormone (LH).[3] Low to low normal free thyroxine, thyroid stimulating hormone, FSH and LH were seen in our patient during recurrence of the disease, most probably secondary to mass effect.

Granulomatous hypophysitis is usually diagnosed on the basis of histopathologic findings of presence of granuloma formation, multinucleated giant cells, plasma cells, and/or lymphocytes. Computed tomography and MRI are unable to differentiate hypophysitis from

pituitary adenoma, as these show similar degrees of enhancement. Granulomatous hypophysitis appears to be homogeneously iso-intense to brain parenchyma on MRI.[4]

Due to its rarity, definitive treatment for granulomatous hypophysitis has not yet been established. A descriptive analysis of different treatment modalities (excision, excision and corticosteroid, and biopsy and corticosteroid) showed a higher recurrence rate in individuals who underwent excision and corticosteroid, compared to biopsy with steroid.[3] It has been suggested that these conditions should be managed conservatively. Transsphenoidal surgery should only be considered when the patient presents with visual symptoms, with the procedure having both diagnostic and therapeutic purpose. Steroid therapy can be initiated postoperatively and maintained for a period of time.[5]

CONCLUSION

Granulomatous hypophysitis is a rare chronic inflammatory disorder of the pituitary gland that may present similar to a pituitary adenoma. The diagnosis can only be made histopathologically. The natural course of granulomatous hypophysitis is not completely understood. As an inflammatory condition, most cases responded well with high dose steroid therapy. In our patient's case, glucocorticoid treatment in tapering doses showed complete resolution of the symptoms and the pituitary lesion, with no noted detrimental effects of steroid therapy. This treatment spared the patient from surgery that may have conferred deleterious consequences. Due to the rarity of this condition as well as its variable response to treatment, long-term follow-up is warranted to detect recurrence early.

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

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

Author Disclosure
The authors declared no conflict of interest.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Cystic Papillary Thyroid Carcinoma: A Case Report

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Abstract

Cystic nodule is an unusual presentation of Papillary Thyroid Carcinoma (PTC), seen in less than 10% of cases. Even by ultrasound, finding a thyroid cyst carries a less than 5% chance of malignancy. We present a case of a 45-year-old male, who came in for incidental finding of a palpable thyroid mass with no significant predisposing history. Thyroidectomy was done and immunohistochemical staining confirmed it to be papillary thyroid cancer. He underwent high dose radiation therapy with post therapy whole body scan showing no evidence of radioavid foci aside from the thyroid bed.

The malignant potential of cystic nodule(s) should never be overlooked in certain select patients even if it carries a low chance of malignancy. The diagnosis of PTC relies primarily on the typical nuclear features, however in cases of histologic uncertainty, immunohistochemical stains such as HBME-1 may be used to help classify unusual presentations of PTC. Treatment and monitoring of Cystic Papillary Thyroid Carcinoma follows the conventional guideline on solid PTC.

Key words: cystic papillary thyroid carcinoma, HBME-1, papillary thyroid carcinoma

INTRODUCTION

Thyroid nodules are a common endocrine problem encountered worldwide. They are defined as lesions arising from thyroid gland that is radiologically separate from the surrounding parenchyma.[1] Clinically, thyroid nodules greater than 1 centimeter are usually palpable while those smaller can only be seen using an ultrasound. The prevalence of palpable thyroid nodules is approximately 5% in women and 1% in men in iodine-sufficient areas. In contrast, the incidental findings of thyroid nodule on ultrasound can be as high as 19-68% with a preponderance towards elderly females.[1] In the Philippines, the most recent prevalence of goiter is estimated to be at 8.9% with 56% having diffuse enlargement and 44% having nodular goiters.[2]

The importance of clinical work up for asymptomatic thyroid nodule is to determine whether the lesion is benign or malignant, as management for both largely differs. The most common well differentiated malignant thyroid nodules are Papillary and Follicular thyroid carcinomas with PTC accounting for about 80% of cases.[1,3] In a local study done by Lo et al., majority of the well differentiated thyroid cancers were PTC with alarmingly aggressive characteristics.[4] Certain ultrasound characteristics can help differentiate benign from malignant thyroid nodules. The finding of a purely cystic nodule has a less than 1% chance of malignancy and biopsy may not even be warranted.[1]

We report a case of a PTC presenting with a purely cystic appearance, diagnosed only after surgery. Histopathology showed a suspicious lesion for thyroid malignancy and it was confirmed using immunohistochemical staining.

CASE

A 45-year-old male initially consulted because of sinusitis with multiple palpable thyroid nodules on examination. He had no hypothyroid or hyperthyroid symptoms or significant radiation exposure to the neck. The family has no history of thyroidal illness but a close relative has colonic cancer. Baseline ultrasound revealed normal thyroid glands with multiple nodules: On the right thyroid was a small 0.58 cm ovoid solid mass (Figure 1A); and a big 3.08 x 2.82 x 2.11 cm ovoid cystic mass (Figure 1B); while on the left thyroid there was a small 0.21 cm ovoid cyst (Figure 1C). Thyroid function tests were normal, and patient was started on levothyroxine suppression therapy.

On follow up, the cystic mass decreased in size until 19 months when the ovoid cyst seen on the right thyroid increased in size by about 2% and now appeared as a well-defined cyst with no vascularity or calcifications. At this time, fine needle aspiration biopsy was done revealing blood and colloid. He underwent right thyroidectomy and the specimens were sent for both frozen and permanent sections. Grossly, the specimen on cut sections showed a cystic cavity measuring 3.2 cm in diameter and at the upper pole, a note or a reddish-brown nodule measuring 0.5 cm in greatest dimension.

Microscopically, the reddish nodule is composed of randomly oriented papillae with fibrovascular cores

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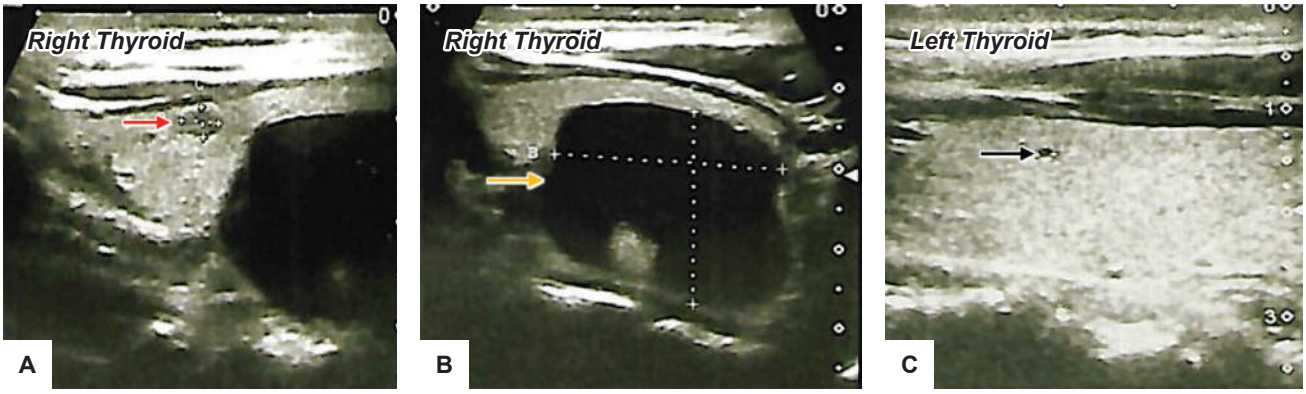

Figure 1. (A) Ultrasound shows a 0.58 cm solid mass *(red arrow)*; **(B)** shows a 3.08 x 2.82 x 2.11 cm ovoid cystic mass *(yellow arrow)* both located at the right thyroid lobe; **(C)** shows a 0.21 cm ovoid cyst *(black arrow)* at left thyroid lobe.

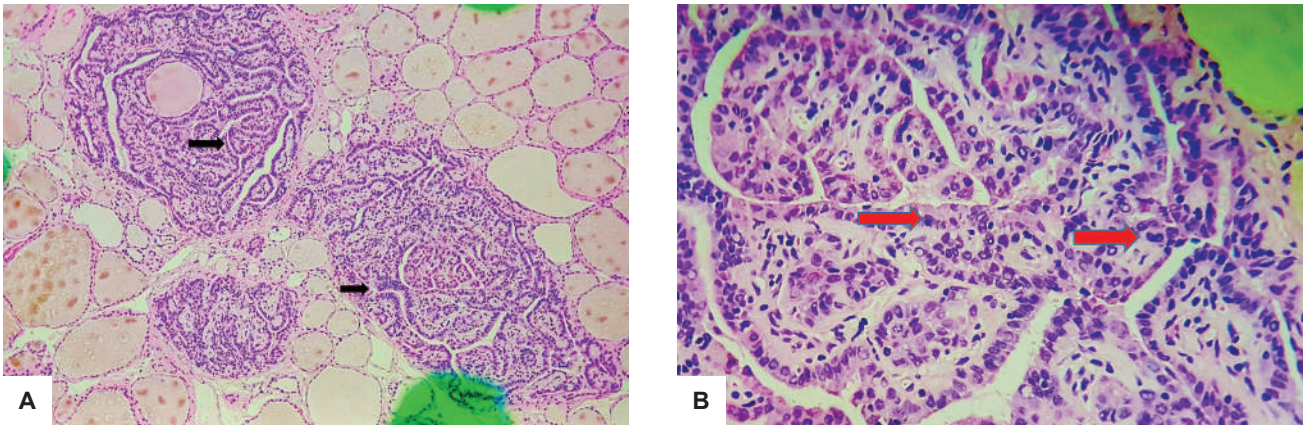

Figure 2. 0.5 cm solid nodule seen on ultrasound. **(A)** Black arrows show papillae with fibrovascular cores (H&E, 40x); **(B)** Red arrows show cuboidal cells with overlapping nuclei (H&E, 100x).

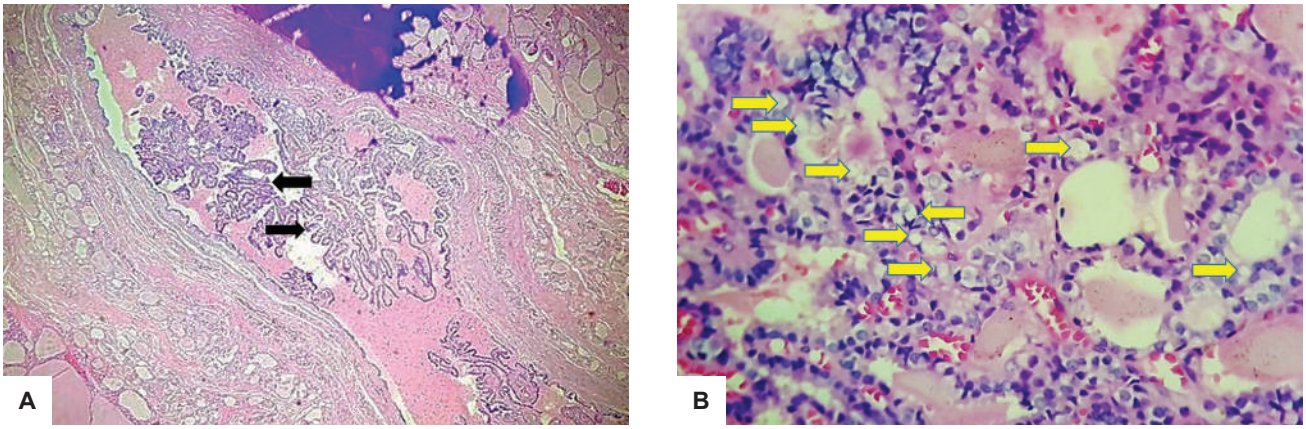

Figure 3. 3.08 x 2.82 x 2.11 cm ovoid cystic mass on ultrasound. **(A)** Black arrows show papillae formation (H&E, 40x); **(B)** On higher magnification (H&E, 400x), yellow arrows show clear or empty nucleus commonly termed as ***"Orphan Annie Eye."*** There is also no extensive infiltration by lymphocytes or macrophages noted and the follicules have abundant colloid material.

(Figure 2A). On higher magnification, the nodule showed papillae lined by cuboidal cells showing round to oval overlapping nuclei with finely dispersed optically clear chromatin, inconspicuous nucleoli and ample cytoplasm. Furthermore, some tumor cells have prominent grooves and occasional pseudoinclusions (Figure 2B).

The cystic cavity, on the other hand, is surrounded by tissues compose of variable sized dilated follicles with flattened to hyperplastic epithelium forming papillae projections into the lumen (Figure 3A). The cells lining the papillary projections were noted to show occasional optical clearing (Figure 3B) thus the pathologist requested for Hector Battifora Mesothelial-1 (HBME-1). The HBME-1 immunostain showed a diffuse membranous staining of the tumor cells (Figure 4).

The patient underwent completion thyroidectomy, and the histopathology results of the left thyroid showed nodular goiter with interstitial fibrosis. Four weeks post

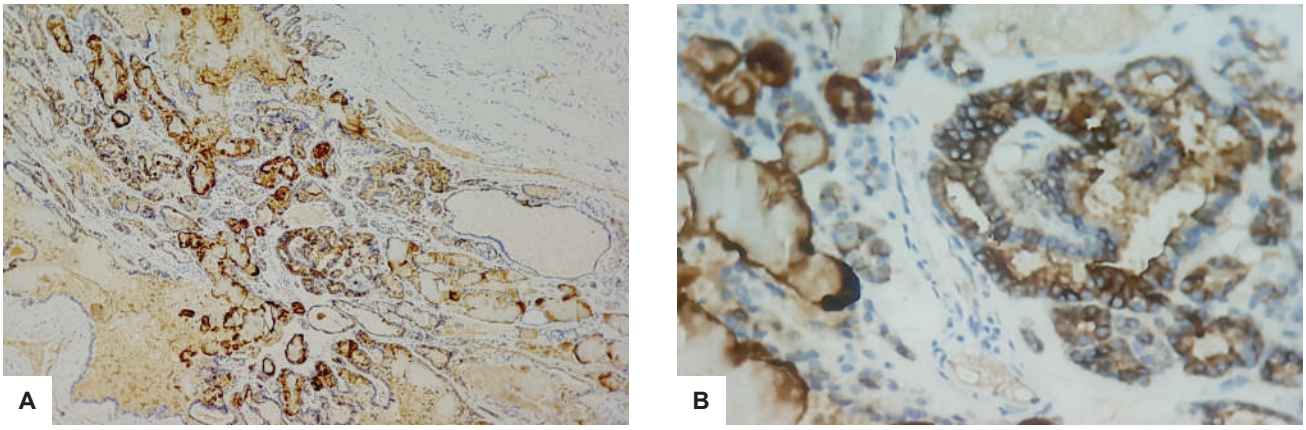

Figure 4. (A) Staining for HBME-1 which appears as a brownish tan stain (HBME-1, 40x); **(B)** On higher magnification, shows HBME-1 positive seen within the plasma membrane of the tumor cells (HBME-1, 400x).

operation, the patient received high dose radioactive iodine therapy. Whole body scan taken 1 week after radiation therapy revealed no evidence of radioavid foci aside from the thyroid bed and patient was categorized as Stage 2 ($T_2N_0M_0$).

DISCUSSION

Well differentiated thyroid cancers usually appear on ultrasonography as solid or complex solid nodules with irregular margins, microcalcifications, a taller than wider appearance, and with rim calcifications. These features have an estimated risk of up to 90% for malignancy and prompts fine needle biopsy for lesions 1 centimeter and above.[1] In this patient, the ultrasound findings were not suggestive of any thyroid malignancy and the indication for fine needle biopsy was to decrease the size of the lesion.

A true thyroid cyst composed of a liquid center lined by cells is rare and most clinically palpated thyroid cysts are solid nodules that have undergone cystic degeneration. These cysts are commonly benign thyroid adenomas.[5] The risk of malignancy in cystic nodules is about 5-10% and it increases as the proportion of the solid part of nodule increases.[5] In a study done by de los Santos et al., it was noted that malignant cystic nodules were Papillary thyroid carcinoma on histopath.[6] Furthermore, it was noted that cystic lesions are as likely as solid lesions to harbor malignancy and this distinction cannot be accurately predicated from the clinical characteristics of the cysts nor the patient's demographic data.[6] As a recommendation, most cysts that are not abolished by aspiration should be excised.[6]

According to the World Health Organization's Classification of Tumors,[7] the histology of PTC is sufficient for its diagnosis and consists of nuclear features showing an enlarged, oval shaped, elongated and overlapping appearance. The nuclei may also show optical clearing or a ground glass appearance. Irregularity of nuclear contours including grooves and nuclear pseudoinclusions are likewise common. Furthermore, in tumors that lack the complexes of papillary structures, the diagnosis of PTC relies heavily on the aforementioned features, which should be present in significant proportions of the neoplasm.[7] The typical papillary architecture of PTC consists of papillae that are complex with branches, and some may appear edematous.[7] The papillae are covered by epithelium with disturbed polarity and pale or eosinophilic cytoplasm.[7] For our case, the solid 0.5 cm undoubtedly was PTC based on both the architectural and nuclear features. However, for the cystic cavity even if it has the typical epithelium of papillae projections, the nucleus only showed occasional optical clearing. The presence of optical clearing although very common in PTC, is not pathognomonic of the tumor,[8] and thus immunohistochemistry was utilized.

PTC are usually reactive to immunohistochemical stains like cytokeratins, thyroglobulin and thyroid transcription factor-1 (TTF-1) and are negative for synaptophysin and chromogranin.[7] Galectin-3 and Hector Battifora Mesothelial-1 (HBME-1) are also expressed in high proportions but according to the WHO consensus, it is not specific for PTC.[7] HBME-1 is an unelucidated membrane antigen found in the microvilli of mesothelial cells, normal tracheal epithelium, and adenocarcinomas of the lung, pancreas and breast.[9] No expression is seen in normal thyroid tissues and when present, suggests malignant lesions that could either be PTC, Follicular Variant of PTC (FVPTC), Follicular Thyroid Carcinoma (FTC), Poorly Differentiated Thyroid Carcinoma (PDC), Undifferentiated Thyroid Carcinoma (UDC) and Hurthle Cell Carcinoma (HCC). FVPTC on histology are composed of small to medium sized, irregularly shaped follicles with virtually no papillary structures.[7] They have variable amount of colloid that appear hypereosinophilic and scalloped and the majority of cells lining the follicles contain large clear nuclei with grooves and nuclear pseudoinclusions that are similar to the classic PTC.[7] However, PTC remains overall to be the most consistent thyroid malignancy that expresses HBME-1.[9]

In a recent study that looked into the clinically utility of HBME-1 for the diagnosis of PTC, it had a sensitivity and specificity of 87% and 96% respectively.[10] Compared to Cytokeratin-19 (CK19), HBME-1 was specific at 96% but CK19 appears more sensitive at 96%.[10] Furthermore, 100% specificity is seen with coexpression of HBME-1/CK19.[10]

According to the WHO consensus, PTC is positive for HBME-1 when it is present primarily within the plasma membrane of the tumor cells.[7] Other authors define

positivity particularly as diffuse membranous positivity.[10] As noted earlier, FVPTC similarly express HBME-1 but since they lack the typical papillary structures, the stain appears within the cell membrane of the follicles.[11] In contrast, no staining is seen for nodular hyperplasia.[11] Nasr et al., looked into the immunohistochemical markers for the diagnosis of PTC, and HBME-1 showed high sensitivity and specificity, although it can similarly be present in focal areas of Hashimoto's Thyroiditis.[12] Since nuclear features of Hashimoto's thyroiditis may overlap with PTC including nuclear clearing, the positivity of HBME-1 *per se* should not be equated with the diagnosis of PTC without considering its histology.[12]

For our case, HBME-1 was primarily requested for the cystic lesion because of the presence of optical clearing that suggested a malignant lesion. Ideally, other stains such as CK19 and Galectin-3 should have been requested together with HBME-1 to improve specificity. However, since the cystic lesion stained positive for HBME-1 but lacked the pathognomonic lymphocytic infiltration seen in Hashimoto's Thyroiditis, it was eventually diagnosed to be classic PTC appearing in a cystic lesion. Moreover, because the architectural characteristic of the cystic lesions had papillae, classic PTC was favored more than FVPTC.

There have been several case reports published on Cystic Papillary Thyroid Carcinoma including those by Patil[13] Baser[14] and Pratinidhi.[15] In those case reports, the patients were all females presenting with large multiple neck masses that were noted on examination. Majority of the ultrasonography findings were cystic with solid components. In contrast, our patient was a male that presented only with an incidental finding of a palpable neck mass. The nodule was noted on ultrasound to be ovoid and purely cystic. Unfortunately, however no pattern can be deduced on patient characteristics that are highly suggestive of Cystic Papillary Thyroid Carcinoma (CPTC) and the American Thyroid Association strongly recommends surgical intervention for cystic lesions greater than 4 cm.[1] In terms of histopathology, no nuclear or architectural characteristic feature can be seen as pathognomonic for CPTC and in the published case reports, the histology appears as classic PTC with prominent cystic degenerative changes. Furthermore, majority of the case reports on CPTC did not utilize immunohistochemical staining and was diagnosed solely on nuclear features. In the case report of Rahamat et al., that described two cases of male patients that have PTC presenting as a lateral neck cyst, the immunohistochemical stains used were TTF-1, thyroglobulin (TGB) and Cytokeratin (CK19).[16] TTF-1, a nuclear protein composed of a single polypeptide of 371 amino acid belongs to the family of homeodomain transcription factors and is the most commonly used immunomarker to identify thyroid or lung primary tumor in the setting of metastasis.[9] Thyroglobulin is a thyroid hormone precursor that is synthesized by the thyrocytes, transported to the apical surface and secreted into the follicles and constitute the major component of colloid.[9] Thyroglobulin and TTF-1 are commonly used as a marker of thyroid organ determination and for that case, it was used to help differentiate a primary from a metastatic malignancy. Like HBME-1, CK19 is an immunohistochemical stain used for the differential diagnosis of thyroid gland neoplasm. It is a low-molecular-weight cytokeratin found in a variety of simple or glandular epithelial seen in both normal and neoplastic epithelium.[9] In some studies, CK19 staining was seen lacking specificity for PTC or malignancy.[9] It is reported to have 82.2% sensitivity for PTC and 44.3% for FTC while it has an overall specificity for thyroid malignancy at 63.1%.[9] Overexpression of CK19 is a good indicator for PTC but should be part of the panel of immunomarkers in the diagnosis of PTC.[9]

Management for this patient's case followed the recommended guideline for well differentiated thyroid carcinoma, including total thyroidectomy followed by post-operative radioactive iodine therapy and lifetime levothyroxine suppression therapy.

CONCLUSION

The chance of malignancy of purely cystic nodule is minimal and estimated at <1% while those with a partially cystic nodule without suspicious features is <3%. Yet, its malignant potential should not be overlooked because thyroid cancers can occasionally present as cystic nodules. Diagnosis of PTC should be made by histology but in case of uncertainty or an unusual appearance, immunohistochemical stains such as HBME-1 are useful tests to help differentiate benign from malignant lesions. The results should be interpreted in the context of the histologic appearance especially if the stain used is not 100% specific. Combination with other stains may also be necessary to improve accuracy. The treatment of CPTC is the same as its solid counterpart and follows an indolent course.

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

Statement of Authorship
All certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

Isochromosome Mosaic Turner Syndrome: A Case Report*

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Abstract

Turner syndrome (TS) with an isochromosome mosaic karyotype 45,X/46,X,i(X) (q10) is an unusual variant, with only an 8-9% prevalence among women with TS based on international studies and 15% of all TS in the Philippines. Clinical features are atypical and any case should be investigated to detect potential complications.

A 20-year-old female came in due to amenorrhea and alopecia. Physical examination revealed short stature, cubitus valgus and Tanner Stage 1 pubic hair and breast development. Transrectal ultrasound revealed absent ovaries and infantile uterus. Hormonal evaluation revealed hypergonadotropic hypogonadism. Bone aging was that of a 13-year-old for females with non-fusion of epiphyseal plates. Cytogenetic study revealed 45,X [37]/46, X, i (X) (q10)[13]. This is consistent with a variant Isochromosome Mosaic Turner Syndrome (IMTS).

She was screened for medical complications. Audiogram and two-dimensional echocardiography were unremarkable. She has dyslipidemia and was given a statin. She has subclinical hypothyroidism with positive test for anti-thyroglobulin antibody. Her intelligence quotient (IQ) was below average. She received conjugated estrogen and progesterone that patterned the hormonal changes in a normal menstrual cycle. On the third week of hormonal therapy, she developed breast mound and on the fourth week, she had her first menstrual period. Her alopecia spontaneously resolved.

The case is a variant of Turner Syndrome requiring supportive, medical and psychological care.

Key words: Turner Syndrome, isochromosome, primary amenorrhea, alopecia, hypergonadotropic hypogonadism, delayed puberty

INTRODUCTION

Isochromosome mosaic Turner Syndrome (IMTS) is a variant of Turner Syndrome (TS) characterized by a cytogenetic profile of 1 or more additional cell lineages aside from 45,X, and the presence of a structurally abnormal X chromosome consisting of either two short or two long arms.[1] IMTS occurs in only 8-9% prevalence among women with TS based on international studies, and 15% of all TS in the Philippines.[2]

Turner Syndrome has a broad range of clinical phenotypes.[3] Patients may present with subtle physical manifestations to more complex conditions such as cardiovascular malformations, aortic dissection and ovarian failure. Manifestations of IMTS may vary and is less severe compared to the most common variant of TS, (pure monosomy X or 45,X).[4]

This report presents a 20-year-old female with primary amenorrhea and alopecia who was diagnosed with IMTS. This case emphasizes the importance of karyotyping in the diagnosis of diseases presenting with atypical manifestations, especially in TS, because clinical phenotype varies with specific karyotypes. It also highlights the need for a multidisciplinary approach in the management of Turner Syndrome to promptly detect and prevent complications.

CASE

MC, a 20-year-old Filipino female was seen at our outpatient clinic because of primary amenorrhea.

One year prior to consult, the patient sought advice with an obstetrician due to amenorrhea despite reaching reproductive age. Transabdominal ultrasound revealed non-visualized ovaries and infantile uterus. No medications were prescribed and the patient was lost to follow up. One month prior to consult, she developed alopecia at the posterior scalp which gradually involved the parietal area thus prompting consultation.

Past medical history revealed no previous hospitalizations and no other comorbidities. She is the 10th child of a 41-year-old mother, born at a tertiary hospital from a

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** This case won as 1st place in the Philippine College of Physician (PCP) National Case Report Contest and was presented in the PCP Annual Convention on May 8, 2017 at SMX Convention Center, Pasay City, Philippines.*

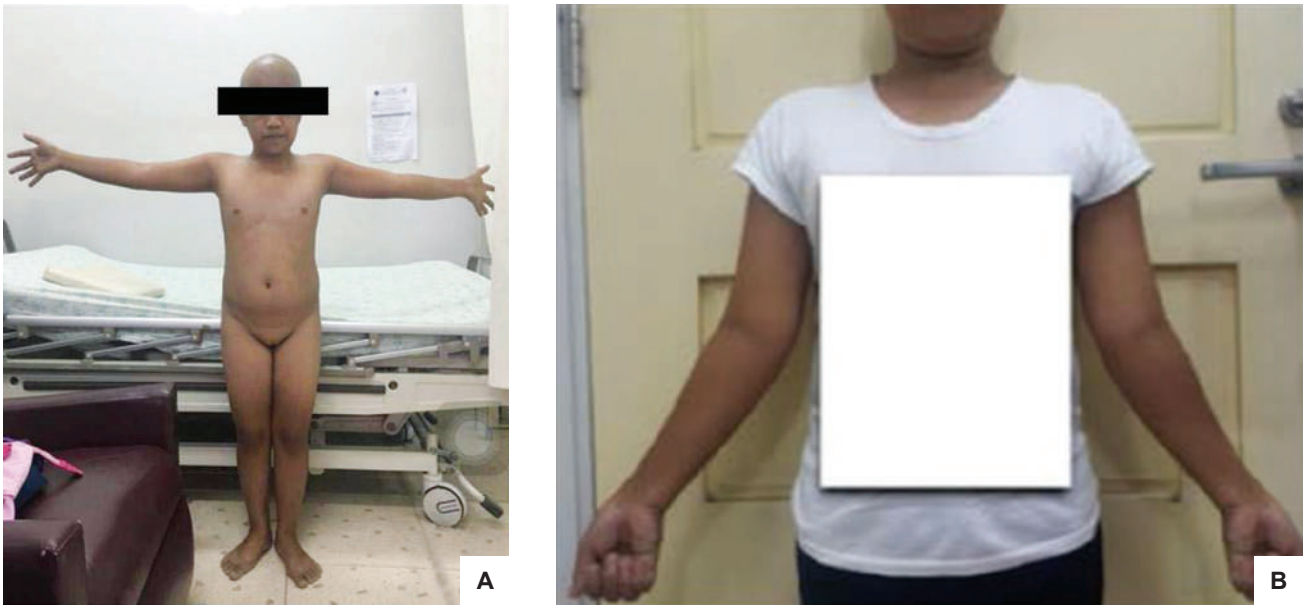

Figure 1. On physical examination, the patient has **(A)** short stature, alopecia and underdeveloped secondary sexual characteristics and **(B)** a wide carrying angle or cubitus valgus.

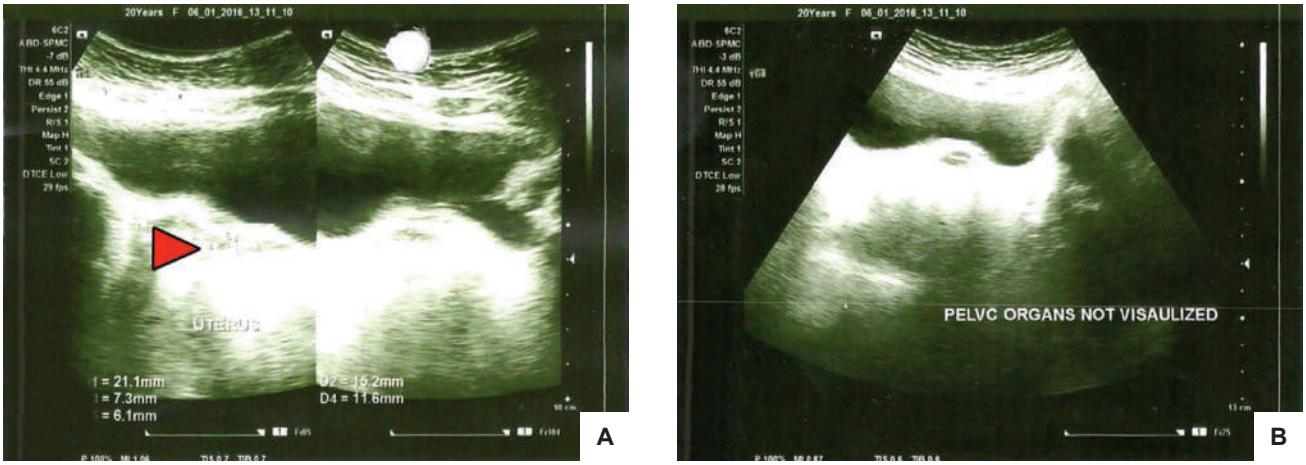

Figure 2. Transrectal ultrasound revealed **(A)** infantile uterus *(red arrow)* and **(B)** non-visualized ovaries.

non-consanguineous marriage with no known pregnancy-related complications. No newborn screening was done. There was no known heredo-familial illness, nor a family history of short stature or delay in menses of female family members. She is nulligravid with no sexual contact, and denied smoking, alcoholic beverage intake and illicit drug use. She finished high school and was assessed to be an average student.

At the time of presentation, she was ambulatory with a height of 134 cm and weight of 37 kg. The patient's height was plotted on the growth chart and revealed short stature. The computed mid-parental height was 152. 25 cm. Her arm span was 139 cm (Figure 1A), and her body mass index (BMI) was 20.67 kg/m^2. Her vital signs were within normal range.

On physical examination, there was alopecia (Figure 1A) and wide carrying angle or cubitus valgus of the elbows (Figure 1B). There was no facial dysmorphism and webbing of the neck. Eyebrows and eyelashes were present and equally distributed. Otoscopic, cardiopulmonary and abdominal examinations were unremarkable. Her pubic hair and breast development were Tanner Stage 1, with no axillary hair. Genital examination revealed a grossly female genitalia with presence of a small clitoris at 0.3 cm and vaginal canal of 5 cm in length. No inguinal masses were palpated. She had no neurologic deficits.

Her complete blood count (CBC) and creatinine were unremarkable. Lipid profile revealed elevated cholesterol (5.70 mmol/L), high density lipoprotein (1.73 mmol/L) and low density lipoprotein (3.61 mmol/L), with normal triglycerides (0.79 mmol/L) and very low density lipoprotein (0.36 mmol/L).

Hormonal evaluation showed hypergonadotropic hypogonadism with elevated follicle-stimulating hormone (FSH) at 82.58 mIU/ml, elevated luteinizing hormone (LH) at 32.38 mIU/ml, low estradiol at <5.00 pg/ml, and low testosterone at <0.025 ng/ ml. Transrectal ultrasound showed a thin endometrium with minimal hydrometra, an infantile uterus measuring 3.6 x 1.6 x 0.8 cm and absent ovaries (Figure 2). Radiograph of the left wrist revealed

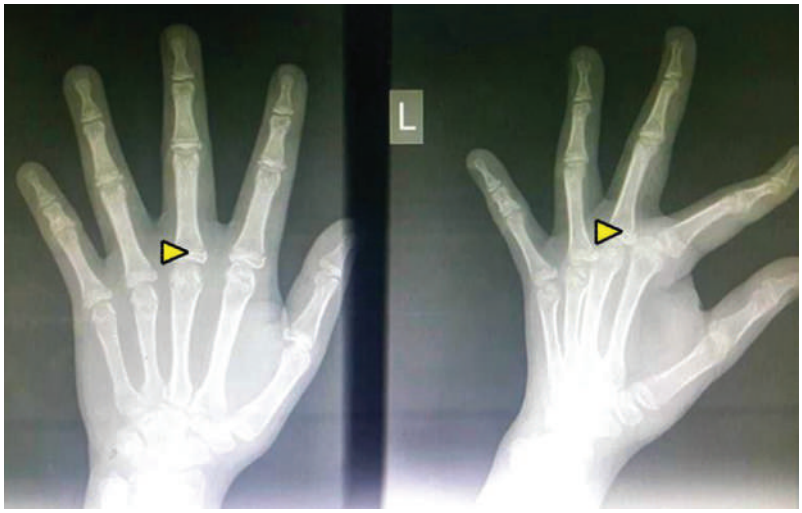

Figure 3. Radiograph of the left wrist revealed non-fusion of epiphyseal plates *(yellow arrowheads)* with bone aging for female of 13 years old by Greulich and Pyle standards.

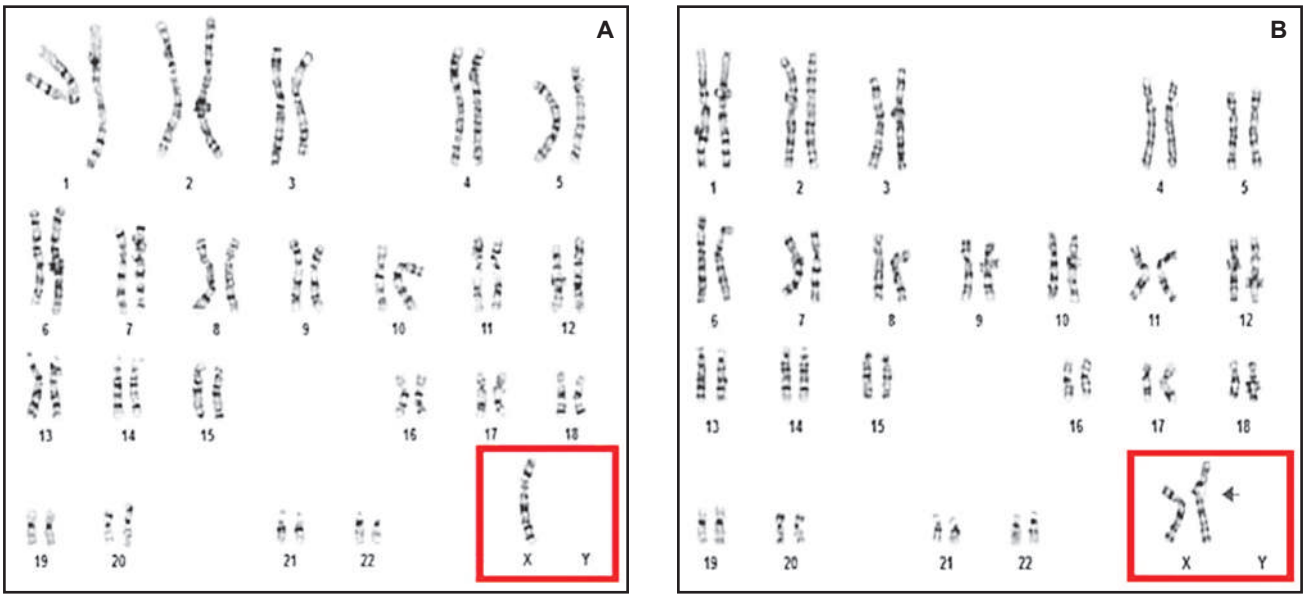

Figure 4. Cytogenetic analysis showing the **(A)** first cell line with loss of one X chromosome, resulting in monosomy X, while **(B)** the second cell line with an isochromosome of the long arm of X chromosome.

non-fusion of epiphyseal plates with bone aging for female of 13 years old by Greulich and Pyle standards (Figure 3). Cytogenetic study of peripheral blood through G-banding technique revealed two cell lines present. The first cell line, seen in 37 cells, showed loss of one X chromosome, resulting in monosomy X (Figure 4A). The remaining 13 cells showed an isochromosome of the long arm of the X chromosome (Figure 4B). Her karyotype is 45,X [37]/46, X,i (X) (q10)[13]. This is consistent with the diagnosis of IMTS variant.

She was screened for potential complications and associated conditions. Her serum thyroid stimulating hormone (TSH) level was elevated at 6.65 mIU/L with normal free thyroxine (T4) and triiodothyronine (T3). Anti-thyroglobulin antibody was elevated at 936.78 IU/ml. Audiogram revealed bilateral normal hearing acuity. Ultrasound of the kidneys was unremarkable (Figure 5). Two-dimensional echocardiography revealed adequate ejection fraction, and absence of bicuspid aortic valve or coarctation of the aorta. Test for intelligence quotient (IQ) by Culture Fair Intelligence Test Scale revealed a score of 70-79 (below average).

The benefits and risks of growth hormone (GH) therapy were discussed with the patient and her family. However, due to financial constraints, GH therapy was not initiated. She was given with oral conjugated estrogen (0.3 mg/day) on the first 6 days, titrated (0.6 mg/day) for the next 22 days. Progesterone was added for 10 days, starting on the 19th day. On the third week of hormonal therapy, she developed breast mound and on the fourth week, she had her first menstrual period. Her alopecia resolved spontaneously *within one month*. In addition, the patient also underwent counseling about her fertility status and the probability and the risks of future pregnancies.

Informed consent was also taken for the publication of this case.

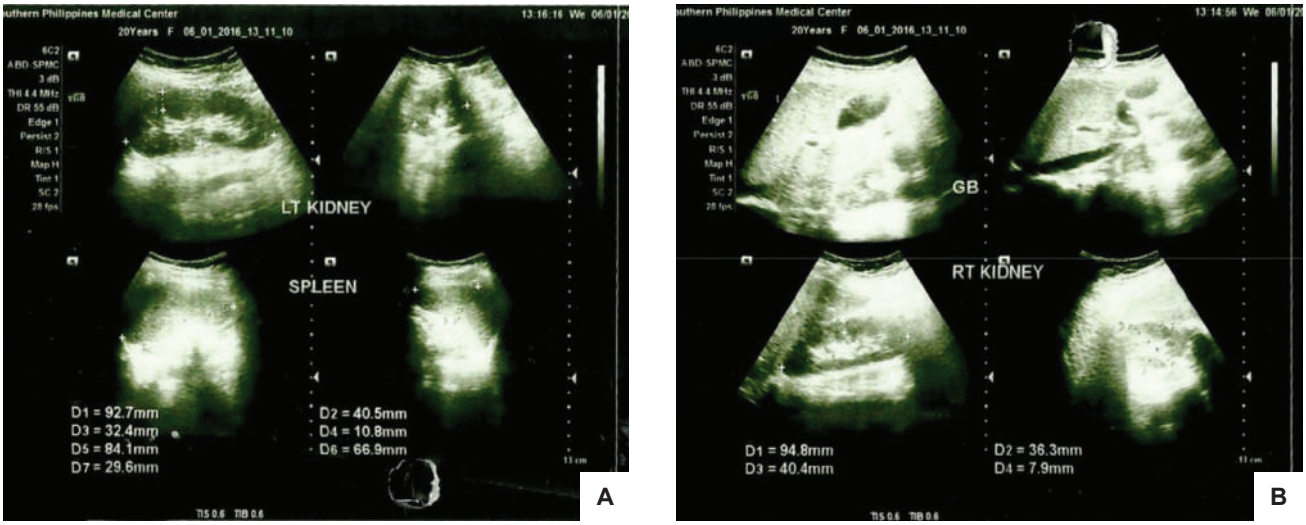

Figure 5. Ultrasound of the abdomen revealed presence of normal left **(A)** and right **(B)** kidneys.

DISCUSSION

Turner Syndrome (TS), or 45,X, is a condition in which a female is partly or completely missing an X chromosome. It is one of the sex chromosome disorders of sexual development (DSD)[5] that affects 1 in 2,500 to 1 in 3,000 female live births.[1] According to the karyotype, there are several variants of TS with monosomy X as the most common.[6] Other types include [1] deletions of the short arm (Xp) or long arm (Xq), [2] formations of ring chromosome (rX), [3] isochromosomization or duplication of the long arm to form an isochromosome (Xi), and [4] mosaicism, where a monosomy X (45,X) cell line is accompanied by one or more cell lines having a complete or structurally abnormal X chromosome.

In this case, karyotype revealed 45, X/46, X, i, (X) (q10) – a combination of mosaicism and isochromosomization. The prevalence of isochromosome mosaic karyotype is 8 - 9%.[1,7] In the Philippines, TS comprises about 80% of all sex chromosome abnormalities, of which 38.9% had the classic pure monosomy X while only 15% had the isochromosome mosaic variant.[2]

The typical manifestations for Turner Syndrome are short stature, gonadal dysgenesis, characteristic facial features, webbed neck, low posterior hairline, broad chest with widely spaced nipples, nevi all over the body, shortened metacarpals, small fingernails, poor breast development, and renal and cardiovascular anomalies. However, most of these clinical symptoms greatly vary depending on the karyotype variant. Of particular note, patients with mosaicism for 46 XX or X isochromosome, have been shown to have milder phenotypes.[8] Hence, for this patient, some of the typical manifestations were not evident.

Short stature is the most readily recognizable finding in women with TS. The deficit in height is caused by the haploinsufficiency of the short stature homeo-box containing gene (SHOX) located within the Xp terminal, the pseudoautosomal region of the X chromosome. Aside from short stature, many of the physical stigmata of TS are a result of structural bone defects as SHOX expression is highly localized at the elbow, knee and wrist.[9] Particularly, cubitus valgus, or increased outward angulation of the arms when they are fully extended, as seen in our patient, is a result of a developmental defect of the ulnar head because of the SHOX gene haploinsufficiency.

Hypergonadotropic hypogonadism is a result of ovarian failure and the lack of feedback inhibition to the pituitary gland. In patients with TS, partial or complete absence of the X chromosome in the germ cells leads to an accelerated degeneration of oocytes and increase in ovarian stromal fibrosis; thus, the absence of ovaries on ultrasound in our patient is an expected finding.[10] Ovarian failure is the reason for the absence of secondary sexual characteristics of our patient.

Alopecia is an immune-related dermatological condition that is 3 times more common in women with TS.[4] There have only been five cases of alopecia in TS reported worldwide.[8,11] One case had a karyotype of 45,XX/45,X[7] while the specific karyotypes of the other 4 cases[10] were not mentioned.

Cardiovascular complications are a common cause of increased mortality in TS,[12] and occurs specifically in 29% of TS with isochromosome mosaicism. Bicuspid aortic valve is the most common congenital malformation affecting the heart[13,14] and may also occur in combination with other anomalies, particularly aortic coarctation. Two-dimensional echocardiography of our patient, however, did not reveal any of these anomalies. In addition, the incidence of developing ischemic heart disease is two-fold among adults with TS compared with the general population[8] and one of the risk factors is hyperlipidemia which was demonstrated to be significantly higher compared to normal controls.[15] This is congruent with the hyperlipidemic profile of our patient who had elevated cholesterol, HDL and LDL; hence, she was given a lipid-lowering agent.

Hypothyroidism affects 25 to 30% of adults with TS and can be attributed to an autoimmune thyroid disease.[16] Thyroid autoantibodies, such as antimicrosomal and antithyroglobulin antibodies, are present in 22-41% of women with TS.[17,18] It is noteworthy that thyroid

autoantibodies have been found to be prevalent in women with the isochromosome [46,Xi(Xq)] karyotype (83%) compared with monosomy 45,X (41%) and other karyotypes (14%).[3] In our patient, elevated antithyroglobulin and subclinical hypothyroidism were present. Although thyroid supplementation was not warranted as of this time, annual evaluation of thyroid function tests is recommended for monitoring.

Structural malformations in the kidneys[19] and the ears[20] are also common among patients with TS. Our patient, however, had unremarkable renal ultrasound, otosopic examination and audiogram.

In terms of cognitive impairment and behavioral function, a significant number of women with TS have deficits in specific areas of intellectual performance and its severity has been shown to be related to the karyotype. Generally, females with TS have normal intelligence -- with the exception of those with mosaic karyotype, particularly IMTS, where 9% present with mental retardation.[4] Our patient's IQ was within the 70-79 range using a standardized tool. This is comparable to an individual with a below average mental ability. It was noted, however, that the subject is educable, although with limited trainability. She is fit and can be employed to fulfill simple tasks or routinized jobs; hence, although with TS, the patient can ordinarily live, work and may overcome deficits in certain aspects of learning.

Management

After screening for and addressing the medical complications, management was aimed at maximizing adult height, development of secondary sexual characteristics and health teaching and counseling on fertility, long term plans and follow up.

Growth Hormone (GH) therapy should be considered for every patient diagnosed with Turner Syndrome. Treatment with recombinant Growth Hormone (GH) (0.375 mg/kg/week divided into seven once-daily doses), with or without oxandrolone (0.0625 mg/kg/day by mouth), is recommended to maximize patient's height.[21] In most cases, treatment starts at around 5-6 years of age and continues until the patients have stopped growing or when the epiphyses have already fused, at around 15-16 years.[8] The bone age, and not the chronological age, will determine how long she can continue to grow. In our case, bone aging revealed non-fusion of epiphyseal plates compatible with a 13-year-old female by Greulich and Pyle standards; ideally, our patient should receive GH therapy but this was not possible due to financial constraints.

For the development of secondary sexual characteristics, the current regimen for pubertal induction in girls with no spontaneous menses mandates low dose estrogen (0.3 mg) at age 14-15 years old, gradually increased to 1.25 to 2.5 milligrams and then cycled with medroxyprogesterone, or less frequently with progesterone.[22] Our patient was initially given low-dose oral conjugated estrogen, with uptitration of dose and addition of progesterone to pattern the physiologic hormonal elevation of normal menstrual cycle.

In terms of fertility and pregnancy, spontaneous pregnancies in women with Turner Syndrome are rare, and may be associated with higher rates of spontaneous abortions, fetal malformations and chromosomal abnormalities. Since most patients are infertile, a modality that has been used for fertility treatment include donor oocyte with in vitro fertilization. However, patients must be counseled that deaths may occur with pregnancies due to the cardiovascular complications such as aortic dissection.[23]

Long term plans for this patient include monitoring of the development of secondary sexual characteristics and appropriate titration of hormonal replacement therapy. Physical examination, lipid profile, fasting blood glucose, and thyroid, liver and renal function tests should be done annually, while echocardiography, bone densitometry and audiogram should also be checked every 3-5 years.

CONCLUSION

Our case of an isochromosome mosaic variant of Turner Syndrome who presented with alopecia, primary amenorrhea, absence of secondary sexual characteristics and short stature has emphasized three points.

First, the value of a karyotyping analysis in the evaluation of patients with atypical presentations is substantial, on top of other preliminary work-ups. In this case, it has confirmed the diagnosis of an isochromosome mosaic Turner Syndrome, thus, facilitating its prompt management.

Second, this report has established that Turner Syndrome has several variants. There is a phenotypic variability in patients with TS depending on the karyotype and for isochromosome mosaicism, the manifestations are less severe compared to the more common form of pure 45,X.

Third, this has highlighted the importance of a multi-disciplinary approach, intensive work-up and thorough screening from the onset of diagnosis in a patient with TS to promptly detect and prevent complications. Understanding the pathophysiology of TS, it is recommended that physicians who handle these patients should use a holistic approach to management that would encompass the medical and psychologic problems.

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

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

Author Disclosure
The authors declared no conflict of interest.

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CASE REPORT

Simultaneous Occurrence of Papillary Carcinoma and Medullary Carcinoma

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Abstract

The cell origin, histopathologic features, and prognosis of medullary and papillary thyroid carcinoma are different and to have them occur simultaneously in a single patient is a rare occurrence.

This is a case of a 38-year-old female who presented with an enlarging anterior neck mass whose fine needle aspiration biopsy could not rule out a papillary lesion. Thus, she was advised to undergo total thyroidectomy, and her final histopath showed a simultaneous medullary and papillary thyroid carcinoma. Her initial serum calcitonin was elevated at 252 pg/ml, and it remained persistently elevated over the course of 7 months. A repeat ultrasound revealed solid nodules with coarse calcifications and enlarged lymph nodes at both submandibular regions. This warranted a repeat surgery with neck dissection with the finding of eight lymph nodes positive for metastatic carcinoma. On follow up after her second surgery, the calcitonin decreased to 42.70 pg/ml.

Knowledge of this simultaneous occurrence of medullary thyroid carcinoma and papillary cancer is important for its prognostic implications and therapeutic plan.

Key words: thyroid cancer, papillary thyroid cancer, medullary thyroid cancer

INTRODUCTION

The cell origin, histopathologic features, and prognosis of medullary thyroid carcinoma and papillary thyroid carcinoma are different and to have them occur simultaneously in a single patient is a rare event. Data about the simultaneous occurrence of these tumors are based mainly on case reports and series.

CASE

This is a case of a 38-year-old female who has simultaneous medullary thyroid cancer in the left thyroid lobe and papillary thyroid cancer in the right thyroid lobe. She was diagnosed to have thyrotoxicosis at 18 years old presenting with palpitations and an anterior neck mass. She was maintained on an unrecalled dose of carbimazole and propanolol for 1 year which was eventually discontinued since her thyroid function test normalized, with noted decrease in size of her anterior neck mass.

Five years prior, she began noticing an enlarging anterior neck mass. There was no associated hoarseness of voice, dysphagia, weight loss, palpitations or difficulty of breathing. She consulted an endocrinologist and work up was done. Thyroid function test showed an elevated TSH at 11.84 uIU/ml and a normal FT4 at 15 uIU/ml. Her ultrasound showed an enlarged left thyroid gland with a 2.38 x 1.4 x 1.69 solid nodule with calcifications and minimal hypervascularity. Few coarse parenchymal calcifications are noted at the mid portion of the right lobe. She underwent fine needle aspiration biopsy (FNAB) of her left thyroid lobe with a result of an adenomatous goiter with concomitant lymphocytic thyroiditis. She was given Levothyroxine 50 mcg daily with serial monitoring of her thyroid function test and ultrasound.

Repeat ultrasound two years later showed interval increase in the size of the previously noted solid nodule with calcifications in the left lobe, with new nodules noted on the right lobe. This warranted a repeat biopsy. Repeat ultrasound guided fine needle aspiration biopsy of the nodule on the right thyroid gland showed nodular hyperplasia but cannot rule out papillary lesion. While the FNAB of the nodule on the left showed nodular hyperplasia of left thyroid lobe. Thus, she underwent total thyroidectomy.

Microscopic examination of the isthmus and left lobe were consistent with medullary carcinoma, with the tumor size 6 cm in its greatest dimension. The right lobe showed papillary thyroid carcinoma, with the tumor size in greatest dimension 1.1 cm, with no lymphovascular or perineural invasion (Figure 1). Immunohistochemistry report for the isthmus and left lobe were chromogranin positive, calcitonin positive supporting the diagnosis of medullary thyroid carcinoma.

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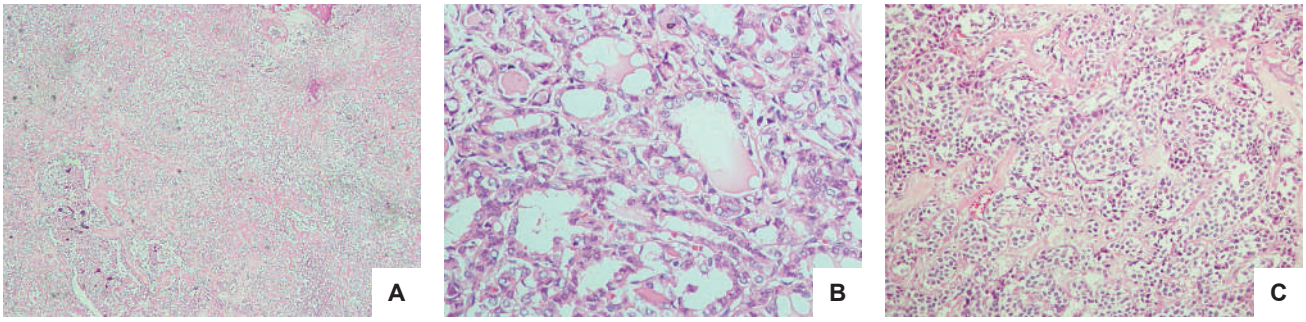

Figure 1. Histopath. **(A)** Areas of normal parenchyma, thyroiditis, and papillary carcinoma (H&E, 40x). **(B)** Papillary Thyroid carcinoma, Right lobe. Overlapping clear ground glass nuclei with eosinophilic inclusions (H&E, 400x). **(C)** Medullary carcinoma. Cells with eccentrically located round nuclei with salt and pepper nuclear chromatin pattern (H&E, 100x).

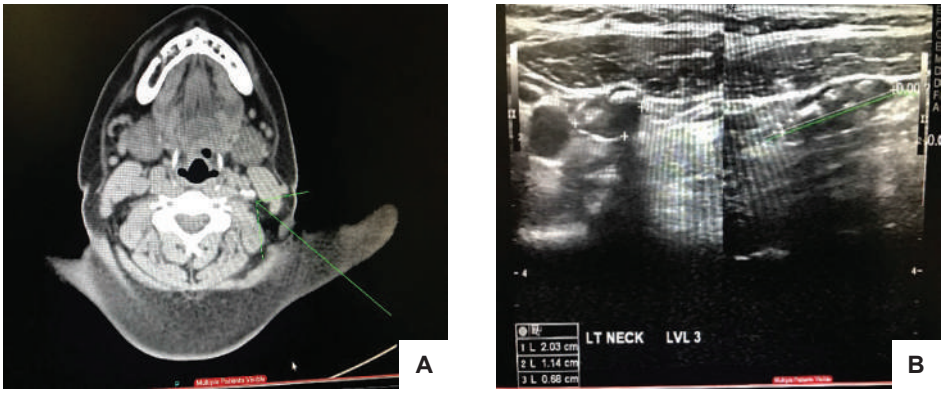

Figure 2. (A) CT scan of the neck with contrast. Calcification in the left infrahyoid carotid space possibly calcified lymph nodes. **(B)** Neck ultrasound. Nodes with calcifications in the left parajugular region (level 3).

After the surgery, serum thyroglobulin was 0.307 ng/ml with normal antithyroglobulin 90.859 IU/ml, while serum calcitonin was elevated at 252 pg/ ml. The elevated serum calcitonin warranted a work up for possible metastasis. Thus, a neck ultrasound was requested which showed post thyroidectomy. Solid nodules with coarse calcifications, left parajugular region. Enlarged lymph nodes, both submandibular regions (Figure 2).

Findings on CT scan of the neck, chest and whole abdomen were nonspecific. CT scan of the neck revealed no evidence of cervical lymphadenopathy (Figure 2).

Chest CT scan showed nonspecific nodules along the left lung fissure and along the posterior hemithoraces. Whole abdomen CT scan showed mild hepatosplenomegaly, uterine myoma and Nabothian cyst. For further work-up, a whole-body fluorodeoxyglucose PET scan was requested. Results showed no hypermetabolic malignant looking disease in the neck and elsewhere. The mildly hypermetabolic calcified left submandibular and left supraclavicular lymph nodes look inflammatory/reactive.

However, serum calcitonin on serial monitoring was persistently elevated (362, 197 pg/ml) over the course of 7 months (Table 1). A repeat thyroid ultrasound showed solid nodules (4) with coarse calcifications at the left parajugular area (level 3).

Thus, she underwent neck exploratory dissection, with the finding of eight of twenty-five lymph nodes with metastatic carcinoma. On follow up three months after the operation, the calcitonin decreased to 42.70 pg/ ml. Nature and prognosis of papillary and medullary thyroid carcinoma were explained to the patient, with plans of monitoring for recurrence. Medullary thyroid carcinoma can occur sporadically or it may be associated with hereditary syndromes such as Multiple Endocrine Neoplasia Type 2. Thus, molecular studies investigating RET germline mutations in exons 11, 15 and 16 were performed, and patient was found to be positive for a mutation in exon 15. She is now recommended for work up for pheochromocytoma and hyperparathyroidism to screen for multiple endocrine neoplasia 2 syndromes.

Table 1. Laboratory Results

	April 2017	May 2017	July 2017
Calcitonin (0 – 11.5 pg/ml)	252	362	197
Thyroglobulin (2 – 70 ng/ml)	0.307		
Antithyroglobulin (up to 100 IU/ml)	90.859		

DISCUSSION

Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma (90%), and it originates from the follicular cells of the endoderm. Medullary thyroid carcinoma, on the other hand, arises from the parafollicular C cells of the ultimobranchial body of the neural crest, and it represents only 5% of all thyroid cancers.[1]

The simultaneous occurrence of an independent medullary thyroid carcinoma, a tumor showing morphological features of medullary thyroid carcinoma (MTC) with

positive immunoreactive calcitonin cells, along with papillary carcinomas in the same thyroid gland is uncommon, but it has been reported.

Although the simultaneous occurrence of papillary and medullary thyroid carcinoma in one patient may be entirely coincidental, several authors have tried to explain as to why it happens. According to Erhamamci (2014), the simultaneous occurrence of MTC and DTC in the same thyroid gland can occur in two ways: as a mixed tumor showing dual differentiation or as a collision tumor showing two separate different carcinomas.[2] They concluded that out of 1420 patients, 0.28% of patients with DTC displayed simultaneous MTC.[2] Machens (2011) followed 1019 patients diagnosed with papillary thyroid carcinoma, and found 26 patients had simultaneous MTC with a prevalence rate of 2.6.[3]

Previous studies have also mentioned several other theories about this concurrence. The first is the 'stem cell theory' which describes a common stem cell that transform into both follicular and C-cell lineages.[4] Another is the 'field effect theory' which proposes that simultaneous transformation of both follicular and C cells is a result of common neoplastic stimuli. On the other hand, the 'collision theory' suggests that two independent tumours are located in the same thyroid by simple coincidence.[4]

Papillary carcinoma generally has a good prognosis since most patients are diagnosed during the early stage of the disease (stage I or II), with 5% having a lethal outcome.[5] Medullary thyroid carcinoma, on the other hand, may have an indolent clinical course or an aggressive variant with a high mortality rate.[5] Distant metastases are present in 13% of patients at initial diagnosis and portend a poor prognosis, with a 10-year survival rate of only 40%.[5] MTC is difficult to cure with a high recurrence rate of 50%.[5] According to WHO, the prognosis of mixed medullary and follicular thyroid carcinoma depends upon the medullary component. Thus, the presence of the medullary component makes the prognosis worse as compared to a pure papillary carcinoma. Patients who have clinically evident disease are best treated with a minimum of a total thyroidectomy and bilateral central neck dissection.[5] The use of adjuvant radioiodine therapy for the papillary carcinoma component of this disease has been mentioned in several case reports with good results. In a study by Diogini et al. (2007), they presented a 65-year-old man with multicentric PTC and MTC associated with diffuse lymphocytic-type thyroiditis who underwent total thyroidectomy with neck dissection and subsequent radioiodine treatment.[5] This patient had normal thyroglobulin and calcitonin levels on follow up.[5]

CONCLUSION

Knowledge of this simultaneous occurrence of medullary thyroid carcinoma and papillary cancer is important because of the poor prognosis associated with medullary thyroid carcinoma. This report also highlights the importance of immunohistochemical markers to make a correct diagnosis.

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

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

Author Disclosure
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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Parathyroid Carcinoma: Analysis of Patient Characteristics and Outcomes in a Retrospective Review of Eight Cases seen in a Single Center

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Abstract

Eight cases of parathyroid carcinoma were identified (8 females; median age 45 years, range 28-72). Half of whom were diagnosed preoperatively. Hypercalcemic symptoms were seen in 87.5% of the patients and the main complication was nephrolithiasis. At presentation, the median calcium was 3.675 mmol/L, median phosphate of 0.68 mmol/L, median intact parathyroid hormone (iPTH) was 211 pmol/L. Five patients had regional nodes metastasis and 1 had distant metastasis to the lungs. Parathyroid gland invasion to adjacent structures was seen in 62.5% of cases while another 62.5% showed capsular or vascular infiltration on histology with median tumour size of 3.2 cm. Recurrent hypercalcemia occurred in 50% of the patients with median time of recurrence of 21 months. In this case series, we found that patients with severe hypercalcemia and high iPTH also exhibited a high index suspicion of PC.

Key words: parathyroid neoplasms, carcinoma, hypercalcemia

INTRODUCTION

Parathyroid carcinoma (PC) is a rare malignancy. It accounts for 1% of patients with primary hyperparathyroidism. It was first described in 1904.[1] 90% of PC is functional and sporadic. It can be a part of the genetic or familial syndrome including Multiple Endocrine Neoplasm (MEN)1, MEN2A, isolated familial hyperparathyroidism and hyperparathyroidism jaw syndrome. The presentation is usually due to complications of hypercalcemia such as bone disease, renal disease or hypercalcemic crisis.[2] Yet, PC remains a challenge due to its rarity and lack of distinct features as compared to benign primary hyperparathyroidism. This is a pilot study conducted in Malaysia to identify the clinicopathologic features of PC and its morbidity and survival in Hospital Putrajaya, one of the leading endocrine institutions in Malaysia.

CASE

We retrospectively reviewed patients diagnosed with PC in Hospital Putrajaya from 2002 to 2018. Data were collected from the electronic medical records by searching for patients who had an International Classification of Diseases, Tenth Revision code for PC. All patients selected in this case series were diagnosed either postoperatively by histology, or based on clinical presentation and radiological images. Data including demographic, clinical, biochemical including calcium and parathyroid hormone (PTH) levels, pathologic characteristics, treatments including surgery and radiation therapy, complications, recurrence, and mortality were collected.

There were eight patients identified in our review, with a median age of 45 years (range 28-72), all were female. Diagnosis of PC was made preoperatively in 50% of patients based on clinical suspicion. Neck swelling was seen in 37.5% and 87.5% had hypercalcemic symptoms including polyuria and polydipsia, abdominal pain, bone pain, and weight loss. All patients presented with hypercalcemia complications including osteoporosis, fractures, nephrolithiasis, pancreatitis, and brown tumours. Median calcium at presentation was 3.675 mmol/L (range: 3.05-4.04), serum phosphate of 0.68 mmol/L (range: 0.58-1.22), serum iPTH 211 pmol /L (range: 72-366) (Table 1).

Ultrasound (US) is the most common imaging procedures used prior to operation. In our case series, 6 neck US was carried out. The analysis of the US findings revealed the characteristics of PC in two patients which includes heterogeneous hypoechoic lesion and presence of intralesional vascularity. In addition, 4 patients underwent CT of the neck and thorax preoperatively and demonstrated median tumour size of 3.2 cm, heterogeneous lesion, calcifications and tumour abutting the adjacent structures.

Surgery was performed in six patients. Two had en bloc resection and four had simple parathyroidectomy at first encounter. The two patients who had en bloc resection were diagnosed with PC preoperatively while others were not. Remaining two patients opted for medical therapy due to advanced age and inoperable tumour. All patients who underwent operation required bisphosphonate and one patient required additional calcitonin to optimize the calcium level. Intraoperatively, five cases show tumour invasion to its adjacent structures including thyroid lobe, esophagus, and recurrent laryngeal nerve. Four patients had developed hungry bone syndrome that required intravenous calcium gluconate postoperatively. One patient developed vocal cord paralysis after a second operation for recurrence, and 1 had surgical site infection.

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Table 1. Clinicopathologic features of eight parathyroid carcinoma patients

N	Gender	Age	Clinical symptoms	Calcium level (mmol/L)	IPTH level (pmol/L)	Preoperative ultrasound / CT finding	Intraoperative findings	Histology	Treatment
1	Female	28	Nephrolithiasis, polyuria, polydipsia	4.0	176	US: Enlarged right parathyroid enlargement. Measured 1.5 x 1.6 x 2.4 cm	Tumour adhered to esophagus and embedded in adjacent thyroid gland	Well circumscribed, focal infiltration of capsule, micro follicular pattern. Mild to moderate nuclear pleomorphic.	Surgery
2	Female	41	Bone pain	3.07	135	NA	Left inferior nodule measured 2 x 2 cm	Tumour infiltrated the fat tissue and skeletal muscle, transverse by fibrous band, mild to moderate pleomorphic nuclei with abnormal mitoses	Surgery
3	Female	66	Constipation, loss of weight	3.75	246	US: Enlarged right inferior parathyroid measured 4 x 2 cm	Adhered to esophagus and highly vascularized	Parathyroid tissue with malignant cell seen, capsule infiltration. Arranged in cord and sheets with micro follicular pattern. Bizarre nuclei with abnormal mitoses. Foci micro calcification seen.	Surgery with adjunct radiotherapy
4	Female	58	Neck mass, polyuria, bone pain, loss of weight	3.05	263	US: Lobulated heterogeneous mass posterior to left thyroid measured 1.9 x 2.1 cm with intralesional vascularity, cervical nodes which indenting to left thyroid gland (largest 1.4 x 0.5 cm) CT: Well defined homogenous non enhancing hypodense mass at posterior aspect of left thyroid 2.9 x 2.0 x 3.3 cm, indenting posterior border of left thyroid lobe	Hard parathyroid gland with intrathyroidal extension and adhered to esophagus and right laryngeal nerve	Malignant tumour infiltrated the surrounding stroma, and capsule. Focal necrosis seen.	Surgery
5	Female	28	Neck mass, polyuria, polydipsia, loss of weight	3.8	72	US: Right inferior parathyroid enlargement	Right superior parathyroid measured 3 x 2 cm densed, adhered and embedded onto thyroid lobe	Circumscribed tumour composed of proliferation of tumour cells arranged in sheets and acini transversed by band of fibrous stroma	Surgery
6	Female	44	Fracture, loss of weight	3.35	366	CT: Heterogeneous enhanced lesion with central hypodensity seen at the left paratracheal region, posterior to the left thyroid lobe measured 3.9 x 2.9 x 5 cm abutted the trachea and esophagus	NA	NA	Palliative
7	Female	72	Fracture, neck mass	4.04	347	CT: Heterogeneous nodules seen in inferior right lobe measured 4x 5.5 x 10.1 cm, extended to carina with calcifications seen	NA	NA	Palliative
8	Female	45	Asymptomatic	3.6	82.5	US: heterogeneous hypoechoic parathyroid mass measured 3 x 1.5 x 6.2 cm, which displaced the thyroid anteriorly, with left cervical nodes CT: Heterogeneous enhanced lobulated parathyroid mass measured 2.5 x 2.8 x 6.4 cm which extended to T1 - T2. It abutted the thyroid gland, esophagus, trachea and left sternocleidomastoid muscle	Left enlarged hard superior parathyroid	NA	Surgery

Recurrence of PC occurred in four patients which required bisphosphonate and two or more surgeries including neck exploration and modified radical neck dissection (MRND). Only one patient received adjuvant radiotherapy post operatively. In the later stage of the disease, two patients had refractory hypercalcemia and required denosumab and cinacalcet to optimize the calcium level.

Histologically, five cases showed vascular and capsular invasion and three cases had abnormal mitoses.

During the course of the disease, five patients had metastatic tumour, mainly to the adjacent nodes and one showed distant metastasis to the lung. Median time of recurrence after diagnosis is 21 months.

At present, four patients are alive, two had defaulted follow up, and two mortalities were reported. Mortality was due to intractable hypercalcemia.

DISCUSSION

PC accounts for <1% of cases of primary hyperparathyroidism. Our cohort study corresponds to a previous clinical review in term of the patients mean age and female predominance traits. Female preponderance

was also reported in other studies. However, it has been previously reported that there is no association of gender in PC. This disease affected women and men in a 1:1 ratio, as compared to that of primary hyperparathyroidism, where there is a marked female predominance, with a ratio of 3-4:1. In terms of geographic, race or income level, there has been no report to show any disparity.[3-4]

Majority of PC are hormonally functional, and patients often exhibit symptoms and complications of profound hypercalcemia at presentation due to elevated parathyroid hormone. Clinical presentation of PC commonly resulted in excessive PTH secretion by the functioning tumour, rather than invasion of the tumour mass into its surrounding structure. It is often associated with simultaneous manifestation of renal and skeletal failure during initial presentation.[5] In our study, all of our PC patients manifested hypercalcemic complications, mostly in bone and kidney. In a recent series, benign primary hyperparathyroidism reported renal involvement in less than 20% of the cases, whereby in PC, renal colic is a common presenting complaint, with 56% with nephrolithiasis and 84% with renal insufficiency were reported in one recent series.[6-8] Neck mass has been reported between 40-70% in several studies and it is an important clinical finding in PC as it is rarely seen in benign parathyroid disease.[9]

Serum calcium and parathyroid hormone were significantly elevated in our cohort study, consistent with previous studies which reported mean serum calcium >3.5 mmol/L[10] and markedly elevated PTH, usually 3-10 times above the upper limit associated with PC. Radiographic imaging was frequently needed prior to surgery for localization, however the procedure is less useful in evaluation of malignancy potential. Large tumours especially more than 2 cm, hypoechogenicity, heterogeneous, irregular borders, calcifications and local invasion were reported in several case series where malignancy should have been suspected.[10-12] In our study, only 2 US were reported preoperatively as PC, indicating invasion to adjacent trachea, cervical nodes involvement and intralesional vascularity.

The pathologic diagnosis of PC is challenging. Histopathologic criteria to diagnose PC include trabecular growth pattern, thick fibrous trabeculae, mitotic figures, and invasion of its capsule and surrounding vessels and lymph nodes.[13] However, these features are not exclusive to PC. In our study, 1 case was diagnosed later after she had undergone 3 surgeries for recurrent hypercalcemia. Therefore, it is crucial to note that the diagnosis of PC cannot depend primarily on histologic criteria as it shares the same features with benign parathyroid disease. Intraoperative findings are also essential to support diagnosis of PC. This includes lobulated firm mass, adhesion to thyroid lobe or adjacent cervical tissue such as strap muscles, recurrent laryngeal nerve, oesophagus and trachea.[14]

Genetic mutations such as CDC73 has been recognized to play an important role in the pathogenesis of PC. CDC73 is responsible to encode for parafibromin, which is involved in the regulation of gene expression and cell proliferation inhibition. It can be found in other mutated genes such as PIK3CA, MTOR, ADCK1, FAT3, AKAP9, and ZEB1, which were also identified in PC. Identification of these mutations carry important implications for management and early detection or prevention of PC among family members of PC patient.[15]

Surgery is the main treatment for PC. Complete surgical resection of tumour and involving tissue (en bloc) with microscopically negative surgical margins offers the best chance of cure and reducing the risk of recurrence. Studies have shown that preoperative suspicion and appropriate resection during primary surgery offers the best prognostic chance.[16-18] In the case of recurrence, surgical resection is still the primary mode of treatment. Significant palliation may result from the resection of recurrence lesions. However, repeated surgeries predispose patients up to a 60% lifetime accumulated surgical risk. To date, there is no established randomized trial available to evaluate radiotherapy and chemotherapy for PC. Incorporation of chemotherapy or radiotherapy needs to be tailored on individual basis.[19]

Hypocalcemia is a common immediate side effect of parathyroidectomy, despite being the cause of the disease. It can be severe, resulting in hungry bone syndrome, which is characterised by a rapid, profound and persistent hypocalcemia. Therefore, it is crucial to ensure that appropriate replacement of calcium and vitamin D are monitored closely. Hungry bone syndrome has been associated with advanced age, preoperative high level of serum calcium, ALP and iPTH, depleted vitamin D level and tumour size. In a randomized control trial among PHPT patients who were going for parathyroidectomy, daily supplementation of high dose vitamin D improves vitamin D status and decreases iPTH level preoperatively. However, this study found no association between preoperative 25(OH)D and postoperative serum Ca level with hungry bone syndrome. Even so, high dose of vitamin D supplement preoperatively is safe and improves bone mineral density and reduces bone resorption. Hence, in our center it is recommended for preoperative administration of vitamin D to minimize the need for prolonged intravenous calcium administration postoperatively.[20]

PC is a slowly progressing disease. It has a high recurrence rate of up to 49-60% of cases after the initial operation.[19] In our study, recurrence of the disease occurred in 4 patients, with mean time to recurrence was 21 months, while other studies reported 24-48 months. Metastasis usually occurs locally in 25-80%, and approximately 25% developed distant metastasis during the duration of the disease, most commonly in the neck, followed by the lung and spine.[21]

Mortality and morbidity in PC are mainly caused by hypercalcemia. Therefore, in treating PC, management needs to be focused on ameliorating the hypercalcemia effects. Apart from surgery, which has been the primary initial therapy in recurrent or refractory cases, medical therapy such as biphosphanate, calcimimetic, denosumab has also shown to control hypercalcemia. In a recent case report, denosumab has demonstrated a rapid normalization of calcium level in a case of refractory hypercalcemia secondary to recurrent PC.[22] Calcimimetic agent is approved by U.S. Food and Drug Administration (FDA) as the treatment for hypercalcemia in PC. One multi-centre study has demonstrated that calcimimetic has a durable clinical effect in achieving control of serum PTH and calcium levels in inoperable patients.[23]

Prognosis of PC is variable. Overall survival from various cancer databases showed of 85% and 49-77% at 5 and 10 years' follow-up, respectively.[16] In several observational studies, mortality has been associated with metastasis, severity of hypercalcemia and lymph nodes involvement. Young age is associated with improved survival.[24,25] Interestingly, a study of PC in a single institution revealed that survival rate and surgical complications were significantly reduced if initial operation was done in a dedicated endocrine centre versus other tertiary or non-tertiary centres. Other studies reported early identification of the tumour and appropriate resection of the neoplasm at the time of primary surgery offered the patients the best prognostic chance.[12]

CONCLUSION

PC is a rare malignancy and has an indolent but progressive course. It remains a challenge to diagnose PC as it mimics benign primary hyperparathyroidism. Clinical judgement is crucial for early diagnosis of PC and to detect its recurrence and/or metastasis. Severe hypercalcemia (>3.5 mmol/L), very high iPTH (3-10 times upper limit) and large parathyroid lesion (>3 cm) should prompt high index suspicion of PC. Complete surgical resection with microscopically negative margins that can be reached with the en bloc excision is the best chance for cure. However, recurrence is not uncommon among PC survivor. Recurrence or metastatic disease should be surgically treated, and often multiple surgical interventions are needed, even though they are not definitely curative. Since PC is an indolent tumour with a long-lasting survival and the cause of death is mainly due to untreatable hypercalcemia, therefore, the main goal of therapy is to control hypercalcemia and its complications. Thus, lifetime follow up is mandatory.

Ethical Consideration

All information in the case series has been provided without mention of any identifier in an effort to ensure anonymity of the patients. The authors have sought ethical clearance from the Medical and Research Committee (MREC), Ministry of Health Malaysia (MOH) to conduct the study and publish the case series.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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

*All authors are required to obtain an ORCID iD. To register, kindly follow this link: https://orcid.org/register.

The **JAFES cover letter template** must be used.

AUTHOR FORM

UPDATE

For submissions to the JAFES to be accepted, all authors must read and accomplish the **JAFES AUTHOR FORMS** consisting of: (1) the Authorship Certification, (2) the Author Declarations, (3) the Author Contribution Disclosure, and (4) the Author Publishing Agreement. The completely accomplished JAFES Author Forms shall be scanned and submitted along with the manuscript. No manuscript shall be received without the completely accomplished JAFES Author Forms.

ADHERENCE TO EQUATOR NETWORK GUIDELINES

To improve and standardize reporting of findings depending on the study type, authors should should ensure compliance with and submit the appropriate accomplished 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

ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

In order to ensure scientific objectivity and independence, the JAFES requires all authors to make a full disclosure of areas of potential conflict of interest. Such disclosure will indicate whether the person and/or his/her immediate family has any financial relationship with pharmaceutical companies, medical equipment manufacturers, biomedical device manufacturers, or any companies with significant involvement in the field of health care.

Examples of disclosures include but not limited to: ownership, employment, research support (including provision of equipment or materials), involvement as speaker, consultant, or any other financial relationship or arrangement with manufacturers, companies or suppliers. With respect to any relationships identified, author(s) must provide sufficiently detailed information to permit assessment of the significance of the potential conflict of interest (for example, the amount of money involved and/or the identification of any value of goods and services).

The form is also downloadable at http://www.icmje.org/conflicts-of-interest/.

ETHICS REVIEW APPROVAL

For Original Articles, authors are required to submit a scanned soft copy of the Ethics Review Approval of their research. For manuscripts reporting data from studies involving animals, authors are required to submit a scanned copy of the Institutional Animal Care and Use Committee approval.

INFORMED CONSENT

UPDATE

For Case Reports, Images in Endocrinology and Clinical Case Seminars, authors are required to submit scanned soft copy of signed informed consent for publication from the involved subject/s ("Patient Consent Form"). In case the involved subject/s can no longer be contacted (i.e., retrospective studies, no contact information, et cetera) to obtain consent, the author must seek ethical clearance from the institutional board to publish the information about the subject/s.

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 (ICMJE 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. Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

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., X400) 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.

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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, affiliations, ORCID iD, specific role/s in writing the manuscript and email address) ☐ 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 and submit checklist (e.g., CONSORT for clinical trials, CARE for case reports)
Author Form	☐ Ensure all authors have read and agreed to the following: (1) the Authorship Certification, (2) the Author Declarations, (3) the Author Contribution Disclosure, and (4) the Author Publishing Agreement ☐ Submit a scanned copy of the fully accomplished form
ICMJE Form for Disclosure of Potential Conflicts of Interest	☐ Ensure all authors have read and agreed to disclose potential Conflicts of Interest ☐ Submit the PDF copy of the fully accomplished form *The form is also downloadable at: http://www.icmje.org/conflicts-of-interest/
Ethics Review Approval	☐ For Original articles, submit a scanned copy of the Ethics Review Approval of research ☐ For manuscripts reporting data from studies involving animals, submit a scanned copy of the Institutional Animal Care and Use Committee approval
Patient Consent Form (if applicable)	☐ For Case Reports, Images in Endocrinology and Clinical Case Seminars, submit a scanned copy of the fully accomplished form; otherwise, obtain appropriate ethical clearance from the institutional review board.
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 ☐ Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references; grants and subsidies from government or private institutions should also be acknowledged
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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Author Form

COMPLETE TITLE OF MANUSCRIPT

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1.		
2.		
3.		
4.		
5.		

***NOTE: Indicate with an asterisk mark the corresponding author.**

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Based on International Committee of Medical Journal Editors (ICMJE) Criteria for Authorship.

In consideration of our submission to the Journal of the ASEAN Federation of Endocrine Societies (JAFES), the undersigned author(s) of the manuscript hereby certify, that all of us have actively and sufficiently participated in:

- ☐ (1) the conception or design of the work, the acquisition, analysis and interpretation of data for the work; AND
- ☐ (2) drafting the work, revising it critically for important intellectual content; AND
- ☐ (3) that we are all responsible for the final approval of the version to be published; AND
- ☐ (4) we all agree 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.

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Adapted from Contributor Roles Taxonomy [CRediT] developed by the Consortia for Advancing Standards in Research Administration Information (CASRAI).

Specific Contributor role	Author 1	Author 2	Author 3	Author 4	Author 5
Conceptualization Ideas; formulation or evolution of overarching research goals and aims.					
Methodology Development or design of methodology; creation of models					
Software Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components					
Validation Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs					
Formal analysis Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data					
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ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

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This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

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Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
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Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
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Royalties: Funds are coming in to you or your institution due to your patent

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Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

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Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Section 6. Disclosure Statement

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Journal of the
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For a patient's consent to publication of information about them in the Journal of the ASEAN Federation of Endocrine Societies (JAFES).

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Subject matter of photograph or article:_____
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about MYSELF/MY CHILD OR WARD/MY RELATIVE relating to the subject matter
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above to appear in the Journal of the ASEAN Federation of Endocrine Societies (JAFES) subject to its publication policies and ethical standards.

I have seen and read the material to be submitted to the JAFES and thoroughly understand the following:

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- The Information may also be placed on the JAFES' website.
- The JAFES shall not allow the Information to be used for advertising or packaging or to be used out of context (i.e., used to accompany an entirely different article or topic).
- I can withdraw my consent at any time before publication, but once the Information has already been sent to press, it is my understanding that it will not be possible to revoke the consent.

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Witness:
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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). 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 practical guidelines, book reviews, et cetera), editorials , letters to the Editor, brief communications and special announcements. Authors may include members and non-members of the AFES.

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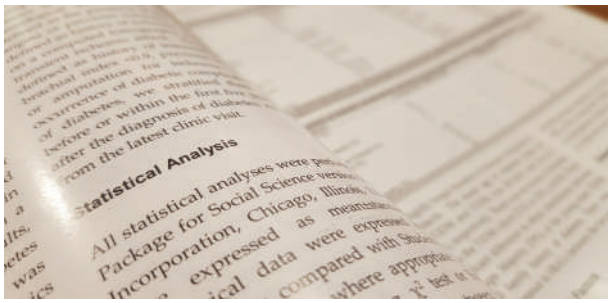

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Articles published in the JAFES from May 2017, Volume 34 No. 1 henceforth, shall be indexed and available 100% Open Access, accessible through Clarivate Analytics™ Web of Science.

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The **International Standard Serial Number (ISSN)** is a digital code used to identify the JAFES as a serial publication in both print and electronic formats.

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As a member of the **World Association of Medical Editors (WAME),** JAFES is dedicated to high ethical and scientific principles in scientific publication. WAME's global network of editors communicate and discuss editorial and publishing issues from which member editors can learn and be guided.

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world association of medical editors

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COMPOSITION: Diamicron MR 60 mg, modified release tablet containing 60 mg of gliclazide, contains lactose as an excipient. **INDICATION:** Non-insulin-dependent diabetes (type 2) in adults, in association with dietary measures and with exercise, when these measures alone are not sufficient. **DOSAGE AND ADMINISTRATION:** One half to 2 tablets per day i.e. from 30 to 120 mg taken orally as a single intake at breakfast time, including in elderly patients and those with mild to moderate renal insufficiency with careful patient monitoring. One tablet of Diamicron MR 60 mg is equivalent to 2 tablets of Diamicron MR 30 mg. The breakability of Diamicron MR 60 mg enables flexibility of dosing to be achieved. In patients at risk of hypoglycemia, daily starting dose of 30 mg is recommended. Combination with other antidiabetics: Diamicron MR 60 mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin (under dose medical supervision). **CONTRAINDICATIONS:** Hypersensitivity to gliclazide or to any of the excipients, other sulfonylurea or sulphonamides; type 1 diabetes; diabetic pre-coma and coma, diabetic ketoacidosis; severe renal or hepatic insufficiency (in these cases the use of insulin is recommended); treatment with miconazole (see interactions section); lactation (see fertility, pregnancy and lactation section). **WARNINGS:** Hypoglycemia may occur with all sulfonylurea drugs, in cases of accidental overdose, when calorie or glucose intake is deficient, following prolonged or strenuous exercise, and in patients with severe hepatic or renal impairment. Hospitalization and glucose administration for several days may be necessary. Patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels. To be prescribed only in patients with regular food intake. Use with caution in patients with G6PD-deficiency. Excipient: contains lactose. **INTERACTIONS:** Risk of hypoglycemia - contraindicated: miconazole; not recommended: phenylbutazone; alcohol; use with caution: other antidiabetic agents, beta-blockers, fluconazole, ACE inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, clarithromycin, NSAIDs. Risk of hyperglycemia - not recommended: danazol; use with caution: chlorpromazine at high doses; glucocorticoids; ritodrine; salbutamol; terbutaline; Saint John's Wort (hypericum perforatum) preparations. Risk of dysglycemia - use with caution: fluoroquinolones. Potentiation of anticoagulant therapy (e.g. warfarin), adjustment of the anticoagulant may be necessary. **PREGNANCY AND BREASTFEEDING:** Pregnancy: Change to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered. Lactation: Contraindicated. **DRIVING & USE OF MACHINES:** Possible symptoms of hypoglycemia to be taken into account especially at the beginning of the treatment. **UNDESIRABLE EFFECTS:** Hypoglycemia, abdominal pain, nausea, vomiting, dyspepsia, diarrhea, constipation. Rare: changes in hematology generally reversible (anemia, leukopenia, thrombocytopenia, granulocytopenia). Raised hepatic enzymes levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). If cholestatic jaundice: discontinuation of treatment. Transient visual disturbances at start of treatment. More rarely: rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS). As for other sulfonylureas: observed cases of erythrocytopenia, agranulocytosis, hemolytic anemia, pancytopenia, allergic vasculitis, hyponatremia, elevated liver enzymes, impairment of liver function (cholestasis, jaundice) and hepatitis which led to life-threatening liver failure in isolated cases. **OVERDOSE:** Possible severe hypoglycemia requiring urgent IV glucose, immediate hospitalization and monitoring. **PROPERTIES:** Diamicron MR 60 mg is a sulfonylurea reducing blood glucose levels by stimulating insulin secretion from beta cells in the islets of Langerhans, thereby restoring the first peak of insulin secretion and increasing the second phase of insulin secretion in response to a meal or intake of glucose. Independent hemovascular properties. **PRESENTATION:** Box of 60 tablets of Diamicron MR 60 mg in blister. **STORAGE:** Store at temperatures not exceeding 30 °C.

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