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Challenging Access, Celebrating the Discovery of Insulin after a Hundred Years

Our continued commitment to open access through the support of the AFES country societies has been affirmed by the renewal of our listing in the Directory of Open Access Journals. Beyond our policy of not requiring fees for article processing, subscription, or download, the Editorial Board affirms key strategies to further improve access to the Journal in the ASEAN.

We firmly believe that science should not be hindered by language. For 2022 and beyond, JAFES plans to organize workshops for ASEAN country societies on scholarly writing and publishing in the English language, to address possible language barriers and improve chances of publication. Through this initiative, data from the ASEAN region can find a greater audience and may even be translated to policies and programs that can improve health outcomes in Southeast Asia.

The team is actively promoting its content through its Facebook, Twitter, and Instagram accounts. Social media platforms are powerful tools and have definitely changed how information is disseminated and shared. We owe it to our authors, readers, and the general public, to address misinformation by delivering correct scientific evidence. Visual abstracts, which we have innovated in 2019 as a way of distilling key findings into graphic, easily understood and shareable formats, also intend to enhance access. We aim to hold workshops for AFES country societies on the creation of visual abstracts, too, to include versions in their own language.

Through the past decade, the JAFES has featured various topics on diabetes: clinical practice guidelines, physiological and demographic characteristics, nutrition, physical activity and medications. In addition to clinical studies, we are coming up with a special molecular and cellular endocrinology issue for May 2022 to cater to regional studies focused on cellular, molecular, genetic, and epigenetic aspects of endocrine research. By making these available for all without paywalls, JAFES hopes to catalyze more opportunities for regional research collaboration, to facilitate scientific discovery through knowledge building upon knowledge.

Figure 1. Sir Frederick Banting (right) and Dr. Charles Best. In the photo is one of the dogs used in their scientific experiments.[1]

The year 2021 ushered in sentimental reminiscences of the time Frederick Banting and Charles Best, James Collip and John MacLeod discovered insulin in Toronto, a hundred years ago, to treat people with diabetes. We remember then 14-year-old Leonard Thompson who was transformed from cachexia to the pink of health with the injection of this life-saving hormone. Along with the international community, JAFES celebrates this momentous scientific milestone that led to better health outcomes for those with diabetes.

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As mentioned by Banting in his Nobel Prize lecture, "insulin was not a cure for diabetes; it is a treatment." A hundred years later, its cure is still elusive. Despite amazing discoveries in our understanding of pathophysiology, enhanced glucose monitoring devices, and insulin-delivery systems, the worldwide epidemic of diabetes continues to prevail.

Through 30 years of clinical practice, I have had many patient interactions, many of whom have led to more than acquaintances, with shared light moments of friendships. Sadly, I continue to see patients in government hospitals who continue to struggle with health care costs for diabetes and its complications, and while the insulin discoverers refused to profit from the discovery in 1921, many today still cannot afford basic insulin. Certainly, greater work needs to be done to overcome the many barriers to access to this century-old scientific breakthrough.

Research information or patient treatment: access is a continuing challenge.

Elizabeth Paz-Pacheco
Editor-in-Chief

Reference

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Discordance between Fasting Plasma Glucose (FPG) and HbA1c in Diagnosing Diabetes and Pre-diabetes in The Malaysian Cohort

Nor Azian Abdul Murad,[1] Noraidatulakma Abdullah,[1] Mohd Arman Kamaruddin,[1] Nazihah Abd Jalal,[1] Norliza Ismail,[1] Nurul Ain Mhd Yusof,[1] Norlaila Mustafa,[2] Rahman Jamal[1]

[1]*UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia (UKM), Kuala Lumpur, Malaysia*
[2]*Department of Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia (UKM), Kuala Lumpur, Malaysia*

Abstract

Objective. In this present study, we aim to evaluate the accuracy of the HbA1c relative to fasting plasma glucose (FPG) in the diagnosis of diabetes and pre-diabetes among The Malaysian Cohort (TMC) participants.

Methodology. FPG and HbA1c were taken from 40,667 eligible TMC participants that have no previous history of diabetes, aged between 35-70 years and were recruited from 2006 – 2012. Participants were classified as normal, diabetes and pre-diabetes based on the 2006 World Health Organization (WHO) criteria. Statistical analyses were performed using ANOVA and Chi-square test, while Pearson correlation and Cohen's kappa were used to examine the concordance rate between FPG and HbA1c.

Results. The study samples consisted of 16,224 men and 24,443 women. The prevalence of diabetes among the participants was 5.7% and 7.5% according to the FPG and HbA1c level, respectively. Based on FPG, 10.6% of the participants had pre-diabetes but this increased to 14.2% based on HbA1c (r=0.86; P<0.001). HbA1c had a sensitivity of 58.20 (95% CI: 56.43, 59.96) and a specificity of 98.59 (95% CI: 98.46, 98.70).

Conclusion. A higher prevalence of pre-diabetes and diabetes was observed when using HbA1c as a diagnosis tool, suggesting that it could possibly be more useful for early detection. However, given that HbA1c may also have lower sensitivity and higher false positive rate, several diagnostic criteria should be used to diagnose diabetes accurately.

Key words: type 2 diabetes mellitus, fasting plasma glucose, HbA1c, The Malaysian Cohort, diagnosis, population differences

INTRODUCTION

The prevalence of Type 2 diabetes mellitus (T2DM) has been increasing worldwide. It is projected that approximately 300 million people will be diagnosed with T2DM by 2025.[1] Malaysia has also observed tremendous hikes in the number of T2DM. The National Health and Morbidity Survey (NHMS) in 2015 reported that the prevalence of T2DM was 17.5%[2] which was similar to findings from The Malaysian Cohort (TMC) study that showed a prevalence of 16.6%.[3] Based on the latest NHMS in 2019, one in five adults or equivalent to 3.9 million people aged 18 years and above in Malaysia have diabetes.[4] The prevalence of diabetes had increased from 13.4% in 2015 to 18.3% in 2019.[4] Early diagnosis is vital for diabetic patients, hence, intervention and treatment can be commenced immediately to prevent macrovascular or microvascular complications of diabetes.

Fasting plasma glucose (FPG) and oral glucose tolerance test (OGTT) have been used as the primary screening tools to diagnose diabetes.[5] FPG, however, is commonly used in both clinical and epidemiological studies due to the inconsistency of the OGTT results that rely on the 2-hour post glucose load (2HPG) which is also laborious to perform.[6,7] Glycalated hemoglobin (HbA1c) is a form of hemoglobin (Hb), produced by non-enzymatic reaction, chemically linked to a sugar and indicative of increased blood sugar in the body over the past 3-4 months.[8,9] The use of HbA1c in monitoring or controlling the glucose metabolism was proposed by Anthony Cerami and colleagues in 1976.[10] Unlike FBG and 2HPG, HbA1c detection is more convenient and patients do not need to fast overnight. In addition, is more accurate and convenient, with less pre-analytical and analytical variability.

The use of HbA1c to diagnose diabetes has been widely recommended and this is further expedited by the worldwide standardization of the HbA1c measurement.[11] In 2009, the diagnosis of diabetes using HbA1c was proposed by the International Expert Committee[12] and was

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Corresponding author: Prof. Datuk Dr. Rahman Jamal
Professor, Paediatric Haematology, Oncology and Molecular Biology UKM,
Senior Principal Fellow, UKM Medical Molecular Biology Institute (UMBI),
Principal Investigator of The Malaysian Cohort project
UKM Medical Molecular Biology Institute (UMBI), Universiti Kebangsaan Malaysia (UKM), Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia
Tel. No.: +603-91456321
Fax: +603-91717185
E-mail: rahmanj@ppukm.ukm.edu.my
ORCiD: https://orcid.org/0000-0002-8354-8957

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endorsed by both ADA and WHO in 2011.[13] Nonetheless, there is evidence showing that HbA1c level varies between different ethnicities or populations.[14-17] For example, Asians have been reported to have higher HbA1c levels than Caucasians.[18] A recent study on the Vietnamese population by Ho-Pham et al., showed that the prevalence of pre-diabetes was about three times higher using the globally recommended HbA1c level of 6.5% or more as compared to using FPG.[19] The prevalence of diabetes and pre-diabetes based on the HbA1c from the Ho Chi Minh City, Vietnam was 9.7% and 34.6% respectively.[19] In Korea, Hee Kim and colleagues analyzed 35,624 non-diabetic Koreans and 1,491 participants were identified as newly diagnosed diabetes.[20] From these 1,491 participants, 31.6% met the FPG criteria only (≥7.0 mmol/l), 23.5% met HbA1c only (≥6.5%) and 44.9% met both FPG and HbA1c.[20] In Malaysia, Nazaimoon and colleagues studied 4,341 individuals from five zones and based on the World Health Organization (WHO), the prevalence of diabetes was 22.9%, with 10.8% was known diabetes and 12.1% was newly diagnosed diabetes.[16] Using HbA1c of 45 mmol/mol (6.3%) as diagnostic criteria, the prevalence of diabetes was only 5.5%

In this present study, we aim to evaluate the accuracy of the HbA1c relative to fasting plasma glucose (FPG) in the diagnosis of diabetes and pre-diabetes among The Malaysian Cohort (TMC) participants.

METHODOLOGY

Study design, study participants and sample size

This study was derived from the prospective cohort study that consists of 106,527 persons whose data infers that of the Malaysian population based on the Census Malaysia Report of 2000. Furthermore, our previous finding indicated that 16.6% of TMC participants were diabetic.[21] Based on this prevalence, with 95% confidence interval and 80% power of study, the sample size needed for this study is only 214. However, since 40,667 participants were eligible, all participants were included into this study. The study was approved by the Research and Ethics Committee, Universiti Kebangsaan Malaysia (UKM) (FF-205-2007), in accordance with the declaration of Helsinki. Written informed consent was taken from all subjects.

Data collection

Anthropometric measurements recorded for each participant included body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR). Weight and height were obtained using a Seca weight scale (SECA, Jerman) and Harpenden stadiometer (Holtain Limited, UK) respectively. Blood pressure was measured using Omron HEM-907 (Omron Corporation, Japan). All measurements were performed three times and the average measurements were recorded. Each participant was interviewed face-to-face by a trained interviewer. Data obtained included age, gender, ethnicity and history of diabetes and other diseases.

Blood collection and bioanalytical analysis

Peripheral blood samples were collected by venipuncture from each participant after an overnight fasting. Biochemical analysis was performed within 24 hours post-blood collection. The blood sample for HbA1c was collected in the EDTA tube whereas the sample for FPG was collected in the sodium fluoride tube. For full lipid profile (total cholesterol, high density lipoprotein (HDL-c) and low-density lipoprotein (LDL-c), samples were collected using the SST II Advance vacutainer. FPG and full lipid profile were analyzed using the COBAS Integra® 800 (Roche Diagnostics Gmbh, Germany). Quality control was performed using Lyphochek Assayed Chemistry Control from Bio-Rad Laboratories. HbA1c was analyzed using the high-performance liquid chromatography (HPLC) in the Variant™ II Turbo machine (Bio-Rad Laboratories Inc, USA). Quality control was performed using Liquichek™ Diabetes Control form Bio-Rad Laboratories. All analyses were performed according to the protocols recommended by the manufacturer.

Subjects with a FPG concentration greater than or equal to 7.0 mmol/l were classified as having T2DM, those with levels between 6.1–6.9 mmol/L as pre-diabetes and level less than 6.1 mmol/l as normal. For HbA1c, those with values at 6.5% and above were classified as T2DM, values between 6.0-6.4% were deemed to have pre-diabetes and values less than 6.0% defined as normal. As for full lipid profile, total cholesterol levels of more than 5.2 mmol/L were classified as elevated and less than 5.2 mmol/L as normal, HDL more than 1.6 were classified as normal and less than 1.6 as deficient, while LDL less than 1.7 were classified as normal and more than 1.7 were classified as elevated. The tests were performed in an accredited bioanalytical laboratory.

Statistical analysis

The prevalence of diabetes and pre-diabetes was determined by percentage. The differences between groups were assessed using the Chi-square test for categorical data and ANOVA for continuous data. The association and agreement between HbA1c and FBG were assessed by Pearson correlation and Cohen's kappa. The diagnostic test including sensitivity, specificity and accuracy of HbA1c in relative to FBG were determined using MedCalc Software. A *p*-value threshold of 0.05 was used for declaring significance. All analyses were performed using IBM SPSS Statistics 21.

RESULTS

Population characteristics

A total of 40,667 subjects were enrolled in this study with the mean age of 51.8 ± 8.2 years. Table 1 shows the status of pre-diabetes and diabetes according to the FPG and HbA1c levels in three Malaysian major ethnic groups including Malay, Chinese and Indian. Based on the FPG measurement, 10.6% and 5.7% of TMC participants were classified as having pre-diabetes and diabetes, respectively. When the HbA1c level measurement was used, we observed significant increases in the prevalence of pre-diabetes (14.2%) and diabetes (7.5%). There were significant differences ($p<0.001$) between diabetes, pre-diabetes and normoglycaemia using the FPG and HbA1c diagnostic criteria for all characteristics (Table 1).

We also examined the relation between the prevalence of diabetes and ethnicity using both criterions. Using the FPG, we noticed that diabetes was more prevalent among Indians (8.3%), followed by Malay (7.0%) and Chinese (3.2%). The pattern was similar when we employed the HbA1c level measurement as the diagnostic tool. However, we observed that the diabetes prevalence in each ethnic group was higher

Table 1. Subjects characteristics and prevalence of pre-diabetes and diabetes using FPG and HbA1c

Characteristics / Guidelines	Fasting Plasma Glucose			*P*-value	HbA1c (WHO)			*P*-value
	Normal (<6.1 mmol/L)	Pre-diabetes (6.1-6.9 mmol/L)	DM (≥7.0 mmol/L)		Normal (<6.0%)	Pre-diabetes (6.0-6.4%)	DM (>6.5%)	
N (%)	34,063 (83.8)	4,292 (10.6)	2,312 (5.7)		31,829 (78.3)	5,778 (14.2)	3,060 (7.5)	
Age (years), Mean (SD)	51.36 (8.25)	54.45 (7.57)	53.51 (7.75)	<0.001	51.24 (8.27)	53.99 (7.71)	53.62 (7.63)	<0.001
Gender (%)								
Male	12,943 (79.8)	2,128 (13.1)	1,153 (7.1)	<0.001	12,064 (74.36)	2,671 (16.46)	1,489 (9.18)	<0.001
Female	21,120 (86.4)	2,164 (8.9)	1,159 (4.7)		19,765 (80.86)	3,107 (12.71)	1,571 (6.43)	
Ethnicity (%)								
Malays	15,150 (81.5)	2,140 (11.5)	1,309 (7.0)	<0.001	14,200 (76.35)	2,734 (14.70)	1,665 (8.95)	<0.001
Chinese	14,537 (88.5)	1,365 (8.3)	533 (3.2)		13,726 (83.52)	2,014 (12.25)	695 (4.23)	
Indians	4,376 (77.7)	787 (14.0)	470 (8.3)		3,903 (69.29)	1,030 (18.29)	700 (12.43)	
Locality (%)								
Urban	27,377 (84.4)	3,382 (10.4)	1,696 (5.2)	<0.001	25,818 (79.55)	4,432 (13.66)	2,205 (6.79)	<0.001
Rural	6,686 (81.4)	910 (11.1)	616 (7.5)		6,011 (73.20)	1,346 (16.39)	855 (10.41)	
Body mass index								
BMI Mean (SD)	25.58 (4.53)	27.64 (4.64)	28.47 (4.67)	<0.001	25.9 (4.66)	25.98 (4.63)	25.96 (4.67)	0.487
Waist circumference (cm)								
Male								
Mean (SD)	88.29 (10.51)	92.31 (10.38)	95.47 (11.10)	<0.001	0.3 (0.61)	0.3 (0.61)	0.31 (0.61)	0.891
Female								
Mean (SD)	81.76 (11.06)	88.29 (11.15)	90.23 (10.75)	<0.001	1.08 (0.85)	1.1 (0.85)	1.07 (0.85)	0.316
Waist -to-hip ratio								
Male								
Mean (SD)	0.90 (0.06)	0.92 (0.06)	0.94 (0.05)	<0.001	0.13 (0.42)	0.16 (0.45)	0.14 (0.41)	0.050
Female								
Mean (SD)	0.83 (0.07)	0.86 (0.07)	0.88 (0.07)	<0.001	1.37 (0.85)	1.38 (0.85)	1.35 (0.86)	0.700
Blood pressure, FBS and HbA1c								
Systolic blood pressure (mmHg), Mean (SD)	127.30 (18.88)	134.60 (18.91)	136.49 (19.84)	<0.001	129.58 (19.27)	129.77 (19.84)	129.2 (18.8)	0.499
Diastolic blood pressure (mmHg), Mean (SD)	81.58 (11.64)	85.17 (11.47)	86.99 (12.05)	<0.001	76.88 (11.35)	77.03 (11.61)	76.8 (11.27)	0.662
FBS, Mean (SD)	5.30 (0.40)	6.43 (0.25)	9.55 (3.08)	<0.001	5.35 (0.53)	5.84 (0.7)	8.47 (3.17)	<0.001
HbA1c, Mean (SD)	5.51 (0.43)	6.00 (0.57)	8.00 (2.04)	<0.001	5.42 (0.35)	6.14 (0.13)	7.86 (1.74)	<0.001
Fasting blood lipid profile								
Total Cholesterol (mmol/L) Mean (SD)	5.67 (1.06)	5.80 (1.09)	5.99 (1.18)	<0.001	5.65 (1.04)	5.83 (1.12)	5.97 (1.18)	<0.001
HDL, Mean (SD)	1.47 (0.42)	1.31 (0.37)	1.24 (0.33)	<0.001	1.48 (0.43)	1.35 (0.38)	1.25 (0.32)	<0.001
LDL, Mean (SD)	3.57 (0.97)	3.73 (1.03)	3.84 (1.08)	<0.001	3.54 (0.99)	3.73 (1.05)	3.83 (1.07)	<0.001

compared to FPG where 12.43% of Indians were classified as diabetes, followed by Malay (8.95%) and Chinese (4.23%). In addition, the prevalence of diabetes was higher among those in the rural areas compared to the urban population using both FPG and HbA1c criteria (p<0.001).

For the mean systolic blood pressure, the patients with diabetes using FBG, had higher readings compared to normal and pre-diabetes subjects. The mean total cholesterol (TC) and LDL cholesterol levels showed increasing trends as the plasma glucose increases across the glucose tolerance groups using either FPG or HbA1c. Obesity, indicated by the increase in body mass index (BMI), waist circumference and waist hip ratio, is associated with high-risk of developing diabetes. In line with this, we observed that those who have diabetes, diagnosed using either FPG or HbA1c criteria, have larger waist circumference, higher BMI and WHR compared to normal and pre-diabetes subjects (Table 1).

Correlation and concordance between HbA1c and FPG

Of the 3,060 individuals with diabetes according to the HbA1c criteria, only 1,781 (58.2%) were concordantly classified as diabetes based on FPG criteria. Table 2 shows the concordance in the classification of diabetes and pre-diabetes between HbA1c and FPG. Out of 5,778 subjects diagnosed with pre-diabetes based on HbA1c diagnostic criterion, 1,462 (25.3%) had similar diagnosis based on FPG. Using HbA1c alone, pre-diabetes was diagnosed about 30% greater than the FPG, and almost 2-fold for diabetes (Table 1). There was a moderate agreement between the diagnosis of diabetes by HbAIc and FPG (Kappa=0.64, p<0.001), whilst the agreement for pre-diabetes was poor (Kappa=0.19, p<0.001). There was a highly significant correlation between HbA1c and FPG, as shown in Figure 1 (r^2=0.86; P<0.001). The use of the HbA1c level of ≥6.5% to diagnose diabetes led to a sensitivity of 58.2% and a specificity of 98.59%, with a positive predictive value of 77.03% and a negative predictive value of 96.67% compared to FPG (Table 3).

Table 2. Concordance in diagnostic classification between HbA1c and FPG

Diagnosis Based on FBG	Diagnosis Based on HbA1c			Total
	Normal	Pre-diabetes	Diabetes	
Normal	29,534 (92.79)	3,995 (69.14)	534 (17.45)	34,063
Pre-diabetes	2,085 (6.55)	1,462 (25.30)	745 (24.35)	4,292
Diabetes	210 (0.66)	321 (5.56)	1,781 (58.20)	2,312
Total	31,829	5,778	3,060	40,667

Table 3. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values of HbA1c over FPG as a gold standard

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Diabetes	58.20 (56.43, 59.96)	98.59 (98.46, 98.70)	77.03 (75.41, 78.58)	96.67 (96.53, 96.80)	95.55 (95.34, 95.75)
Pre-diabetes	16.62 (16.02, 17.23)	92.91 (92.59, 93.22)	57.27 (55.87, 58.66)	66.10 (65.92, 66.28)	65.17 (64.70, 65.63)

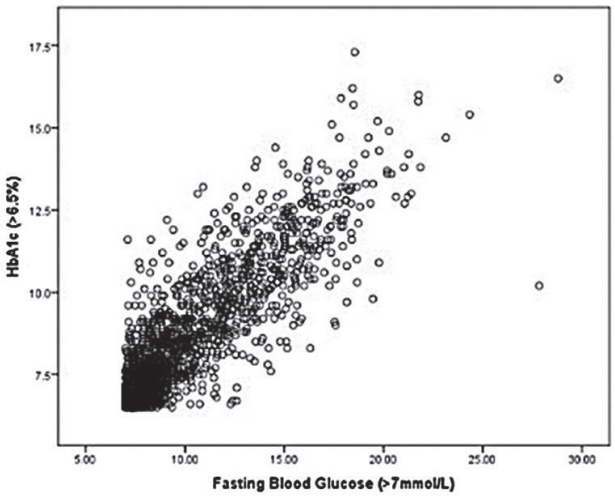

Figure 1. Scatterplot between FPG>7mmol/L and HbA1c >6.5%.

DISCUSSION

The screening methods used to diagnose T2DM have evolved over time, from the measurement of FPG, OGTT and to the use of HbA1c. Our study showed that using the HbA1c threshold level of ≥6.5%, resulted in about 14.2% and 7.5% of the studied population was identified as pre-diabetes and diabetes. This finding is of concern because if the FPG criterion is used for screening, these subjects will not be diagnosed as having diabetes and will live with persistent hyperglycemia without treatment for a significant period of time. This will eventually lead to diabetic complications, including cardiovascular disease (CVD), diabetic nephropathy and diabetic retinopathy. In addition, the increase in pre-diabetes prevalence by about four-fold using the HbA1c level criteria needs immediate attention and action. Untreated pre-diabetes is 37% likely to developed diabetes in 4 years' time.[22] However, with proper lifestyle intervention, the risk of developing diabetes can be reduced to 20%.[22] Based on our results, HbA1c is more sensitive to identify diabetes. However, there were also patients with diabetes by FBG but normal based on HbA1c (n=210, 0.66%). About 321 (5.56%) participants with diabetes by FBG were found to be pre-diabetes by HbA1c. A total of 2,085 (6.55%) normal individuals based on HbA1c were identified as pre-diabetes by FBG. These results suggested that HbA1c may also have a lowered specificity in diagnosing diabetes with high false positive rate.

Although this study showed a high correlation (r^2=0.86) and moderate agreement between fasting plasma glucose and HbA1c in the diagnosis of diabetes, the two tests showed a poor agreement in detecting pre-diabetes. Discordance in the diagnosis of diabetes between HbA1c and FPG screening methods have been reported mainly among Asian populations.[19] A smaller scale population-based study in Malaysia about a decade ago involving 4,341 subjects showed consistent results with the studies from other Asian populations.[16] The discordance might be explained by the different information given by both HbA1c and FPG on the glycaemic exposure. FPG is the measurement of blood glucose at the particular time point, whereas HbA1c reflects the blood glucose level for the past 3 months.[14,21] It is suggested that the use of HbA1c can avoid the problem of within-subject fluctuation in glucose measurements. Thus, it is not surprising that individuals were classified differently by both methods based on the exposure of the blood glucose. It is also important to be aware about the different processes involved in measuring HbA1c and FPG, and the variation in the glycation process between individuals which might also contribute to the variations.[22]

The findings of this present study are likely to be representative of the actual diabetes prevalence in the general population who come from different ethnic groups. A study by Booth and colleagues in Canada showed similar findings where different ethnic groups will have different HbA1c levels in order to detect dysglycemia or diabetes.

Measuring HbA1c is a convenient approach for diabetes diagnosis due to its pre-analytical stability, less intra-individual variability and more importantly, unlike the oral glucose tolerance test, HbA1c level measurement does not require an overnight fast. However, there are several limitations using HbA1c for the diagnosis of diabetes. First, HbA1c cannot be used in individuals with haemoglobinopathies, anemia and disorders where the patients had abnormal red cell turnover.[23] Other processes such as erythropoiesis, glycation, erythrocyte destruction as well as different HbA1c assays used may also lead to differences in the HbA1c levels.[24]

For example, in erythrocyte destruction, increased erythrocyte life span and splenectomy could lead to increase HbA1c levels, whereas decreased erythrocyte life span, haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as anti-retrovirals, ribavirin and dapsone may decreased HbA1c levels.[24]

Appendix 1 shows several factors that could influence the HbA1c measurement and Appendix 2 shows the advantages and disadvantages of glucose and HbA1c assays (adapted from Gallagher et al., and WHO, 2011). Based on the WHO report in 2011, HbA1c can be used when rigorous quality assurance tests are applied, the assays are standardize based on the international reference value and the diabetic patients have no conditions as mentioned above that could result in imprecise measurement.[8] In addition, The American Association of Clinical Endocrinologists recommended that the HbA1c test should be considered as an additional, not as a primary diagnostic criterion.[25]

CONCLUSION

In summary, our results showed a higher prevalence of pre-diabetes and diabetes upon using the HbA1c compared to FPG. We also showed the differences in prevalence of diabetes across the different ethnic groups. We believe there is a basis to use the HbA1c for diagnosis of pre-diabetes and diabetes among the Malaysian population for early intervention and prevention. However, given that HbA1c may also led to lower specificity and high false positive rate, several criteria should be used in diagnosing and controlling diabetes.

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

Author Disclosure
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APPENDICES

Appendix 1. Several factors that could influence HbA1c levels[24] (adapted)

Description	Increased HbA1c	Decreased HbA1c
Erythropolesis	iron, vitamin B12 deficiency, decreased erythropoiesis	administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease
Altered Haemoglobin	genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.	
Glycation	alcoholism, chronic renal failure, decreased intra-erythrocyte pH	aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. variable HbA1c: genetic determinants.
Erythrocyte destruction	increased erythrocyte life span: Splenectomy.	decreased erythrocyte life span: haemoglobinopathies splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone
Assays	hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. variable HbA1c: haemoglobinopathies.	hypertriglyceridaemia

Appendix 2. Advantages and disadvantages of glucose and HbA1c assays in the diagnosis of diabetes[13]

Description	Glucose	HbA1c
Patient preparation prior to collection of blood	Stringent requirements if measured for diagnostic purposes	None
Processing of blood	Stringent requirements for rapid processing, separation and storage of plasma or serum at 4°C	Avoid conditions for more than 12 hr at temperatures >23°C. Otherwise keep at 4°C (stability minimally 1 week).
Measurement	Widely available	Not readily available world-wide
Standardization	Standardization for procedures is needed	Standardization for procedures is needed
Routine calibration	Adequate	Adequate
Interferences: illness	Severe illness may increase glucose concentration	Severe illness may shorten red-cell life and could reduce HbA1c levels
Haemoglobinopathies	Less problematic unless the patient is ill	May interfere with measurement in some assays
Haemoglobinopathy traits	No problems	Not affected by most assays
Affordability	Affordable in most low and middle income country settings (Cheap)	Unaffordable in most low and middle-income country settings (Expensive)

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ORIGINAL ARTICLE

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Association Between Metformin Use and Mortality among Patients with Type 2 Diabetes Mellitus Hospitalized for COVID-19 Infection

Angeli Nicole Ong,[1] Ceryl Cindy Tan,[1] Maria Teresa Cañete,[2] Bryan Albert Lim,[3] Jeremyjones Robles[1,4]

[1]*Section of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines*
[2]*Section of Neurology, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines*
[3]*Section of Infectious Diseases, Department of Internal Medicine, Chong Hua Hospital, Cebu City, Philippines*
[4]*Department of Internal Medicine, Cebu Institute of Medicine – Cebu Velez General Hospital, Cebu City, Philippines*

Abstract

Introduction. Metformin has known mechanistic benefits on COVID-19 infection due to its anti-inflammatory effects and its action on the ACE2 receptor. However, some physicians are reluctant to use it in hypoxemic patients due to potential lactic acidosis. The primary purpose of the study was to determine whether metformin use is associated with survival. We also wanted to determine whether there is a difference in outcomes in subcategories of metformin use, whether at home, in-hospital, or mixed home/in-hospital use.

Objectives. This study aimed to determine an association between metformin use and mortality among patients with type 2 diabetes mellitus hospitalized for COVID-19 infection.

Methodology. This was a cross-sectional analysis of data acquired from the COVID-19 database of two tertiary hospitals in Cebu from March 1, 2020, to September 30, 2020. Hospitalized adult Filipino patients with type 2 diabetes mellitus who tested positive for COVID-19 via RT-PCR were included and categorized as either metformin users or metformin non-users.

Results. We included 355 patients with type 2 diabetes mellitus in the study, 186 (52.4%) were metformin users. They were further categorized into home metformin users (n=109, 30.7%), in-hospital metformin users (n=40, 11.3%), and mixed home/in-hospital metformin users (n=37, 10.4%). Metformin use was associated with a lower risk for mortality compared to non-users (p=0.001; OR=0.424). In-hospital and mixed home/in-hospital metformin users were associated with lower mortality odds than non-users (p=0.002; OR=0.103 and p=0.005; OR 0.173, respectively). The lower risk for mortality was noted in metformin, regardless of dosage, from 500 mg to 2 g daily (p=0.002). Daily dose between ≥1000 mg to <2000 mg was associated with the greatest benefit on mortality (p≤0.001; OR=0.252). The survival distributions between metformin users and non-users were statistically different, showing inequality in survival ($\chi 2$=5.67, p=0.017).

Conclusion. Metformin was associated with a lower risk for mortality in persons with type 2 diabetes mellitus hospitalized for COVID-19 disease compared to non-users. Use of metformin in-hospital, and mixed home/in-hospital metformin use, was also associated with decreased risk for mortality. The greatest benefit seen was in those taking a daily dose of ≥1000 mg to <2000 mg.

Key words: metformin, diabetes mellitus, COVID-19, mortality

INTRODUCTION

In December 2019, the SARS-CoV-2 infection, which initially started in China, spread internationally and was declared a pandemic.[1] In over a year since its discovery, cases have reached more than 200 million globally, with more than four million deaths worldwide.[2] The Philippines has more than two million cases confirmed, with nearly forty thousand deaths attributed to the virus.[3]

The lungs are the primary target due to the high expression of the ACE2 receptor, which serves as its entry point.[4-6] The virus induces a cytokine storm causing alveolar epithelial damage, and in severe cases, may lead to acute respiratory disease syndrome and death.[7]

The most prevalent comorbid conditions noted with COVID-19 infection are hypertension, diabetes mellitus, cardiovascular disease, and obesity.[8,9] Studies also show that type 2 diabetes mellitus (T2DM) is a risk factor for more severe disease and is associated with an increased mortality rate.[10-13] Persons with diabetes have a greater risk for viral infection, adverse clinical outcomes, and mortality, as noted in previous coronavirus epidemics, namely

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Corresponding author: Angeli Nicole S. Ong, MD
Section of Endocrinology, Diabetes and Metabolism,
Department of Internal Medicine, Chong Hua Hospital,
Don Mariano Cui Street, Fuente Osmeña, Cebu City,
Cebu 6000 Philippines
Tel. No.: +63-032-255-8000
E-mail: anj0321ong@gmail.com
ORCiD: https://orcid.org/0000-0001-6671-0636

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the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[14-16]

The cure for COVID-19 remains elusive. Continual shifts in the therapeutic recommendations occur as clinical trials evaluate the effectiveness of potential agents. Investigators are looking into possible risks and added benefits of current antihyperglycemic medications to ascertain their impact on the course and prognosis of COVID-19 patients with diabetes.

Metformin is an established antidiabetic agent. Despite the introduction of new drugs in the treatment of type 2 diabetes mellitus, metformin is commonly used and is considered a mainstay treatment.[17] Aside from its glucose-lowering action, other potential underlying mechanisms explaining the favorable impact of metformin on the COVID-19 patients with diabetes have been explored, including its effect on reducing cytokine storm.[18,19]

A study by Cheng et al., supported the findings of a higher incidence of lactic acidosis in metformin users, especially with severe COVID-19 disease. Acidosis occurred in patients with higher (<3 g per day) metformin doses compared to when given lower (<1 g per day) or moderate (<2 g per day) doses of the drug.[20] However, metformin rarely causes lactic acidosis on its own. Clinical conditions associated with increased circulating lactate levels include hypoxia, sepsis, chronic kidney disease, or decreased renal function and heart failure.[21] Due to the risk of lactic acidosis with infections, clinicians discontinue metformin in most patients with severe illness, including COVID-19 infection.[22,23] Despite the risk, the degree of mortality was comparable between the metformin and non-metformin groups in COVID-19 infected patients,[20] which supports its continued use in COVID-19 patients with diabetes, despite physician reluctance.

Because metformin is a cornerstone of management in patients with type 2 diabetes mellitus due to its therapeutic effects on glucose control and low cost, it is important to determine the outcome with its use in COVID-19 patients.

METHODOLOGY

Our study was a cross-sectional analysis done in two tertiary hospitals in Cebu, Philippines. The study population included patients admitted and subsequently included in the COVID-19 database of Chong Hua Hospital – Fuente and Chong Hua Hospital – Mandaue from March 1, 2020, to September 30, 2020.

All hospitalized Filipino patients who tested positive for COVID-19 via RT-PCR, are 18 years or older, and have type 2 diabetes mellitus, either preexisting or newly diagnosed using the American Diabetes Association criteria, were included in the analysis. We excluded patients if they had type 1 diabetes mellitus, were pregnant, of a different race or ethnicity, had unknown final disposition and those who were transferred to another institution or discharged against medical advice.

We categorized patients as to use or non-use of metformin, subdividing the metformin group into home metformin users, in-hospital metformin users, and mixed home/in-hospital metformin users. We retrospectively reviewed the characteristics and medications of these patients using an electronic medical record system.

The primary outcome was in-hospital mortality defined by a recorded final disposition of either discharged improved or death. Survival function between both groups was also an additional outcome measured.

Sample size

In the study by Lalau et al.,[24] which included 2449 people with type 2 diabetes mellitus, mortality on day 28 was 16% among metformin users, and 28.6% among non-users. To show a similar difference in mortality, we estimated that the sample size would have to be at least 311 persons with type 2 diabetes mellitus, similar to the population of Lalau. The Chong Hua Hospital database of COVID-19 patients from March 2020 to September 2020 revealed 952 patients, 355 of which had type 2 diabetes mellitus. It is these persons with diabetes who were included in our present study.

Ethical considerations

The Chong Hua Hospital Institutional Ethics Review Committee approved the study. Confidentiality was ascertained using a coding system. The principal investigator was responsible for the accuracy and integrity of the data presented. Data collection was compiled and stored in a personal computer system and tabulated in Microsoft Excel format.

Data analysis

The independent variable was metformin use, whether home use, in-hospital use, or mixed home/in-hospital use. Also, assessed were potential confounding comorbidities and medications that may cause protection or harm for patients with COVID-19 infection.

Age and glycemic control using admission HbA1c were expressed in mean ± standard deviation. Categorical variables, namely sex, body mass index, preexisting medical conditions, preadmission and in-hospital medications, and disease severity, were expressed in percentages. Chi-square test of independence was used to compare variables between metformin users and non-users and between the three subgroups of metformin users. Univariate logistic regression analysis was done for these variables, computing for odds ratios for mortality.

Any significant variables were then included in the multivariate logistic regression model to adjust for any imbalance noted between study groups. The stepwise backward deletion was also done. We analyzed survival function using the Kaplan-Meier survival curve, and a log-rank test was run to determine if there were differences in the survival distributions between both groups. Stata BE version 17 was used. A p-value of less than 0.05 was considered significant.

RESULTS

Our hospital COVID-19 database observed 952 individuals admitted with COVID-19 between March 1, 2020, and September 30, 2020. Of these, 381 patients had type 2

diabetes mellitus, 26 were excluded (3 being non-Filipino, 22 being transferred or discharged against medical advice, and 1 with unknown disposition). Of the 355 persons with type 2 diabetes, 186 (52.4%) were metformin users, further categorized into home metformin users (n=109, 30.7%), in-hospital metformin users (n=40, 11.3%), and mixed home/in-hospital metformin users (n=37, 10.4%).

Tables 1A and 1B show the comparison of the demographic profile, clinical characteristics, and in-hospital use of anti-COVID medications of patients with type 2 diabetes mellitus hospitalized for COVID-19 who are metformin users versus non-users, and between the three subcategories of metformin users, respectively.

The total mean age of the population was 62.69 ± 12.21 years. The total population was composed of 198 (55.8%) males, 109 (58.6%) metformin users. Among the metformin users, 13.4% were overweight and 62.4% were obese, compared to 13% overweight and 65.1% obese in the non-metformin group. Age, sex, and body mass index between both groups were statistically similar.

Table 1A. Comparison of demographic profile, clinical characteristics, and in-hospital anti-covid medications among patients with type 2 diabetes mellitus hospitalized for COVID-19 infection who are metformin users versus metformin non-users

	Variable	Metformin users n=186	Metformin non-users n=169	*p*-value
Age (years)	Mean	61.61 ± 11.555	63.91 ± 12.837	0.174
	<45	14 (7.5%)	12 (7.1%)	
	45-55	40 (21.5%)	29 (17.2%)	
	56-65	62 (33.3%)	51 (30.2%)	
	66-75	52 (28%)	44 (26%)	
	76-85	13 (7%)	24 (14.2%)	
	>85	5 (2.7%)	9 (5.3%)	
Sex	Male	109 (58.6%)	89 (52.7%)	0.288
	Female	77 (41.4%)	80 (47.3%)	
Body Mass Index	Underweight (<18.5 kg/m^2)	4 (2.2%)	1 (0.6%)	0.763
	Normal (18.5-22.9 kg/m^2)	40 (21.5%)	35 (20.7%)	
	Overweight (23-24.9 kg/m^2)	25 (13.4%)	22 (13%)	
	Obese I (>25-29.9 kg/m^2)	64 (34.4%)	58 (34.3%)	
	Obese II (≥30 kg/m^2)	52 (28%)	52 (30.8%)	
Pre-existing Medical Conditions	Hypertension	136 (73.1%)	129 (76.3%)	0.460
	Bronchial asthma	13 (7%)	14 (8.3%)	0.773
	Acute coronary syndrome	4 (2.2%)	12 (7.1%)	0.044*
	Coronary artery disease	13 (7%)	21 (12.4%)	0.112
	Heart failure	2 (1.1%)	8 (4.7%)	0.076
	Chronic obstructive pulmonary disease	4 (2.2%)	2 (1.2%)	0.779
	Liver disease	8 (4.3%)	5 (3%)	0.711
	Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	9 (4.8%)	37 (21.9%)	<0.001*
	Cerebrovascular disease	8 (4.3%)	9 (5.3%)	0.822
	Cancer	10 (5.4%)	9 (5.3%)	1.00
Preadmission injectable antihyperglycemic agent	Insulin	18 (9.7%)	34 (20.1%)	0.008*
	GLP-1 agonist	2 (1.1%)	1 (0.6%)	1.00
Preadmission oral antihyperglycemic agent	DPP-4 inhibitor	69 (37.1%)	52 (30.8%)	0.24
	Sulfonylurea	29 (15.6%)	21 (12.4%)	0.508
	Thiazolidinediones	2 (1.1%)	1 (0.6%)	1.00
	SGLT-2 inhibitors	19 (10.2%)	7 (4.1%)	0.05
	Glucosidase inhibitors	0	1 (0.6%)	0.957
Baseline severity of disease	Mild	32 (17.2%)	28 (16.6%)	0.460
	Moderate	81 (43.5%)	68 (40.2%)	
	Severe	35 (18.8%)	43 (25.4%)	
	Critical	16 (8.6%)	11 (6.5%)	
	Missing	0	1 (0.6%)	
Admission HbA1c		6.997 ± 2.351	7.590 ± 1.894	0.016*
In-hospital medications				
Tocilizumab		97 (52.2%)	88 (52.1%)	1.000
Antimalarials		14 (7.5%)	17 (10.1%)	0.492
Antivirals		120 (64.5%)	115 (68%)	0.543
Systemic steroids		109 (58.6%)	100 (59.2%)	0.904
Hemoperfusion		9 (4.8%)	11 (6.5%)	0.634
Convalescent plasma therapy (CPT)		8 (4.3%)	9 (5.3%)	0.822
Injectable antihyperglycemic agent	Insulin	47 (25.2%)	71 (42%)	0.001*
	GLP-1 agonist	1 (0.5%)	1 (0.6%)	1.000
Oral antihyperglycemic agent	DPP-4 inhibitor	64 (34.4%)	56 (33.1%)	0.861
	Sulfonylurea	10 (5.4%)	7 (4.1%)	0.785
	Thiazolidinediones	0	0	N/A
	SGLT-2 inhibitors	11 (5.9%)	4 (2.4%)	0.115
	Glucosidase inhibitors	0	0	N/A

Table 1B. Comparison of demographic profile, clinical characteristics, and in-hospital anti-COVID medications between the 3 subcategories of metformin users

Variable		Home Metformin Use n=109	In-hospital Metformin Use n=40	Mixed home/ in-hospital Use n=37	*p*-value
Age (years)	<45	6 (5.5.%)	5 (12.5%)	3 (8.1%)	0.256
	45-55	18 (16.5%)	13 (32.5%)	9 (24.3%)	
	56-65	38 (34.9%)	11 (27.5%)	13 (35.1%)	
	66-75	35 (32.1%)	7 (17.5%)	10 (27%)	
	76-85	10 (9.2%)	2 (5%)	1 (2.7%)	
	>85	2 (1.8%)	2 (5%)	1 (2.7%)	
Sex	Male	68 (62.4%)	26 (65%)	15 (40.5%)	0.098
	Female	41 (37.6%)	14 (35%)	22 (59.5%)	
Body Mass Index	Underweight (<18.5 kg/m^2)	2 (1.8%)	2 (5%)	0	0.685
	Normal (18.5-22.9 kg/m^2)	20 (18.3%)	9 (22.5%)	11 (29.7%)	
	Overweight (23-24.9 kg/m^2)	17 (15.6%)	4 (10%)	4 (10.8%)	
	Obese I (>25-29.9 kg/m^2)	39 (35.8%)	15 (37.5%)	10 (27%)	
	Obese II (≥30 kg/m^2)	30 (27.5%)	10 (25%)	12 (32.4%)	
Pre-existing Medical Conditions	Hypertension	84 (77.1%)	24 (60%)	28 (75.7%)	0.076
	Bronchial Asthma	9 (8.3%)	2 (5%)	2 (5.4%)	0.694
	Acute Coronary Syndrome	3 (2.8%)	1 (2.5%)	0	0.592
	Coronary Artery Disease	7 (6.4%)	5 (12.5%)	1 (2.7%)	0.235
	Heart Failure	2 (1.8%)	0	0	0.481
	Chronic obstructive pulmonary disease	1 (0.9%)	2 (5%)	1 (2.7%)	0.316
	Liver Disease	3 (2.8%)	3 (7.5%)	2 (5.4%)	0.440
	Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	6 (5.5%)	3 (7.5%)	0	0.271
	Cerebrovascular Disease	6 (5.5%)	1 (2.5%)	1 (2.7%)	0.608
	Cancer	5 (4.6%)	3 (7.5%)	2 (5.4%)	0.802
Preadmission injectable antihyperglycemic agent	Insulin	14 (12.8%)	2 (5%)	2 (5.4%)	0.201
	GLP-1 agonist	1 (0.9%)	0	1 (2.7%)	0.509
Preadmission oral antihyperglycemic agent	DPP-4 inhibitor	50 (45.9%)	1 (2.5%)	18 (48.6%)	<0.001*
	Sulfonylurea	20 (18.3%)	3 (7.5%)	6 (16.2%)	0.249
	Thiazolidinediones	0	0	2 (5.4%)	0.019*
	SGLT-2 inhibitors	14 (12.8%)	0	5 (13.5%)	0.052
	Glucosidase inhibitors	0	0	0	N/A
Admission HbA1c		6.960 ± 1.914	7.071 ± 2.124	7.026 ± 1.560	0.951
In-hospital use of anti-COVID medications					
Tocilizumab		59 (54.1%)	19 (47.5%)	19 (51.4%)	0.680
Antimalarials		10 (9.2%)	2 (5%)	2 (5.4%)	0.569
Antivirals		70 (64.2%)	26 (65%)	24 (64.9%)	0.991
Systemic steroids		59 (54.1%)	28 (70%)	22 (59.5%)	0.293
Hemoperfusion		9 (8.3%)	0	0	0.033*
Convalescent plasma therapy (CPT)		8 (7.3%)	0	0	0.048*
Injectable antihyperglycemic agents	Insulin	27 (24.8%)	9 (22.5%)	11 (29.7%)	0.770
	GLP-1 agonist	0	0	1 (2.7%)	0.137
Oral antihyperglycemic agents	DPP-4 inhibitor	18 (16.5%)	21 (52.5%)	25 (67.6%)	<0.001*
	Sulfonylurea	4 (3.7%)	2 (5%)	4 (10.8%)	0.266
	Thiazolidinediones	0	0	0	N/A
	SGLT-2 inhibitors	2 (1.8%)	4 (10%)	5 (13.5%)	0.011*
	Glucosidase inhibitors	0	0	0	N/A

More patients suffered from acute coronary syndrome (p=0.044) and chronic kidney disease (p≤0.001) in the non-metformin group. More patients in the non-metformin group were on insulin therapy before admission (p=0.008).

Both groups were similar in other clinical profiles, including hypertension, bronchial asthma, coronary artery disease, heart failure, chronic obstructive pulmonary disease, liver disease, cerebrovascular disease, malignancy, and preadmission use of GLP-1 agonists and oral antihyperglycemic agents.

Among the three subgroups of metformin users, most patients with preadmission use of DPP4-inhibitors (p≤0.001) were on home metformin use, while patients on preadmission thiazolidinediones were in the mixed home/in-hospital metformin users (p=0.019). Other characteristics, clinical profile, and preadmission medications among the three subgroups were statistically similar.

Most metformin users (n=81, 43.5%) and metformin non-users (n=68, 40.2%) had moderate COVID-19 disease severity. There was no notable difference in the baseline severity of disease between both groups (p=0.460).

Better glycemic control was observed in patients taking metformin than non-users (p=0.016), while there was no difference in glycemic control between the three metformin groups (p= 0.951).

More metformin non-users required insulin therapy during hospitalization (p=0.001). Fewer patients on metformin at home were treated with DPP-4 inhibitors (p≤0.001) and SGLT-2 inhibitors (p=0.011) during hospitalization, but they required convalescent plasma therapy (p=0.048) and hemoperfusion (p=0.033) more frequently. The use of other in-hospital treatments, including tocilizumab, antivirals, antimalarials, and systemic steroids, were similar among the treatment groups. Among the antihyperglycemic agents, the use of GLP-1 agonists, sulfonylureas, and glucosidase inhibitors was identical between the three metformin subgroups.

In the metformin group, 33 (17.7%) died during hospitalization for COVID-19, compared to 57(33.7%) in the non-metformin group (p=0.001). More deaths occurred in those with critical COVID-19, with 31 (93.9%) deaths in the overall metformin group compared to 53 (93%) in the non-metformin group. No deaths were noted in patients with mild disease in the two groups.

Although more patients died among home metformin users (n=28, 84.8%), compared to both in-hospital (n=2, 6.1%) and mixed home/in-hospital users (n=3, 9.1%) (p=0.003), there was an overall low rate of mortality in overall metformin users compared to the metformin non-users.

Logistic regression analysis using each variable in a univariate fashion showed an increased odds ratio for mortality in patients with increased age (p≤0.001; OR=1.041), chronic kidney disease (p≤0.001; OR=3.248), and acute coronary syndrome (p≤0.001; OR=14.744).

Patients who were given tocilizumab (p=<0.001; OR=2.556), systemic steroids (p=0.048; OR=1.662), convalescent plasma therapy (p=0.042; OR=2.775), hemoperfusion (p=0.003; OR=3.960) and those started on in-hospital insulin therapy (p=0.010; OR=1.917) were also noted to have increased odds for mortality. The odds ratio for glycemic control using preadmission HbA1c and baseline severity of disease were not significant.

Metformin use was associated with lower odds for mortality (p=0.001; OR 0.424) compared to non-users. In-hospital metformin users (p=0.002; OR=0.103) and mixed home/in-hospital metformin users (p=0.005; OR=0.173) were also associated with lower odds for mortality compared to non-users.

Table 2 shows univariate logistic regression analysis using factors that may affect mortality and crude odds ratio for mortality between metformin users and non-users.

Metformin use, regardless of dosage from 500 mg to 2 g daily, was associated with a lower risk for mortality compared to patients not taking metformin (p=0.002). There was also a lower crude odds ratio for mortality among patients on ≥1 g to <2 g daily of metformin, compared to non-users and other dosages (p≤0.001; OR=0.252). However, analyzing metformin users only showed no association between metformin dosage and mortality noted (p=0.166) (Supplementary Table).

We did a multivariate logistic regression analysis on significant variables, namely: age, chronic kidney disease, acute coronary syndrome, tocilizumab, systemic steroid use, convalescent plasma therapy, hemoperfusion, in-hospital insulin use, and HbA1c. After controlling for these variables, metformin use was associated with reduced odds for mortality (p=0.01; OR=0.433). The stepwise deletion was also done in this model and still showed metformin use was associated with better mortality outcomes (p=0.008; OR= 0.430).

Table 3 shows multivariate logistic regression analysis for mortality controlled for significant confounders.

The survival distributions between metformin users and non-users were statistically different, showing the inequality of survival (χ2=5.67, p=0.017).

Figure 1 illustrates the Kaplan-Meier survival curve between metformin users versus non-users.

DISCUSSION

Findings from several studies demonstrate the negative impact of type 2 diabetes mellitus on the morbidity and mortality of COVID-19 infected patients.[10-13] Thus, the potential role of antihyperglycemic agents, especially metformin, in this viral infection should also be explored.

COVID-19 patients with diabetes have one or more accompanying comorbidities, higher levels of circulating inflammatory markers, worse lung involvement by chest imaging, and thus are associated with more severe disease, more complications, and higher mortality rate.[10-13] Poor glycemic control is associated with severe COVID-19 infection and increased mortality.[11,25]

Aside from its effects on glucose metabolism, another potential role of metformin is immunomodulation. It inhibits the mTOR pathway, which plays a role in viral protein production, viral replication and release, and is critical for apoptosis and senescence.[26] It can also cause modulation of the ACE2 receptor, which serves as the viral entry point via the AMP-activated protein kinase.[27,28] This medication provides anti-inflammatory effects, reducing the cytokine storm by decreasing TNFα and IL-6 levels and increasing IL-10.[18,19] A reduction in the neutrophil extracellular traps and neutrophil to lymphocyte count have also been observed.[29]

Patients with stage 3 to 5 chronic kidney disease or dialysis therapy were less likely to be on metformin therapy before and during admission. This was an expected finding since metformin is contraindicated in patients with end-stage renal disease, and those with an eGFR of less than 30 mL/min/1.73 m^2. Initiation of metformin therapy is also contraindicated in patients with eGFR of less than 45 mL/min/1.73 m^2.

Metformin has previously been reported to decrease the incidence of cardiovascular events in the landmark UK Protective Diabetes Study (UKPDS) which showed lower all-cause mortality and incidence of myocardial infarction with its use versus conventional treatment.[30] The SPREAD-DIMCAD study also showed a significantly lower cardiovascular endpoint for persons with type 2 diabetes with coronary artery disease in its metformin

Table 2. Univariate logistic regression analyses using factors that may affect mortality

Variable	Survivors (n=265)	Non-survivors (n=90)	Odds Ratio (95% CI)	*p*-value
Age	61.33 (12.20)	67.04 (1.81)	1.04137 (1.01961 - 1.06360)	<0.001*
Sex – Male	149 (56.23%)	49 (54.44%)	0.93043 (0.57538 - 1.50457)	0.769
Body Mass Index	27.81 (6.11)	27.49 (7.16)	0.99191 (0.95467 - 1.03062)	0.769
Hypertension	196 (74%)	69 (76.7%)	1.15671 (0.66056 - 2.02551)	0.611
Bronchial asthma	22 (8.3%)	5 (5.6%)	0.64973 (0.23855 - 1.76961)	0.399
Chronic obstructive pulmonary disease	5 (1.9%)	1 (1.1%)	0.58427 (0.06735 - 5.06873)	0.626
Liver disease	9 (3.4%)	4 (4.4%)	0.315 (0.033-2.986)	0.314
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	24 (9.1%)	22 (2.4%)	3.24878 (1.71640 - 6.14922)	<0.001*
Heart failure	7 (2.6%)	3 (3.3%)	1.27094 (0.32161 - 5.02242)	0.732
Acute coronary syndrome	3 (1.1%)	13 (14.4%)	14.74458 (4.09613 - 53.07515)	<0.001*
Coronary artery disease	29 (10.9%)	5 (5.6%)	0.47870 (0.17950 - 1.27667)	0.141
Cerebrovascular disease	13 (4.9%)	4 (4.4%)	0.90161 (0.28632 - 2.83914)	0.860
Cancer	12 (4.5%)	7 (7.8%)	1.77811 (0.67773 - 4.66510)	0.242
Severity of disease (using mild as a comparator at baseline)				
Mild	49 (18.5%)	11 (12.2)		
Moderate	103 (39.9%)	46 (51.1%)	1.98941 (0.94864 - 4.172)	0.069
Severe	61 (23%)	17 (18.9%)	1.24143 (0.53247 - 2.89436)	0.617
Critical	23 (8.7%)	4 (4.4%)	0.77470 (0.22262 - 2.69588)	0.688
Missing	0	1 (1.1%)		
HBA1c	7.29987 (1.99)	7.17014 (2.55)	0.97148 (0.85608 - 1.10243)	0.654
Preadmission medications				
Insulin	36 (9.8%)	16 (17.8%)	1.37538 (0.72191 - 2.62035)	0.582
GLP-1 agonists	3 (1.1%)	0	0.000	1.000
Metformin	113 (42.97%)	30 (33.71)	0.67496 (0.40826 - 1.11590)	0.125
DPP-4 inhibitors	89 (33.58%)	32 (35.56%)	1.09105 (0.66092 - 1.80111)	0.733
Sulfonylureas	41 (15.5%)	9 (10%)	0.60705 (0.28250 - 1.30443)	0.201
Thiazolidinediones	2 (0.8%)	1 (1.1%)	1.47753 (0.13238 - 16.49124)	0.751
SGLT-2 inhibitors	23 (8.7%)	3 (3.3%)	0.36282 (0.10628 - 1.23858)	0.106
Glucosidase inhibitors	1 (0.4%)	0	0.000	0.999
In-hospital medications				
Tocilizumab	123 (46.42%)	62 (68.89%)	2.55633 (1.53909 - 4.24591)	<0.001*
Antimalarials	22 (8.3%)	9 (10%)	1.22727 (0.54309 - 2.77339)	0.622
Antivirals	176 (66.42%)	59 (65.56%)	0.96243 (0.58141 - 1.59313)	0.882
Systemic steroids	148 (55.85%)	61 (67.78%)	1.66286 (1.00434 - 2.75316)	0.048*
Convalescent plasma therapy	9 (3.4%)	8 (8.9%)	2.77506 (1.03704 - 7.42598)	0.042*
Hemoperfusion	9 (3.4%)	11 (12.2%)	3.96062 (1.58417 - 9.90206)	0.003*
Insulin	78 (29.43%)	40 (44.44%)	1.91795 (1.17193 - 3.13886)	0.010*
GLP-1 agonists	2 (0.8%)	0	0.132	1.000
Metformin	72 (27.1%)	5 (5.56%)	0.15768 (0.06149 - 0.40433)	<0.001*
DPP-4 inhibitors	93 (35.09%)	27 (30%)	0.79263 (0.47283 - 1.32872)	0.378
Sulfonylureas	14 (5.3%)	3 (3.3%)	0.61823 (0.17352 - 2.20266)	0.458
Thiazolidinediones	-	-	-	-
SGLT-2 inhibitors	15 (5.7%)	0	0.000	0.998
Glucosidase inhibitors	-	-	-	-
Crude odds ratio for mortality between metformin users versus non-users, with non-users as the reference group				
Metformin use	153 (57.7%)	33 (36.7%)	0.42438 (0.25881-0.69397)	0.001*
Crude odds ratio for mortality between 3 subgroups of metformin users, with non-users as the reference group				
Metformin use				
Home	81 (30.6%)	28 (31.3%)	0.67922 (0.39777-1.15984)	0.157
In-hospital	38 (14.3%)	2 (2.2%)	0.10341 (0.02408-0.44407)	0.002*
Mixed Home/In-hospital	34 (12.8%)	3 (3.3%)	0.17337 (0.05104-0.58888)	0.005*
Crude odds ratio between different metformin dosages, with metformin non-use as reference group				
Metformin dosage (mg/day)				
500 - <1000 (n=85)	66 (24.9%)	19 (21.1%)	0.56565 (0.30990-1.03247)	0.063
≥1000 - <2000 (n=79)	70 (26.4%)	9 (10%)	0.25263 (0.11769-0.54225)	<0.001*
≥2000 (n=19)	15 (5.7%)	4 (4.4%)	0.52397 (0.16622-1.65169)	0.27

group compared to its glipizide group.[31] This may explain the higher prevalence of acute coronary syndrome in patients admitted without prior metformin use in our study population.

After computing for crude odds ratio, our study showed that metformin use was associated with a lower risk for mortality compared to the non-metformin group. More patients in the non-metformin group in our study population had chronic kidney disease and acute coronary syndrome, which can also be associated risk factors for mortality.

Tocilizumab, systemic steroids, hemoperfusion, convalescent plasma therapy, and in-hospital insulin use were also associated with mortality. The association noted between mortality and the use of these medications, especially tocilizumab, may be because of more severe diseases requiring these treatments.

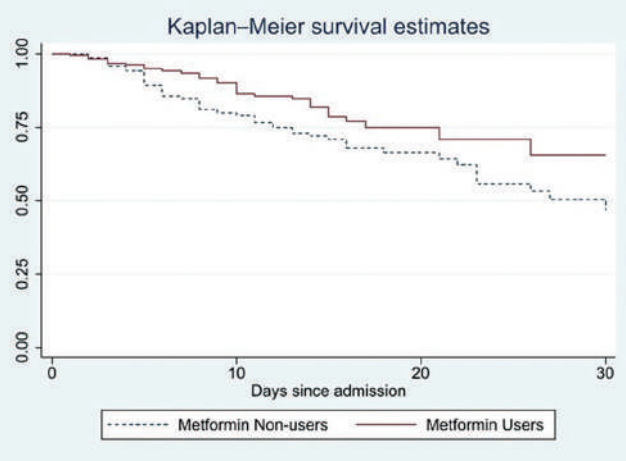

Figure 1. Kaplan-Meier survival curve between metformin users versus non-users.

Table 3. Multivariate logistic regression analyses for mortality controlled for significant confounders

Variable	Odds Ratio (95% CI)	*p*-value
Metformin use	0.43320 (0.22869-0.82061)	0.010*
Age	1.02510 (0.99773-1.05322)	0.073
Chronic kidney disease	2.08117 (0.78501-5.51749)	0.141
Acute coronary syndrome	14.80458 (2.89512-75.70515)	0.001*
Tocilizumab	2.31083 (1.11154-4.80409)	0.025*
Systemic steroids	1.35679 (0.64987-2.83268)	0.417
Convalescent plasma therapy	2.07477 (0.62739-6.86119)	0.232
Hemoperfusion	3.56889 (1.03360-12.32302)	0.044*
In-hospital insulin use	1.25407 (0.63349-2.48259)	0.516
HbA1c	0.96426 (0.82677-1.12461)	0.643
Using stepwise deletion		
Metformin use	0.43064 (0.23006-0.80609)	0.008*
Age	1.02656 (0.99984-1.05399)	0.051
Chronic kidney disease	2.18395 (0.84120-5.67001)	0.109
Acute coronary syndrome	15.36630 (3.00181-78.66032)	0.001*
Tocilizumab	2.65869 (1.35206-5.228065)	0.005*
Hemoperfusion	3.72632 (1.07222-12.9502)	0.038*
Convalescent plasma therapy	2.14171 (0.65775-6.97367)	0.206

After adjusting for these significant variables using multivariate logistics regression, metformin use, whether in the hospital or mixed home/in-hospital use, was still associated with a lower risk for mortality. This correlates with studies by Bramante[32] and Luo[33] who showed mortality benefits in patients with preadmission and in-hospital metformin use, respectively. Three other studies similarly showed the beneficial effects on overall mortality by this medication.[24,34,35] The CORONADO study also noted a lower risk for death in patients on metformin therapy.[36,37]

Our study finding, however, differed only from the study by Cheng et al., which concluded there was no difference in outcomes of patients with and without metformin use.[20] Our study showed a metformin dose from 500 mg to 2000 mg per day was associated with a lower risk for mortality. The greatest benefit was seen with a dosage between 1000 mg to <2000 mg daily. Patients taking higher metformin doses had fewer deaths, but estimates of benefit across dose categories cannot be made due to the small study population. No reports have currently surfaced recommending an optimal protective dose of metformin, and prospective studies are suggested or ongoing.

Luo et al. found no significant difference in the length of hospital stay between both groups.[33] The CORONADO study noted lower death rates at day seven and higher chances of discharge among patients on metformin therapy.[36-37] The study done by Lalau[24] showed lower mortality rates for metformin users on day seven and day 28. Our study showed that metformin users were associated with longer survival than non-users.

Results of this retrospective observational study showed beneficial effects of metformin on mortality in patients with type 2 diabetes mellitus hospitalized for COVID-19. Randomized controlled trials are still ongoing, and their results may or may not be similar to our study findings.

CONCLUSION

Metformin was associated with a lower risk for mortality in patients with type 2 diabetes mellitus hospitalized for COVID-19 disease, especially in patients with in-hospital and mixed home/in-hospital metformin use. Metformin, regardless of dosage, was associated with a lower risk for mortality compared to its non-use. The greatest benefit was seen in those on a daily dose of ≥1000 mg to <2000 mg. Despite the results from this study, the decision whether to initiate metformin in patients hospitalized for COVID-19 infection is upon the physician's discretion.

Limitation and Recommendation

Most patients in our study population had moderate disease. Therefore, our study results may not apply to patients with severe or critical COVID-19 infection.

We only collected data from admitted Filipinos with type 2 diabetes, and results may differ in the outpatient setting and among different ethnicities or races. The duration of metformin intake is not specified in this study. Compliance with preadmission metformin was also lacking and could not be assured. Several cells had frequencies less than 5, and significance may not be valid. Mortality prediction scoring, such as APACHE II and qSOFA, was not applied to help determine baseline risk for death between metformin users and non-users. Other confounding variables such as comorbid conditions and medications not included in this study analysis may also affect study results.

Findings were obtained from a retrospective observational study, and due to limitations, any results derived should be considered only hypothesis-generating. We recommend prospective studies to ensure complete data, fewer potential biases, and confounders.

A randomized prospective study can best determine the definitive effect of metformin on mortality in COVID-19 disease. Further sub-analysis on the beneficial effects of metformin on mortality outcome and survival time between different disease severities may also be investigated with a bigger study population.

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APPENDIX

Supplementary Table 1. Association between metformin dosage and mortality

Metformin users with dosage from 500 mg to 2000 mg daily versus no metformin use					
Metformin dosage (mg/d)				**Mortality**	***p*-value**
0				57	
500-<1000				19	0.002*
≥1000-<2000				9	
≥2000				4	
Dosage from 500 mg to 2000 mg daily among metformin users					
Metformin dosage (mg/d)		**Alive**		**Mortality**	***p*-value**
500-<1000		66		19 (22.4%)	
≥1000-<2000		70		9 (11.4%)	0.166
≥2000		15		4 (21.1%)	
Dosage from 500 mg to 2000 mg daily among three subcategories of metformin users					
Metformin dosage (mg/d)	**Home metformin use n=109**	**In-hospital metformin use n=40**	**Mixed home/in-hospital use n=37**	**Mortality**	***p*-value**
500-<1000 n=85	56	15	14	19 (22.4%)	
≥1000-<2000 n=79	36	23	20	9 (11.4%)	0.166
≥2000 n=19	14	2	3	4 (21.1%)	

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ORIGINAL ARTICLE

The Impact of the Filipino Plate Method versus Standard Nutrition Education on Food Group Proportions and 2-hour Postprandial Blood Glucose for Type 2 Diabetes

Richultz Montevirgen,[1] Kristine Bea Mendoza,[2] Lizette Kristine Lopez[1]

[1]*Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, The Medical City, Pasig City, Philippines*
[2]*Nutrition Management Services, The Medical City, Pasig City, Philippines*

Abstract

Objectives. To compare the efficacy of the Filipino plate method against standard nutrition education in the selection of food group proportions and in reducing 2-hour postprandial blood glucose levels (2h-PPG) among patients with type 2 diabetes.

Methodology. This randomized, open-label trial assigned 148 subjects with type 2 diabetes to receive nutrition education using either the Filipino plate method or standard nutrition education, as recommended by the American Diabetes Association (ADA). The subjects were given meals before and three days after the intervention, at which time the contents of their plate were scored based on food group proportions. After the meal, 2h-PPG levels were obtained. Pre- and post-intervention plate scores and 2h-PPG were compared in both groups.

Results. Plate scores were significantly increased from pre to post-teaching for both groups (*p value* <0.001). There was no statistically significant difference in post-teaching scores between the two modes of nutrition education (Filipino plate method median score 8/9 vs standard nutrition education 7/9, *p*=0.018). The 2h-PPG results decreased significantly from baseline to post-teaching for both groups (*p*=0.008). There was no significant difference in the reduction in 2h-PPG between the two groups (*p*=.741).

Conclusion. The Filipino plate method was comparable to standard nutrition education in improving food group choices and proportions as well as 2h-PPG in patients with type 2 diabetes.

Key words: diabetes, nutrition, post prandial glucose

INTRODUCTION

According to the World Health Organization (WHO), diabetes mellitus is one of the non-communicable diseases which is increasing in prevalence.[1] Various studies have demonstrated that uncontrolled hyperglycemia increases the risk for microvascular and macrovascular complications.[2-5] Therefore, optimal diabetes management to achieve glycemic control is important in delaying or preventing complications.

Medical nutrition therapy (MNT) is well-recognized as a cornerstone of diabetes management. Per the American Diabetes Association (ADA) guidelines, all patients with diabetes should have a teaching encounter for individualized medical nutrition therapy, preferably with a registered dietitian. These encounters should last from 45 to 90 minutes and should include the determination of the individual's goal macronutrient content.[6] By the description, the recommended standard nutrition education sessions are time-consuming and require the specialized knowledge of a dietitian or a diabetes educator, which may not be available in most settings.

To simplify nutrition education, the plate method was developed. As early as 1987, the plate method was already used by various countries in Europe to teach patients with diabetes, because it was straightforward and easy to teach, minimizing any language barrier between the patient and the educator.[7] In the plate method, a dinner plate serves as a pie chart to show proportions of the plate that should be covered by various food groups. Portions of food and appropriate food choices are depicted for meals and snacks in assorted forms of the model. This model was presented as a simple alternative to the traditional exchange-based method for teaching meal planning.[7] In acknowledgement of the usefulness and possible benefits of the plate method and the continuing gap in providing the need for nutrition education for patients with diabetes, the University of Idaho developed their own plate method to be used specifically for educating patients with diabetes. This was termed "The Healthy Diabetes Plate" or the Idaho Plate Method (IPM).[8]

In 2014, the Department of Science and Technology-Food and Nutrition Research Institute (DOST-FNRI) developed the Filipino plate method to address the

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Corresponding author: Richultz C. Montevirgen, MD
Fellow, Section of Endocrinology, Diabetes and Metabolism,
Department of Medicine, The Medical City
Ortigas Avenue, Pasig City, Philippines
Tel. No.: (632) 898-81000
E-mail: chokmd29@gmail.com
ORCiD: https://orcid.org/0000-0003-2699-8238

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growing prevalence of obesity in the Philippines.[9] It is an easy-to-understand, visual tool for educating patients on healthful eating habits, requiring less time and less specialized skills and knowledge to teach. However, in the local setting, this tool has not been incorporated in protocols for managing persons with diabetes. Nutrition education is provided at the discretion of each physician giving the advice. Unfortunately, such advice may not be extensive, as nutrition education is often time-consuming. Consequently, patients with diabetes often have poor knowledge of a healthy diet and nutrition.

This study aims to evaluate the efficacy of the Filipino plate method against standard nutrition education in the selection of food group proportions and in reducing 2-hour postprandial blood glucose levels (2h-PPG) among patients with type 2 diabetes. If proven efficacious, this simpler plate method may be used to make nutrition education easier to teach and accessible to more patients with diabetes.

METHODOLOGY

This is a prospective randomized controlled trial which used pre- and post-intervention assessments across time. We recruited participants with diabetes mellitus type 2 who were either a member of the Diabetes Club or were being treated in a community health center in Obando, Bulacan, Philippines. By word-of-mouth through the Diabetes Club and the health workers in the health center, those interested in participating were invited to come in during the specific date in which the study was held and thus recruited by convenience sampling. We included patients if they were aged 19 years old and above and spoke either English or Filipino. We excluded patients who were pregnant, those who had formal diabetes and nutrition education via individual consultation with a registered nutritionist-dietitian, those who were already actively using any plate method for planning meals, and those who were fully dependent on others to plan their meals. Randomization was done via a coin toss, with one group assigned to the Filipino plate method, while the other was assigned to the standard nutrition education for diabetes.

Sample size

A minimum of 124 subjects are required for this study or 62 per arm assuming a mean ± SD change in HbA1c from baseline to 6 months equal to -1.13 ± -1.196 and -0.25 ± -1.847 in the modified plate method and control groups, respectively. The values were based on the RCT study of Bowen, et al, at 80% power, 5% alpha level of significance, and accounted for an anticipated 20% dropout rate.

Formulation of test products

The primary outcomes were knowledge of appropriate meal portions and compliance with the food proportions on the plate (Figure 1). This was measured via meal planning sheets obtained from the participants, as well as plate portions of the actual meals, scored simultaneously by two registered nutritionist-dietitians. Figure 2 shows an example of the meal planning sheet and plate portion sheet.

The meal planning sheet is a large blank piece of paper on which the participants drew the plates and estimated portions of the different food groups that they usually eat. The plate portion sheet was pre-filled with the proper food groups and portions. The large circle symbolizing the plate should ideally be exactly 9 inches.

The meal planning sheets with the participants' drawings were scored from 0 to 10 points. The completeness of food groups and appropriate portions were taken into consideration. One point each was given if there was water, a carbohydrate source, a protein source, fruits, and vegetables on the sheet. The presence of all of these garnered a total of 5 points for completeness of food groups. The correct portion size per food group also corresponded to one point each, for a perfect score of 10.

Participants were provided with meals in a buffet style, from which they were freely allowed to take food. Two nutritionist-dietitians then scored the contents of the plates of the respondents from 0 to 9, using a plate portion sheet as a guide. One point each was given if the participant took proper plate portions of carbohydrates, protein, fruits, and vegetables, for a total of 4 points. We also

Figure 1. Filipino Plate Method (Adopted from the FNRI-DOST).[9]

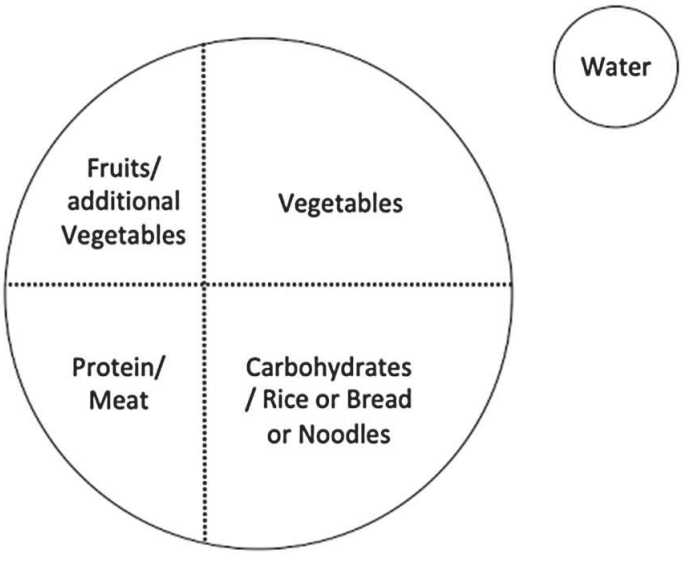

Figure 2. Sample meal planning sheet.

provided at least two options per food group, with one option being healthier (less fatty or less starchy) than the other. An additional point per food group was given if the healthier option was chosen. Plates of various sizes were also provided. If the correct plate size of no larger than 9 inches was chosen, another point was given. The perfect plate score was 9 points.

Another outcome measured was the 2-hour plasma postprandial blood glucose levels (2h-PPG) of the participants, after their meals at days 1 and 3. The blood drawn was sent to the laboratory for processing.

Determining baseline practices

After recruitment, we tested participants for their food group choices and portions using the blank meal planning sheets (Day 1). Participants drew the usual size of their plates and the food portions of their meals on the plate. They also drew a representation of the fluids they usually drank and any food that they may consume outside of their plate (fruits, dessert, etc.). The sheets were then submitted to a nutritionist-dietitian who scored the sheets. The scores were recorded in a database under assigned numerical codes.

Plate portion scoring sheet and 2h-PPG

Participants were given 100 pesos as dummy money to buy a meal, to simulate the limited budget for food in the real-world setting. They were brought to the cafeteria area, which offered different options from all the major food groups. Plates of different sizes were provided at the start of the food line, where a menu with the "prices" of the different dishes was posted. The participants were invited to freely choose the food and drink given the limited budget. After making their choices and placing the food and beverages on their plate and tray, they lined up at the cashier to "pay" for their food. Two nutritionist-dietitians stood by the cashier behind a counter to independently score each participant's plate using a plate portion scoring sheet. The plate portion scoring sheet were labeled with the participants' codes, as determined from their code tags. The average of the scores of both dietitians for the plate portion scoring sheet of each participant were then recorded in the database.

Participants were also asked to consume their chosen meals within 30 minutes. Two hours from the time of the first bite, venous blood was drawn to check for 2h-PPG, the results of which were recorded.

Nutrition education

After the above procedures, two nutritionist-dietitians performed group nutrition counseling simultaneously. One nutritionist-dietitian taught the Filipino plate method to one group, while the other gave standard nutrition education to the second group. Both groups received a standard 1,900 kcal/day nutrition education,[6] with differing teaching materials as appropriate for each methodology.

Nutrition education using the Filipino plate method was completed within 15 minutes, while the standard nutrition education for diabetes took approximately 60 minutes to teach. The standard nutrition education discussed all the nutrition recommendations of the ADA, such as determining individual macronutrient content, the intake of complex rather than simple carbohydrates, the use of nonnutritive or hypocaloric sweeteners, the intake of mono- or polyunsaturated fatty acids, limiting saturated fatty acids to less than 10% of calories, and advice on micronutrient, sodium, and alcohol intake. On the other hand, nutrition education using the Filipino plate method emphasized eating the food groups in their proper portions, as visualized in the tool. All participants were also advised against drinking sweetened drinks.

Post-education testing

Participants were asked to return after 3 days. The procedures described above under "Plate portion scoring sheet and 2h-PPG" were repeated at day 3. The participants were asked to draw on the meal planning sheets, then given a meal with the contents of their plates being surreptitiously scored by two nutritionist-dietitians. Blood was drawn for 2h-PPG after the meals. Figure 3 shows the overview of the participant's flow during the whole study.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the participants. Frequency and proportion were used for categorical variables such as sex, BMI class, education, and annual income. The Shapiro-Wilk test was used to check for normality of continuous variables such as age, duration of diabetes, plate scores, meal planning scores, and 2h-PPG. Medians and ranges were then used to describe non-normally distributed continuous variables. The Mann-Whitney U test was used to compare medians of the Filipino plate method group and Standard nutrition education group. Chi-square test was used to compare the frequency of the two groups. For variables that did not meet the assumptions for chi-square test, we used Fisher's exact test instead. All valid data were included in the analysis. No imputation was done on any variables. Null hypothesis was rejected at 0.05 α-level of significance. STATA 15.0 was used for data analysis.

Ethical approval

The study was approved by the Institutional Review Board of The Medical City, Philippines, in partnership with the Clinical and Translational Research Institute (CTRI) of the same institution with the registration number GCSMED2019-044. 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. Informed consent was obtained from all participants included in the study.

RESULTS

A total of 197 participants were recruited. Of these, 148 participants were included for the study endpoint (Figure 4), with 75 (50.68%) being randomized to the Filipino plate method group and 73 (49.32%) to the standard nutrition education group.

The median age of the participants was 62 years (range 22 to 86 years). The participants were mostly female (72.97%). Half of the participants were within the normal BMI range. Approximately four in ten participants had completed only elementary school level. 87.16% of the

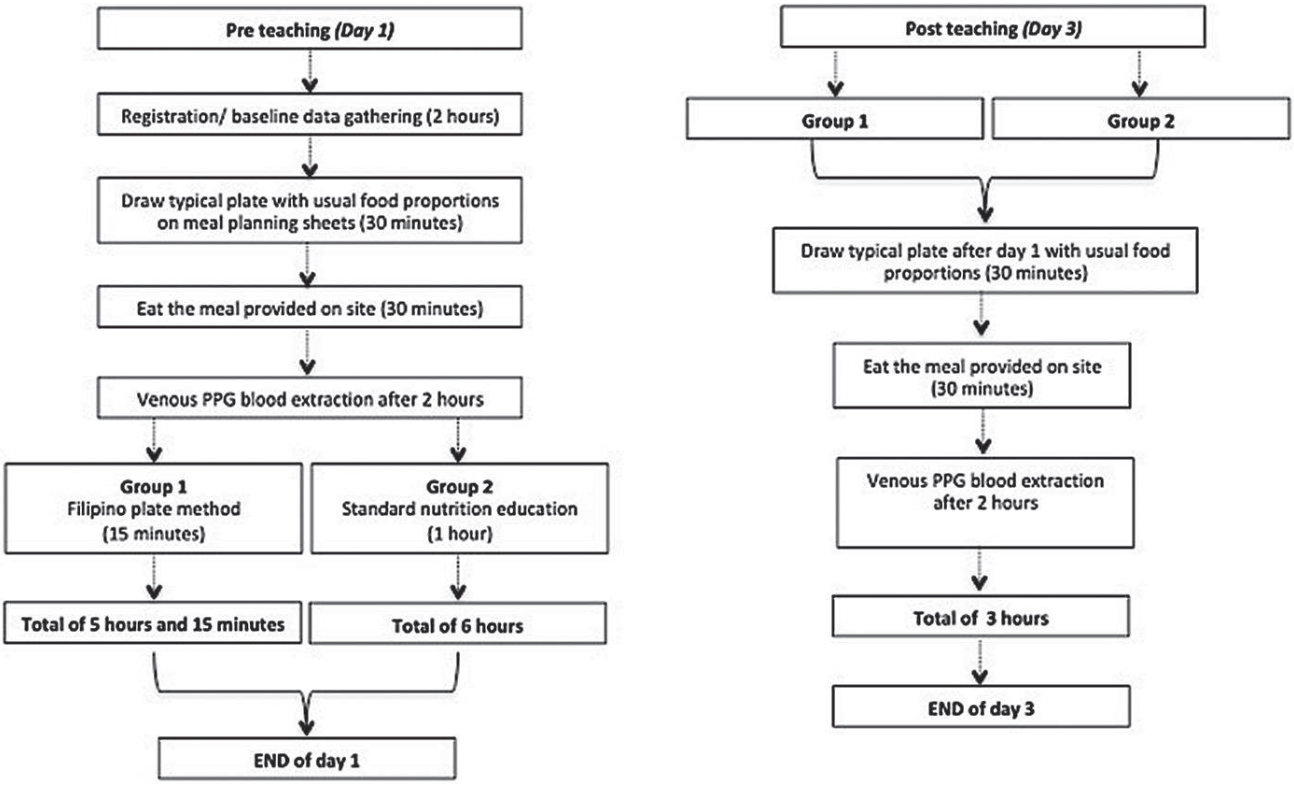

Figure 3. Participant's flow during the study.

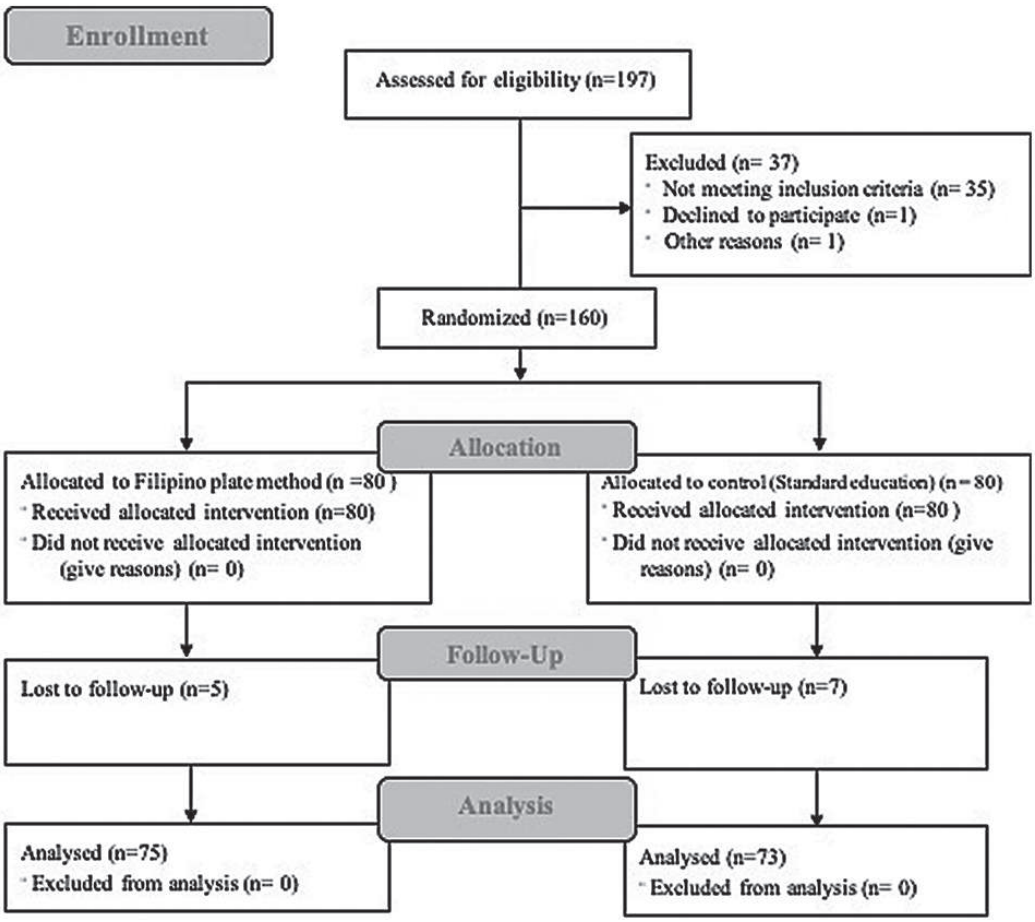

Figure 4. A total of 197 participants were recruited and 148 were included for the study endpoint.

participants had an annual household income of PhP 250,000 and below. There was no statistical difference in the demographic profile of participants in the Filipino plate method group versus those in the standard nutrition group (Table 1). The participants were diagnosed with diabetes for a median of five years prior to the study, with 29 (19.59%) on insulin. More than half of the participants reported compliance with their maintenance medications (Table 2).

In terms of actual plate scores, the scores significantly increased from pre-teaching to post-teaching overall for both groups (pre-teaching score 5/9 vs post-teaching score 8/9, $p<0.001$). Across groups, the Filipino plate method group had a higher median post-teaching score of 8/9 compared to 7/9 for the standard nutrition education group ($p=0.018$) (Table 3).

For the meal planning scores, there was a significant increase from pre-teaching to post-teaching for both groups (pre-teaching score 4/10 vs post-teaching score 5/10, $p<0.001$). Across groups, the post-teaching scores were similar with a median of 5/10 for both groups ($p=0.274$). There was no statistically significant difference in post-teaching scores between the two interventions.

On baseline and on post-teaching, the 2h-PPG absolute values for both groups demonstrated a significant decrease from pre- to post-teaching (pre-teaching score 223.3 mg/dl vs post-teaching score 183.4 mg/dl, $p<0.001$). The post-teaching values for 2h-PPG were significantly lower for the Filipino plate method compared to standard nutrition education (Filipino plate method 173.75 mg/dl vs standard nutrition education 212.1 mg/dl, $p=0.008$). However, the average difference of 2h-PPG values pre- to post-teaching was not statistically significant between the two groups (Filipino plate method -15.6 mg/dl vs standard nutrition education -18.7 mg/dl, $p=0.741$).

DISCUSSION

Medical nutrition therapy is an integral component of diabetes management which greatly impacts glycemic control and clinical outcomes.[6,10-12] Several studies have evaluated the effectiveness of diabetes self-management

Table 1. Demographic profile of participants (n = 148)

	Total (n=148)	Group A Filipino plate method (n=75)	Group B Standard nutrition education (n=73)	p-value
		Median (Range); Frequency (%)		
Age, years	62 (22 – 86)	62 (22 – 86)	62 (28 – 84)	0.855*
Sex				0.312†
Male	40 (27.03)	23 (30.67)	17 (23.29)	
Female	108 (72.97)	52 (69.33)	56 (76.71)	
BMI, kg/m²	24.62 (14.88 – 37.2)	24.56 (15.4 – 34.48)	24.73 (14.88 – 37.2)	0.500*
BMI Classification				
Underweight	10 (6.76)	5 (6.67)	5 (6.85)	0.857†
Normal	75 (50.68)	37 (49.33)	38 (52.05)	
Overweight	52 (35.14)	26 (34.67)	26 (35.62)	
Obese	11 (7.43)	7 (9.33)	4 (5.48)	
Education				0.795†
No formal education	6 (4.05)	3 (4)	3 (4.11)	
Elementary	61 (41.22)	34 (45.33)	27 (36.99)	
High school	37 (25)	19 (25.33)	18 (24.66)	
Vocational	7 (4.73)	4 (5.33)	3 (4.11)	
College	35 (23.65)	14 (18.67)	21 (28.77)	
Post-graduate	2 (1.35)	1 (1.33)	1 (1.37)	
Family annual income (in thousands), Php				0.201†
0-250	129 (87.16)	68 (90.67)	61 (83.56)	
250-400	12 (8.11)	3 (4)	9 (12.33)	
400-800	7 (4.73)	4 (5.33)	3 (4.11)	

Statistical test used: * - Mann-Whitney U test; † - Fisher's exact/Chi-square test

Table 2. Diabetes profile of participants (n = 148)

	Total (n=148)	Group A Filipino plate method (n=75)	Group B Standard nutrition education (n=73)	p-value
		Median (Range); Frequency (%)		
Duration, years [n=136]	5 (0.42 – 44)	6 (0.42 – 30)	5 (0.58 – 44)	0.370*
Regimen				
Diet	7 (4.73)	4 (5.33)	3 (4.11)	1.000†
Oral agents	116 (78.38)	58 (77.33)	58 (79.45)	0.754†
Insulin	29 (19.59)	10 (13.33)	19 (26.03)	0.052†
Adherence to pharmacologic therapy				0.123†
Never	9 (6.08)	7 (9.33)	2 (2.74)	
Seldom	16 (10.81)	6 (8)	10 (13.7)	
Sometimes	38 (25.68)	22 (29.33)	16 (21.92)	
Often	2 (1.35)	2 (2.67)	0 (0)	
Always	83 (56.08)	38 (50.67)	45 (61.64)	

Statistical test used: * - Mann-Whitney U test; † - Fisher's exact/Chi-square test

Table 3. Plate score, meal planning score, and 2h-PPG levels of the Filipino plate method group vs the standard nutrition education group

	Total (n=148)	Group A Filipino plate method (n=75)	Group B Standard nutrition education (n=73)	p-value
	Mean ± SD; Median (Range); Frequency (%)			
Actual plate score	[n=147]	[n=74]	[n=73]	
Pre-teaching	5 (0 – 9)	5 (0 – 9)	5 (1 – 9)	
Post-teaching	8 (3 – 9)	8 (4 – 9)	7 (3 – 9)	0.018*
p-value	<0.001‡	<0.001‡	<0.001‡	
Actual change in scores	3 (-4 – 8)	2 (-4 – 7)	3 (-1 – 8)	0.020*
% change in scores	50 (-44.44 – 800)	60 (-20 – 800)	50 (-44.44 – 700)	0.065*
Meal planning score	[n=145]	[n=73]	[n=72]	
Pre-teaching	4 (0 – 10)	4 (0 – 10)	4 (0 – 8)	
Post-teaching	5 (1 – 10)	5 (1 – 10)	5 (1 – 9)	0.274*
p-value	<0.001‡	<0.001‡	0.004‡	
Change in scores	1 (-7 – 7)	1 (-7 – 6)	1 (-5 – 7)	0.501*
% change in scores	33.33 (-83.33 – 700)	33.33 (-83.33 – 700)	33.33 (-83.33 – 700)	0.475*
2h-PPG	[n=113]	[n=54]	[n=59]	
Pre-teaching	223.2 (101.1 -502.3)	202.25 (101.8 – 502.3)	241 (101.1 – 435.6)	
Post-teaching	183.4 (99.8 – 424.5)	173.75 (104.3 – 424.5)	212.1 (99.8 – 376.4)	0.008*
p-value	<0.001‡	0.002‡	0.004‡	
Change in PPG values	-18.5 (-219.9 – 123.1)	-15.6 (-200.3 – 87.9)	-18.7 (-219.9 – 123.1)	0.741*
% change in PPG values	-8.99 (-61.35 – 86.35)	-8.99 (-50.9 – 63.45)	-9.38 (-61.35 – 86.35)	0.972*

Actual change was calculated as the difference of post- values and pre- values. Percent change was calculated as the actual change/pre- values x 100%.
PPG – Post-prandial glucose
Statistical test used: * - Mann-Whitney U test; † - Fisher's exact/Chi-square test

nutrition training and education,[11,13] such as standard individualized education with a nutritionist, video tapes and lunch demonstrations, providing dietary guides, and group education. These methods have demonstrated an improved knowledge among patients, which further supports the need for nutrition education.

Unfortunately, a large percentage of people with diabetes do not receive any standard diabetes education and/or nutrition therapy.[14,15] Therefore, to bridge the gap in providing the need for nutrition education in the diabetes population, the University of Idaho developed "The Healthy Diabetes Plate," or the Idaho Plate Method in 2004, which was found to be effective in managing nutrition in patients with diabetes.[8] In the Philippines, the Filipino plate method is being used as a tool for nutrition education for general healthy eating,[6] but its effectiveness in teaching patients with diabetes and achieving glycemic control was not studied previously.

The results of our study showed that the Filipino plate method is non-inferior to the standard nutrition education given by registered nutritionist-dietitians, as prescribed by the ADA. The improvement in the meal planning sheet scores and the decrease in the 2h-PPG values were similar for the two groups. On the other hand, the median actual plate scores were better for the Filipino plate method group compared to the standard nutrition education group (Filipino plate method score 8/9 vs standard nutrition education score 7/9, p=0.018). It is likely that the actual plate scores for the Filipino plate method group may have been better, because the tool is easier to comprehend and remember than the standard nutrition education.

It is notable that despite reaching significance, there was very little improvement in the meal planning sheet scores from pre-teaching to post-teaching for both groups (pre-teaching median score 4/10 vs post-teaching median score 5/10 for both groups). This is possibly because the participants had poor drawing skills or did not comprehend how to draw the appropriate proportions and plate sizes. The instructions may have been vague and non-specific, leading to a greater variation in the drawings. On the other hand, the significant improvement in the actual plate scores suggest that the participants had better food choices and proportions after nutrition education, despite the somewhat disappointing results of the meal planning sheets.

The significant reduction in 2h-PPG from pre- to post-teaching for both groups also suggests that better food choices and proportions led to better glycemic control. Although the absolute 2h-PPG of the Filipino plate method group was lower than that of the standard nutrition education group, we chose to compare the average individual reduction in 2h-PPG from pre-teaching to post-teaching between the groups. This is due to the wide variation in the pre-teaching 2h-PPG of the participants, which also led to a wide variation in the post-teaching 2h-PPG; therefore, the absolute 2h-PPG values were not good comparative measures.

There are certain limitations to this study: First, the post-teaching results only determined short-term outcomes. Ideally, the meal planning sheet and actual plate scores, as well as the 2h-PPG, should be repeated over several weeks or months after the nutrition education to determine if these interventions had an impact on the long-term outcomes. Second, the post-intervention outcomes were not repeated; thus, the consistency of the results were not established. Third, the study interventions were not blinded to the participants, and the results were not blinded to the researchers. We also recommend that the meal planning sheets and actual plate scores be used in future studies, since there is currently no universally accepted test to determine knowledge and behavior in meal planning and food choices. Lastly, venous blood glucose levels before the meals should ideally be obtained, and the change

from postprandial to preprandial glucose levels should be compared before and after the teaching interventions. This was not done due to budget constraints.

Based on our study results, either the Filipino plate method or the standard nutrition education may be used in teaching patients with diabetes regarding medical nutrition therapy. The Filipino plate method reduces postprandial glucose levels similar to standard nutrition education. The visual Filipino plate method requires less time, knowledge, and skill to teach, thus providing an alternative to standard nutrition education. Because it is simpler, it may also be easier to understand, facilitating comprehension and memory of the healthy food groups and their proportions. The use of the Filipino plate method in the nutrition education of patients with diabetes may make nutrition education more accessible to the population of patients with diabetes.

CONCLUSION

The Filipino plate method is comparable to standard nutrition education in improving meal planning and food choices, as well as improving postprandial glucose in patients with type 2 diabetes.

Practice Implication

The Filipino plate method may be used as a simpler and easier alternative to standard nutrition education in teaching patients with type 2 diabetes about medical nutrition therapy. This method may make nutrition education more accessible to a wider population of patients with diabetes.

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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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Rate of Weight Gain and its Association with Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) among Obese Children attending Paediatric Endocrine Clinic, Hospital Universiti Sains Malaysia

Siti Hasmiza Che Mat,[1] Najib Majdi Yaacob,[2] Suhaimi Hussain[1]

[1]*Department of Paediatrics, Hospital Universiti Sains Malaysia*
[2]*Department of Biostatistic and Research Methodology, School of Medical Science, Universiti Sains Malaysia*

Abstract

Objective. We aimed to study the median time to gain weight from baseline and factors that were associated with rate of weight gain among obese children attending pediatric endocrine clinic Hospital USM.

Methodology. We recruited 70 participants with the mean age of 10.1 ± 2.94 years with exogenous or simple form of obesity from June 2019 until September 2020. We analyzed their demography (age, gender, ethnicity, family background), measured their anthropometry (weight, height, BMI) and monitored monthly weight increment and finally analyzed their HOMA-IR at baseline and after 6 months of follow up.

Results. The mean time to gain 5 kg from baseline was 16 weeks (95% CI): (15.2, 16.7). Multivariate analysis showed only HOMA-IR after 6 months was a significant predictor affecting time to gain 5 kg; Adjusted HR: (95% CI) 1.617 (1.232, 2.123), (p=0.001).

Conclusion. The time to gain 5 kg from baseline weight was increased 1.6 times in the presence of insulin resistance at 6 months follow up in patients with obesity. More intensive education and closed follow-up are recommended for children with obesity.

Key words: HOMA-IR, prognostic factor, obesity, insulin resistance

INTRODUCTION

Obesity in children and adolescents has become a massive health problem in many countries. Childhood obesity, especially in developed countries, has increased dramatically in the last 20 years.[1] North America and the Eastern Mediterranean regions have higher prevalence of overweight and obesity (30-40%) than European (20-30%) while South-East Asia, Western Pacific, and African regions contributed about 10-20%.[2]

The worldwide prevalence of childhood overweight and obesity increased from 4.2% (95% CI: 3.2%, 5.2%) in 1990 to 6.7% (95% CI: 5.6%, 7.7%) in 2010.[3] This trend was expected to reach 9.1% (95% CI: 7.3%, 10.6%) or 60 million in 2020. The prevalence of obesity was lower in Asia (4.9% in 2010) than in Africa (8.5% in 2010) but the numbers of affected children (18 million) was higher in Asia.[3]

The problem of childhood obesity is global and extends into the developing world. The prevalence of obesity in Thailand among 5-12 years old children increased from 12.2% to 15.6% within two years (WHO, 2003). The National Health and Morbidity survey (NHMS) by Institute of Public Health, 2015 reported that the prevalence of obesity among children aged 10-14 years in Malaysia was 14.4%.

Obesity is caused by an imbalance in energy input versus output, resulting in a positive energy balance. The International Obesity Task Force developed an international standard BMI for age, in which the 85th percentile and the 95th percentile for age roughly correspond to BMI of 25 kg/m^2 and 30 kg/m^2 respectively among those above 18 years old.[4]

Childhood obesity is associated with an increased risk for several metabolic complications, such as insulin resistance, glucose intolerance and type 2 diabetes mellitus (T2DM). In particular, insulin resistance is the most common metabolic alteration related to obesity, it represents an important link between obesity as well as cardiovascular complications.

Insulin Resistance is defined as a condition in which plasma insulin at normal concentration has an impaired ability to adequately promote peripheral glucose disposal, hepatic glucose suppression and inhibition of very low-density lipoprotein output.[5] In IR, insulin production

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Corresponding author: Suhaimi Hussain, MD
Consultant Paediatric Endocrinologist
Department of Paediatrics, School of Medical Sciences,
Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan
Tel. No.: +6097676536
Fax No.: +6097673370
E-mail: hsuhaimi@usm.my
ORCiD: https://orcid.org/0000-0002-7146-3076

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by the pancreatic β-cell is increased, causing hyperinsulinemia. Failure of the compensatory response leads to IGT and eventually T2DM.

The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) is the most commonly used method in clinical practice and it is a way to measure insulin resistance in children.[6] It is used to yield an estimate of insulin sensitivity and cell function from fasting plasma insulin and glucose concentration. The HOMA value was calculated as follows: fasting insulin (mU/L) x fasting glucose (nmol/L)/22.5 (using HOMA calculator version 2.2).[6]

According to a study by Chang-Rueda et al, among children and adolescents, HOMA-IR had a moderately significant correlation with an increase in BMI percentile for age (r=0.198, *p*=0.037).[7] The result showed that the combined prevalence of obesity and overweight was 66% with insulin (*p*=0.010) and HOMA-IR (*p*=0.015) values higher than those in the normal weight group. The HOMA-IR values correlated positively with age (r=0.636), weight (r=0.569), height (r=0.578) and BMI percentile (r=0.198).

A large prospective cohort study by Peplies et al., on the longitudinal association of lifestyle factor and weight status with insulin resistance (HOMA-IR) in preadolescent children was the first prospective study on IR in that population.[8] The result of this study showed the strongest positive association of IR with BMI z-score (OR=2.6 for unit change from the mean, 95% CI 2.1-3.1) and z score of waist circumference (OR=2.2, for unit change from the mean, 95% CI 1.9-2.6), audio-visual media time (OR=1.2 for an additional hour per day, 95% CI 1.0-1.4 in both models) and an inverse association determined physical activity (OR =0.5 for 3rd compared to 1st quartile, 95% CI 0.3-0.9 in both models. A longitudinal reduction of HOMA-IR was accompanied with a parallel reduction of BMI.

This study supported the common hypothesis that excess body weight and obesity were the main determinants of IR. Their data also indicate that physical activity and a sedentary lifestyle was likewise associated with the development of IR, independent of weight status.

Insulin resistance syndrome is the most common co-morbidity for obesity in many clinical trials, and the higher the weight or body mass index (BMI), the greater the risk to develop insulin resistance syndrome. As far as we know, there is no study looking for an association between rate of weight gain and insulin resistance syndrome in children. Therefore, the main purpose of this study is to investigate whether the rate of weight gain contributes to Insulin Resistance Syndrome or not.

Research objectives

To analyze the median time to gain 1 kg, 3 kg and 5 kg weight from the baseline and identify factors associated with the rate of weight gain.

METHODOLOGY

Study design

A prospective study with the recruitment period from June 2019 until September 2020. The participants were followed up every 3 month at the Endocrine clinic HUSM.

Subjects and procedures

We recruited 70 obese subjects according to inclusion and exclusion criteria. The inclusion criteria were all exogenous or primary obesity which was defined as BMI more than 95th centile according to age and gender, age less than 18 years old and waist circumference more than 90th percentile according to WHO waist circumference chart. The exclusion criteria were secondary forms of obesity such as monogenic disorder, syndromes, neurogenic, endocrine, drug induced and hypothalamic causes. Patient who failed to follow up and were not compliant with monthly weight measurement were excluded from this study.

Waist circumference was measured over the skin midway between the tenth rib and the iliac crest at the end of normal expiration, using the same measuring tape. Body mass index (BMI) was calculated using the formula: weight (kg)/height (m)^2. Obesity was defined as BMI >95th centile of standard WHO BMI. Pubertal maturation was evaluated according to standardized Tanner staging.

A total of 10 ml venous blood sample was obtained in the morning using standard venipuncture after an overnight fast by trained health staff. Fasting lipid profile (FLP), fasting blood glucose (FBG), fasting insulin, liver function tests (LFT) and renal function tests (RFT) were analyzed. LFT, FBS were analyzed using spectrophotometry method while fasting insulin was measured using immunoassay methods. Modified Oral Glucose Tolerance Test (MOGTT) was performed in all participants as they were at risk of diabetes. The index for insulin resistance was calculated using the Homeostasis Model Assessment (HOMA) calculator version 2.2 taking scores >3.16 as the threshold for the presence of insulin resistance.[6] HOMA-IR was measured twice: at presentation and 6 months after their first visit.

All participants who had consented to be in the study were given questionnaires to answer. The questionnaires were answered by parents in children less than 13 years old and if they were older, both the subject and the parents would answer together. The family was provided with a diary to record monthly body weight at the nearest health clinic. We estimated the daily caloric consumption based on 24-hour food recall and food portions were compared to a standard food atlas. The weight of the subject was measured by trained nurses using a standard height measurement/ stadiometer that was calibrated monthly. A monthly phone call was made to remind the family to record proper weight in the diary and to stick to the lifestyle modifications. The clinic anthropometric measurement was performed every 3 months and blood extraction was done at base line and after 6 months.

Weight was measured while the subject dressed minimally, upright, without shoes using the same standing stadiometer and it was recorded to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm in a standing position, without shoes on a standard height board. Blood pressure was measured with the digital method using appropriate cuff and standard sphygmomanometer.

Statistical analysis

SPSS IBM version 26.0 was used to analyze the data. Numerical data were presented as mean (SD) or median

(IQR) based on their normality distribution. Categorical data were presented as frequency (percentage). Median time to gain 1, 3 and 5 kg weight were analyzed with Kaplan-Meier survival analysis. Sample size was calculated with PS software (survival analysis), alpha=0.05, power =0.8 for primary objective and we used sample size G power software (survival analysis) with r=0.3, alpha=0.05 and power=0.8 for secondary objective. The calculated sample size was 80 patients for objective 1 and 84 for objective 2. The final sample size for objective 1 was 100 patients with 20% dropout and 105 patients with 20% dropout for objective 2. Predictive factors that influence the rate of weight gain were analyzed with Cox-Proportional Hazard regression test. All the demographic and clinical data were initially analyzed with simple Cox regression test. Variables with $p<0.25$ were further analyzed with multiple Cox regression. Forward LR and backward LR were used in the method. Two-way interaction and multicollinearity were checked for independent variables. We then checked the proportional hazard assumption and outliers with scatterplots and finally the fitness of the final model was checked with partial residuals.

Ethical approval

This study was approved by the Human Research Ethics Committee USM with its references USM/JEPeM/19020132.

RESULTS

Demographic characteristics of 70 patients in this study are summarized in Tables 1 and 2. There were 43 patient (61.4%) males and 27 patient (38.6%) females. Majority of the patients were Malay, 67 patients (95.7%); and 3 patients (4.3%) were Chinese. The mean age of the subjects was 10.1 ± 2.94 years. Thirty nine patients (55.7%) were between 10-18 years old and 31 patients (44.3%) were between 3-9 years old.

For the care-taker education background, the parents received primary education in 15.7%, secondary education level in 32.8% and tertiary education in 51.4%. In Malaysia, household income of less than USD 909 was defined as urban poverty or known as B40 group as categorized by Social Welfare Department of Malaysia and Ministry of Housing and Local Government. From this study, 46 patients (65.7%) were from the high income family group and 24 patients (24.3%) were from the low-income family group. Fifty patients (71.4%) had sedentary lifestyle group and 20 patients (28.6%) were non-sedentary. Sedentary lifestyle was defined as more than 2 hours of screen time per day and less than 60 minutes of moderate to vigorous physical activity per day according to WHO recommendation. In this study, only 22 patients (31.4%) met more than 60 minutes of moderate to vigorous physical activity per day but the others (68.6%) did not meet the recommendation.

Table 2 shows clinical and biochemical parameters of obese patients in this study. Thirty-two patients (45.7%) had BMI >30 kg/m^2 and 38 patient (54.3%) had BMI <30 kg/m^2. The BMI cutoff of 30 was used because it was more likely to be associated with obesity complications or co-morbidity.

Forty-seven patients (67.1%) had normal blood pressure during follow-up but 23 patients (32.9%) were diagnosed to have hypertension during this study period. Seven patients (10%) were pubertal and 63 patients (90%) were prepubertal.

From this study, 37 patients (52.8%) had normal MOGTT results while 33 patients (47%) had abnormal MOGTT results that comprised of 15 patients (21.4%) with impaired fasting glucose (IFG), 17 patients (24.2%) with impaired

Table 1. Baseline characteristics of patients with obesity

Variable	n (%)
Gender	
Male	43 (61.4)
Female	27 (38.6)
Age (years)	
1-9	31 (44.3)
10-18	39 (55.7)
Race	
Malay	67 (95.7)
Chinese	3 (4.3)
Family income	
Low income	24 (34.3)
High income	46 (65.7)
Caretaker education	
Primary	11 (15.7)
Secondary	23 (32.8)
Tertiary	36 (51.4)
Sedentary lifestyle	
Yes	50 (71.4)
No	20 (28.6)
Exercise	
None	7 (10)
<15 min	13 (18)
15-30 min	11 (15.7)
30-60 min	17 (24.3)
>60 min	22 (31.4)

n (%) for categorical variables

Table 2. Baseline clinical and biochemical parameters of patients with obesity

Variable	n (%)
BMI	
<30	38 (54.3)
>30	32 (45.7)
BP	
Normal	47 (67.1)
Hypertension	23 (32.9)
Tanner staging	
Prepubertal	63 (90)
Pubertal	7 (10)
Age Onset obesity (years)*	5.59 ± 3.29
Current Weight (kg)*	63.89 ± 23.75
Current Height (cm)*	142.79 ± 15.83
Waist circumference (cm)*	91.96 ± 20.00
Calories/day (kcal)*	3503.62 ± 887.03
HOMA Baseline*	2.31 ± 0.96
HOMA at 6 months*	3.80 ± 1.65
MOGTT	
Normal	37 (52.8)
IFG	15 (21.4)
IGT	17 (24.2)
DM	1 (1.4)
Dyslipidemia	
Yes	21 (30)
No	49 (70)
Transaminitis	
Yes	25 (35.7)
No	45 (64.3)

*Mean+SD for numerical variables
n (%) for categorical variables

glucose tolerance (IGT) and 1 patient (1.4%) with diabetes mellitus (DM). Twenty-one patients (30%) had dyslipidemia and 49 patients (70%) had normal fasting lipid profile. Twenty-five patients (35.7%) had transaminitis and 45 patients (64.3%) had normal ALT. The mean age of obesity onset was 5.59 ± 3.29 years with mean weight of 63.89 ± 23.75 kg, mean height of 142.79 ± 15.83 cm and mean WC of 91.96 ± 20.00 cm. The mean caloric intake was 3503.62 ± 887.03 kcal/day with mean HOMA at baseline of 2.31 ± 0.96; and the mean HOMA at 6 months was 3.80 ± 1.65.

From the Kaplan Meier analysis, the mean time to gain 1 kg was 7.9 weeks with (98% CI): (6.6, 9.2), mean time to gain 3 kg weight was 12 weeks (98% CI): (9.7,14.2), and mean time to gain 5 kg from baseline was 16 weeks (98% CI): (15.2, 16.7).

Significant factors that were associated with 5 kg weight gain after univariate analysis were older age with patients 10-18 years, crude OR (95% CI); 0.557 (0.277,1.120), BMI >30 kg/m^2; 0.551 (0.278,1.091), non-Malay; 0.384 (0.117,1.263), transaminitis; 1.591 (0.851,2.975), dyslipidemia; 1.523 (0.813,2.852), total calories (kcal/day); 1.000 (1.000,1.001), current weight (kg); 1.010 (0.998,1.023), current height (cm); 1.022 (1.00,1.044), WC (cm); 1.014 (1.000,1.028), HOMA at baseline; 1.364 (0.984,1.889) and HOMA after 6 months; 1.617 (1.232, 2.123) (Table 3).

However, multivariate analysis revealed only HOMA-IR after 6 months was a significant predictor affecting time to gain 5 kg; Adjusted HR: (95% CI) 1.617 (1.232, 2.123), (p=0.001). The time to gain 5 kg from the baseline was 1.6 times increased in the presence of insulin resistance at 6 months follow up in patients with obesity. As there is only one variable from final analysis, there is no interaction/ multicollinearity. The plot of dfBeta against survival time is less than 1. The partial residuals in the plot for the variable is distributed in a band around zero which is acceptable.

Table 3. Factors associated with 5 kg weight gain

Variables	Crude HR[a] (95% CI)	*p* value
Race		
Malay	0.384 (0.117, 1.263)	0.115
Chinese	1.0	
Age (years)		
1-9	0.557 (0.277, 1.120)	0.101
10-18	1.0	
BMI		
<30	0.551 (0.278, 1.091)	0.087
>30	1.0	
Transaminitis		
Yes	1.59 (0.851, 2.975)	0.146
No	1.0	
Dyslipidemia		
Yes	1.523 (0.813, 2.852)	0.189
No	1.0	
Total calories (kcal/day)	1.000 (1.000, 1.001)	0.140
Current weight (kg)	1.010 (0.998, 1.023)	0.099
Current height (cm)	1.022 (1.000, 1.044)	0.050
Waist circumference (cm)	1.014 (1.000, 1.028)	0.056
HOMA at baseline	1.364 (0.984, 1.889)	0.062
HOMA after 6 months	1.617 (1.232, 2.123)	0.001

[a] Simple Cox proportional hazard regression. The model reasonably fits well. Proportional hazard assumption is met. There are no interaction and multicollinearity problem.

DISCUSSION

Previous research had identified numerous socio-demographic and factors associated with childhood obesity in Malaysia. A survey done by Ismail et al., had demonstrated increased prevalence of obesity with increasing age: 6.6% among 7-year-olds, which went up to 13.8% among 10-year-old group and a higher prevalence seen among males than females (12.5% compared to 5%).[9]

Another study among children (6239 respondents) aged between 7 to 16 years in Kuala Lumpur by Kasmini et al., published in Asia Pacific Journal Clinical Nutrition, also showed that males were found to be more obese than females particularly in the pubertal age group (11 to 14 years old).[10] Our study showed that the majority of obese children were male (61.4%) aged 10-18 years old (55.7%). This study had similar findings compared to others in which there were more obese males in the older age group.

Comparing our study with neighboring countries also showed similar findings. A study in Singapore showed that the overall prevalence rate of obesity was 3.51% with a significantly higher rate in boys (3.95%) than in girls (3.06%), p<0.0001. There was a higher prevalence of obesity among 10-year-olds (4.29%) compared to 7-year-old students (2.75%) p<0.0001. This study suggested that the tendency to become obese increases with age and boys are more prone to obesity.[11] In many Asian countries, boys are encouraged by their parents to take higher portions of energy dense food compared to girls and together with sedentary lifestyle practices resulted in positive energy balance and an increase in weight among boys.

A study of socioeconomic determinants of childhood obesity in Guangzhou, China (2016) also showed that the prevalence of obesity increased with increasing age (9.1% in 5–6 years compared with 22.0% in 11–12 years) and it was also higher in males (23.5%) compared with females (11.6%).[12] The prevalence of obesity also increased with increasing quartile of household per-capita income and with higher maternal education.[12]

Our study findings contradicted the findings of a study of socio demographic and life style determinants among preschool children in Babol, Northern Iran.[13] This study showed no significant difference between genders and the odds ratio significantly decreased in tertiary parental education compared to primary parental education. However, our findings were similar with this study in terms of age distribution in which the higher prevalence of obesity was seen with increasing age. The odds of obesity was raised more than double among age 4-5 years compared with 2-3 years (OR=2.53, 95% CI:1.71-3.73).

Our study showed that majority of obese children were of Malay ethnicity (95.7%), with tertiary education background in the family (51.4%), with high income (65.7%) and with sedentary lifestyle (71.4%). Ismail and Tan et al., found ethnicity differences in their study with 16.8% of Malay being obese compared to approximately 11.0% of Chinese and Indian.[9] However based on study by Kasmini et al., there was no significant difference between 3 major ethnic groups among obese children.[10]

There are no studies that compare ethnicity among pediatric patients in neighboring countries. The higher prevalence of obesity among Malay in our paper is primarily due to the greater proportion of Malay subjects that were recruited, reflecting the predominant Malay ethnicity in the state.

A cross sectional study by Alagappan et al., among secondary school student (7247 respondents) in Batang Padang, Perak Malaysia, showed that obesity was significantly (p<0.05) associated with higher family education and low physical activity group.[14] This study supported our finding that the higher prevalence of obesity was seen in those with good education background in the family and among those who were sedentary.

A study by Amuthaganesh et al., regarding physical activity and media environment as antecedent of childhood obesity in Malaysia support that excessive media viewing is consistently shown to be linked to increased BMI independent of physical activity.[15] In comparison to our study, the prevalence of obesity was higher among sedentary lifestyle group which did not meet the WHO recommendation of physical activity for children; 71.4% were in sedentary lifestyle group with more than 2 hours of screen time and less than 60 minutes of moderate to vigorous physical activity per day. The physical activity level of the children in our study was low, only a small proportion (31.4%) reached the daily activity level recommended by WHO.

In contrast to the study in Iran, there was no significant association between higher prevalence of obesity with physical activity and sedentary lifestyle. Results showed spending ≥2 hours per day for TV watching and ≥1 hour for playing with computer games tend to increase the odds of overweight/obesity (OR=1.31, P=0.13 and OR=1.46, P=0.06 respectively) but it was not significant.[13] However, the author did not explain the reason for the insignificant difference between physical activity and sedentary lifestyle.

The mean caloric intake per day among our participants was 3503.62 ± 887.03 kcal/day which was mainly high carbo diet based on 24 hour food recall. The high caloric consumption per day contributes to imbalance of energy input versus output, resulting in a positive energy balance. The sedentary lifestyle together with high caloric food consumption were factors that contribute to an increase in the rate of weight gain in this study.

High socio-economic status has also been associated with an increased prevalence of obesity among children in this study. A study in Peninsular Malaysia among 10-17 years obese children by Nurul et al., revealed that high socioeconomic status with household income of more than USD 708 was associated with a two fold increase in the odds ratio (OR 2.240, p=0.049).[16] This finding was consistent with our study in which 65.7% were in the high income group, defined as monthly household income of more than USD 913 as categorized by Social Welfare Department of Malaysia and Ministry of Housing and Local Government. The children that belong to higher income families had more access to various food resources and might have an increase in the food consumption while their parents were away.

In this study, we analyzed the time to gain weight from the baseline. As far as we know, there were no previous publications that reviewed time to gain weight from the baseline. Based on expert opinion, the usual increment of 5 kg weight from the baseline was 6 months on average. Guidelines also stated that weight reduction is between 0.5 kg-1.0 kg per month.[17]

We found that the patients gained 5 kg within 16 weeks (98% CI): (15.2, 16.7). The rate was more rapid compared to what was recommended by the general consensus guidelines for obesity prevention.[17]

A recent meta-analysis on impact of dietary and exercise intervention on weight change and metabolic outcomes in obese children by Ho et al., demonstrated that those children that were given intervention showed significant improvement in all anthropometric measurements as well as mean glucose and HbA1c.[18] The early findings from 6 months of family-based intervention demonstrated decrease in BMI, fat mass, total cholesterol and insulin resistance.[18] The main and first line management of obesity in children is diet and life style intervention. However, most of the families find it hard to consistently maintain healthy diet and lifestyle; and with poor motivation, this would result in weight increment as proven by our study. We found that those with persistent weight gain among obese children were older patients 10-18 years; and had higher BMI, presence of transaminitis, dyslipidemia and abnormal MOGTT result.

Skeletal muscle mass affects locomotion and maintenance of posture. It is the most abundant insulin sensitive tissue that plays a crucial role in systemic glucose metabolism. Decreased muscle mass, known as sarcopenia, typical of the aging process, is a risk factor for insulin resistance and is associated with metabolic risk in children and adolescents.[19] Furthermore, elevated body fat level may act in synergism with decreased skeletal muscle mass because adiposity is also closely linked to insulin resistance and thus, a low ratio of skeletal muscle to body fat (MFR) importantly predicts the development of metabolic syndrome.[19]

Transaminitis was associated with increase of weight gain. A study by Wei et al., shown that 16% of obese children from a UK-based obesity clinic had raised alanine aminotransferase (ALT) and patient with transaminitis were more likely to fulfill the criteria for metabolic syndrome (p<0.001) and had abnormal OGTT.[20] In this prospective trial, there was a significant relationship between 12 months changes in BMI and corresponding change in ALT. Improvement in BMI over 1 year correlated with improvement in ALT levels.

Another study by Tock et al., showed that 11% of patients in the subgroup with raised ALT at the beginning of weight management program who have normalized their level after 12 months displayed a 9% reduction in BMI.[21] Transaminitis in the form of raised ALT has been used as a surrogate marker for the diagnosis of nonalcoholic fatty liver disease (NAFLD). NAFLD is linked to adiposity, and is commonly associated with metabolic syndrome. The etiology of NAFLD in obese patients is multi-factorial. Increased portal concentration of free fatty acid is found in patients with obesity and insulin resistance.

The increased level of free fatty acid causes damage to intracellular membrane and leads to the development of NAFLD.

Transaminitis in obese children has been associated with features of the metabolic syndrome such as obesity, hyperinsulinism and hyperlipidemia. In our study, obese patients who had elevated ALT showed significant increase of 5 kg weight from the baseline and some of these patients had dyslipidemia and abnormal MOGTT.

Although a relationship between insulin resistance and fat gain has been demonstrated, it is not clear whether insulin resistance is a promoting factor or simply a consequence of fat gain. A study by Odeleye et al., regarding fasting hyperinsulinemia as a predictor of increased body weight gain and obesity among 5 to 9 years old Pima Indian children found that high fasting insulin level was associated with greater weight gain during 9 years of follow up.[22]

Moreover, similar results were reported from a number of Caucasian and African-American children, with a mean age of 8.1 ± 1.6 years and studied for over 3-6 years.[23] The finding suggested that hyperinsulinemia and insulin resistance favor fat gain during childhood and adolescent.

The findings are also reported in other studies in which there was a significant correlation of increase BMI with HOMA- IR; and a longitudinal reduction of BMI cause decline in HOMA-IR.[7] These studies are consistent with our study in which there was a significant correlation between weight gain with HOMA-IR at 6 months follow up (r=0.737; p<0.001). The time to gain 5 kg from the baseline was 1.6 times increased in the presence of insulin resistance at 6 months follow up in patients with obesity.

Obesity is the excessive growth of adipose tissue depots arising from the chronic consumption of calories in excess of the energy need of the individuals. There is a specific link between visceral adipose tissue accumulation and insulin resistance that will explain why insulin resistance is higher in obese groups.

One possibility is that visceral fat is diabetogenic, because it secretes adipokines that impair the insulin sensitivity in tissue such as liver and muscle. The second reason is that the presence of visceral fat indicates the existence of ectopic lipid accumulation and lipotoxicity that cause insulin resistance in the liver and muscle. The third explanation is the excess lipid accumulation in visceral adipose tissue causes release of inflammatory cytokines that will impair insulin sensitivity. Another possibility is that the lipotoxicity in peripheral and visceral adipose tissue increases cytokine production that contributes to systemic insulin resistance.[24]

In this study, we found the significant association of weight gain and HOMA-IR after 6 months follow up among our study population. This favors the development of insulin resistance syndrome. Most of the patients that had high HOMA-IR index were also found to have clinical and biochemical findings compatible with metabolic syndrome. Without proper interventions, they are at risk of complications related to metabolic syndrome such as diabetes and cardiovascular complications.

Limitations of the study

We aimed to get a larger sample size, however we had difficulty in recruitment due to the COVID19 pandemic and movement restriction order (MCO) in our country. Our initial recruitment was 84 patients; however, the final sample size was only 70 patients because fourteen of them dropped out. The duration of follow up should be longer in order to ascertain whether the weight gain persists, however since this trial is only a short term of up to 6 months, we were unable to determine this.

CONCLUSION

In this prospective study, the mean time to gain 5 kg was 16 weeks. There were many factors associated with the time to gain 5 kg weight, however, only HOMA-IR after 6 months was a significant predictor affecting time to gain 5 kg with adjusted HR: (95% CI) 1.617(1.232, 2.123), (p=0.001) from multiple Cox Proportional Hazard regression. Intensive education and more frequent follow-up are recommended for children with obesity.

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Statement of Authorship

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Author Disclosure

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ORIGINAL ARTICLE

Weekly Versus Daily Levothyroxine Tablet Replacement in Adults with Hypothyroidism: A Meta-Analysis

Harold Henrison Chiu,[1] Ramon Larrazabal Jr.,[2] Angelique Bea Uy,[1] Cecilia Jimeno[1]

[1]*Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Taft Avenue, Ermita, Manila, Philippines*
[2]*Division of Medical Oncology, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Taft Avenue, Ermita, Manila, Philippines*

Abstract

Objectives. Daily levothyroxine is the treatment of choice and standard of care in hypothyroidism, sufficient to restore thyroid stimulating hormone (TSH) to normal range. For many patients, daily lifelong therapy is required, making adherence a major issue. In such cases, weekly replacement may be a suitable alternative to improve adherence. In this study, we aimed to determine the efficacy and safety of weekly levothyroxine replacement among adults with hypothyroidism.

Methodology. Electronic databases were searched. Two reviewers (HCC and RBL) independently screened the abstracts, reviewed full-text papers, critically appraised the quality of included studies using PRISMA guidelines. Meta-analysis was performed using the random-effects model. The primary outcome is the difference in serum TSH levels between weekly and daily administration, while secondary outcomes included adverse events and symptoms of hypothyroidism.

Results. The primary outcome is the difference in serum TSH levels between weekly and daily administration. Secondary outcomes included adverse events and clinical symptoms. The study included two randomized trials (n=109) in the primary analysis. The difference in TSH levels was 1.78 mIU/mL higher [(95% confidence interval (CI): 1.28 to 2.28, p<0.00001] at 6 weeks and 1.22 mIU/mL higher (95% CI: 0.76 to 1.67, p<0.00001) at 12 weeks for the weekly regimen. There was no significant heterogeneity between the two groups. There was no significant difference in hypothyroid symptoms and adverse events before and after levothyroxine treatment within each group.

Conclusions. Weekly levothyroxine resulted in less suppression and higher mean serum TSH levels, while still remaining within the normal reference range. It may be a suitable alternative for non-adherent patients. However, larger randomized trials with longer duration of follow-up are needed to firmly establish its role.

Key words: hypothyroidism, levothyroxine, thyroid hormone, adherence, weekly replacement

INTRODUCTION

Hypothyroidism is a common hormone deficiency with a prevalence ranging from 4 to 5% worldwide.[1] It presents with classic signs and symptoms as a result of low thyroxine levels. Treatment in the form of thyroid hormone replacement carries an overall excellent prognosis if patients are adherent to regular treatment.[1] Daily levothyroxine (LT4) at a dose of 1.6 to 1.8 μg/kg of body weight per day is the treatment of choice and standard of care, sufficient to restore the thyroid stimulating hormone (TSH) to normal range.[2] However, for many patients with primary hypothyroidism and post-procedural hypothyroidism, lifelong therapy is needed, and adherence then becomes a major issue. When higher than usual doses are needed to maintain TSH in the normal range, clinicians must determine the reason for high dose requirements.[2-4] One of the most commonly cited reasons is non-adherence brought about by the following reasons: (1) the need to take the medication while fasting, (2) the need to wait for 30 to 60 minutes before the next meal, (3) the need to take the medication on a daily basis, and (4) the need to avoid various medications that may interfere with absorption, as many drugs have the potential to interfere with LT4 metabolism.[3,5,6]

To overcome these issues leading to non-adherence, various strategies have been employed including once-weekly therapy, twice-weekly therapy, alternate-day therapy, liquid formulations, use of patient education manuals, intramuscular and parenteral administration.[2-4,7-18] Since LT4 has an elimination half-life of approximately 7 days and an even longer biological effect, giving it once weekly may be a logical alternative.[2-4] Normalization of serum TSH in patients suspected of being non-adherent to their therapy was achieved with weekly or twice weekly oral therapy.[2-4,7-13]

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Corresponding author: Harold Henrison C. Chiu, RCh, MD
Senior Fellow, Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines Manila
Taft Avenue, Ermita, Manila, Philippines
Telefax: +632-85548400
E-mail: harold.c.chiu@gmail.com; hcchiu@up.edu.ph
ORCiD: https://orcid.org/0000-0002-2021-7843

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Ingested LT4 is further converted in the peripheral tissues to the more metabolically active triiodothyronine (T3) by deiodinase enzymes. Given its long elimination half-life and metabolic conversion *in vivo*, the available depot of LT4 suggests the possibility of using LT4 at a longer dosing interval.[3] In addition, the weekly dosing regimen may also be advantageous to caregivers taking care of patients who are unable to or have physical difficulty taking daily doses.

A few published studies consisting mostly of case reports and prospective studies have reported on weekly administration of LT4.[7-11] The first trial comparing daily and weekly administration of levothyroxine was done by Grebe and colleagues in 1997, who found that weekly LT4 replacement was well-tolerated with no evidence of cardiac toxicity.[4] Since then, only two additional trials have been completed over the past two decades.[3,4] Currently, only three relevant randomized cross-over trials have been performed comparing the effect of weekly and daily LT4 replacement on serum TSH, clinical symptoms and adverse events.[2-4] However, all trials were as short-term, limited to 12 weeks in duration, and none were conducted in truly non-adherent patients.[2-4] Results of the three studies have demonstrated no statistically significant differences between daily and weekly dosing in terms of both clinical and biochemical parameters.

In this study, we aimed to determine the efficacy and safety of daily versus weekly levothyroxine tablet replacement in adults with hypothyroidism with the effect on serum TSH as our primary outcomes, and clinical symptoms using the hypothyroidism symptom scale (HSS) and adverse events as our secondary outcomes.

METHODOLOGY

Our study was approved by the Institutional Review Board and Research Ethics Board of the University of the Philippines Manila (UPM-REB Code 2020-399-EX, RGAO Registration No. 2020-0328) prior to commencement.

The study included only randomized controlled trials that determined the effect of weekly versus the daily administration of levothyroxine on thyroid function tests as a standard of care for replacement therapy. Trial settings were restricted to participants ≥19 years of age, and with hypothyroidism of any etiology. All studies were required to have measured thyroid function in study participants using thyroid stimulating hormone.

We performed a comprehensive search strategy from inception to February 2021 in the following databases: PubMed/MEDLINE, Ovid MEDLINE, Google Scholar, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science and ClinicalTrials.gov. The search was limited to adults (age ≥19 years), randomized controlled trials, systematic reviews and meta-analyses. There was no language restriction on the searches performed. To identify all the relevant studies, the following descriptors were used to build the search strategies: levothyroxine, L-thyroxine, L-T4, hypothyroidism, daily replacement and weekly replacement, among others. Terms were combined with the Boolean operators AND and OR using the following strategy: "weekly"[All Fields] AND ((((("levothyroxine"[All Fields] OR "thyroxine"[MeSH Terms]) OR "thyroxine"[All Fields]) OR "levothyroxine"[All Fields]) OR "levothyroxine"[All Fields]), Filters: Clinical Trial.

The eligibility criteria were as follows: (1) the study was a randomized controlled trial; (2) the study compared daily levothyroxine administration to weekly levothyroxine administration in patients on replacement therapy; (3) the formulation must be in tablet, not in soft gel capsule or liquid form; (4) the reported outcome included serum TSH levels; and (5) the study was published as full text with complete outcomes. The studies that did not fulfill the eligibility criteria were excluded. We supplemented our electronic search with manual searches and by cross-referencing included papers, relevant sections of clinical practice guidelines, and relevant systematic and narrative reviews.

Two investigators (HCC and RBL) independently screened citations from the electronic search, reviewed full text papers for inclusion, critically appraised the quality of the included studies using PRISMA guidelines and abstracted the data. Consensus was achieved for inclusion of papers by discussion between reviewers. A third reviewer/clinical content expert (ABU/CAJ) was consulted in the event of any discrepancies that could not be resolved by reviewer discussion. Each study was evaluated for their risk of bias of using the Risk of Bias evaluation tool developed by the Cochrane Collaboration. All outcomes were reported according to PRISMA standards. Continuous data for thyroid functions tests (TSH) and clinical symptoms using the hypothyroidism symptom scale were reported as means with corresponding standard deviations. Adverse events were presented as narratives. A random-effects model meta-analyses was performed estimating the levels of thyroid function tests and HSS scores with 95% confidence intervals using the Review Manager Software (Revman) Version 5.3.

RESULTS

Search strategy

A total of 354 articles were retrieved after a comprehensive search of databases. Forty three duplicate studies were eliminated, 303 were excluded based on title and abstract, and six articles were excluded after full text assessment (four case reports, one prospective study and one unable to fully extract data). Eventually, two articles were included in this meta-analysis. The study selection schematic diagram is shown in Figure 1.

Study characteristics

The baseline characteristics of the studies included in this meta-analysis are summarized in Table 1. The studies were carried out in two countries, India and Brazil.[2,3] These were published in 2017 and 2012, respectively. Overall, there were 114 participants in both studies. Both trials included patients with primary hypothyroidism who were maintained on hormone replacement and were euthyroid for at least three months at the time of recruitment. The mean age of the subjects ranged from 35.4 to 42.5 years old. The duration of the interventions for both trials was 12 weeks. A summary of the risk of bias of included trials is shown in Figure 2.

Table 1. Characteristics of the included studies

Author	Design	N	Mean Age (y)	Intervention	Comparison	Outcome	Duration
Bornschein (2012)	Randomized cross-over study	14	Group 1: 41.2 ± 8.41 Group 2: 42.5 ± 7.48	Weekly dose of LT4[a] (seven times higher than usual dose) for 6 weeks then switched to daily dosing	Usual daily dose of LT4[a] for 6 weeks then switched to weekly dosing	TSH,[b] Total T4,[c] Total T3[d]	12 weeks
Raiput (2017)	Randomized cross-over study	100	Group 1: 36.1 ± 10.7 Group 2: 35.4 ± 8.4	Weekly dose of LT4[a] (seven times higher than usual dose) then switched to therapeutic regimen after 6 weeks	Usual daily dose of LT4[a] for 6 weeks then switched to weekly dosing; switched to therapeutic regimen after 6 weeks	TSH,[b] free T4,[c] Total T3[d]	12 weeks

[a]LT4, levothyroxine; [b]TSH, thyroid stimulating hormone; [c]T4, thyroxine; [d]T3, triiodothyronine

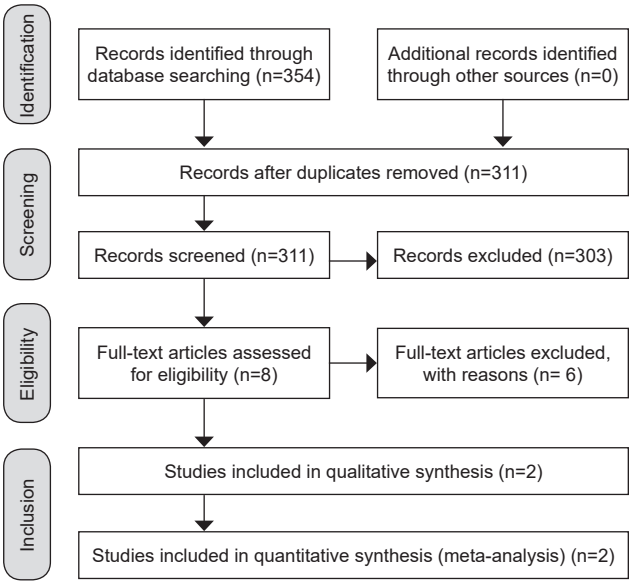
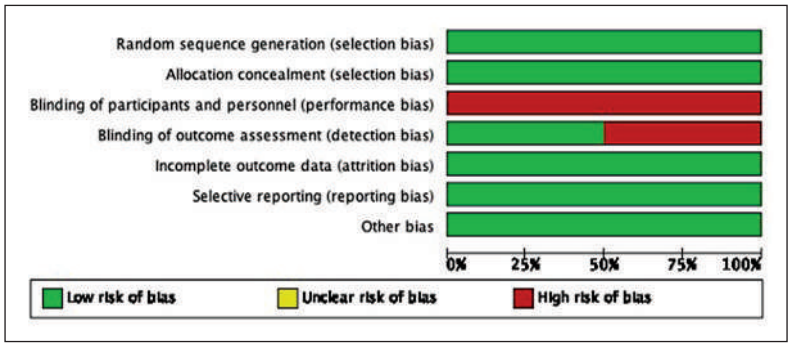


Figure 1. Schematic diagram of the literature search and study selection.

Effect of weekly administration on TSH

The pooled estimate from the random-effects model performed on the two studies showed that weekly administration of levothyroxine had significantly higher serum TSH levels at 6 weeks [standard mean difference (SMD) = 1.78, 95% confidence interval (CI): 1.28 to 2.28, $p<0.00001$). There was no significant heterogeneity between the two groups ($P = 0.71$, $I^2 = 0$) (Figure 3).

Similarly, the pooled estimate from the random-effects model performed on the two studies showed that weekly administration of levothyroxine still had significantly higher serum TSH levels at 12 weeks (SMD = 1.22, 95% CI: 0.76 to 1.67, $p<0.00001$). There was no significant heterogeneity between the two groups ($P = 0.75$, $I^2 = 0$) (Figure 4).



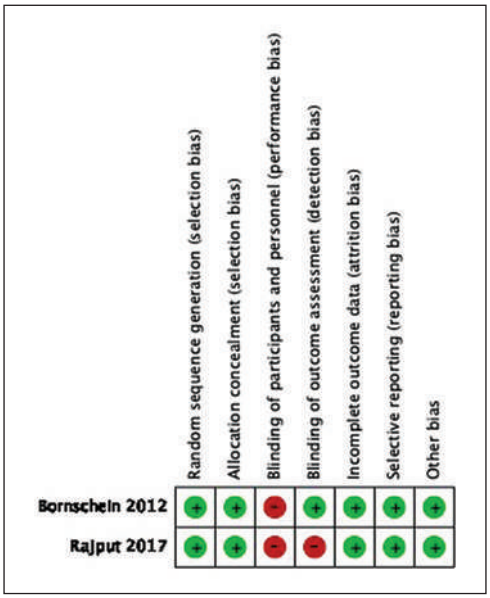


Figure 2. Quality assessment of the included randomized controlled trials.

Clinical symptoms and adverse events

Both studies measured hypothyroid symptoms using the HSS scale. In the Rajput study, there was no significant difference in HSS scores between weekly and daily administration of LT4 (6.4 ± 2.8 after daily therapy and 6.4 ± 2.3 after weekly therapy, $p=0.771$).[2] Similarly, Bornscheiner and colleagues noted that the HSS scores were similar in both groups at all times: group 1, daily regimen (5.5 to 6.00 afterwards, $p>0.05$) followed by weekly regimen (5.75 to 5.75, $p>0.05$); and group 2, weekly regimen (5.33 to 5.50, $p>0.05$) followed by daily regimen (5.5 to 5.33, $p>0.05$).[3]

Bornscheiner and colleagues also assessed cardiac adverse events by measuring echocardiographic parameters during systole, specifically pre-ejection period (PEP), aortic ejection time (ET), isovolumetric contraction time (ICT) and heart rate (HR).[3] There were no significant differences in all echocardiographic parameters before and after LT4 within each group. The study done by Rajput did not assess cardiac adverse events.[2]

DISCUSSION

This is the first meta-analysis that compared the effects of weekly versus daily LT4 administration on thyroid function of adult patients with hypothyroidism. There is an overall low risk of bias for both studies except for the blinding of participants which was difficult to achieve given the stark difference in terms of the method of administration being obvious to the participants (weekly versus daily

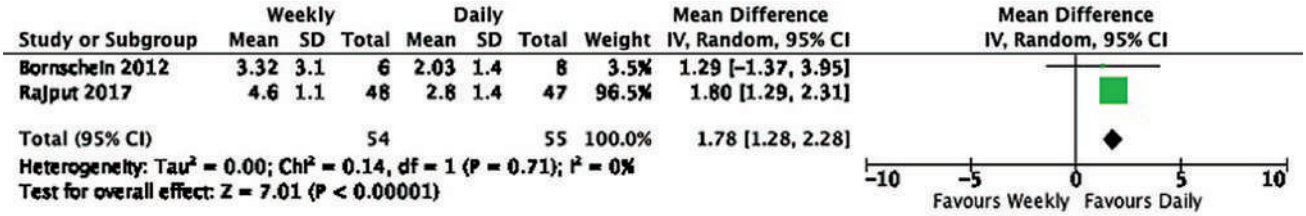


Figure 3. Forest plot showing the effect of weekly levothyroxine administration on TSH at 6 weeks.

TSH, thyroid stimulating hormone; SD, standard deviation; CI, confidence interval.

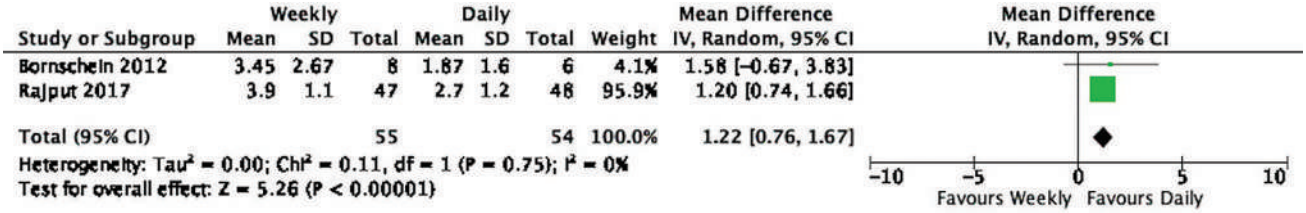


Figure 4. Forest plot showing the effect of weekly levothyroxine administration on TSH at 12 weeks.

TSH, thyroid stimulating hormone; SD, standard deviation; CI, confidence interval.

regimen). The lack of participant blinding has no effect on serum TSH levels, since these are objectively quantified using either radioimmunoassay or chemiluminescence methods. However, it can affect subjective parameters such as hypothyroid symptoms as measured using the hypothyroidism symptom scale. There was no significant heterogeneity between the studies. However, the analysis is limited by the very few numbers of studies available in literature, as well as the overall small sample size in both studies. We still believe that despite these limitations, this meta-analysis is still a crucial contributor to new scientific knowledge, as it highlights novel and practical insights and approaches in terms of the use and administration of levothyroxine among our patients with hypothyroidism.

Overall, we observed a significant difference in the levels of TSH when weekly LT4 was compared to daily administration. The weekly replacement regimen showed a statistically higher level of mean serum TSH at both 6 and 12 weeks, respectively. From a clinical and biochemical standpoint, this meant less TSH suppression. Despite the observed higher mean TSH in the weekly regimen, levels remained within the reference range of normal at all times. This is consistent with the treatment target of maintaining the TSH level within the normal range as recommended by the American Thyroid Association (ATA) in the treatment of hypothyroidism.[1] In addition, patients did not experience cardiac adverse events, symptoms of overtreatment, as well as symptoms of hypothyroidism during weekly administration of LT4. Our limited data suggests that weekly LT4 is safe from a cardiac point of view; however, due to the small number of patients and short follow-up period, firm safety data for weekly therapy has not yet been established definitively.

There are only very few studies worldwide that compared weekly and daily administration of LT4 in hypothyroid patients. Three clinical trials and one prospective study have shown that weekly LT4 is as effective as daily treatment for non-adherent patients and have concluded that once weekly LT4 is a safe regimen.[2-4,19] However, Grebe and colleagues showed that while weekly therapy was well tolerated, the thyroid function tests are biochemically consistent with mild hypothyroidism with an overall increase in mean serum TSH levels and a decrease in thyroxine before the next weekly dose.[2] It can be hypothesized that the type 2 deiodinase enzyme might be responsible for sufficient peripheral conversion of LT4 to T3 which would have resulted in maintenance of euthyroidism despite the rise in TSH level from less negative feedback observed in the weekly group. This mechanism may be responsible for the maintenance of euthyroidism while on the weekly regimen.[4,13]

Patient adherence is a significant factor in the achievement of treatment goals.[20] Non-adherence to medications remains a major challenge in the management of hypothyroidism, particularly the requirement of daily drug intake after prolonged fasting.[1-16] This is often elicited by physicians during patient consults as persistently elevated TSH, despite the patient being given very high LT4 doses. However, it must be noted that there have been many concerns regarding the potential toxicity of high doses being administered in the weekly regimen (as high as seven times the daily dose). Serious complications have been reported in toxicologic and overdose investigations. Those taking levothyroxine ranging from 3 to 4 mg can develop cardiac complications, and these patients should be closely monitored.[20-22] The dose of the weekly regimen is far below this potentially toxic dose range of 3 to 4 mg of LT4 daily. However, cardiac safety cannot be generalized for the entire population, especially for the elderly, since both studies have utilized relatively younger patients. Furthermore, the short period of follow-up in both studies makes it difficult to predict long-term differences between the two regimens.

Given our results showing that serum TSH levels remain within reference ranges with weekly administration of LT4, changing the drug administration to a weekly regimen may increase adherence among non-adherent patients. However, it must be highlighted that the weekly regimen is not suitable for patients who are planning to conceive in view of more stringent TSH targets in that group.

Assay difference is also another limitation in our study. Fortunately, both third generation assays using the immunoradiometric (IRMA) and chemiluminescence immunoassay (CLIA) methods are precise up to 0.1 mIU/mL.[2,3] Furthermore, the reference range of these assays are almost identical and utilize the same unit of measurement for TSH in mIU/mL.

To summarize, the current meta-analysis is mainly limited by the few numbers of trials and participants, differences in TSH assays (IRMA versus CLIA), generalizability of cardiac safety especially in the elderly, short period of follow-up, as well as the lack of measurement of treatment adherence as an outcome among participants in both trials. Given the paucity of data on efficacy and safety, future randomized trials with larger sample sizes and a longer duration of follow-up are needed to firmly establish the definite role of weekly LT4 in the management of hypothyroidism.

CONCLUSION

In summary, weekly LT4 administration has less suppression and higher overall serum TSH levels, while remaining within the normal reference range as recommended in international treatment guidelines. It may be a feasible alternative for patients with hypothyroidism, especially when adherence is a concern. However, more randomized trials with larger sample sizes and longer duration of follow-up are needed to firmly establish the role of weekly LT4 in the management of hypothyroidism.

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

Author Disclosure
Dr. Chiu, Dr. Larrazabal and Dr. Uy have declared no conflict of interest. Dr. Jimeno is the Vice Editor-in-Chief of JAFES.

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ORIGINAL ARTICLE

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Predictors of Response to Therapy Among Post Thyroidectomy Adult Filipino Patients with Papillary Thyroid Carcinoma Based on the 2015 American Thyroid Association Guidelines*

Aivind Gabrielle Santiago,[1] Maria Jocelyn Isidro,[1] Joseph Parra[2]

[1]*Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Makati Medical Center, Makati City, Philippines*
[2]*Oncology Unit, Makati Medical Center, Makati City, Philippines*

Abstract

Objective. To identify factors independently associated with incomplete response to therapy based on the 2015 ATA guidelines in surgically treated Filipino patients with papillary thyroid carcinoma (PTC).

Methodology. This is a retrospective cohort study of adults aged 21-74 years with papillary thyroid carcinoma (PTC) treated with surgery with or without radioactive iodine therapy (RAI) in Makati Medical Center from 2013 to 2017. We collected the following factors through a review of charts: age at diagnosis, gender, family history of thyroid cancer, date of surgery, tumor size, capsular/lymphovascular invasion, lymph node/distant metastases, stage, risk of recurrence, dose of post-surgical RAI therapy, initial post-treatment serum Thyroglobulin (Tg) and anti-Tg antibody levels (Negative Tg level: suppressed non-stimulated Tg <0.2 ng/mL or TSH-stimulated Tg <1 ng/mL; Positive Tg level: suppressed Tg ≥1 ng/mL or a TSH-stimulated Tg ≥10 ng/mL or rising anti-Tg antibody levels), thyroid stimulating hormone suppression, post-operative imaging studies and levothyroxine dose. Response to therapy was checked 6-24 months post-therapy.

Results. We analyzed a total of 115 patients with PTC who underwent thyroidectomy. Patients who had family history of thyroid cancer were less likely to have an incomplete or indeterminate response (p=0.045). None of the patients with excellent response had lymphovascular invasion. Having a positive Tg (p=0.001) and positive anti-Tg postoperatively (p<0.001) were strongly associated with incomplete or indeterminate response.

Conclusion. Patients who were positive for thyroglobulin and anti-thyroglobulin post-operatively were strongly associated with incomplete or indeterminate response to therapy in PTC.

Key words: papillary thyroid cancer, response to papillary thyroid cancer therapy, well-differentiated thyroid cancer

INTRODUCTION

The most common endocrine malignancy is well-differentiated thyroid cancer.[1] In a report based upon the Surveillance, Epidemiology, and End Results (SEER) database from 1975 to 2012, the incidence of papillary cancer increased from 4.8 to 14.9 per 100,000. Compared to any other malignancies in recent years, the age- and gender-adjusted incidence of thyroid cancer has increased more rapidly. This was observed in both genders and all ethnic backgrounds.[2]

Several studies showed that Filipinos have a higher risk of recurrence rates and mortality in thyroid malignancies.[3-8] Kus et al., showed that Filipinos in Canada have a significantly increased risk of thyroid cancer recurrence in 5 years at 25% compared with all other racial/ethnic groups where the recurrence rate was at 9.5%, even after adjusting for confounders.[4] Lo et al., reported that papillary thyroid cancer (PTC), which is generally known to have a good prognosis, had more aggressive features in cases in the Philippines. Filipino patients are younger, have larger tumor sizes, and had a higher degree of distant metastases and recurrence rate.[5]

According to the 2015 American Thyroid Association (ATA) Guidelines, initial therapy for patients with differentiated thyroid cancer such as PTC should aim to improve survival (overall and disease-specific), reduce the risk of persistent/recurrent disease and associated morbidity, and accurate disease staging with risk stratification, while minimizing treatment-related complications and unnecessary therapy. The treatment recommendation for PTC is complete surgical resection, with postoperative adjunctive therapy such as radioactive iodine (RAI) and thyroid stimulating hormone (TSH) suppression. The ATA 2015 guidelines classify response to therapy as: (1) excellent response when there is no clinical, biochemical, or structural evidence of

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Corresponding author: Aivind Gabrielle G. Santiago, MD
Fellow-in-training, Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Makati Medical Center
No. 2 Amorsolo St., Legaspi Village, Makati City 1229
Tel. No.: +632-84207460
E-mail: ags0311@yahoo.com
ORCiD: https://orcid.org/0000-0002-7429-5206

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disease, (2) biochemical incomplete response when there is abnormal thyroglobulin (Tg) or rising anti-thyroglobulin (anti-Tg) antibody levels in the absence of localizable disease, (3) structural incomplete response for persistent or newly identified loco-regional or distant metastases and (4) indeterminate response for nonspecific biochemical or structural findings that cannot be confidently classified as either benign or malignant including patients with stable or declining anti-Tg antibody levels without definitive structural evidence of disease.[8] Each category has its own predicted clinical outcomes and management implications.

Response to therapy is one of the parameters that can be utilized to assess clinical outcomes of the disease and direct the clinical decision with regards to management and follow-up. This is especially important in Filipino patients, who tend to have a more aggressive course of PTC. Currently, we have little evidence regarding the response to therapy of Filipinos with papillary thyroid cancer using the 2015 ATA Guidelines. This study aims to identify factors independently associated with having an incomplete response to therapy in surgically treated Filipino patients with papillary thyroid cancer.

METHODOLOGY

The study is a retrospective cohort of all patients with papillary thyroid carcinoma who underwent surgery, with or without radioactive iodine therapy in Makati Medical Center from 2013 to 2017. The Institutional Review Board (IRB) of the hospital approved the study design. The inpatient and outpatient medical records of all adult patients aged at least 18 years old, who underwent thyroidectomy (lobectomy, near total, or total) with or without neck dissection, diagnosed through histopathology as having papillary thyroid carcinoma, with documented response to therapy up to 24 months post-surgery were reviewed and included in the study. No randomization was done because all charts that satisfied the inclusion criteria were included. We cross-referenced medical records, in-hospital cancer registry, and outpatient charts with attending endocrinologists for a comprehensive review of charts.

We collected the following information: age at diagnosis, gender, family history of thyroid cancer, date of surgery, tumor size, capsular or vascular invasion, presence of lymph node or distant metastases, stage, risk of recurrence, dose of post-surgical RAI therapy if done, initial post-ablative and post-surgical thyroglobulin (Tg) and anti-Tg antibody levels in serum, thyroid stimulating hormone (TSH) suppression, results of imaging studies done post-operatively (ultrasound, RAI whole body scan, CT scan, PET scan) and levothyroxine suppressive dose.

A negative Tg level refers to either a suppressed non-stimulated Tg <0.2 ng/mL or TSH-stimulated Tg <1 ng/mL, while a positive thyroglobulin level refers to either a suppressed Tg ≥1 ng/mL or a TSH-stimulated Tg ≥10 ng/mL or a rising anti-Tg antibody levels. The assay used for Tg levels is Immunoradiometric Assay (IRMA).

The primary outcome of the study is the response to therapy after six to 24 months, as defined by the 2015 American Thyroid Association Guidelines.[8] They were classified as having an (1) excellent response if they had a negative imaging and either a suppressed Tg <0.2 ng/mL or TSH-stimulated Tg <1 ng/mL, (2) biochemical incomplete response if they had a negative imaging and suppressed Tg more than or equal to 1 ng/mL or stimulated Tg more than or equal to 10 ng/mL or rising anti-Tg antibody levels, (3) structural or functional evidence of disease with any Tg level with or without anti-Tg antibodies, or (4) indeterminate response for nonspecific findings on imaging studies, faint uptake in the thyroid bed on RAI scanning, detectable non-stimulated Tg but <1 ng/mL, detectable stimulated Tg but <10 ng/mL or stable or declining anti-Tg antibodies in the absence of structural or functional disease. Patients who did not have RAI as part of their initial therapy were still included and grouped with the same definitions of response to therapy.

We required a minimum sample of 122 patients at 90% power to detect an odds ratio of 3.674 of multifocal type papillary thyroid carcinoma for an incomplete response in Filipino patients.[9] Of the 136 records reviewed, 115 satisfied the inclusion criteria. Our sample of 115 was greater than the 80% power requirement at a minimum of 91 patients. Descriptive statistics were used to summarize the general and clinical characteristics of the patients. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality of continuous variables. Continuous quantitative data that did not meet the normality assumption were summarized using median and range. Simple and multiple logistic regression analysis was used to determine the factors associated with an incomplete or indeterminate response to therapy post-thyroidectomy. Simple logistic regression was performed to determine whether there was an association between each independent variable and the dependent variable (incomplete/indeterminate response), before adjusting for other factors. Levothyroxine intake, TNM stage, tumor size, surgical margins, extrathyroidal extension, TSH level, thyroglobulin, anti-thyroglobulin and RAI were all included and analyzed in the multiple regression analysis due to their relevance in the AMES, ATA and MACIS criteria. The variables were adjusted by age, sex, and family history of thyroid cancer. Crude and adjusted odds ratios and corresponding 95% confidence intervals were reported. Missing observations were not imputed. Null hypothesis was rejected at 0.05 α-level of significance. STATA 15.0 (StateCorp SE, College Station, TX, USA) was used for data analysis (Figure 1).

RESULTS

We analyzed a total of 115 patients with papillary thyroid carcinoma who underwent thyroidectomy (Table 1). Overall, there were 68 (59%) with excellent response. Biochemical incomplete response was observed in 12 (10%), structural incomplete response in 30 (26%), and

Table 1. Response to therapy among post-thyroidectomy adult Filipinos patients with PTC (n=115)

	Total (n=115)	RAI + (n=90)	RAI – (n=25)
	Frequency (%)		
Excellent response	68 (59.13%)	51 (56.67%)	17 (68%)
Biochemical incomplete	12 (10.43%)	12 (13.33%)	0 (0%)
Structural incomplete	30 (26.09%)	23 (25.56%)	7 (28%)
Indeterminate response	5 (4.35%)	4 (4.44%)	1 (4%)

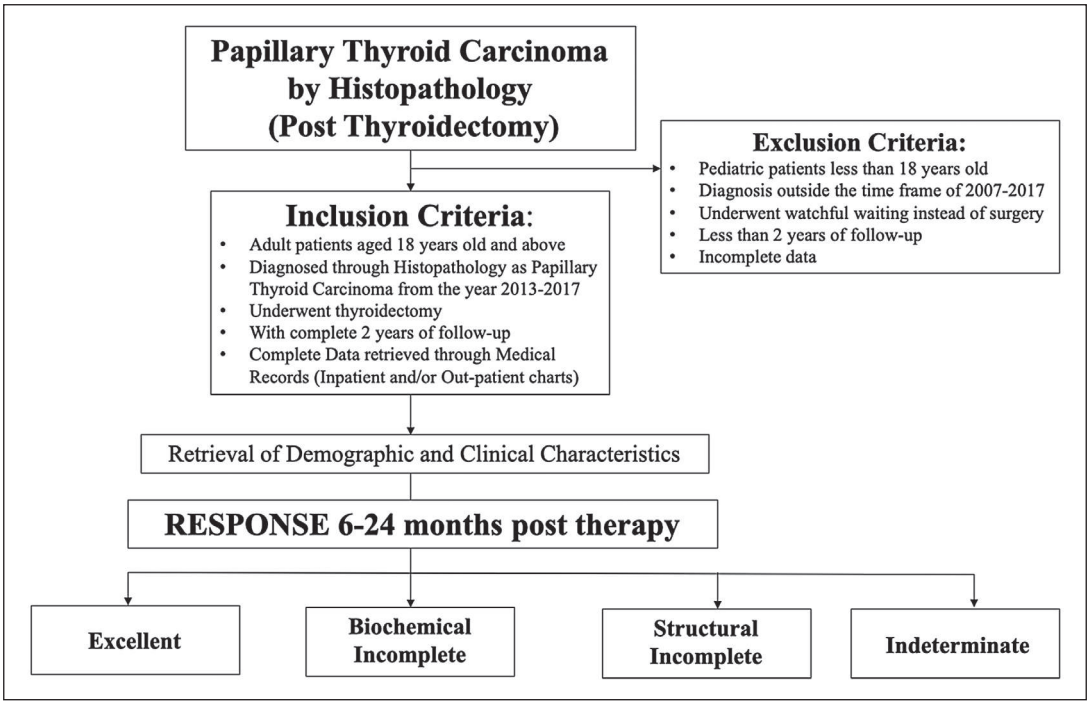

Figure 1. Study flowchart for data collection.

indeterminate response in five patients. When grouped according to RAI therapy, there were 90 (78%) who had received RAI. Among patients who received RAI, excellent response was observed in 51 (57%) patients. Among those who did not receive RAI, there were 17 (68%) who had an excellent response.

Comparing groups according to response type, the excellent response group had a higher proportion of patients who had reported having a family history of thyroid cancer (23.53% versus 8.51%, p=0.037), and none of them had lymphovascular invasion (0% versus 15%, p=0.001). The group who did not have an excellent response had a higher proportion of initially positive post-operative results for thyroglobulin (p<0.001) and anti-Tg (p=<0.001).

A higher proportion of high-risk patients on AMES and MACIS had incomplete or indeterminate responses (Table 2), but this was not statistically significant. On ATA, 53% of those with incomplete or indeterminate responses were classified as high risk, which was significantly higher than the excellent response group (p<0.001).

Patients who reported that they had a family history of thyroid cancer were approximately 70% less likely to have an incomplete or indeterminate response (cOR 0.302, 95% CI 0.09 to 0.97, p=0.045). Having a positive Tg (aOR 121.88, 95% CI 7.74 to 1918.46, p=0.001) and positive anti-Tg post-operatively (aOR 46.61, 95% CI 7.36 to 295.05, p<0.001) were strongly associated with incomplete or indeterminate response, even after performing multiple logistic regression to adjust for age, sex, and family histo hyroid cancer (Table 3).

DISCUSSION

The four responses to therapy were coined by Tuttle et al., and were utilized by the 2015 American Thyroid Association to assess the clinical status of patients with well-differentiated thyroid cancer post-therapy (total thyroidectomy and radioactive remnant ablation).[10] The four classifications of treatment responses namely: excellent, biochemical incomplete, structural incomplete and indeterminate have different clinical outcomes.

Patients classified as having excellent response had 1-4% recurrence, with only <1% disease specific death. Thirty percent of patients with biochemical incomplete response spontaneously evolved to No Evidence of Disease (NED), 20% achieved NED after additional therapy, 20% developed structural disease, and <1% had disease specific death.

According to the ATA, for structural incomplete response, 50-80% of patients continue to have persistent disease despite additional therapy, disease specific death rates at 11% with locoregional metastases and 50% with distant metastases.[8]

Patients with indeterminate response had 15-20% structural disease, <1% had disease specific death and the rest had resolved or stable disease.

Because of the clinical outcomes that each response represents, it impacts the type of management for each treatment response. A patient with excellent response to therapy is expected to have less intense follow-up and less TSH suppression. In biochemical incomplete response, monitor serum thyroglobulin and anti-thyroglobulin levels to determine the appropriate levothyroxine dose for TSH suppression, any additional tests and therapy, if indicated. Patients with structurally incomplete response usually need additional treatment modalities depending on the findings. In our study, the patients who did not receive RAI but had structurally incomplete response had either positive lymph nodes, metastatic tissue (bone or lung) or recurrence on the thyroid bed. Lastly, in

Table 2. Demographic and clinical characteristics of adult Filipino patients with papillary thyroid carcinoma (n=115)

	Total (n=115)	Incomplete/Indeterminate (n=47)	Excellent (n=68)	*p*
	Median (Range); Frequency (%)			
Age at diagnosis	48 (21–74)	53 (24–74)	45 (21–74)	0.073*
Sex				0.158†
Male	19 (16.52%)	5 (10.64%)	14(20.60%)	
Female	96 (83.48%)	42 (89.36%)	54(79.40%)	
Family history of thyroid cancer	20 (17.39%)	4 (8.51%)	16(23.53%)	**0.037†**
Levothyroxine dose per week, mcg	700 (250–2100)	800 (375–2100)	700 (350–1400)	0.467*
Tumor size, cm	1.6 (0.1– 8)	1.5 (0.1–7)	1.8 (0.1–8)	0.838*
Focality				0.485†
Unifocal	80 (69.57%)	31 (65.96%)	49(72.06%)	
Multifocal	35 (30.43%)	16 (34.04%)	19(27.94%)	
Surgical margin				0.738‡
Negative	105 (91.30%)	42 (89.46%)	63(92.65%)	
Positive	10 (8.70%)	5 (10.64%)	5 (7.35%)	
Capsular invasion				0.699‡
Negative	108 (93.91%)	45 (95.74%)	63(92.65%)	
Positive	7 (6.09%)	2 (4.26%)	5 (7.35%)	
Lymphovascular invasion				**0.001‡**
Negative	108 (93.91%)	40 (85.11%)	68 (100%)	
Positive	7 (6.09%)	7 (14.89%)	0 (0%)	
Extrathyroidal extension				0.777‡
Negative	99 (86.09%)	39 (82.98%)	60(88.24%)	
Positive	8 (6.96%)	4 (8.51%)	4 (5.88%)	
Grossly positive	8 (6.96%)	4 (8.51%)	4 (5.88%)	
Lymph node metastases				0.057†
Negative	97 (84.35%)	36 (76.60%)	61(89.71%)	
Positive	18 (15.65%)	11 (23.40%)	7 (10.29%)	
Metastases on whole body scan				0.483‡
Negative	106 (92.17%)	42 (89.36%)	64(94.12%)	
Positive	9 (7.83%)	5 (10.64%)	4 (5.88%)	
TNM stage				**0.003‡**
1	93 (80.87%)	36 (76.60%)	57(83.82%)	
2	15 (13.04%)	4 (8.51%)	11(16.18%)	
3	0 (0%)	0 (0%)	0 (0%)	
4	7 (6.09%)	7 (14.89%)	0 (0%)	
TSH post-op	0.34 (0.01–117.97)	0.43 (0.02–107.42)	0.31 (0.01–117.97)	0.352†
Thyroglobulin post-op				**<0.001†**
Negative	95 (82.61%)	27 (57.45%)	68 (100%)	
Positive	20 (17.39%)	20 (42.55%)	0 (0%)	
Anti-thyroglobulin post-op				**<0.001†**
Negative	95 (82.61%)	28 (59.57%)	67(98.53%)	
Positive	20 (17.39%)	19 (40.43%)	1 (1.47%)	
AMES risk				0.197†
Low	81 (70.43%)	30 (63.83%)	51 (75%)	
High	34 (29.57%)	17 (36.17%)	17 (25%)	
MACIS risk	4.9 (3.13–10.39)	4.93 (3.25–10.39)	4.89 (3.13–9.2)	0.179*
Low	99 (86.09%)	37 (78.72%)	62(91.18%)	0.058†
High	16 (13.91%)	10 (21.28%)	6 (8.82%)	
ATA				**<0.001**
Low	67 (58.26%)	20 (42.55%)	47(69.12%)	
Intermediate	14 (12.17%)	2 (4.26%)	12(17.65%)	
High	34 (29.57%)	25 (53.19%)	9 (13.24%)	

Statistical tests used: *Mann Whitney U test; †Chi-square test; ‡Fisher's Exact test

patients with indeterminate response, they are continually observed with appropriate biochemical (thyroglobulin, anti-thyroglobulin) and serial imaging tests; biopsy can be offered for suspicious looking lesions as well.[8]

This study had a total of 115 patients, majority of which are females (83.48%) with a mean age of 48 at diagnosis and have negative family history (17.39%). This is compatible with the usual profile of patients with PTC as characterized by previous studies.[11-13] Majority had an excellent response, as expected, as PTC is a disease with a a generally good prognosis. We looked at some of the factors that might affect the patient's response to therapy such as age, gender, family history, tumor size, surgical margin, capsular invasion, extrathyroidal extension, lymph node and distant metastases. A more advanced age was predisposed to having an incomplete response to therapy – this maybe due to a long duration of disease prior to diagnosis. However, the value was not significant.

Initial findings suggested female gender did not have an excellent response as expected, more commonly male gender is a poor prognostic indicator. However, upon further analysis, this was not found to be significant

Table 3. Predictors of incomplete or indeterminate response (n=115)

	Crude Odds Ratio (95% CI)	*p*	Adjusted Odds Ratio (95% CI)	*p*
Age at diagnosis	1.025 (0.997 – 1.05)	0.078		
Sex				
Male	Reference	-		
Female	2.178 (0.73 – 6.53)	0.165		
Family history of thyroid cancer	0.302 (0.09 – 0.97)	**0.045**		
Levothyroxine dose per week, mcg	1.001 (0.999 – 1.002)	0.461	1.001 (0.999-1.004)	.244
Tumor size, cm	0.989 (0.79 – 1.24)	0.926	1.022 (0.66-1.57)	.922
Focality				
Unifocal	Reference	-		
Multifocal	1.331 (0.60 – 2.97)	0.485		
Surgical margin				
Negative	Reference	-	Reference	-
Positive	1.5 (0.41 – 5.50)	0.541	0.663 (0.02-24.03)	.823
Capsular invasion				
Negative	Reference	-		
Positive	0.56 (0.10 – 3.02)	0.500		
Extrathyroidal extension				
Negative	Reference	-	Reference	-
Positive/grossly positive	1.538 (0.53 – 4.44)	0.426	1.380 (0.32-6.04)	.669
Lymph node metastases				
Negative	Reference	-	Reference	-
Positive	2.663 (0.95 – 7.48)	0.063	0.697 (0.06-8.77)	.780
Metastases on whole body scan				
Negative	Reference	-	Reference	-
Positive	1.905 (0.48 – 7.50)	0.357	2.131 (0.27-17.12)	.477
TSH post-op	0.999 (0.98 – 1.01)	0.863	0.990 (0.96-1.03)	.579
RAI+	1.625 (0.64 – 4.15)	0.310	1.713 (0.27-10.68)	.564
Positive thyroglobulin post-op	102.127 (5.97-1748.14)	**.001**	121.886 (7.74-1918.46)	**.001**
Positive anti-thyroglobulin post-op	30.789 (5.53-171.51)	**<.001**	46.611 (7.36-295.05)	**<.001**
AIC=50.26; BIC=88.57; Cox-Snell/ML R^2 =50.8				

probably because the number of females in the study far outnumbered males.

Initially, having a family history significantly showed an association with having an excellent response to therapy. Patients with a family history are likely to be more vigilant and consult much earlier with timely diagnosis and treatment. Upon multiple regression analysis however, the finding did not reach statistical significance.

The presence of lymphovascular invasion in the study equated to an incomplete response, which was true for 7 patients. Lymph node metastasis is the most common route of spread for papillary thyroid carcinoma, but its prognostic implication in several studies is conflicting.[14] Multifocality, lymphovascular invasion, absence of tumor capsule and extrathyroidal extension are multiple factors reported as predictors of nodal disease.[14] This finding might change the outlook of clinicians regarding the response to therapy in those with positive lymph node metastases. Tumor size, focality, capsular invasion as well as extrathyroidal extension did not appear to be significant predictors of response in this study.

A positive thyroglobulin (aOR 121.88, 95% CI 7.74 to 1918.46, p=0.001) and positive anti-Tg post-operatively (aOR 46.61, 95% CI 7.36 to 295.05, p<0.001) were strongly associated with incomplete or indeterminate response, even after performing multiple logistic regression to adjust for age, sex, and family history of thyroid cancer. A study by Matthews et al., showed an increase in relative risk of developing recurrence of papillary thyroid cancer if the serum thyroglobulin at the time of RAI is greater than 27.5 ug/L, with a positive predictive value of 31.3%.[15] Another study by Spencer showed a positive predictive value of 23.1% if the thyroglobulin level is 2 ug/L or higher.[16] However, prescribing a cut-off value for serum thyroglobulin level at the time of RAI that would reach clinical prognostic difference is difficult due to the heterogeneity of thyroglobulin assays, and other factors that may affect Tg levels such as positive anti-Tg and residual normal thyroid tissue.[15] The Tg level cut-off used in this study for being positive is a suppressed Tg of ≥1 ng/mL, a TSH-stimulated Tg of ≥10 ng/mL, or a rising anti-Tg antibody level as defined by ATA for biochemically incomplete response.

Based on the different risk scores utilized in the study, there is a higher proportion of patients classified as high risk on AMES and MACIS that had incomplete response but this was not statistically significant. However, when the 8th edition of AJCC/TNM staging and ATA 2009 risk stratification were used, there is significant difference between the 2 groups.[8] The patients with a higher TNM stage and classified as high risk in the ATA guidelines had incomplete response to therapy.

A limitation of the study is that the data collected were highly dependent on the records and charts retrieved. The parameters used in categorizing the patients' responses to therapy were dependent on facilities in which laboratory tests and imaging were available with accurate interpretation and reading. Also, there were 25 patients who were included in the study but did not undergo RAI, and were still classified and grouped according to the ATA response post-therapy.

The study by Matthews et al., and Spencer noted that the measurement of thyroglobulin level still plays a significant role even when taken at the time of RAI.[15-16]

Although there were a number of factors analyzed, another limitation is the small sample size. The level of significance was reached, but with a wide confidence interval.

The authors acknowledge that the sample size was calculated based on a variables already known to be strongly linked to recurrence rather than a factor that had the least association but could potentially have a biologically meaningful association. We recommend a similar multicenter prospective study, with a larger cohort of patients, that can more accurately identify the factors associated with poor responses to treatment among Filipino patients who will undergo thyroidectomy with or without RAI for papillary thyroid cancer.

A study done by Espiritu et al., among Filipino patients with papillary thyroid cancer showed the presence of BRAF V600E mutation in 70% of the study population. This finding may explain the difference in the behavior and course of the disease in this selected population.[17] The inclusion of such cytogenetic tests as an additional parameter to assess the prognosis of patients with PTC post therapy is recommended in future studies.

CONCLUSION

In conclusion, patients who were positive for thyroglobulin and anti-thyroglobulin post-operatively were strongly associated with incomplete or indeterminate response to therapy in papillary thyroid cancer. However, we recommend to have our results validated in a larger cohort of patients with papillary thyroid cancer.

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ORIGINAL ARTICLE

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The Effect of DPP4 Inhibitor on Glycemic Variability in Patients with Type 2 Diabetes treated with twice-daily Premixed Human Insulin*

Florence Hui Sieng Tan,[1] Chin Voon Tong,[2] Xun Ting Tiong,[3] Bik Kui Lau,[1] Yueh Chien Kuan,[1] Huai Heng Loh,[4] Saravanan A/L Vengadesa Pillai[2]

[1]*Endocrine Unit, Department of Medicine, Sarawak General Hospital, Malaysia*
[2]*Department of Medicine, Hospital Melaka, Malaysia*
[3]*Clinical Research Center, Sarawak General Hospital, Malaysia*
[4]*Faculty of Medicine and Health Sciences, University of Malaysia Sarawak (UNIMAS), Malaysia*

Abstract

Objective. To evaluate the effect of adding DPP4 inhibitor (DPP4-i) on glycemic variability (GV) in patients with type 2 diabetes mellitus (T2DM) treated with premixed human insulin (MHI).

Methodology. We conducted a prospective study in patients with T2DM on twice-daily MHI with or without metformin therapy. Blinded continuous glucose monitoring was performed at baseline and following 6 weeks of Vildagliptin therapy.

Results. Twelve patients with mean (SD) age of 55.8 (13.1) years and duration of disease of 14.0 (6.6) years were recruited. The addition of Vildagliptin significantly reduced GV indices (mmol/L): SD from 2.73 (IQR 2.12-3.66) to 2.11 (1.76-2.55), *p*=0.015; mean amplitude of glycemic excursions (MAGE) 6.94(2.61) to 5.72 (1.87), *p*=0.018 and CV 34.05 (8.76) to 28.19 (5.36), *p*=0.010. In addition, % time in range (3.9-10 mmol/l) improved from 61.17 (20.50) to 79.67 (15.33)%, *p*=0.001; % time above range reduced from 32.92 (23.99) to 18.50 (15.62)%, *p*=0.016; with reduction in AUC for hyperglycemia from 1.24 (1.31) to 0.47 (0.71) mmol/day, *p*=0.015. Hypoglycemic events were infrequent and the reduction in time below range and AUC for hypoglycemia did not reach statistical significance.

Conclusion. The addition of DPP4-I to commonly prescribed twice-daily MHI in patients with T2DM improves GV and warrants further exploration.

Key words: glycemic variability, dipeptidyl peptidase 4 inhibitors, premixed human insulin, continuous glucose monitoring, type 2 diabetes mellitus

INTRODUCTION

Glycemic variability (GV) has become an emerging target for optimal glycemic control in patients with diabetes independent of HbA1c.[1-3] Recent studies have highlighted the association of GV to hypoglycemia and its associated adverse consequences.[4-6] In addition, there are increasing data in the literature supporting association of GV to microvascular and macrovascular diabetic complications although definitive evidence on hard clinical outcomes remains limited.[1,6-9] Nonetheless, with the advent of continuous glucose monitoring (CGM), the focus of glycemic management in diabetes has moved beyond HbA1c to include reduction of GV and hypoglycemic events.

Type 2 diabetes mellitus (T2DM) is a progressive disease and many patients will require insulin therapy in order to achieve glycemic control. In Asia, premixed insulin, often in combination with metformin, is commonly used for the treatment of T2DM.[10,11] While more convenient for the patients, premixed insulin with a fixed ratio of prandial and intermediate insulin is less flexible and may be associated with more hypoglycemic risk and greater GV. In addition, in resource-limited countries and public institutions, premixed human insulin is still commonly prescribed. Premixed human insulin may further increase the GV compared to premixed insulin analogues due to its less physiological pharmacokinetic profile.[12,13] Hence, a strategy to reduce GV in patients on premixed human insulin is highly desired.

Incretin-based therapies especially the dipeptidyl peptidase 4 inhibitors (DPP4-i) have been increasingly used for the treatment of T2DM. Few studies have shown DPP4-i to be effective in reducing GV in patients treated

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Corresponding author: Florence Hui Sieng Tan, MD
Endocrinologist, Department of Medicine, Sarawak General Hospital
Jalan Hospital, 93586 Kuching, Sarawak, Malaysia
Tel. No.: +60 82 276666
Fax No.: +60 82 240767
E-mail: ftanhs@gmail.com
ORCiD: https://orcid.org/0000-0002-1258-6788

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with metformin.[14-17] Studies on the effect of DPP4-i on GV in patients with T2DM treated with insulin are very limited. We, therefore, undertook this study to evaluate the effect of Vildagliptin on GV in patients with T2DM treated with premixed human insulin.

METHODOLOGY

Subjects and study design

This was a prospective study involving adult patients with T2DM attending diabetes clinics in 2 state hospitals in Malaysia. Patients with HbA1c of 7-10% who were treated with stable dose of twice-daily premixed human insulin (30% regular insulin, 70% Neutral Protamine Hagedorn) for at least 3 months, with or without metformin as combination therapy, were recruited. Participants who consented attended baseline visit with a diabetes nurse educator and were briefed on the use of continuous glucose monitoring (CGM) before undergoing a 7-day blinded CGM (Medtronic MiniMed, Northridge, CA) to collect baseline GV data. They were instructed to perform self-monitoring of blood glucose (SMBG) 4 times daily for CGM calibration during the 7-day period and record any symptomatic hypoglycemic episode in the SMBG diary. Baseline demographics, insulin dosage as well as HbA1c and renal function were collected. Subjects and investigators were blinded to the results of the CGM until the end of the study.

Participants returned after completion of the 7-day CGM and were then started on vildagliptin (Novartis Pharma AG, Basel, Switzerland) for 6 weeks. The dose of Vildagliptin was determined based on calculated eGFR using MDRD (Modification of Diet in Renal Disease) IDMS (isotope dilution mass spectrometry) traceable formula. Vildagliptin 50 mg twice daily was prescribed for patients with eGFR ≥50 ml/min while patients with eGFR <50 ml/min received vildagliptin 50 mg daily as per prescription information recommendation. Drug accountability was assessed by tablet count. Throughout the study period, insulin doses were kept stable but may be adjusted by the investigators in the event of recurrent or severe hypoglycemia. The participants were also given the diabetes team's contact number for adjustment of insulin should they experience more frequent hypoglycemia with initiation of vildagliptin, as per usual clinical practice.

After 6 weeks of vildagliptin therapy, participants returned for the third trial visit and a repeat 7-day CGM was performed. Changes in weight, insulin dosage and any symptomatic hypoglycemic episode occurring during the study period were recorded. Data collected from the CGM device were analyzed with EasyGV software to derive the glycemic variability parameters. Primary outcome measures for GV were changes in mean amplitude of glycemic excursions (MAGE), standard deviation of the mean glucose levels (SD) and % coefficient of variation (CV). We also examined other secondary GV measures including M value, mean absolute glucose (MAG), continuous overlapping net glycemic action (CONGA), low blood glucose index (LBGI), high blood glucose index (HBGI) and lability index (LI). In addition, we explored quality of glycemic control with addition of DPP4-i treatment by assessing the % time in range (TIR) with blood glucose in target range of 3.9-10.0 mmol/L, % time above range (TAR), % time below range (TBR) and % of time spent in clinically significant level 2 hypoglycemia (blood glucose <3.0 mmol/L regardless of symptoms). Area under the curve (AUC) above and below blood glucose target of 3.9 and 10.0 mmol/L respectively, as well as glycemic estimate, i.e. estimated HbA1c (eA1c) from CGM data were also assessed before and after vildagliptin treatment.

Sample size and statistical analysis

A prior study investigating GV variable (MAGE) from matched pairs of study subjects indicated that the difference in the response of matched pairs was normally distributed with an estimated standard deviation of 3.0.[18] Based on the true difference in the mean response of matched pairs estimated at 3.5, we needed to study a minimum of 8 pairs of subjects to be able to reject the null hypothesis that this response difference was zero with a probability of (power) 0.8. The Type I error probability associated with the test of this null hypothesis was 0.05.[19] After incorporating 30% for non-response rate, the required sample size was 12 subjects.

Data analysis was performed using the IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). Continuous data were expressed as mean (standard deviation) or median (interquartile range); whereas, categorical data were reported as counts (percentages). Normality distributions were determined by Shapiro-Wilk test, a p-value of ≥0.05 considered the data distributions as normal. Means of normally distributed continuous data at baseline vs. end of study and before vs. after vildagliptin therapy were compared using paired t-test. For non-normally distributed variables, Wilcoxon Sign Rank test was used. A two-sided p-value <0.05 was considered to be statistically significant for both tests.

The study was registered at the Malaysian National Medical Research Register (NMRR 18-2293-43523) and approved by the Malaysian Medical Research and Ethics Committee. Written informed consents were obtained from all participants. The study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

RESULTS

Patient characteristics

Twelve patients (6 males) with a mean (SD) age of 55.8 (13.1) years old and mean duration of diabetes of 14.0 (6.6) years participated in the study. Their baseline demographic and clinical characteristics are presented in Table 1. They had significant microvascular and macrovascular complications and majority of them had concomitant hypertension and dyslipidemia. Mean HbA1c at baseline was 8.4 (1.0) % and mean eGFR was 62.1 (25.8) ml/min/kg/m^2. 42% of the participants had stage 3 chronic kidney disease. Two-thirds of them received metformin therapy in combination with their premixed insulin. Mean insulin dose was 0.63 u/kg/day. Treatment adherence was good with drug accountability of 98%.

Glycemic variability parameter

Table 2A summarizes the GV parameters derived from the CGM before and after DPP4-i treatment. The addition of Vildagliptin significantly reduced GV indices in our

Table 1. Demographic and clinical characteristics at baseline and end of study

	Baseline	End of study	*P* value
Age (years)	55.8 (13.1)		
Duration of diabetes (years)	14.0 (6.6)		
Duration on premixed insulin (years)	6.8 (3.6)		
Baseline HbA1c (%)	8.4 (1.0)		
Diabetes complication rate (%)			
Retinopathy	9 (75.0%)		
Nephropathy	10 (83.3%)		
Peripheral neuropathy	3 (25.0%)		
Ischemic heart disease	3 (25.0%)		
Cerebrovascular accident	1 (8.3%)		
Hypertension	11 (92.0%)		
Dyslipidemia	11 (92.0%)		
Drugs			
Metformin	8 (67.0%)		
RAAS blockade	11 (92.0%)		
Statin	11 (92.0%)		
Antiplatelet	6 (50.0%)		
Body Weight (kg)	75.1 (11.9)	73.7 (13.7)	0.54
BMI (kg/m^2)	29.4 (4.7)	28.6 (5.4)	0.42
Insulin dosage (unit/day)	47.2 (14.8)	46.5 (15.3)	0.26
Insulin dosage (unit/kg/day)	0.6 (0.2)	0.6 (0.2)	0.75
eGFR (ml/min/1.73m^2)	62.1 (25.8)	58.4 (24.3)	0.30

HbA1c: glycated hemoglobin, RAAS: renin–angiotensin–aldosterone system, BMI: body mass index, eGFR: estimated glomerular filtration rate. Data are mean (SD) and n (%) on 12 adult patients with Type 2 diabetes mellitus treated with premixed human insulin.

patients on twice-daily premixed human insulin. While the mean blood glucose was not different before or after Vildagliptin, standard deviation of the mean glucose levels (SD) and coefficient of variation (CV) were significantly reduced. Mean amplitude of glycemic excursions (MAGE), one of the most commonly used parameters to reflect GV, was reduced from 6.94 (2.6) mmol/L at baseline to 5.72 (1.9) mmol/L (p=0.018). CONGA was not different but there was a significant reduction in mean absolute glucose (MAG), M value and liability index (LI).

Glycemic control parameters

Estimated HbA1c derived from CGM data improved significantly from 7.36% to 6.60% (p=0.031). Body weight, insulin dose and renal function did not change significantly before and after Vildagliptin treatment (Table 1). There was an improvement in the time in range (TIR) at blood glucose of 3.9-10.0 mmol/L, contributed by significant reduction in time above range (TAR) as well as AUC for TAR (Table 2B). HBGI was significantly reduced. Overall hypoglycemic events were infrequent and there was no episode of severe level 3 hypoglycemia reported by the participants during the study period. There was a reduction in % time below range (TBR), AUC for TBR, as well as % of time with level 2 hypoglycemia (blood glucose below 3.0 mmol/L) with addition of Vildagliptin, but these parameters did not reach statistical significance. LBGI and GRADE also showed a non-significant reduction with Vildagliptin treatment.

DISCUSSION

Traditionally, patients with T2DM initiated on or intensified to twice-daily premixed insulin often have their oral anti-diabetes medication further simplified. Metformin therapy is usually maintained while other oral anti-diabetes agents including DPP4-i are typically discontinued.[20] Blood glucose control is then achieved by titration of insulin dosage or further intensification to basal-bolus insulin regimen. While these strategies may lower blood glucose and improve HbA1c, they are associated with increased risk of hypoglycemia and weight gain. The effect on GV may also be heterogeneous.

Premixed human insulin is commonly used for treatment of patients with T2DM, either at initiation of insulin therapy or during intensification from basal insulin.[10,21] While simpler, more convenient, and acceptable to patients due to reduced injection burden, it is less flexible and may be associated with higher glucose fluctuations. In addition, in

Table 2. Indices of glycemic variability and glycemic control parameters before and after vildagliptin therapy

	Before Vildagliptin	After Vildagliptin	*P* value
2A. GV parameters (mmol/L)			
Mean blood glucose	8.81 (2.43)	8.17 (1.63)	0.325
SD	2.73 (2.12 - 3.66)	2.11 (1.76 - 2.55)*	0.015[a]
% CV	34.05 (8.76)	28.19 (5.36)**	0.010
MAGE	6.94 (2.61)	5.72 (1.87)*	0.018
MAG	1.34 (1.16 - 1.82)	1.12 (0.89 - 1.39)**	0.002[a]
CONGA	8.13 (2.39)	7.58 (1.46)	0.400
M Value	9.18 (5.45 - 17.05)	3.56 (2.55 - 7.12)*	0.023[a]
LI	2.44 (1.43 - 4.48)	1.54 (0.92 - 2.31)[a, **]	0.002[a]
2B. Glycemic control parameters			
Estimated HbA1c (eA1c)	7.36 (1.51)	6.60 (0.92)*	0.031
% time in range	61.17 (20.50)	79.67 (15.33)**	0.001
% time above range	32.92 (23.99)	18.50 (15.62)*	0.016
% time below range	5.92 (9.74)	1.84 (2.58)	0.183
% time below 3.0 mmol/L	1.50 (2.88)	0.25 (0.62)	0.187
LBGI (mmol/L)	3.50 (3.38)	1.66 (1.28)	0.077
HBGI (mmol/L)	7.29 (4.60 - 12.67)	4.86 (2.99 - 7.42)*	0.034[a]
AUC above 10.0 mmol/day	1.24 (1.31)	0.47 (0.71)*	0.015
AUC below 3.9 mmol/day	0.03 (0.54)	0.01 (0.02)	0.163

MAGE: mean amplitude of glycemic excursions, MAG: mean absolute glucose, CONGA: continuous overlapping net glycemic action, LI: liability index, HbA1c: glycated hemoglobin, LBGI: low blood glucose index, HBGI: high blood glucose index, AUC: area under the curve.
Data are mean (SD) or median (interquartile range) on 12 adult patients with Type 2 diabetes mellitus treated with premixed human insulin.
* P<0.05 vs. before vildagliptin; ** P≤0.01 vs. before vildagliptin

resource-limited countries, premixed human insulin is still widely used. Compared to premixed insulin analogues, premixed human insulin is associated with a higher risk of hypoglycemia as well as higher postprandial glucose excursion.[13,22] Hence, a strategy to reduce GV in patients treated with premixed human insulin is highly desirable. Newer anti-diabetic drugs including the incretin-based therapy have been shown to reduce GV in addition to their glucose lowering effect.[23,24] Since its introduction more than a decade ago, DPP4-i has been widely used for glycemic management of patients with T2DM. Hence, we undertake the current study to examine if the addition of DPP4-i will improve GV in patients with T2DM treated with premixed human insulin.

The addition of a DPP4-i to an insulin regimen has been reported to have moderate efficacy in a meta-analysis,[25] reducing HbA1c around 0.5% without increasing the risk of hypoglycemia or weight gain. DPP4-i effect on GV has been less well-studied. A systematic review and meta-analysis performed by Lee et al., to evaluate the effect of DPP4-I compared to other oral anti-diabetes drugs on GV in patients with T2DM included 304 patients in 7 studies and found a significant reduction of MAGE for patients treated with DPP4-i compared to sulfonylurea.[26] All patients in the studies were drug-naive or on metformin monotherapy.

Comparatively, data regarding the effect of DPP4-i on GV in insulin-treated patients with T2DM are very limited. Nomoto et al., found dapagliflozin was not superior to DPP4-i in reducing GV in 29 patients with T2DM treated with insulin.[27] Li et al.,[18] examined the effect of vildagliptin in Chinese patients with uncontrolled T2DM treated with either basal or premixed insulin analogues with or without metformin and found significant improvement of GV in the group with vildagliptin added on. There was a significant reduction in MAGE and mean blood glucose but no improvement in SD nor AUC >10 mmol/L in the vildagliptin-treated group compared to placebo. Apart from the difference in the insulin regimen used (around 35% basal, and the remaining premixed insulin analogues), the CGM was performed in-hospital with controlled mealtime and meal composition.

In contrast, all our patients were on human premixed insulin with or without metformin and the CGM was performed in real-life outpatient home setting. Our study showed that while mean blood glucose was the same, the addition of vildagliptin significantly improved various GV parameters including a reduction in MAGE, SD, CV, MAG, M value and LI. Vildagliptin also significantly improved estimated HbA1c (eA1c) and time in range. There was a significant reduction in % time above range and AUC for blood glucose >10.0 mmol/L. This has been attributed to enhanced insulin release from pancreatic beta cells as well as suppression of glucagon secretion during hyperglycemia.[23,27] Furthermore, the reduction in hyperglycemia was achieved without increasing the AUC of hypoglycemia, due to its glucose-dependent insulinotropic effect. In fact, in our cohort of patients with long-standing diabetes with multiple co-morbidities and reduced renal function, the addition of vildagliptin reduced the % of time below range and AUC for blood glucose <3.9 mmol/L as well as % below clinically-significant level 2 hypoglycemia with blood glucose of <3.0 mmol/L. However, as overall hypoglycemic events were infrequent, these parameters did not reach statistical significance.

This study is limited by the lack of a control group. However, we tried to minimize confounding factors by keeping intervention to a minimum. We recruited patients who were on stable doses of insulin for at least 3 months and the insulin dose was not adjusted during the study, except for hypoglycemia. Baseline CGM results were kept blinded until the end of the study, study visits were primarily for insertion and removal of the CGM sensor and interaction with the diabetes nurse was solely for the use of CGM and for hypoglycemia management. In addition, the study period was kept short to reduce changes in lifestyle and other confounding variables. Indeed, we observed no significant changes in insulin dosage or body weight for the study period. Our vildagliptin treatment duration of 6 weeks was relatively short. Although pharmacokinetic study had shown that vildagliptin and its metabolite reached a steady state after 14 days of dosing,[28] we cannot be sure that a complete therapeutic effect had been achieved.

Our study strengths include the participation of insulin-treated high-risk patients with long duration of diabetes and multiple co-morbidities, in whom reduction of GV and hypoglycemic risk are of particular clinical relevance. Strategies to reduce GV in this group of patients are limited in the literature. In addition, compared to other studies which performed CGM for 3 days only (14-18), some under inpatient setting with standardized mealtime and composition, we examined GV via 7-day CGM under real-world ambulatory setting without interfering with the patients' usual lifestyle. Thus, we believe our results are applicable clinically and better reflect the effect of DPP4-i on GV in the real-world setting.

CONCLUSION

Our study examined an important treatment strategy in real-world setting for a vast number of patients receiving premixed human insulin where addition of DPP4-i inhibitor has not been considered a standard practice.[20] Our study added to the scarce literature that DPP4-i improved GV in patients with T2DM treated with twice-daily premixed human insulin. We suggest that its role and long-term benefits in this group of patients more vulnerable to hypoglycemia and diabetic complications should be further explored.

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ORIGINAL ARTICLE

Association between Degrees of Malnutrition and Clinical Outcomes among Non-critically Ill Hospitalized Adult Patients with Type 2 Diabetes Mellitus*

Freyja Diana Ramos,[1] Joy Arabelle Fontanilla,[1,2] Reginna Emiliene Lat[2]

[1]*Center for Diabetes, Thyroid and Endocrine Disorders, St. Luke's Medical Center, Global City, Taguig, Philippines*
[2]*Center for Weight Intervention and Nutrition Services, St. Luke's Medical Center, Global City, Taguig, Philippines*

Abstract

Introduction. Malnutrition among hospitalized patients is highly prevalent. This adversely affects outcomes with longer length of stay (LOS), higher treatment costs and increased mortality. People with diabetes mellitus (DM) are particularly vulnerable to malnutrition and its consequences.

Objective. To determine the association of nutritional status with LOS and mortality among adults with Type 2 DM.

Methodology. This was a retrospective study of 439 adult patients with type 2 diabetes admitted in the medical ward of a tertiary hospital from January 1, 2018 to December 31, 2018. Demographics, anthropometrics, feeding route, LOS and outcomes were taken from the Clinical Nutrition Service database; biochemical data were taken from the Healthcare System, and were analyzed.

Results. In our analysis, 83.8% were found to be malnourished with 50.3% moderately-malnourished (MM) (Nutrition risk level 1-2) and 33.5% severely-malnourished (SM) (Nutrition risk level ≥3). BMI category and malnutrition were the significant confounders for LOS. After controlling for BMI, LOS was longer by a mean of 2.2 days in SM compared to well-nourished (WN) patients (95% CI=0.49-3.95, p=0.012). Of the malnourished patients, 6.1% of SM and 0.5% of MM patients died. None of the WN patients died. Feeding route, admitted for neoplasm, low albumin levels and malnutrition were the confounding factors associated with mortality. After controlling for these factors, SM had higher odds of dying compared to MM patients [adjusted OR=8.91 (95% CI=1.04-76.18, p=0.046)].

Conclusion. Among hospitalized non-critically ill adult patients with type 2 diabetes, SM patients but not MM patients had significantly longer LOS compared to WN patients, and greater degrees of malnutrition were associated with higher mortality.

Key words: malnutrition, hospital outcome, diabetes mellitus

INTRODUCTION

Malnutrition, as defined by the World Health Organization (WHO), refers to deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients.[1] It is classified into undernutrition, which include stunting, wasting, underweight and micronutrient deficiencies or insufficiencies; and overweight, obesity and diet-related non-communicable diseases such as heart disease, stroke, diabetes and cancer. Using current WHO BMI guidelines, it is usually associated with a body mass index (BMI) of less than 18.5 kg/m^2 (underweight) or 30 kg/m^2 and above (obese).[2]

Hospitalized patients, regardless of their BMI, typically suffer from undernutrition because of reduced food intake due to illness-induced poor appetite, gastrointestinal symptoms, reduced ability to chew or swallow, or *nil per-os* status for diagnostic and therapeutic procedures.[3] Malnutrition is a debilitating and highly prevalent condition in the acute hospital setting. It is estimated that at least one-third of patients have some degree of malnutrition upon admission to the hospital. If left untreated, approximately two thirds of these patients will experience a further decline in their nutritional status during in-patient stay.[4] Its prevalence in the hospital setting has been widely documented in the literature to be between 20% to 50%.[5]

In the Philippine setting, the prevalence of malnutrition among hospitalized patients is between 48 to 53%. With these data, it is concluded that every hospital in the Philippines has malnourished patients.[6] Patients with

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Corresponding author: Freyja Diana A. Ramos, MD
Fellow, St. Luke's Medical Center – Global City
Rizal Drive corner 32nd Street and 5th Avenue,
Taguig City, 1634 Metro Manila
Tel. No.:8-789-7700 local 2086
E-mail: freyjadiana@yahoo.com
ORCiD: https://orcid.org/0000-0001-8395-3293

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diabetes mellitus are susceptible to malnutrition due to disease complications such as poor dentition, eating disorders, alterations in bowel movement or gastroparesis and cognitive disorders. Malnutrition in patients with diabetes was highly prevalent in the acute hospital setting, in which 37% had moderate risk, and 63% had high risk for malnutrition. Fifty-five percent of patients had mild to moderate malnutrition, and 45% of patients had severe malnutrition.[7]

An average of 10% loss of lean body mass results in immune suppression and increases the risk of infection, 15% to 20% loss will impair wound healing, and a 30% loss leads to the development of spontaneous wounds, such as pressure ulcers, an increased risk of pneumonia, and a complete lack of wound healing.[4] Malnutrition is associated with many adverse outcomes including depression of the immune system, impaired wound healing, muscle wasting, longer lengths of hospital stay, higher treatment costs and increased mortality.[8]

Patients who were admitted with some degree of malnutrition, and those patients who experienced a decline in nutritional status during their admission, had significantly longer hospital stay by an average of 4 days than patients both admitted and discharged as well-nourished.[9]

Due to the high prevalence of malnutrition and adverse outcomes in the hospital setting, every patient admitted should be screened for malnutrition risk. Nutrition Risk Screening (NRS) is the first step in identifying patients at risk for malnutrition. It uses recent weight loss, BMI and reduced dietary intake, combined with a subjective assessment of disease severity. Such subjective grading of illness severity may not accurately reflect current nutritional status and this tool does not allow for definitive diagnosis of malnutrition. However, it has been recommended for use in hospitalized patients and may be useful for prompting the initiation of nutrition support.[10] Patients who were screened to be nutritionally at-risk are further evaluated using nutritional assessment tool/s to label and classify malnourished patients.

Subjective Global Assessment (SGA) is a tool used to confirm the result of NRS. There are five questions focusing on history of unintentional weight loss over the past six months, dietary intake change, gastrointestinal symptoms of more than 2 weeks, functional capacity and metabolic demands of the underlying condition. Physical examination explores muscle, fat mass, and the existence of edema. Each feature is noted as normal, mild, moderate, or severe according to clinician's subjective impression. The nutritional status is classified as well-nourished, moderately-malnourished, or severely-malnourished.[5]

Malnutrition was prevalent on admission and discharge, and malnourished patients were older, suffered more serious disease, had comorbidities, and had longer hospital stay and higher risk of mortality.[9] Particularly among patients with diabetes, the factors associated with high nutritional risk for malnutrition were abnormal BMI, lower albumin, and lower total lymphocyte count (TLC).[7]

It is not clear what level of malnutrition is associated with poor hospital outcome specifically in patients with diabetes in the local setting. We studied the association of degrees of malnutrition and hospital outcomes in terms of length of stay and mortality among hospitalized patients with diabetes in the medical ward of a tertiary institution. In addition, we analyzed confounding factors affecting nutritional status in these patients and correlated them to the degrees of malnutrition.

Definition of terms

A. *Nutritionally at risk* is defined based on the NRS tool, with at least one of the following three criteria:
   1. BMI <18.5 kg/m^2 or ≥30 kg/m^2
   2. Weight loss within the last 3 months
   3. Severely ill, i.e., head injury, cancer, Intensive Care Unit (ICU) patients, sepsis, burns (>50 total body surface area or TBSA), bone marrow or solid transplantation, severe acute pancreatitis, patients on regular hemodialysis or peritoneal dialysis
B. *Well-nourished* or normal is a nutritional status defined by a nutritional risk level score of zero (Appendix).
C. *Moderately-malnourished* or moderate malnutrition is a nutritional status defined by a nutritional risk level score of 1 to 2.
D. *Severely-malnourished* or severe malnutrition is a nutritional status defined by a nutritional risk level of 3 and above.

Objective

To determine the association of nutritional status with length of hospital stay and mortality among adult patients with type 2 diabetes mellitus.

METHODOLOGY

Patients

This study included non-critically ill adult patients with type 2 diabetes mellitus aged 19 years and above, admitted for at least 24-hours in the medical ward. We excluded patients initially admitted in the intensive care unit (ICU) within the first 24-hours, patients admitted for executive check-up or chemotherapy, pregnant and surgical patients, and type 1 DM. This study was approved by the Institutional Ethics and Review Board with reference number CT-18251 on 21 February 2019.

Design

This was a retrospective analytical study that involved patients admitted in the medical ward of St. Luke's Medical Center – Global City in Taguig City, Philippines from January 1, 2018 to December 31, 2018. All patients admitted in the hospital were screened for nutrition risk by the nurse-on-duty using the NRS. Patients who were found to be nutritionally at risk on admission were assessed by the Clinical Nutrition Service (CNS) to determine their nutritional status (Appendix). Patients' nutritional status are then recorded in the database of the CNS. Eligible subjects were selected from this database.

Nine hundred forty-five patients were eligible for the study. Out of the 945 patients, 506 had incomplete laboratory results including one with type 1 diabetes and were thus excluded. A total of 439 patients were included in the study. The data collected from the CNS database were the

age, sex, diagnosis/reason for admission, co-morbidities, anthropometric measurements, route of feeding, NRS, SGA, LOS, and hospital outcomes (discharged or deceased). The white blood cell (WBC) count, glycosylated hemoglobin (HbA1c), and serum albumin of these patients were taken from the Healthcare System record of the hospital. The total lymphocyte count was calculated using the formula TLC = WBC x lymphocyte count %.

Sample size estimation

Sample size was calculated based on the comparison of the length of hospital stay among severely malnourished and well-nourished patients. Assuming that mean length of hospital stay among severely malnourished patients is 5.1 ± 4.9 SD days and for well-nourished patients, 2.9 ± 1.9 SD days,[7] with an alpha error of 5%, power of 95% and one-tailed alternative hypothesis, sample size calculated is 62 per group or 186 for three groups. Controlling for 4 more variables in the analysis, with an additional 20% for each control variable, final sample size required is 336.

Data analysis

Descriptive statistics was done using the mean and standard deviation for quantitative variables and frequencies and proportions for categorical variables.

Determination of the association between nutritional status and length of hospital stay was analyzed using univariate and multivariate statistics. ANOVA/t-test and linear regression were used for categorical and continuous independent variables, respectively, in the univariate analysis. Multiple linear regression was then utilized in the multivariate analysis using forward elimination.

Determination of the association of nutritional status and mortality was also analyzed using univariate and multivariate statistics. Malnutrition status was categorized as severely and moderately-malnourished in the analyses. Chi-square test and logistic regression for categorical and continuous independent variables, respectively were done in the univariate analysis. Crude odds ratio and the 95% confidence interval were also calculated. Multiple logistic regression was then utilized in the multivariate statistics using backward elimination.

To control for confounders, different demographic and clinical profiles were tested for their association with nutritional status in the univariate analysis using Chi-square test and ANOVA/t-test. Variables with p-value less than 0.30 were included in the multivariate analysis.

Analysis was done using Stata v.14. P-value less than 0.05 was considered significant.

RESULTS

Four hundred thirty-nine patients were included in the study, of whom 61.5% were males. The mean age was 67.4 years and mean BMI was 28.2 kg/m^2. Only 5.9% of the patients were fed via enteral tube feeding (nasogastric tube or gastrostomy tube), and the rest were fed *per orem*. The most common reason for admission was pneumonia/respiratory insufficiency (20.7%). Most (96.1%) of the patients had co-morbidities with cardiovascular (72.2%) being the most common (Table 1).

The prevalence of malnutrition among the 439 hospitalized patients with type 2 diabetes in the study was 83.8%. The proportion of moderately-malnourished and severely-malnourished patients were 50.3% and 33.5%, respectively. Older mean age was observed as the degrees of malnutrition increased. In terms of BMI, most of the patients were normal and obese I (both 27.3%), and a few were obese III (4.3%). Enteral tube route of feeding was noted in the malnourished group and none in the well-nourished group (Table 1). Among the variables, age group, BMI category, feeding route, metabolic derangement and neoplasm (as reasons for admission), and presence of co-morbidities (specifically cancer and lung disease) were the confounders of nutritional status (p<0.05).

Overall, the average LOS of patients was 6.7 days. Pairwise comparison showed that severely-malnourished patients had significantly longer LOS than patients who were moderately-malnourished and well-nourished. Furthermore, moderately-malnourished patients had significantly longer LOS than well-nourished patients (Table 2). Ten (2.3%) patients died as observed in the study. The proportion of deceased patients is also significantly different among the 3 groups: 9 (6.1%) patients and 1 (0.5%) patient died from the groups of severely-malnourished and moderately-malnourished patients, respectively. No deaths occurred in the group of well-nourished patients (Table 2).

Body mass index (BMI) and malnutrition were the factors significantly affecting length of stay. Holding nutritional status constant, for every one unit increase in BMI, the LOS decreased on the average by 0.2 day, or for every 5 units increase in BMI, the LOS decreased on the average by 1 day. Holding BMI constant, LOS increased on the average by about 2.2 days in severely-malnourished patients compared to well-nourished patients (Table 3).

In the univariate analysis, feeding route, admission for neoplasm, low albumin levels, and malnutrition were significantly associated with mortality. The odds of dying among patients on oral feeding were 0.13 or 87% less likely than patients on enteral tube feeding. Patients admitted for neoplasm had more than 4 times the odds of dying compared to those who were not admitted for this reason (Table 4).

Other reasons for admission were ear, throat and systemic infections, veno-occlusive disease, syncope, hypersensitivity reaction, neurodegenerative disorders and hematologic conditions.

The following reasons for admission had relative risks (RR) to be discharged alive: urinary tract infection [RR=1.02 (95% CI=1.01-1.04, p=0.496)], acute gastrointestinal disease [RR=1.03 (95% CI=1.01-1.04, p=0.262)], cerebrovascular disease [RR=1.02 (95% CI=1.01-1.04, p=0.592)], skin infections [RR=1.02 (95% CI=1.01-1.04, p=0.534)], acute musculoskeletal disease [RR=1.02 (95% CI=1.01-1.04, p=0.562)], and others [RR=1.03 (95% CI=1.01-1.04, p=0.362)].

The following co-morbidities had relative risks to be discharged alive: genitourinary [RR=1.02 (95% CI=1.01-1.04, p=0.576)], endometabolic [RR=1.03 (95% CI=1.01-1.04, p=0.257)], neurologic [RR=1.03 (95% CI=1.01-1.04, p=0.268)],

Table 1. Baseline demographics and clinical profile of patients

	Well-nourished n=71 (16.2%)	Moderately-malnourished n=221 (50.3%)	Severely-malnourished n=147 (33.5%)	Overall n=439	*p*-value
Age, mean years ± SD	55.9 ± 15.14	69.0 ± 12.70	70.6 ± 13.42	67.4 ± 14.27	<0.001**
Age groups (years), n (%)					<0.001
Young adult (19-35)	6 (8.5)	3 (1.4)	1 (0.7)	10 (2.3)	
Middle aged (36-55)	25 (35.2)	28 (12.7)	23 (15.6)	76 (17.3)	
Older adult (56-64)	20 (28.2)	43 (19.5)	23 (15.6)	86 (19.6)	
Young elderly (65-74)	7 (9.9)	79 (35.7)	70 (47.6)	156 (35.5)	
Old elderly (≥75)	13 (18.3)	68 (30.8)	30 (20.4)	111 (25.3)	
Sex, n (%)					0.161
Male	50 (70.4)	128 (57.9)	92 (62.6)	270 (61.5)	
Female	21 (29.6)	93 (42.1)	55 (37.4)	169 (38.5)	
BMI, mean kg/m^2 ± SD	33.6 ± 5.23	27.4 ± 6.10	26.8 ± 6.78	28.2 ± 6.63	<0.001**
BMI class (kg/m^2), n (%)					
Normal (18.5-<25)	3 (4.2)	69 (31.2)	48 (32.7)	120 (27.3)	<0.001
Underweight (<18.5)	0 (0.0)	9 (4.1)	14 (9.5)	23 (5.2)	
Overweight (25-<30)	8 (11.3)	71 (32.1)	35 (23.8)	114 (26.0)	
Obese I (30-<35)	36 (50.7)	51 (23.1)	33 (22.4)	120 (27.3)	
Obese II (35-<40)	20 (28.2)	10 (4.5)	13 (8.8)	43 (9.8)	
Obese III (≥40)	4 (5.6)	11 (5.0)	4 (2.7)	19 (4.3)	
Feeding route, n (%)					<0.001
Oral	71 (100.0)	217 (98.2)	125 (85.0)	413 (94.1)	
Enteral tube	0 (0.0)	4 (1.8)	22 (15.0)	26 (5.9)	
Reasons for admission, n (%)					
AKI/insufficiency	5 (7.0)	21 (9.5)	17 (11.6)	43 (9.8)	0.562
Pneumonia/respiratory insufficiency	12 (16.9)	44 (19.9)	35 (23.8)	91 (20.7)	0.456
UTI	5 (7.0)	8 (3.6)	6 (4.1)	19 (4.3)	0.460
Acute GI disease	10 (14.1)	22 (10.0)	16 (10.9)	48 (10.9)	0.624
CVD	0 (0.0)	7 (3.2)	5 (3.4)	12 (2.7)	0.301
Metabolic derangement	11 (15.5)	12 (5.4)	11 (7.5)	34 (7.7)	0.022
CAD	6 (8.5)	18 (8.1)	9 (6.1)	33 (7.5)	0.731
HTN/heart failure	9 (12.7)	15 (6.8)	10 (6.8)	34 (7.7)	0.237
Skin infection	3 (4.2)	5 (2.3)	8 (5.4)	16 (3.6)	0.269
Neoplasm	2 (2.8)	49 (22.2)	14 (9.5)	65 (14.8)	<0.001
Acute MS disease	3 (4.2)	7 (3.2)	4 (2.7)	14 (3.2)	0.839
Others	5 (7.0)	14 (6.3)	14 (9.5)	33 (7.5)	0.517
Comorbidities, n (%)					
Without comorbidities	8 (11.3)	6 (2.7)	3 (2.0)	17 (3.9)	0.002
With comorbidities	63 (88.7)	215 (97.3)	144 (98.0)	422 (96.1)	
Cancer	2 (2.8)	85 (38.5)	35 (23.8)	122 (27.8)	<0.001
Cardiovascular	47 (66.2)	166 (75.1)	104 (70.7)	317 (72.2)	0.307
Lung disease	5 (7.0)	22 (10.0)	25 (17.0)	52 (11.8)	0.048
Gastrointestinal	1 (1.4)	15 (6.8)	10 (6.8)	26 (5.9)	0.213
Kidney disease	18 (25.4)	79 (35.7)	61 (41.5)	158 (36.0)	0.066
Genitourinary	3 (4.2)	6 (2.7)	4 (2.7)	13 (3.0)	0.790
Endometabolic	12 (16.9)	22 (10.0)	15 (10.2)	49 (11.2)	0.244
Neurologic	5 (7.0)	21 (9.5)	21 (14.3)	47 (10.7)	0.192
Rheumatologic	2 (2.8)	2 (0.9)	6 (4.1)	10 (2.3)	0.128
Hematologic	1 (1.4)	3 (1.4)	0 (0.0)	4 (0.9)	0.362
Dermatologic	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	0.610
Total lymphocyte count, mean mm^3 ± SD	2045.3 ± 839.09	1761.7 ± 1602.49	1889.7 ± 4356.06	1850.4 ± 2781.74	0.741**
Albumin, mean g/dL ± SD	3.8 ± 3.69	3.1 ± 0.71	2.8 ± 0.67	3.1 ± 1.64	<0.001**
HbA1c, mean % ± SD	8.3 ± 2.25	7.2 ± 1.56	7.1 ± 1.65	7.3 ± 1.76	<0.001**

AKI=acute kidney injury. BMI=body mass index. CAD=coronary artery disease. CVD=cerebrovascular disease. DM=diabetes mellitus. GI=gastrointestinal. HbA1c=glycosylated hemoglobin. HTN=hypertension. MS=musculoskeletal. UTI=urinary tract infection. SD=standard deviation. **compared using one-way analysis of variance (ANOVA) (the rest were compared using chi-square)

Table 2. Length of stay and number of patients deceased according to nutritional status

	Well-nourished n=71 (16.2%)	Moderately-malnourished n=221 (50.3%)	Severely-malnourished n=147 (33.5%)	Overall n=439	*p*-value
LOS, mean days ± SD	4.1 ± 3.55	6.5 ± 6.03	8.3 ± 8.14	6.7 ± 6.66	<0.001*
Deceased, n (%)	0 (0.0)	1 (0.5)	9 (6.1)	10 (2.3)	0.001**

LOS=length of stay. *compared using one-way analysis of variance (ANOVA) **compared using chi-square

Table 3. Multivariate analysis of the association between factors and length of stay (number of days)

	Beta Coefficients (95% CI)	*p*-value
Body mass index	-0.2 (-0.29 – -0.10)	<0.001
Normal vs severely-malnourished	2.2 (0.49 – 3.95)	0.012
Normal vs moderately-malnourished	1.2 (-0.40 – 2.74)	0.142

rheumatologic [RR=1.02 (95% CI=1.01-1.04, *p*=0.625)], hematologic [RR=1.02 (95% CI=1.01-1.04, *p*=0.759)], dermatologic [RR=1.02 (95% CI=1.01-1.04, *p*=0.879)].

For every one unit increase in albumin, the odds of dying decreased by 63%. No mortality was recorded in the well-nourished group, hence only malnourished groups were analyzed. Severely-malnourished patients had more than 14 times the odds of dying compared to moderately-malnourished patients (Table 4). In the multivariate analysis

Table 4. Univariate analysis of the association between factors and nutritional status with mortality

	Unadjusted Odds Ratio (CI 95%)	*p*-value
Age group		
Elderly vs non-elderly	2.66 (0.55-12.51)	0.209
Sex		
Male vs female	2.55 (0.54-12.15)	0.224
Feeding route		
Oral vs enteral tube	0.13 (0.03-0.55)	0.001
BMI		
Normal vs other categories	0.95 (0.85-1.05)	0.282
Reasons for admission		
AKI/insufficiency vs none	1.02 (0.13-8.28)	0.982
Pneumonia/respiratory insufficiency vs none	0.42 (0.05-3.35)	0.397
UTI vs none	-	-
Acute GI disease vs none	-	-
CVD vs none	-	-
Metabolic derangement vs none	1.33 (0.16-10.85)	0.787
CAD vs none	3.21 (0.65-15.77)	0.130
HTN/heart failure vs none	3.10 (0.63-15.22)	0.142
Skin infection vs none	-	-
Neoplasm vs none	4.02 (1.10-14.67)	0.023
Acute MS disease vs none	-	-
Others vs none	-	-
Co-morbidities		
With vs without	0.98 (0.96-0.99)	0.521
Cancer vs none	1.76 (0.49-6.34)	0.383
Cardiovascular vs none	1.55 (0.33-7.42)	0.578
Lung disease vs none	0.82 (0.10-6.64)	0.855
Gastrointestinal vs none	1.80 (0.22-14.74)	0.581
Kidney disease vs none	1.80 (0.51-6.33)	0.350
Genitourinary vs none	-	-
Endometabolic vs none	-	-
Neurologic vs none	-	-
Rheumatologic vs none	-	-
Hematologic vs none	-	-
Dermatologic vs none	-	-
Total lymphocyte count	1.00 (1.00 -1.00)	0.298
Albumin	0.37 (0.17-0.81)	0.013
HbA1c	0.86 (0.56-1.32)	0.490
Nutritional status Severely-malnourished vs moderately-malnourished	14.35 (1.80-114.49)	0.001

Table 5. Association between malnutrition and mortality

Nutritional status	Adjusted Odds Ratio (CI 95%)	*p*-value
Severely-malnourished vs moderately-malnourished	8.91 (1.04-76.18)	0.046

however, only malnutrition was significantly associated with mortality. Those severely-malnourished had almost 9 times the odds of dying compared to moderately-malnourished patients (Table 5).

DISCUSSION

A total of 83.8% of hospitalized patients with type 2 diabetes were malnourished in our study. This is much greater than previously reported prevalence rates of hospital malnutrition in general (48-53%).[6] This suggests that patients with type 2 diabetes have a higher prevalence of malnutrition in the hospital setting.

Most of the patients were elderly, and increasing age was associated with higher degrees of malnutrition. Elderly patients are at risk for malnutrition due to frailty, polypharmacy, general health decline including physical disability, dementia, cognitive decline, poor appetite, eating dependencies, dysphagia, delirium and constipation.[11,12] Most of the patients admitted were male, however sex was not a significant factor for nutritional status. The most common reasons for admission were pneumonia/respiratory insufficiency, neoplasm, and acute gastrointestinal disease. Only neoplasm was associated with mortality but not length of stay. More than 96% of patients had co-morbidities, and cardiovascular disease was the most prevalent co-morbid condition. However, this did not significantly affect the nutritional status and hospital outcome.

In general, hyperglycemia on admission has been associated with poorer outcomes.[13] In our study, however, glycemic control based on HbA1c showed that a lower value was observed with more severe malnutrition. More chronically ill patients such as those with debilitating diseases and cancer may have better glycemic control related to reduction in food intake, presence of liver and/or kidney dysfunction. Furthermore, factors affecting the level of hemoglobin such as anemia and renal insufficiency may have contributed to these findings. Therefore, our study suggests that admission HbA1c may not be a robust predictor of mortality or length of stay in the face of malnutrition.

Among the different factors, age group, BMI category, feeding route, admission for metabolic derangement and neoplasm, presence of cancer and lung co-morbidities, albumin and HbA1c were the confounders of nutritional status. However, in the univariate and multivariate analyses, in addition to malnutrition in the hospital setting (i.e., moderately-malnourished and severely-malnourished), only BMI significantly affected and was negatively correlated with LOS, while feeding route, admission for neoplasm, and low albumin levels were significantly associated with mortality.

Well-nourished patients had the highest mean BMI among the 3 groups. Moderately-malnourished patients had higher mean BMI than severely-malnourished patients. Higher BMI was associated with shorter LOS but not associated with mortality based on the results of the study. Patients with type 2 diabetes tended to be more overweight or obese at baseline. Chronically-ill patients may have experienced weight loss possibly due to poor intake or appetite, depression, hypercatabolic state, systemic inflammation, etc., hence lower BMI compared to patients with more acute conditions. This may have contributed to higher BMI seen among patients with diabetes, who had shorter LOS. Severe malnutrition was also associated with longer LOS.

All well-nourished patients were fed through oral route or by mouth. Feeding through enteral tube was only observed in the malnourished groups. Patients who were fed by enteral tube had higher odds of dying compared to patients who were fed by mouth. Based on their clinical profiles, patients who were on tube feeding were more likely to be chronically-ill and have co-morbidities, hence these patients tended to be malnourished, predisposing them to higher risk of poor hospital outcomes. Among the reasons for admission, neoplasm was associated with 4 times the odds of dying. Malignant neoplasms are known to be associated with depressed immune system, reduced appetite and hypercatabolism, which can significantly affect nutritional status.

Higher levels of albumin were associated with reduced mortality in our study. Hypoalbuminemia has traditionally been seen as a marker for poor nutritional status. However, it is now posited rather to reflect an inflammatory state.[14] Inflammation often results in hypercatabolism with increased protein and caloric requirements. Measuring albumin levels may be useful for diagnosing inflammation and assessing nutrition risk by identifying patients at risk for adverse outcomes if adequate nutrition is not administered.[15] As inflammation resolves, albumin levels increase and nutrition risk is thus reduced. We also confirmed that malnutrition in hospitalized type 2 diabetes was associated with mortality. No mortality was reported among well-nourished patients. Mortality rate was highest in the severely-malnourished group with almost 9 times the odds of dying than the moderately-malnourished group.

This study analyzed the association between HbA1c and other factors affecting nutritional status to hospital outcomes among patients with type 2 diabetes. Contrary to other published literature, we observed that TLC was not associated with poor nutritional status. We confirmed the results of other studies done in elderly patients (who comprise the majority of our study population) that have likewise failed to find a correlation between TLC and malnutrition.[16] Our study was limited only to type 2 diabetes as we only had one case of type 1 diabetes among the eligible patients.

Type 1 and type 2 diabetes have different phenotypes in general, one of which is BMI. Patients with type 1 diabetes are generally not obese and patients with type 2 diabetes are generally overweight or obese.[17,18] The type of diabetes may have an impact on the results of BMI and other parameters. Available data were also limited to include patients who had complete laboratory results. Since HbA1c is affected by multiple factors such as anemia, renal insufficiency, and those associated with red blood cell turnover, point-of-care testing for glucose could have provided more information but was not available. Since the study was limited to non-ICU patients (to remove the confounding factor of being critically-ill as a cause of poor outcome), mortality rate was expectedly lower.

We recommend a prospective multicenter study involving patients with type 1 and type 2 diabetes on the effects of age, sex, BMI categories, types of diabetes, glycemic control, and TLC on the nutritional status and outcomes of hospitalized patients. Although BMI is part of the nutrition risk assessment for patients at risk for malnutrition in the hospital setting, further studies on optimal BMI category/range affecting hospital outcomes are recommended. Studies including other parameters indicating glycemic control such as point-of-care testing for glucose and continuous glucose monitoring are also suggested. We also recommended to study factors affecting the level of TLC, and the significance and consideration of this parameter on nutritional risk assessment in persons with diabetes.

CONCLUSION

Malnutrition is highly prevalent among hospitalized adult patients with type 2 diabetes. Lower BMI categories and severe malnutrition were associated with greater LOS. Severely-malnourished patients had longer LOS compared to well-nourished patients by an average of 2.2 days. Mortality was observed only in malnourished patients. Artificial feeding route, admission for neoplasm, lower albumin levels, and malnutrition were associated with mortality. Lower HbA1c levels were seen in malnourished patients, but did not correlate with length of stay or mortality. Greater degrees of malnutrition were associated with higher mortality.

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APPENDIX

St. Luke's Medical Center Global City

CLINICAL NUTRITION SERVICES

NUTRITIONAL ASSESSMENT AND RISK LEVEL FORM (ADULT)

Date Admitted	Room / Bed No.	File No.	PIN	
Patient's Name (Last, First, Middle Name)			Age	Sex
Height (m)	Weight (kg)	BMI		
Attending Physician	Diagnosis			

Criteria	Normal / Mild	Moderate	Severe
Weight Loss	☐ none	☐ < 10% of usual weight	☐ > 10% of usual weight
Food Intake (last 1-2 months)	☐ no change	☐ suboptimal	☐ starvation
Gastro symptoms (>2 weeks)	☐ none	☐ nausea, vomiting	☐ anorexia, diarrhea severe
Functional Capacity	☐ no change	☐ dysfunction < 3 weeks suboptimal work bedridden < 2 weeks	☐ bedridden > 2 weeks
Disease and relation to nutritional requirements	☐ no or low stress	☐ moderate stress	☐ severe stress
Physical Examination	☐ 0 subcutaneous fat and/or muscle loss	☐ +1 to 2 subcutaneous fat and/or muscle loss	☐ +3 subcutaneous fat and/or muscle loss
Edema / Ascites	☐ none	☐ none	☐ +1 or +2

SGA Grade	A	0 ☐	B	1 ☐	C	3 ☐
BMI	18.5 – 24.9	0 ☐	25 – 29.9	1 ☐	< 18.5 or ≥ 30	2 ☐
Albumin g/dL	> 3.4	0 ☐	2.5 – 3.4	1 ☐	< 2.5	2 ☐
TLC	≥ 1500	0 ☐	900 but < 1500	1 ☐	< 900	2 ☐

TOTAL SCORE	NUTRITION RISK LEVEL	NUTRITIONAL STATUS
☐	0 ☐ Level 1 LOW RISK 1-2 ☐ Level 2 MODERATE RISK ≥ 3 ☐ Level 3 HIGH RISK	☐ Normal ☐ Moderate malnutrition ☐ Severe malnutrition

Assessed by:

REGISTERED DIETITIAN
(Signature over Name Stamp)

Date/Time

GC-MPG-CNS-***-4-02-00 02/16

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Accuracy of Waist Circumference Measurement using the WHO versus NIH Protocol in Predicting Visceral Adiposity Using Bioelectrical Impedance Analysis among Overweight and Obese Adult Filipinos in a Tertiary Hospital

Leslie Daphne Kawaji[1] and Joy Arabelle Fontanilla[1,2]

[1]*Center for Diabetes, Thyroid and Endocrine Disorders, St. Luke's Medical Center, Global City, Taguig, Philippines*
[2]*Center for Weight Intervention and Nutrition Services, St. Luke's Medical Center, Global City, Taguig, Philippines*

Abstract

Objectives. The study aimed to compare the performance of weight circumference (WC) measurement using the World Health Organization (WHO) versus National Institutes of Health (NIH) protocol in identifying visceral adiposity, and to determine the association of WC with cardiometabolic risk factors among overweight and obese adult Filipinos.

Methodology. A retrospective study involving 221 subjects (99 males, 122 females) evaluated at an outpatient weight intervention center of a tertiary hospital. The WC was measured at the superior border of the iliac crest (WC-NIH) and midway between the lowest rib and the iliac crest (WC-WHO) for each patient. Using visceral fat rating (VF) derived via bioelectrical impedance analysis (BIA) as reference standard, diagnostic accuracy tests for both protocols (using cut-offs of ≥90 cm in males and ≥80 cm in females) were done. Cardiometabolic parameters were also obtained, and binary logistic regression was performed to determine associations with WC.

Results. Among males, WC-WHO had 96% sensitivity (95% CI 88.8%-99.2%) and 25% specificity (95% CI 9.77%-46.7%) while WC-NIH had 94.7% sensitivity (95% CI 86.9%-98.5%) and 29.2% specificity (95% CI 12.6%-51.1%) to predict high VF >12. Among females, WC-WHO had 100% sensitivity (95% CI 90%-100%) and 24.1% specificity (95% CI 15.6%-34.5%) while WC-NIH had 100% sensitivity (95% CI 90%-100%) and 4.6% specificity (95% CI 1.3%-11.4%). Prevalence of high VF was significantly greater among males – 75.8% (95% CI 66.1%-83.8%) vs. 28.7% (95% CI 20.9%-37.6%) in females (p<0.001). Among females, WC-NIH tended to have higher measurements than WC-WHO by an average of 4.67 cm. Females with WC-WHO measurements of at least 80 cm were approximately four times more likely to have low (<50 mg/dL) HDL levels (cOR 3.82, p=<0.05), even after adjusting for age (aOR 3.83, p=<0.05).

Conclusion. WC measurement using the WHO and NIH protocols were both highly sensitive but had low specificity in predicting high VF estimated via BIA among overweight and obese adult Filipinos in this study. WC-NIH measurements tended to be higher among the females, which may affect classification of central obesity when using this protocol. WC ≥80 cm measured using the WHO protocol was associated with low HDL levels among female subjects. Prospective studies conducted among the general Filipino population are recommended to verify these findings.

Key words: waist circumference, central obesity, visceral adiposity

BACKGROUND

Obesity is a complex condition increasingly recognized as an important risk factor in the development of cardiovascular disease and diabetes mellitus. In the Philippines, the prevalence of overweight and obesity among adults is 37.2%.[1] Although body mass index (BMI) is most commonly used to classify obesity, it cannot obtain a measurement of fat distribution, particularly central or visceral, which has been associated with increased cardiometabolic risk.[2] Central obesity is characterized by increased intraabdominal adipose tissue, which has been linked with altered lipoprotein metabolism,[3] promotion of insulin resistance,[4] and production of inflammatory adipokines.[5] In Asians, accumulation of intraabdominal fat can occur without overt increase in overall body mass. A study by Pagsisihan et al., among rural Filipino subjects noted the occurrence of cardiometabolic diseases at lower BMI cut-offs of 24 kg/m^2 and 23 kg/m^2 in males and females, respectively.[6]

While computed tomography (CT) and magnetic resonance imaging (MRI) are currently the gold standards for the quantification of visceral adiposity, they are considered too expensive, cumbersome and/or invasive for routine clinical use.[7] Waist circumference (WC) is a reliable surrogate marker of visceral fat mass, and its measurement is recommended in evaluating patients for obesity-related disease risk. Large population studies[8-10] have shown a significant association between WC and the risk of developing type 2 diabetes

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Corresponding author: Leslie Daphne R. Kawaji, MD
Fellow-in-training, Center for Diabetes, Thyroid and Endocrine Disorders,
St. Luke's Medical Center, Global City,
Rizal Drive corner 32nd Street and 5th Ave., Taguig 1634, Philippines
Tel. No.: +63-8-7897700
E-mail: ldkawaji@gmail.com
ORCiD: https://orcid.org/0000-0001-5285-8074

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mellitus (DM) and coronary heart disease independent of other risk factors such as hypertension, blood glucose elevation and dyslipidemia. The relationship between WC and health outcomes persists across different age groups, in males and females, and among several ethnic groups.[2]

Different clinical studies on cardiovascular morbidity and mortality have used different WC measurement sites such as above the iliac crest (recommended by the National Institutes of Health[11]), midway between the lowest rib and iliac crest (recommended by the World Health Organization[12]), the narrowest portion of the waist or below the lowest rib. In general, it is recommended to use bony anatomic landmarks to serve as easily identifiable fixed guides for measurement.[2] While there is no universal protocol for WC measurement, several cross-sectional studies have attempted to determine which WC measurement site better reflects visceral adiposity and cardiometabolic outcomes in the different ethnic groups.

Bosy-Westphal et al., conducted a study among Caucasian adults and children comparing 3 WC measurement sites, and concluded that WC is better correlated to subcutaneous (SFA) rather than visceral fat areas (VFA).[13] They determined that WC measured below the lowest rib was the better index of VFA and cardiometabolic risk. Another study in Ireland had similar findings, with WC measured below the lowest rib showing the strongest associations with hypertension, dyslipidemia and DM in both genders.[14]

In a study by Ma et al., conducted in Taiwan, WC measurement at the iliac crest (WC-IC) and midway between the lowest rib and iliac crest (WC-mid) were compared – they found greater correlations between WC-mid and VFA, blood pressure, blood glucose, hemoglobin A1c and lipid levels.[15] Identification of central obesity using WC-mid was also able to predict the development of DM after 31 months.

A systematic review of 120 studies evaluating different WC measurement criteria showed that the different sites had no impact on morbidity and mortality.[16] However, these studies determined that the site of WC measurement plays an important role in the evaluation of central obesity and cardiometabolic status. Hence, it may be important to determine which WC measurement site is better used for Filipino subjects in order to identify those at risk for adiposity-related complications and institute timely prevention.

OBJECTIVES

The general objective of the study was to compare the performance of WC measurement using the WHO versus the NIH protocol in predicting high visceral fat estimated by bioelectrical impedance analysis among overweight and obese adult Filipino patients at St. Luke's Medical Center, Global City.

Specific objectives were to: (1) Compare the sensitivity, specificity, predictive values, likelihood ratios and accuracy of the WHO and NIH protocols; (2) Determine the statistical agreement between the WHO and NIH protocols, disaggregating for males and females; and (3) Compare the association of WC measurements using the WHO versus NIH protocols with the clinical and biochemical cardiometabolic risk factors present among the subjects.

METHODOLOGY

Study Design

This was a single-center retrospective study conducted on Filipino patients aged 19 years old and above who were enrolled and evaluated at the Center for Weight Intervention and Nutrition Services (WINS) of St. Luke's Medical Center, Global City from January 2017 to December 2018.

Study Population

All overweight and obese Filipino patients aged 19 years old and above who were enrolled and evaluated at WINS from January 2017 to December 2018 and who did not fulfill the exclusion criteria were included in this study. Patients with the following conditions that could have interfered with accurate waist circumference measurement were excluded from the study population: abdominal mass, abdominal hernia, abdominal surgery in the past 3 months, and bariatric surgery in the past 3 months. Subjects found to have incomplete data were also excluded from analysis.

Study Procedures

Patient data which include charts, logbooks and electronic medical records were reviewed by the primary investigator. Demographic data such as age and sex were included.

Anthropometric data obtained were the height, weight, WC and visceral fat rating. Waist circumference expressed in centimeters (cm) was measured using a flexible, non-stretchable plastic tape measure at two sites for every patient: 1. At the horizontal plane on the superior border of the iliac crest (WC-NIH); and 2. At the horizontal plane midway between the lowest rib and the iliac crest (WC-WHO). Measurement to the nearest 0.5 cm was done at the end of a normal expiration and done twice for each site. The higher value was recorded in the event of a discrepancy between the two determinations. All anthropometric measurements were carried out by either of 2 clinical dietitians at WINS.

Visceral fat rating (VF) was obtained after the patient has fasted for at least 2 hours, using a multifrequency segmental body composition analyzer (TANITA MC-980MA PLUS) which uses bioelectrical impedance technology. Bioelectrical impedance analysis (BIA) is a practical, rapid and radiation-free modality widely used to analyze body composition. BIA measures the electric resistance between fat and components of other organs, and is used in clinical and epidemiological settings to estimate regional fat distribution.[17]

Studies comparing the accuracy of BIA in determining visceral fat accumulation have been done among Chinese,[18] Korean[19] and Japanese[17,20,21] subjects showing moderate to high correlation (r 0.605-0.904) with abdominal imaging using CT and MRI. However, there were observed differences in correlation attributed to the sex and BMI[19] of the subjects as well as the specification of the BIA machines used (such as single vs multifrequency,[18,22] bipolar vs tetrapolar electrodes,[22] or segmental vs whole body BIA[23,24]). Currently, CT and MRI remain the gold standards for quantification of visceral adipose tissue.

Cardiometabolic risk factors present during the initial evaluation of each patient were included, such as blood pressure (BP), fasting blood sugar (FBS), 2-hour post-glucose load values (2-hr OGTT), hemoglobin a1c (HbA1c), lipid profile, as well as the presence of hypertension, diabetes, dyslipidemia and use of relevant medications.

Operational definitions

Body mass index (BMI) was defined as the subject's weight in kilograms (kg) divided by the height in meters squared (m^2). Using the WHO criteria for Asians,[12] the subject is classified as overweight if the BMI is 23.0-24.9 kg/m^2 and obese if the BMI is ≥25.0 kg/m^2.

Central obesity was defined as WC of ≥90 cm in males and ≥80 cm in females according to WHO recommendations.[12]

High VF was defined as visceral fat rating above 12 units, while acceptable level ranges from 1-12 using BIA (TANITA MC 980MA). Visceral fat rating (presented as a value ranging from 1-59) is derived by applying predictive equations to the segmental impedance measurements.[22] An algorithm was developed by the manufacturer to assign VF values that were based on abdominal imaging by MRI, showing good correlation (r 0.84-0.886).[25-27]

Hypertension (HTN) was defined by systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg on repeated examination,[28] intake of anti-hypertensive medications, or prior diagnosis by a physician.

Diabetes mellitus (DM) criteria include use of oral hypoglycemic agents and/or insulin, a prior diagnosis by a physician, or if any of the following criteria were present: fasting blood sugar (FBS) ≥126 mg/dL, or hemoglobin A1c (HbA1c) ≥6.5%, or 2-hour oral glucose tolerance test (OGTT) result ≥200 mg/dL using 75 g anhydrous glucose load, or random blood sugar (RBS) ≥200 mg/dL accompanied by signs and symptoms of hyperglycemia such as polydipsia, polyuria and polyphagia.[29]

Diagnosis of dyslipidemia was based on intake of lipid-modifying drugs (such as statins, fibrates etc.), prior diagnosis by a physician, or presence of any of the following abnormal lipid profile results: total cholesterol (TC) ≥200 mg/dL, triglyceride (TG) ≥150 mg/dL, low density lipoprotein (LDL) ≥100 mg/dL, high density lipoprotein (HDL) <40 mg/dL in males and <50 mg/dL in females.[30]

Sample size

A minimum of 174 adults satisfying the inclusion/exclusion criteria is required, to compare, with 10% precision at 5% level of significance, the performance of WC measurements based on the NIH and WHO protocols in assessing central obesity among overweight and obese adult Filipino patients based on the assumptions that sensitivity and specificity of abdominal circumference are 76% and 79%, respectively,[15] and prevalence of central obesity among overweight and obese patients is 63.3%.[31]

Statistical analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for categorical variables. Shapiro-Wilk test was used to determine the normality distribution of continuous variables. Continuous quantitative data that met the normality assumption was summarized using mean and standard deviation (SD), while those that do not was described using median and range.

Continuous variables which were normally distributed were compared using the independent t-test. Otherwise, the non-parametric Mann-Whitney U test was used. For categorical variables, Chi-square test was used to compare the outcomes. If the expected percentages in the cells are less than 5%, Fisher's Exact test was used instead.

Sensitivity, specificity, predictive values, and likelihood ratios of WC-WHO and WC-NIH (using accepted cut-offs ≥90 cm in males and ≥80 cm in females[12,32]) to predict high VF (>12 via BIA) were calculated.

Bland-Altman analysis was used to determine the limits of agreement and the mean difference between WC measurements using the NIH and WHO protocols. Crude and age-adjusted odds ratios with 95% confidence intervals from binary logistic regression were computed to determine the association between WC and cardio-metabolic parameters.

All valid data were included in the analysis. Missing data were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

Ethical considerations

The protocol of this study adhered to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, and National Ethics Guidelines for Health Research. The investigators have completed the Good Clinical Practice (GCP) training on the responsible conduct of research with human data. The study only commenced upon the approval of the St. Luke's Medical Center Institutional Ethics Review Committee.

Identifiable data were purged from the study records and each patient was assigned a code number. A master list containing the code number and subject's hospital PIN was kept separately from the research data. The master list and all research data were stored on a password-protected computer which only the investigators could access. These records will be kept for a minimum of 5 years following completion of the study, after which electronic data will be deleted and any existing hard copies will be shredded.

RESULTS

We enrolled a total of 221 adult Filipinos who were either overweight or obese. They had a median age of 38 years, ranging from 19 to 71 years old. The median BMI was 35.17 kg/m^2 for males and 31.59 kg/m^2 for females. Median WC-NIH measurement was 115.2 cm for males and 107 cm for females. Median WC-WHO measurement was 111.5 cm for males and 99 cm for females. The median VF was 17 units for males and 10 units for females. Average values for the blood pressure, metabolic parameters, and co-morbidities are enumerated in Table 1.

Table 1. Clinical characteristics of the overweight and obese adult Filipinos (n = 221)

	All (n = 221)	Males (n = 99)	Females (n = 122)
Age (years)	38 (19-71)	38 (19-71)	38.5 (19-71)
Anthropometrics			
BMI (kg/m^2)	33.17 (23.37-92.64)	35.17 (24.59-92.64)	31.59 (23.37-67.15)
23.0-24.9 (%)	10 (4.52)	2 (2.02)	8 (6.56)
≥25.0 (%)	211 (95.48)	97 (97.98)	114 (93.44)
Waist circumference (cm)			
WC-NIH	111 (75-181)	115.2 (83-181)	107 (75-154)
WC-WHO	106 (71-199)	111.5 (81-199)	99 (71-156)
Visceral fat rating	12 (4-51)	17 (6-51)	10 (4-33)
Blood pressure (mmHg)			
Systolic BP	120 (90-170)	120 (100-170)	120 (90-140)
Diastolic BP	80 (60-120)	80 (60-120)	80 (60-100)
Metabolic parameters			
FBS (mg/dL)	97 (73-296)	100 (76-296)	94.5 (73-213)
2-hr OGTT (mg/dL)	128.5 (92-329)	135.5 (97-226)	124 (92-329)
HbA1c (%)	5.8 (4.9-12.5)	5.8 (5.2-12.5)	5.7 (4.9-8.4)
Total cholesterol (mg/dL)	185 (85.2-348)	182.9 (85.2-295)	186.5 (124-348)
Triglycerides (mg/dL)	126 (49-497)	132 (55-497)	124 (49-295)
HDL (mg/dL)	46 (27-87)	42 (27-84)	47.5 (28-87)
LDL (mg/dL)	118 (32-249)	117 (32-249)	118.5 (54-244.5)
Comorbidities			
Hypertension (%)	79 (35.75)	45 (45.45)	34 (27.87)
With HTN medications	75 (94.94)	42 (93.33)	33 (97.06)
Diabetes mellitus (%)	51 (23.08)	29 (29.29)	22 (18.03)
With DM medications	44 (86.27)	25 (86.21)	19 (86.36)
Dyslipidemia (%)	149 (67.42)	68 (68.69)	81 (66.39)
With lipid medications	63 (42.28)	31 (45.59)	32 (39.51)

Data are presented as median (range) or frequency (%)

Overall, WC had a high sensitivity and low specificity to detect VF above 12 via BIA across both NIH and WHO protocols for both sexes (Table 2). The prevalence of high visceral fat was at 75.8% (95% CI 66.1% to 83.8%) for males and 28.7% (95% CI 20.9% to 37.6%) for females. Consequently, positive predictive values were high for males, while negative predictive values were higher in females. Notably, accuracy was the same for males at 78.8% for both WC-NIH and WC-WHO. For females, the accuracy was at 32.0% for WC-NIH and 45.9% for WC-WHO.

Using Bland-Altman plots (Figures 1-3), we identified the agreement in WC measurement using the NIH protocol with the WHO protocol. To define the limits of agreement, at least 95% of the data points should lie within ±1.96SD of the mean difference. Pitman's test of difference in variance was also done concurrently.

On the average, WC-NIH tended to have higher measurements compared to WC-WHO by 2.19 cm (2.5%). Among males, WC-NIH had lower measurements than WC-WHO by an average of 0.85 cm (0.39%). In contrast, WC-NIH tended to have higher measurements than WC-WHO by an average of 4.67 cm (4.88%) among the female subjects. There is a statistically significant difference in variance between the NIH and WHO protocols of WC measurement (p<0.05) overall, in males and in females (Tables 3, 3.1).

Using log-transformed values, the mean difference (log NIH - log WHO) was calculated in the overall study population, then disaggregated by sex (Figures 4-6). There is a statistically significant difference in variance between the WC measurement protocols (p<0.05). The difference in variance was maintained even after classifying by gender (Table 3.2). On linear regression, there is a negative trend between the differences and averages of the WC values

Table 2. Diagnostic performance of WC-NIH and WC-WHO in predicting high visceral fat at recommended cut-off values, by sex

	Males (n = 99)			Females (n = 122)		
	WC-NIH	WC-WHO	*p*	WC-NIH	WC-WHO	*p*
Prevalence of high visceral fat (%)	75.8 (66.1-83.8)			28.7 (20.9-37.6)		<0.001[a]
Sensitivity (%)	94.7 (86.9-98.5)	96 (88.8-99.2)		100 (90.0-100)	100 (90.0-100)	
Specificity (%)	29.2 (12.6-51.1)	25 (9.77-46.7)		4.6 (1.3-11.4)	24.1 (15.6-34.5)	
PPV (%)	80.7 (70.9-88.3)	80 (70.2-87.7)		29.7 (21.6-38.8)	34.7 (25.5-44.8)	
NPV (%)	63.6 (30.8-89.1)	66.7 (29.9-92.5)		100 (39.8-100)	100 (83.9-100)	
LR+	1.34 (1.03-1.74)	1.28 (1.01-1.62)		1.05 (1.0-1.1)	1.32 (1.17-1.48)	
LR-	0.18 (0.06-0.57)	0.16 (0.04-0.59)		0	0	
Accuracy (%)	78.8 (69.4-86.4)	78.8 (69.4-86.4)		32 (23.8-41.0)	45.9 (36.9-55.2)	

Data are presented as an estimate (95% confidence interval)
Test positive: Females, WC ≥80 cm; Males, WC ≥90 cm
Disease positive: VF >12
a, p-value <0.05 on males vs females

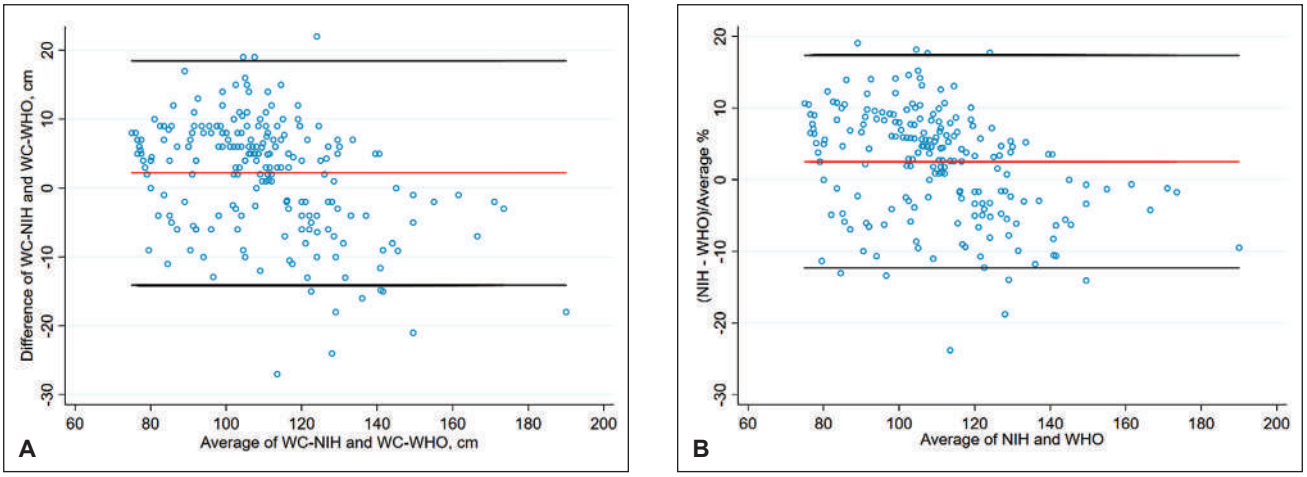

Figure 1. Bland Altman plot depicting agreement between WC-NIH and WC-WHO measurements in the overall study population. **(A)** Differences presented in cm, with an agreement range from -14.12 to +18.50 cm; **(B)** Percentage difference presented, with an agreement range from -12.33% to +17.37%.

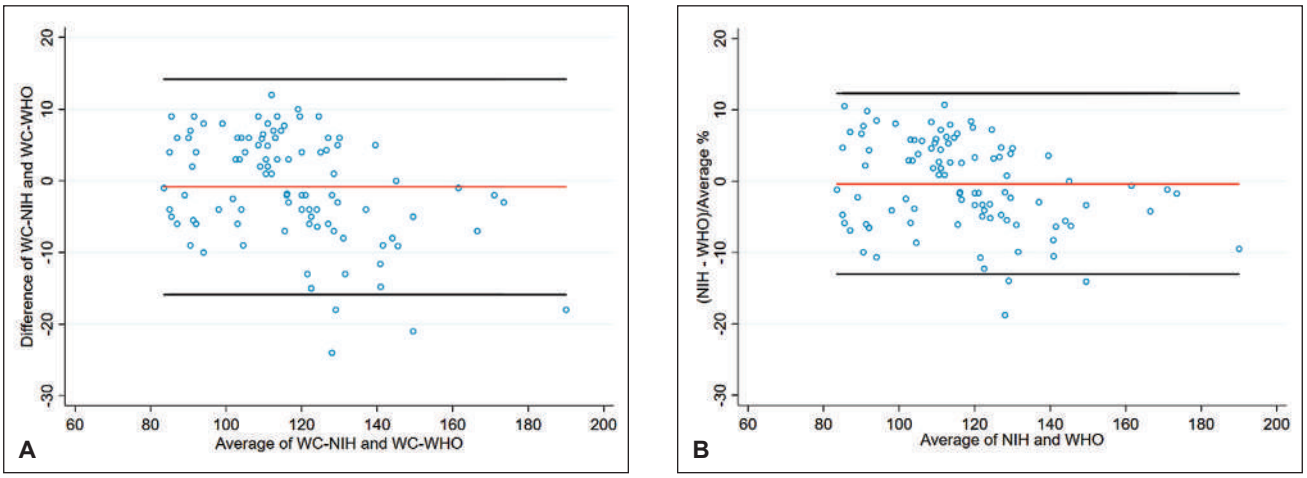

Figure 2. Bland Altman plot depicting agreement between WC-NIH and WC-WHO measurements among the male subjects. **(A)** Differences presented in cm, with an agreement range from -15.89 to +14.18 cm; **(B)** Percentage difference presented, with an agreement range from -13.04% to +12.27%.

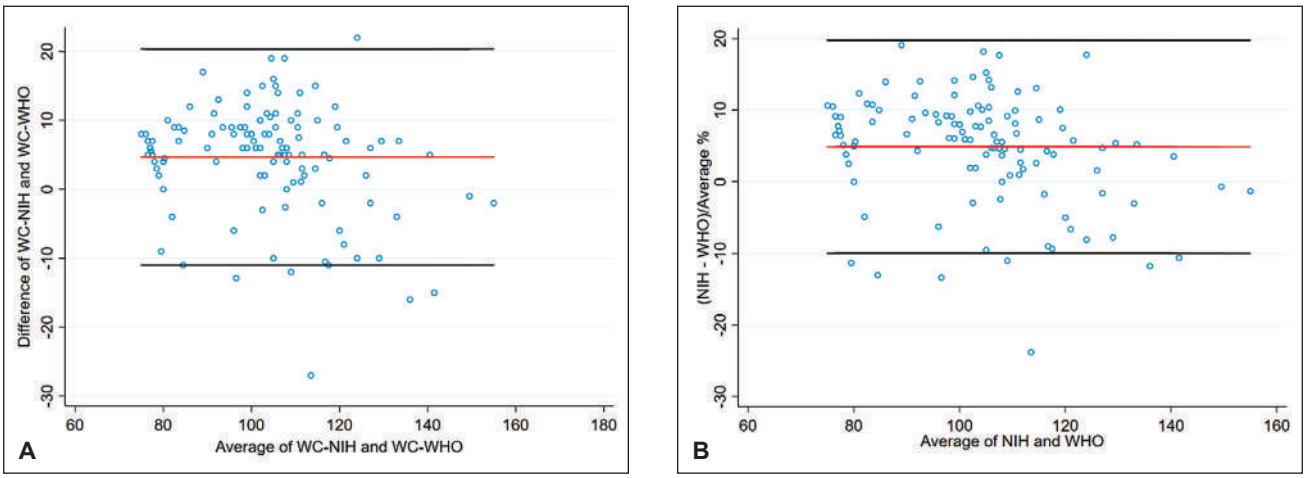

Figure 3. Bland Altman plot depicting agreement between WC-NIH and WC-WHO measurements among the female subjects. **(A)** Differences presented in cm, with an agreement range from -11.01 to +20.34 cm; **(B)** Percentage difference presented, with an agreement range from -9.99 to +19.75%.

Table 3. Bland-Altman agreement between WC-NIH and WC-WHO

	Overall	Males	Females
N	221	99	122
Limits of Agreement	-14.12 to 18.50	-15.89 to 14.18	-11.01 to 20.34
Mean difference between WC-NIH and WC-WHO (95% CI), cm	2.19 (1.11 to 3.27)	-0.85 (-2.35 to 0.65)	4.67 (3.26 to 6.07)
Range, cm	75.0 to 190.0	83.5 to 190.0	75.0 to 155.0
Pitman's Test of difference in variance (r)	-0.382	-0.375	-0.24
P-Value	<0.001*	<0.001*	0.008*

Limits of agreement = mean diff. ± 1.96*std dev. We expect that 95% of the differences will lie within the limits of agreement.
*p-value <0.05

Table 3.1. Bland-Altman agreement between WC-NIH and WC-WHO using percentage differences

	Overall	Males	Females
N	221	99	122
Limits of Agreement, %	-12.33 to 17.37	-13.04 to 12.27	-9.99 to 19.75
Mean difference between WC-NIH and WC-WHO (95% CI), %	2.52 (1.52 to 3.52)	-0.39 (-1.66 to 0.88)	4.88 (3.54 to 6.23)
Range, cm	75.0 to 190.0	83.5 to 190.0	75.0 to 155.0
Pitman's Test of difference in variance (r)	-0.38	-0.305	-0.301
P-Value	<0.001*	0.002*	0.001*

Limits of agreement = mean diff. ± 1.96*std dev. We expect that 95% of the differences will lie within the limits of agreement.
*p-value <0.05

Table 3.2. Bland-Altman agreement between log-transformed values of WC-NIH and WC-WHO

	Overall	Males	Females
N	221	99	122
Limits of Agreement	-0.12 to 0.17	-0.13 to 0.12	-0.10 to 0.20
Mean difference between WC-NIH and WC-WHO (95% CI)	0.025 (0.015 to 0.035)	-0.004 (-0.017 to 0.009)	0.049 (0.036 to 0.062)
Range	4.32 to 5.25	4.43 to 5.25	4.32 to 5.04
Pitman's Test of difference in variance (r)	-0.368	-0.289	-0.282
P-Value	<0.001*	0.004*	0.002*

Limits of agreement = mean diff. ± 1.96*std dev. We expect that 95% of the differences will lie within the limits of agreement.
*p-value <0.05

using the NIH and WHO protocols (p<0.05), suggesting the presence of proportional bias. The negative trend was still observed after classifying by gender (Table 3.3).

Females with WC of at least 80 cm via the WHO protocol were approximately four times more likely to have a low HDL level <50 mg/dL (cOR 3.82, 95% CI 1.36-10.65).

Table 3.3. Relationship between the mean and difference of waist circumference measurements using WC-NIH and WC-WHO

	Beta Coefficient (95% CI)	*p*
Average of WC-NIH and WC-WHO		
Overall	-0.15 (-0.20 to -0.10)	<0.001*
Males	-0.10 (-0.18 to -0.03)	<0.001*
Females	-0.13 (-0.21 to -0.05)	0.002*

*p-value <0.05

This association was maintained even after adjusting for age (aOR 3.83, 95% CI 1.37-10.70). We have insufficient evidence to demonstrate an association of WC with the rest of the cardiometabolic parameters in the subjects (Tables 4, 4.1).

DISCUSSION

To the best of our knowledge, this is the first study comparing WC measurement sites in evaluating central adiposity among Filipino subjects. Using the current recommended cutoffs (≥90 cm for males and ≥80 cm for females), sensitivity of both WC measurement sites for identification of elevated VF on BIA was similarly high in both genders. As a screening tool for central obesity, this attribute may be beneficial. However, specificity of both WC measurement sites was poor in both males

Table 4. Association between waist circumference and cardiometabolic factors in overweight and obese Filipino adults (N = 122)

	Males		Females	
	WC-NIH	WC-WHO	WC-NIH	WC-WHO
SBP ≥130	3.58 (0.73-17.54)	6.40 (0.77-53.32)	2.33 (0.12-44.82)	2.65 (0.57-12.24)
DBP ≥85	11.99 (0.68-210.44)	9.58 (0.54-170.11)	1.06 (0.05-20.80)	6.01 (0.34-105.46)
FBS ≥100	1.44 (0.41-5.07)	2.50 (0.59-10.63)	0.53 (0.07-3.92)	1.93 (0.65-5.69)
2-hr OGTT ≥140	3.96 (0.18-89.19)	2.60 (0.11-62.57)	0.15 (0.01-1.74)	1.35 (0.06-30.00)
HbA1c >5.6	1.75 (0.32-9.50)	1.28 (0.26-6.29)	1.38 (0.08-23.17)	1.11 (0.27-4.60)
TC ≥200	0.62 (0.40-0.18)	0.66 (0.16-2.62)	1.92 (0.19-18.99)	2.28 (0.77-6.70)
TG <150	1.22 (0.33-4.53)	0.57 (0.11-2.92)	0.60 (0.20-1.85)	0.56 (0.17-1.79)
Low HDL (<40 males; <50 females)	1.85 (0.46-7.44)	5.85 (0.70-48.73)	3.81 (0.38-37.68)	3.82 (1.36-10.65)*
LDL >100	0.82 (0.22-3.02)	0.95 (0.22-4.07)	1.48 (0.15-14.70)	0.75 (0.28-2.00)

Data are presented as crude OR (95% CI)
*p-value <0.05 vs. Low HDL

Table 4.1. Association between waist circumference and cardiometabolic factors, adjusted for age (N = 221)

	Males		Females	
	WC-NIH	WC-WHO	WC-NIH	WC-WHO
SBP ≥130 mmHg	3.82 (0.76-19.18)	6.57 (0.78-55.18)	2.37 (0.12-46.75)	3.31 (0.65-16.77)
DBP ≥85 mmHg	11.05 (0.62-195.53)	8.98 (0.51-159.64)	0.98 (0.05-19.56)	6.61 (0.37-118.94)
FBS ≥100 mg/dL	1.93 (0.65-5.69)	4.29 (0.83-22.12)	0.53 (0.07-4.12)	2.51 (0.72-8.71)
2-hr OGTT ≥140 mg/dL	4.18 (0.18-99.13)	2.70 (0.11-66.24)	0.18 (0.01-2.06)	1.20 (0.05-29.61)
HbA1c >5.6%	1.11 (0.27-4.60)	1.53 (0.28-8.32)	1.49 (0.09-26.17)	1.60 (0.35-7.44)
TC ≥200 mg/dL	2.28 (0.77-6.70)	0.64 (0.16-2.56)	1.98 (0.20-19.80)	2.37 (0.79-7.12)
TG <150 mg/dL	0.56 (0.17-1.79)	0.58 (0.11-2.97)	0.61 (0.20-1.85)	0.56 (0.17-1.79)
Low HDL mg/dL (<40 males; <50 females)	1.52 (0.36-6.33)	5.66 (0.66-48.20)	3.78 (0.38-37.44)	3.83 (1.37-10.70)*
LDL >100	0.75 (0.28-2.00)	1.09 (0.25-4.81)	1.44 (0.14-14.34)	0.76 (0.28-2.02)

Data are presented as adjusted OR (95% CI)
*p-value <0.05 vs. Low HDL

and females. This may be due to the nature of the study population, which consisted of overweight and obese individuals with almost all subjects exceeding the WC cutoffs. Accuracy of both WC-WHO and WC-NIH was also lower for the female subjects compared to the males, which may be due to the significantly lower prevalence of high VF among the female study population.

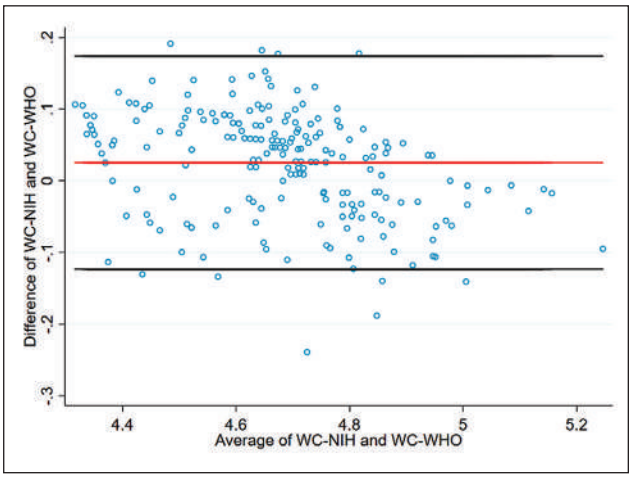

Figure 4. Bland-Altman plot depicting agreement between log-transformed WC-NIH and WC-WHO values in the overall study population. Agreement range was from -0.12 to +0.17.

In this study, diagnostic parameters of WC-WHO and WC-NIH were similar, with overlapping 95% confidence intervals of the sensitivity, specificity, predictive values, likelihood ratios, and diagnostic accuracy between both methods. This is in contrast to the findings of Ma et al., which determined that WC measured according to the WHO protocol was superior in detecting high visceral fat in females.[15] However, an important difference in their study is that they used CT to quantify VFA.

Based on Bland-Altman analysis, there was no agreement between WC measurements using the WHO and NIH protocols in this study. While we noted statistically significant differences in the variance of both WC measurement protocols (i.e., they are statistically not interchangeable), the average difference of 4.67 cm between WC-NIH from WC-WHO among the female subjects (compared to only 0.85 cm in males) may be more clinically significant – likely due to sex differences in body fat distribution. As seen in other similar studies, WC measurement location has a greater impact in females.[13,15] Classification of central obesity therefore might differ depending on the WC measurement protocol used, particularly among women. This supports the recommendation of the International Atherosclerosis Society (IAS) and International Chair on Cardiometabolic Risk (ICCR) Working Group on Visceral Obesity to be consistent in the use of WC measurement protocols.[33]

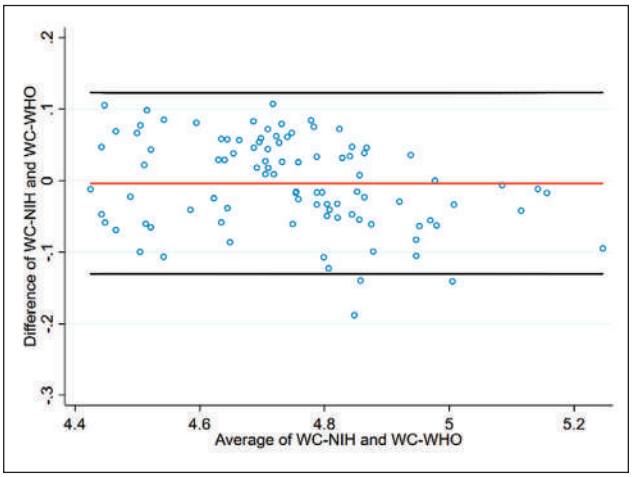

Figure 5. Bland-Altman plot depicting agreement between log-transformed WC-NIH and WC-WHO values among the male subjects. Agreement range was from -0.13 to 0.12.

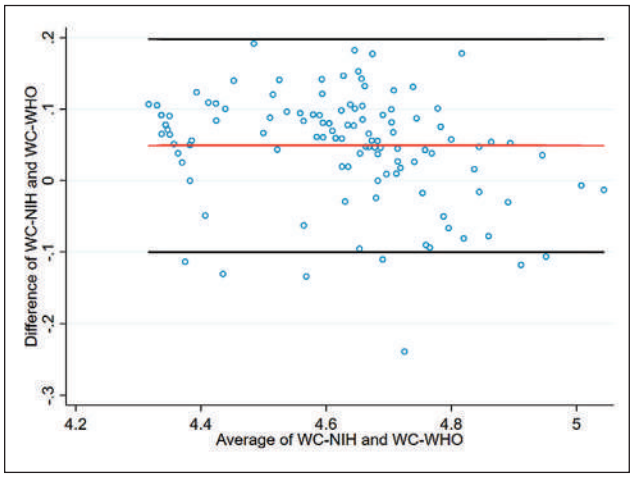

Figure 6. Bland-Altman plot depicting agreement between log-transformed WC-NIH and WC-WHO values among the female subjects. Agreement range was from -0.10 to +0.20.

Among the clinical and biochemical cardiometabolic parameters, only low HDL (<50 mg/dL) among the females had an association with WC-WHO even after adjusting for age. In contrast, Ma et al., determined that both WC-NIH and WC-WHO were associated with blood pressure, glucose levels, TG and HDL.[15]

Our study compared the relationships of WC-WHO and WC-NIH with visceral fat and cardiometabolic risk factors. While adequate comparison of parameters was attempted, several limitations are present in the current study. First is that other WC measurement sites were not evaluated. Other studies have concluded that WC measurement using the lowest rib was more reproducible and easier to obtain compared to WC-WHO[2,13,14]; hence its assessment could be clinically relevant.

Second, the gold standard methods (CT or MRI) for quantification of visceral adipose tissue were not utilized. While there are several studies that explored the correlation of BIA with the gold standards for visceral fat quantification, these studies were conducted on a relatively small number of subjects. BIA equations may also be population-specific,[22] and currently there are no studies evaluating the accuracy of BIA and visceral fat rating conducted among Filipinos.

Third, there were 2 observers who performed WC measurements throughout the study period, although only 1 observer performed both WC measurement methods in each patient, and interobserver variability could be a factor.

Fourth, temporal relationships between WC measurement and cardiometabolic diseases could not be established due to the cross-sectional study design.

Lastly, the single-center study population was composed of overweight or obese subjects hence our findings may not be generalizable to the non-overweight/non-obese Filipino.

CONCLUSION

Based on this study, WC measurement using the WHO and NIH protocols showed similarly high sensitivity but low specificity in identifying high VF estimated via BIA among overweight and obese adult Filipinos. WC-NIH measurements tended to be higher among the females owing to sex-related body fat distribution, which may affect classification of central obesity when using this protocol.

In this study, female subjects with an elevated WC measured using the WHO protocol were more likely to have low HDL levels, even after adjusting for age. We were unable to demonstrate an association between WC and the rest of the cardiometabolic factors among the subjects.

Prospective studies conducted among the general Filipino population using gold standard methods such as CT or MRI to quantify visceral adiposity are recommended to further determine the most appropriate WC measurement site and cut-offs to define central obesity, and further establish associations with cardiometabolic risk factors.

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Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
Both authors declared no conflicts of interest.

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ORIGINAL ARTICLE

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Predictors of Outcomes of Foot Ulcers among Individuals with Type 2 Diabetes Mellitus in an Outpatient Foot Clinic

Roy Raoul Felipe and Ma. Teresa Plata-Que

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, East Avenue Medical Center, Quezon City, Philippines

Abstract

Objectives. To determine the risk factors for recurrence and persistence of non-healing foot ulcers resulting in minor and major amputations.

Methodology. This was an ambispective cohort analysis of persons with diabetic foot ulcers consulting at the diabetic foot clinic of East Avenue Medical Center. Data were analyzed through multiple logistic regression.

Result. Two hundred sixteen patients with Type 2 Diabetes Mellitus and diabetic foot ulcers were included in the analysis; 50.9% were males and the mean age of the cohort was 55.8 ± 9.9 years. Outcomes of foot ulcers were: healed 44.5% (healed with no recurrence 30%, healed but with recurrence 14.5%) and not healed 55.5% (major amputation 11%, minor amputation, 21.5%, and persistently non-healing 23%). Multivariate logistic regression showed the following were independent risk factors for persistent non-healing ulcer: osteomyelitis (OR 66.5; CI 19.7, 217.8), smoking (OR 28.9; CI 6.8, 129.3, and peripheral arterial disease (PAD) (OR 56.8; CI 2.5, 877.2). Independent risk factors for ulcer recurrence were: plantar location of ulcer (OR 16.8; CI 6.8, 89.4), presence of more than one ulcer (OR 7.8; CI 3.6,31.6), and neuropathy (OR 11.2; CI 7.2, 19.9). For healed foot ulcers, mean healing time was 14 ± 3 weeks. Healing time was significantly reduced from 12 weeks to 4.5 weeks (p<0.001) if patients consulted earlier (within 4 weeks from sustaining an ulcer).

Conclusion. Only half (55%) of patients with diabetic foot ulcers consulting in a dedicated outpatient foot clinic had an adverse outcome of foot ulcers (major amputation 11%, minor amputation, 21.5%, and persistently non-healing ulcer 23%) while a small portion (14.5%) of patients had recurrent foot ulcers. Arterial obstruction, smoking, low hemoglobin, neuropathy, and osteomyelitis increase the likelihood of healing failure while the presence of multiple ulcers, plantar location of ulcers, and neuropathy increase the risk of ulcer recurrence.

Key words: foot ulcer, amputation, neuropathy, peripheral artery disease

INTRODUCTION

Foot ulcerations are still the leading cause of limb amputations in persons with diabetes.[1] In South East Asia, major amputation rates vary from as low as 9% to as high as 56%; while minor amputation rates are estimated at 27% and mortality from diabetic foot ulcers can be as high as 11%.[2,3] Internationally, major amputation rates vary - the major amputation rate in Pakistan was 14% while it was only 10.7% in the UK. These studies were both done in a dedicated outpatient foot clinic.[4,5] Ulcer recurrence is also a serious outcome next to amputations, and two important risk factors for ulcer recurrence are peripheral vascular disease and ulcer location. Patients with an ulcer on the plantar surface of the big toe are more likely to have recurrent ulcers.[6] The healing time of diabetic foot ulcers vary from as short as 52 days to as long 78 days. Factors that affect time of healing are Wagner staging, bacterial infection, osteomyelitis, and peripheral arterial disease (PAD).[5,7] Finally, ulcers may also fail to heal – risk factors associated with persistent ulcers are longer wound duration, number of ulcers, presence of infection, Wagner stage, age of patient, dialysis therapy, and peripheral vascular disease.[8]

In the Philippines there are no published foot ulcer related outcome studies done in dedicated outpatient foot clinics to date. However, numerous inpatient studies have shown major amputation rates as high as 56%. Predictors for major amputation include neuropathy, PAD, severity of ulcer staging, longer duration of diabetes, smoking, delayed consultation, delayed administration of antibiotics, and delayed surgical management.[9-12]

Data collected from this study will be used to aid clinicians to properly identify patients at risk for amputations and adverse foot outcomes so early referral to a diabetic foot clinic may be immediately done. Likewise, patients at risk for recurrence will be monitored more intensively and home routine foot care is taught at first consult.

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Corresponding author: Roy Raoul H. Felipe, MD
Section of Endocrinology, Diabetes and Metabolism,
Department of Medicine, East Avenue Medical Center
East Avenue, Quezon City, Philippines 1100
Tel. No.: +632-89280611
ORCiD: https://orcid.org/0000-0003-3255-9821

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The East Avenue Medical Center is the only tertiary government hospital in the Philippines to have a dedicated out-patient foot clinic (established in 1996). The goal of the clinic is to lower extremity amputation prevention by doing high risk foot screening, regular annual foot exam and applying standards of care for diabetic foot ulcers like off-loading, antibiotic therapy, weekly debridement and wound dressings.

The objective of the study was to determine the risk factors for foot ulcer recurrence and complications such as major amputation, minor amputation, or persistent ulceration. As a secondary objective, this study aimed to identify factors associated with healing time (defined as the number of weeks until complete epithelialization).

METHODOLOGY

The outpatient treatment of foot ulcers is done at the diabetic foot clinic of East Avenue Medical Center in Quezon City, Philippines - which is managed by an endocrine consultant and four endocrine fellows working in collaboration with orthopedic and vascular surgeons. The clinic sessions are held once a week. Patient management follows standards of care as given by international recommendations.[13] Upon consult patients are evaluated by etiology, presence of infection, and limb threatening/ life threating state. Those with limb threatening infection, extensive osteomyelitis, or needing major amputation or revascularization are subsequently admitted. Appropriate antibiotics are prescribed according to severity of infection; sharp debridement is done to remove gangrene and slough tissue; ulcer dressings and autolytic ointments are given by taking into consideration the wound bed, presence of granulation tissue, and degree of exudation. Patients are educated on off-loading, and follow-up is scheduled weekly at the minimum.

This was an ambispective study and ulcer outcomes were defined 1 year after initial consult. The retrospective cohort arm reviewed all charts from 2014-2017. For the prospective arm, patients consulting at the Out-Patient Foot Clinic recruited consecutively from January 2018 to May 2018 and were followed up for 1 year. Informed consent was obtained and privacy and confidentiality were emphasized. Individual case record forms contained only the initials of patient plus the code numbers assigned. Approval was obtained from the Institutional Ethics Review Board.

Inclusion criteria include: All adult patients, 18 years old and above, able to give written informed consent, consulting in the Diabetic foot clinic, diagnosed with Type 2 Diabetes Mellitus, presenting with ischemic/neuropathic/ neuroischemic foot ulcers, of any duration, and all charts of patients in the Diabetic foot clinic from 2014-2017.

Exclusion criteria include: patients unable to give written informed consent, patients with mental illness, patients with disease that may impair judgment and consent, non-diabetic foot ulcers, venous ulcers, cellulitis without ulcer, Charcot arthropathy without diabetic foot ulcer, and other unrelated skin diseases. Patients with missing data from the retrospective chart review were likewise excluded from the study. All charts from the retrospective arm with missing data and all patients from the prospective arm who were lost to follow up were excluded from the study.

Data collection included demographic data, duration of diabetes, presence of hypertension, atherosclerotic cardiovascular disease (ASCVD), or chronic kidney disease; laboratories collected were fasting blood sugar, HbA1c, lipid profile, creatinine, and hemoglobin at the time of initial consult (i.e., lipid profile were categorized as either "high" or "low" following clinical practice guideline targets of total cholesterol 200 mg/dL, Triglycerides 150 mg/dL, and HDL 40 mg/dL for male and 50 mg/dL for female[14] and hemoglobin, defined as "low" if lower than normal range); also noted were history of past foot ulcers and previous amputations, onset and duration of foot ulcer, presence of infection, PAD, neuropathy, osteomyelitis and Wagner staging.

The presence of peripheral neuropathy was assessed using the Michigan Neuropathy Screening Instrument.[15,16]

PAD was assessed by palpation of the posterior tibial and dorsalis pedis pulses and by measuring the Ankle Brachial Index using a hand held Doppler. PAD is defined as at least one of the following: ABI <0.9, a history of a peripheral artery revascularization procedure or angiography confirming PAD, non-compressible arteries (defined as ABI >1.4), abnormal waveforms (monophasic or biphasic) with ABIs of 0.9 –1.4, or absence of two or more pedal pulses on palpation.[17]

Osteomyelitis was diagnosed through probe to bone or X-ray findings.

Outcomes of this study were defined as:

1. Healed: (complete epithelization of a foot ulcer)
    a. Healed (complete epithelialization) with no recurrence within the observation period of 1 year.
    b. Recurrent foot ulcers (those who presented with foot ulcers that eventually healed within the observation period of 1 year but had another foot ulcer on the same site as the healed ulcer). If the recurrent ulcer eventually healed within the observation period, this was still included in the population of "recurrence."
2. Not healed:
    a. Resolved foot ulcer through Minor amputation (amputation below the malleolus)
    b. Resolved foot ulcer through Major amputation (amputation above the malleolus)
    c. Persistence of ulcer (non-healing of ulcer beyond the study period)

These outcomes were assessed by the primary investigator. Healed foot ulcers are defined as complete epithelialization of a foot ulcer with no signs of infection such as erythema, swelling, or exudative discharge. Recurrence is defined as a new foot ulcer occurring at the same site of a previous foot ulcer at any time during the study period. For persistent ulcers, these were diabetic foot ulcers that required major or minor amputation, or ulcers that failed to epithelialize beyond the study period.[13] Healing time was defined as the number of weeks it took for a foot ulcer to have complete re-epithelialization with resolution of any sign of infection.

Statistical analysis

Summary statistics were reported as mean ± standard deviation for continuous data with normal distribution or as median (interquartile range) for quantitative data with skewed distribution or as count (percent) for qualitative measures. Minimum and maximum values were also reported. Shapiro-Wilk's test was used to check for normality of quantitative data. Checks for homogeneity of patient characteristics were also performed. Multivariate regression analyses were performed to identify demographic and clinical characteristics independently associated with healed and unhealed ulcers, and healing time.

Subgroup analysis was done for 2 data sets: the first was for patients with "healed" ulcers – factors for recurrence vs. no recurrence were compared using all data collected. The second subgroup analysis using the Mann Whitney U test was done for patients with "healed" ulcers with no recurrence – specifically, the factors for number of weeks it took for complete epithelialization (healing time) were identified. Odds-ratios and 95% confidence intervals were estimated. Statistical significance was based on *p*-value ≤0.05. STATA v13 was used in data processing and analysis. The sample population was computed at a minimum of 196 patients with diabetic foot ulcer satisfying the inclusion/exclusion criteria to determine as significant, at 75% power and 95% confidence level, risk factors of major amputation at medium effect of 0.15 based on 18.46% rate of major amputation.[3]

RESULTS

Cohort description

There were a total of 216 adults with Type 2 diabetes mellitus and diabetic foot ulcers seen in this study. There were 130 charts for the retrospective arm and 86 patients for the prospective arm. The demographic and clinical characteristics of the study are summarized in Table 1. The average age was 55.8 years and there was an equal distribution of male and female (male 50.9%). Average duration of diabetes was 5 years. Only 22% of the cohort were smokers (n=48) and the most common comorbidity was hypertension seen in 38.9% of the cohort (n=84). Only 4.6% of the entire cohort had regular or routine foot care at home. The mean fasting blood sugar (FBS) was 145 mg/dL, mean HBA1c was 7.9%, mean creatinine was 0.9 mg/dL and the mean lipid profile of the cohort has total cholesterol less than 200 mg/dL but LDL greater than 100 mg/dL.

A plantar foot ulcer was seen in 25.5% of patients (n=54) and only 14.8% (n=17) had more than 1 foot ulcer upon consult. The average duration of diabetic foot ulcers prior to initial consult was 9 weeks.

Upon presentation, 38.4% (n=83) had PAD, while a similar percentage had osteomyelitis 34.7% (n=75). Majority of all patients (58.3%, n=126) had neuropathy.

Table 1. Characteristics of patients with diabetic foot ulcer according to healing outcome

	All (n = 216)	Not Healed Ulcers (n = 120) [Major amputation 24; Minor amputation 46; Persistently unhealed 50]	Healed Ulcers (n = 96) [Recurrence 31; No recurrence 65]
Age in years	55.8 ± 9.9	55.1 ± 10.7	56.2 ± 9.2
Male gender	110 (50.9%)	60 (50.0%)	50 (52.1%)
Duration of diabetes in years	5.0 (9.6)	8.0 (9.5)	3.0 (9.7)
Smoker	48 (22.2%)	40 (33.3%)[a]	8 (8.4%)[b]
Comorbidities			
Hypertension	84 (38.9%)	46 (38.3%)	38 (39.5%)
Chronic kidney disease	22 (10.2%)	8 (15.0%)	14 (14.6%)
Retinopathy	52 (24.1%)	30 (25.0%)	22 (22.9%)
With routine foot care	10 (4.6%)	4 (3.33%)	6 (6.25%)
Serum biochemistry			
FBS in mg/dL	145.0 (86.0)	173.5 (96.5)	121.0 (83.0)
HBA1c in %	7.9 (3.2)	8.9 (4.0)	7.7 (2.0)
Creatinine in mg/dL	0.9 (0.3)	0.9 (0.2)	0.8 (0.3)
Hemoglobin in g/dL	14.0 (2.4)	11.1 (3.4)	14.1 (1.6)
Cholesterol in mg/dL	189.0 (47.0)	196.0 (50.0)	151.0 (43.0)
Triglyceride in mg/dL	146.0 (67.0)	189.5 (91.0)	110.0 (54.5)
HDL in mg/dL	37.2 (11.0)	35.0 (11.3)	41.0 (11.0)
LDL in mg/dL	122.7 (46.0)	146.5 (39.5)	99.5 (32.5)
Plantar location of ulcer	54 (25.5%)	36 (30.0%)	18 (18.8%)
More than 1 ulcer on foot	17 (14.8%)	37(30.8%)[a]	7 (7.3%)[b]
Duration of ulcer in weeks	9.0 (3.4)	12.0 (4.8)	3.0 (1.0)
Peripheral Arterial Disease	83 (38.4%)	68 (56.7%)[a]	15 (15.6%)
Osteomyelitis	75 (34.7%)	60 (50.0%)[a]	15 (15.6%)
Neuropathy	126 (58.3%)	86 (71.7%)	30 (31.3%)
Wagner staging system			
I	11 (5.1%)	1 (0.8%)[a]	10 (10.4%)
II	120 (55.6%)	44 (36.7%)[a]	76 (79.2%)
III	12 (5.6%)	9 (7.5%)[a]	3 (3.1%)
IV	76 (35.2%)	70 (58.3%)	6 (6.25%)
V	6 (2.8%)	6 (5.0%)	-

FBS: fasting blood glucose, HbA1c: glycated hemoglobin, HDL: High density lipoproteins, LDL: low-density lipoproteins
Data presented as mean ± standard deviation, median (interquartile range) or count (percent).
[a]Single case

Non-healing foot ulcers

For non-healing foot ulcers vs. healed foot ulcers a significant proportion were smokers (33.3% vs 8.4%); had evidence of PAD (56.7% vs 15.6%); neuropathy (71.7% vs 31.3%); osteomyelitis (50.0% vs. 15.6%); had multiple ulcers (30.8% vs 7.3%); had higher levels of fasting blood glucose (173.5 vs. 121 mg/dL); cholesterol (196 vs. 151 mg/dL); triglyceride (189.5 vs. 110 mg/dL); LDL (146.5 vs. 99.5 mg/dL); plus lower levels of hemoglobin (11.1 vs. 14.1 mg/dL); lower HDL (35 vs. 41 mg/dL) and a longer ulcer duration prior to consult (12 vs 3 weeks). A higher proportion of the non-healing group had worse ulcer severity - majority presenting with Wagner IV (58.3% vs. 6.25%) or Wagner V (5% vs. 0%).

The prevalence of non-healing ulcer was 55.5% (n=120). The major amputation rate was 11% (n=24), minor amputation rate 21.5% (n=46), and persistently unhealed 23% (n=50). The major amputation rates in an outpatient setting are expectedly lower compared to inpatient rates of 50%.[11,12] In the outpatient setting, patients present with less severe ulcer staging and milder infections – these, along with prompt antibiotic treatment, weekly sharp debridement, offloading education, all contribute in lowering major amputation rates.[11]

Risk factors independently associated with major amputation, minor amputation, or persistent non-healing are shown in Table 2. Independent factors with the highest odds for non-healing are osteomyelitis (OR 66.5; CI 19.7, 217.8), PAD (OR 56.8; CI 2.5, 877.2), and smoking (OR 28.9; CI 6.8, 129.3). The data concurs with current literature that osteomyelitis and infection are the leading causes of major amputation in diabetic foot ulcers.[18-21] Our study did not analyze the location of osteomyelitis as a predictor of amputation – but other studies have found that osteomyelitis is more frequently found in the forefoot (90% of the time) - which has a better prognosis than if the osteomyelitis was in the hindfoot, because a hindfoot osteomyelitis significantly increases the chance of major amputation.[22]

Dyslipidemia (high TG and LDL, low HDL) is significant but only barely increased the odds for non-healing: high TG (OR 1.09; CI 1.0, 2.4), high LDL (OR 1.1; CI 1.0, 1.1), low HDL (OR 0.9; CI 0.8, 0.9).

We also found that every 1 g/dL decrease in hemoglobin from normal increased the chance of non-healing of a diabetic foot ulcer by 29% (p<0.0001).

Table 2. Independent risk factors for non-healing of diabetic foot ulcer (major amputation, minor amputation, and persistently unhealed)

Factor	Adjusted OR	95% CI	*p*-value
Smoking	28.9	(6.8, 129.3)	<0.0001*
Hemoglobin in g/dL	0.7	(0.4, 0.9)	<0.0001*
Triglyceride in mg/dL	1.1	(1.0, 2.4)	0.010*
HDL in mg/dL	0.9	(0.8, 0.9)	0.010*
LDL in mg/dL	1.1	(1.0, 1.1)	0.009*
Peripheral Arterial Disease	56.8	(2.5, 877.2)	<0.0001*
Osteomyelitis	66.5	(19.7, 217.8)	<0.0001*
Neuropathy	9.9	(7.4, 19.0)	0.010*

HDL: High density lipoproteins, LDL: low-density lipoproteins, OR: odds-ratio, CI: confidence interval
*Significant at 5% level

Recurrence

The prevalence for healed foot ulcers was 44.5% (n=96). Out of the 96 patients who had healed foot ulcers, only 14% of them had ulcer recurrence (n=31). Three important factors (Table 3) were found that predicted recurrence in healed foot ulcers: plantar location of ulcer (OR 16.8; CI 6.8, 89.4), presence of more than one ulcer (OR 7.8; CI 3.6,31.6), and neuropathy (OR 11.2; CI 7.2, 19.9).

Healing time

Table 4 shows the factors that affect healing time. Of the 65 adults with completely healed ulcer (no recurrence), the mean healing time was 14 weeks (98 days) ±3 weeks. Many studies have established various factors that affect healing time of ulcers which include: duration of ulcer, size and depth of ulcer, smoking, increased HbA1c, male gender, and presence of infection.[23-25] In our study, the only significant factor associated with time of healing was ulcer duration – those who consulted within 4 weeks of sustaining the ulcer healed faster (healing time 4.5 weeks) than those who delayed more than 4 weeks (healing time 12 weeks).

DISCUSSION

Out of 216 patients with diabetic foot ulcers the prevalence of healed foot ulcers was 44% (n=96) and the prevalence of non-healing was 55% (n=120). For the non-healing foot ulcers, major amputation rate outcome 20% (n=24), minor amputation outcome 38% (n=46), and non-healing outcome was 42% (n=50). For the healed foot ulcers, 32% (n=31) had recurrence within 1 year.

The major and minor amputation rates in an out-patient setting are expectedly lower than those of in-patient studies such as those located at the Philippine General Hospital (PGH) where the major amputation rate is 50%.[11,12] This can be attributed to factors such as ulcer severity presenting in the out-patient setting is less severe compared to the in-patient setting; or that an out-patient

Table 3. Independent risk factors for recurrence in healed ulcers

Factor	Adjusted OR	95% CI	*p*-value
Plantar location of ulcer	16.8	(6.8, 89.4)	0.031*
More than 1 ulcer on foot	7.8	(3.6, 31.6)	0.006*
Neuropathy	11.3	(7.2, 19.9)	0.010*

OR: odds-ratio, CI: confidence interval
*Significant at 5% level

Table 4. Factors affecting healing time

Factors	Healing Time In Weeks		*p*-value
Duration of diabetes: <10 years vs. ≥10 years	12 (8)	15 (17)	0.147
Smoker: yes vs. no	17 (14)	12 (9)	0.509
Routine foot care: with vs. without	3[a]	12 (11)	0.096
Plantar location of ulcer: yes vs. no	13.5 (10)	12 (12)	0.225
More than 1 ulcer on foot: yes vs. no	12 (8)	20 (8)	0.078
Foot ulcer duration on presentation: <4 weeks vs. ≥4 weeks	4.5 (7)	12 (11)	<0.0001*
Peripheral Arterial Disease: yes vs. no	9.5 (12)	12 (11)	0.885
Osteomyelitis: yes vs. no	14.5 (21)	12 (8)	0.485
Neuropathy: yes vs. no	12 (11)	10 (11)	0.560

Data presented as median (interquartile range).
[a]Single case
*Significant at 5% level

setting provides patients early consult, prompt antibiotic treatment, and weekly sharp debridement that are not done in most cases that are eventually admitted.[11]

Risk factors independently associated with non-healing of ulcers were smoking, low hemoglobin, dyslipidemia, and the presence of PAD, osteomyelitis, and neuropathy. Although dyslipidemia increased non-healing by only a small percentage, smoking was found to increase the risk of non-healing nearly 29 times compared to non-smokers. The significance of smoking in these patients reflect an acceleration of macrovascular disease and atherosclerosis prevalent in many persons with diabetes and is in itself, together with dyslipidemia, already an independent risk factor for developing peripheral arterial disease.[19]

Our study also found that for every 1 g/dL decrease in hemoglobin, the chance of non-healing of diabetic foot ulcer is increased by 52%.

The data also concurs with the study of Jeffcoate et al.,[5] where PAD was an independent risk factor for major amputation. As mentioned previously, the co-existence of CAD and PAD in patients with diabetes is well established. In a study by Poredos and Jug,[26] 50% of patients with macrovascular disease have co-existing PAD – reflecting the underlying atherosclerosis that plagues these patients predisposing to foot ulcer formation resulting in major amputation.

Neuropathy is an established risk factor for recurrence because this predisposes the feet to "unrecognized repetitive trauma."[27] Neuropathy also delays and impairs detection of new foot ulcers which tend to recur on the same site as old ulcers when healed patients begin to walk again.[28] Multiple ulcers are twice as likely to recur than single ulcers, have poor 12-month outcomes, and are almost invariably associated with ischemic ulcers and PAD.

Peters et al., found that patients had a 61% chance of increase in recurrence if the ulcer was located in the plantar area.[6] An ulcer on the plantar surface, when not offloaded properly, is subjected to repeated pressures which delay its healing.

This concurs with our finding that a plantar ulcer increased risk of recurrence; and if the ulcer was on the dorsal side of the foot, the non-healing outcome was reduced by 83%.

For ulcer recurrence, other risk factors were neuropathy and presence of more than 1 ulcer at the time of consult. These risk factors differ from two studies of Cardino and Panuda et al.,[11,12] where smoking and PAD were both significant risk factors for non-healing.

Possible sources of difference in these risk factors are that our patients are treated and seen in an outpatient foot clinic where their presentation is less severe than the population seen by in the PGH studies where the patients were admitted and had severe infection or ischemia.

The mean healing time was 14 weeks (98 days) ±3 weeks and only one factor was significant in affecting healing time, namely, the duration of foot ulcer prior to consult. Patients who consulted within 1 month of sustaining a foot ulcer tended to heal within 4.5 weeks while patients who waited after 1 month healed within 12 weeks (p<0.001). This again reinforces the findings of Cardino et al., that delayed treatment of foot ulcers lead to untoward foot complications.[2,11]

Compare this to the study of Messenger et al., where 335 patients consulting in an out-patient podiatry clinic were analyzed and foot ulcers had a median healing time of 52 days (7.5 weeks) and the factors that affected healing time were more severe wound staging, bacterial infection, osteomyelitis, and PAD.[7] In the study by Jeffcoate et al.,[5] of 449 patients with diabetic foot ulcers, the median healing time was 78 days (11 weeks) and again factors that affected healing time were severity of infection and presence of PAD. Once persons with diabetes sustain a foot ulcer it is imperative they consult immediately for prompt assessment and treatment of PAD, neuropathy, and infection to prevent non-healing.

Glycemic control (as tracked by fasting blood sugar and HbA1c) plays a major role in wound healing and diabetic foot ulceration. In two reasonably large prospective studies by Xiang et al., and Christman et al., their data found that an HbA1c of 7-8% increased the healed outcome of diabetic foot ulcers by 3 (OR 3.01, CI 1.32, 6.86) and "for each 1.0% point increase in HbA1c, the daily wound area healing rate decreased by 0.028 cm^2/day."[29,30]

Other studies done on diabetic foot ulcers in the inpatient and outpatient settings found no correlation between blood sugar control and healing of diabetic foot ulcers. In a prospective study by Fesseha et al., they found that "baseline A1c was not associated with wound healing in univariate or fully adjusted models." Furthermore, as they monitored the HbA1c changes in their 4-year study, they found that mean HbA1c changes were not associated with wound healing.[31] This finding was also seen by Ozenc et al., in 137 patients with diabetic foot ulcers that HbA1c was not a factor in developing diabetic foot ulcers or healing.[32] Sarinnapakorn et al., in a prospective study of 593 patients in Thailand found that blood glucose control is not markedly related to foot ulcer onset and healing. Their study identified that the significant factors for foot ulcer healing are age, duration of diabetes, dyslipidemia, neuropathy, cardiovascular disease, foot deformities, decreased pulses, prior amputation, and abnormal ankle-brachial index.[33]

Taking into account all these studies, the information at hand indicates foot ulcer healing is affected not just by glycemic control but also by the additional interplay of other factors like smoking, osteomyelitis, peripheral arterial disease, number of ulcers on consult, severity of infection, and delay of consult and treatment – important factors also found in our study.

The data obtained from this study are from patients presenting at a dedicated outpatient clinic. The profile of patients who are admitted for diabetic foot ulcers are much different because by definition, their admission may already be an indicator of a more severe infection necessitating intravenous antibiotics, limb threatening ischemia, or life-threatening sepsis. Thus, the data and independent risk factors presented in this study should be able to guide

clinicians seeing patients with foot ulcers in the outpatient setting – facilitating early referral to a diabetic foot clinic or specialist for those patients who have risk factors for non-healing, or intensive monitoring and education for patients who are at risk for foot ulcer recurrence.

CONCLUSION

Outcomes of foot ulcers can be classified into two groups: Healed and Not Healed. For unhealed foot ulcers whose specific outcomes can lead to major amputation, minor amputation, and persistent ulceration - the presence of PAD, smoking, dyslipidemia, low hemoglobin, neuropathy, and osteomyelitis all increase the likelihood of amputation or persistent non-healing.

For patients who have healed foot ulcers the presence of multiple ulcers, plantar location, and neuropathy all increase the risk for ulcer recurrence. When patients present to a foot clinic early (less than 4 weeks) the healing time is significantly shortened from 12 weeks to 4.5 weeks.

We recommend early identification of risk factors in patients with type 2 Diabetes Mellitus presenting with foot ulcers so that timely and early referral to an outpatient foot clinic or diabetic foot specialist may be immediately initiated.

Likewise, for patients with a past history of foot ulcers that have healed, identification of risk factors should lead to closer monitoring and education for routine home foot care. Ultimately, primary prevention is still the key to avoiding adverse foot outcomes. We encourage all persons with diabetes to have regular foot screening and foot care education.

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CASE REPORT

A Rare Occurrence of Premature Birth and Recurrent Acute Pulmonary Oedema in the Mother due to Cushing's Syndrome: A Case Report

Dorothy Maria A/p Anthony Bernard,[1] Ooi Xin Yi,[1] Hema Lata A/p Veerasamy,[1] Mohamed Badrulnizam Long Bidin,[2] See Chee Keong[1]

[1]*Hospital Sultan Haji Ahmad Shah, Pahang, Malaysia*
[2]*Hospital Kuala Lumpur, Kuala Lumpur, Malaysia*

Abstract

Presentation of Cushing's syndrome during pregnancy is extremely rare. We report a 21-year-old female with Cushing's syndrome diagnosed at 23 weeks of gestation and had recurrent acute pulmonary oedema during the antepartum and postpartum period. She delivered prematurely via emergency caesarean section at 28 weeks of gestation. This case highlights the rare occurrence of recurrent acute pulmonary oedema during pregnancy and consequential premature birth in a patient with adrenal Cushing's. She was diagnosed with adrenal Cushing's during the postpartum period based on unsuppressed serum cortisol after overnight and low-dose dexamethasone suppression test with a suppressed ACTH. CT scan of the adrenal glands revealed a right adrenal cortical adenoma. The risk of complications in infants and mothers who suffer from Cushing's syndrome needs to be handled carefully. The diagnosis of Cushing's syndrome in pregnant women often overlaps and is difficult to establish in early pregnancy.

Key words: Cushing's syndrome, pregnancy, acute pulmonary oedema

BACKGROUND

Cushing's syndrome is rarely reported during pregnancy as most women with Cushing's syndrome usually present with subfertility secondary to hypercortisolism-induced ovulatory dysfunction. Only 220 cases of Cushing's syndrome in pregnancy have been reported in a recent systematic review over a 52-year period.[1] The diagnosis of Cushing's syndrome in pregnancy is difficult and often missed as weight gain, development of striae, hyperglycemia and hypertension overlap with pregnancy itself. The levels of serum cortisol, corticosteroid-binding globulin and ACTH are increased during normal pregnancy and result in potential diagnostic difficulty.[2] There are also no standardized serum cortisol and urinary cortisol reference ranges in pregnancy.[3] In cases of successful conception, acute pulmonary oedema has been rarely reported. We report a patient with Cushing's syndrome diagnosed during pregnancy complicated by severe and life-threatening recurrent acute pulmonary oedema and premature birth.

CASE

A 21-year-old Malay female of middle socioeconomic status, first presented with acute pulmonary oedema at 23 weeks of gestation when she was admitted to the intensive care unit for four days for non-invasive ventilation. She had a BMI of 32.9kg/m^2 with hypertension documented during pregnancy. Further assessment also revealed presence of gestational diabetes. She was investigated for Cushing's syndrome as she had facial acne, purplish abdominal striae, skin thinning and easy bruising (Figure 1). She had elevated 24-hour urinary cortisol and mildly elevated morning serum cortisol detected. However, her diagnosis of Cushing's syndrome was never confirmed as she defaulted her follow-up and was subsequently managed in multiple hospitals due to logistic reasons.

At 27 weeks of gestation, she was readmitted for acute pulmonary oedema (Figure 2) with hypertensive crisis. She required non-invasive ventilation during this admission and blood pressure was controlled with intravenous infusion of magnesium sulphate. A bedside echocardiogram showed an ejection fraction of 55% with presence of pericardial effusion at the base of the right atrium measuring 1.1 cm with presence of right atrial systolic collapse. In view of her unstable cardiac condition and hypertensive crisis, the collective decision between the obstetrician and cardiologist was to proceed with emergency caesarean section. A 1.1 kg baby girl was delivered prematurely at 27 weeks and 3 days period of gestation and was subsequently admitted to NICU for further care.

Following delivery, her condition improved with diuretics and blood pressure was controlled with 3 oral antihypertensive agents. Unfortunately, her hospitalization was prolonged due to dehiscence over her caesarean section surgical wound. Despite being discharged well after delivery, she was admitted for 2 further episodes of acute pulmonary oedema with hypertensive crisis, in which both episodes required ICU admission and ventilation.

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Corresponding author: Dorothy Maria A/p Anthony Bernard, MBBS (IMU), MRCP (UK)
Internal Medicine Physician and Endocrine Fellow, Hospital Sultan Haji Ahmad Shah, Temerloh, Jalan Paya Luas, Taman Harapan, 28300 Temerloh, Pahang
Tel. No.: +6092955333
Fax No.:+6092972468
E-mail: dorothy.bernard@gmail.com
ORCiD: https://orcid.org/0000-0001-8392-7909

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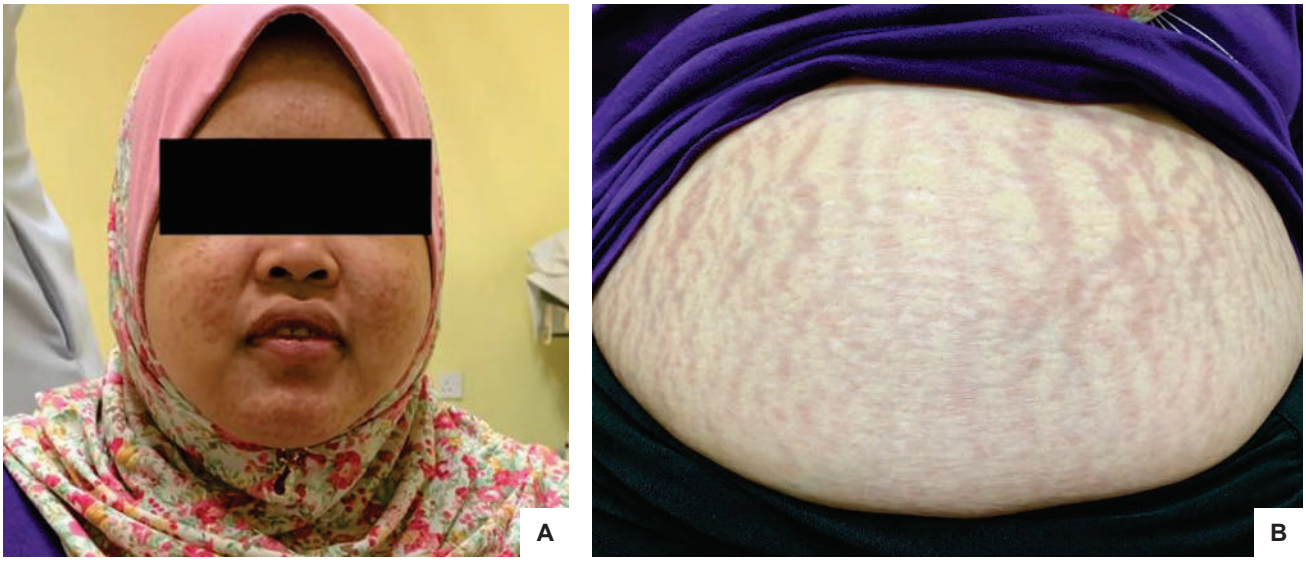

Figure 1. (A) Generalized acne on the patient's face; **(B)** Wide purplish striae on the patient's abdomen.

Table 1. Initial laboratory values

Laboratory	Patient values (Normal ranges)
24-hour urinary cortisol	1712.4 nmol/L (53.2-876.3 nmol/L)
8 am serum cortisol after 1mg overnight dexamethasone suppression	646 nmol/L (unsuppressed)
8am serum cortisol after low-dose dexamethasone suppression	699 nmol/L (unsuppressed)
Adrenocorticotrophic Hormone (ACTH)	1.1 pmol/L (<10.2 pmol/L)
Renal profile	
Blood urea nitrogen	7.3 mmol/L (2.8 - 8.1 mmol/L)
Serum sodium	144 mmol/L (136 -145 mmol/L)
Serum potassium	3.31 mmol/L (3.5 - 4.5 mmol/L)
Serum chloride	102 mmol/L (98 - 107 mmol/L)
Serum creatinine	38 mmol/L (62 - 106 mmol/L)
Liver function tests	
Total protein	63 g/L (66 - 87 g/L)
Albumin	34 g/L (35 - 52 g/L)
Total bilirubin	9.1 umol/L (≤21 umol/L)
Alanine transaminase	62 U/L (≤33 U/L)
Alkaline phosphatase	148 U/L (35 - 104 U/L)
Complete blood count	
Hemoglobin	12.3 g/dL (11.5 - 17.0 g/dL)
Haematocrit	35.5% (37.0 - 54.0%)
White blood cell count	18.2 x 10^9/L (4.0 - 10.0 x 10^9/L)
Platelet count	469 x 10^9/L (150 - 500 x 10^9/L)

The first episode occurred two months after delivery, and again two weeks later. She received furosemide and BP lowering medication. Her diagnosis of ACTH-independent Cushing's Syndrome was only confirmed in between the two acute pulmonary oedema admissions during the postpartum period. She had unsuppressed serum cortisol after overnight and low-dose dexamethasone suppression test with suppressed ACTH (Table 1).

Outcome and follow-up

During her clinic review at 4 months postpartum, she complained of severe lower back pain which corresponded to T9 to L1 osteoporotic compression fracture (Figure 3). She required multiple analgesic medications to relieve her severe pain and she was given an immobilization brace. The pain resulted in her being home-bound and dependent on wheelchair for ambulation.

She also defaulted her follow-up during the postpartum period on several occasions resulting in a delay in her adrenal computerized tomography (CT) scan. Adrenal CT scan was only performed at 6 months postpartum which revealed a right medial limb adrenal adenoma measuring 3.1 x 1.9 x 2.9 cm with pre-contrast HU of 31 and 96% absolute contrast washout (Figure 4).

After much deliberation and counselling, she finally agreed to surgery. She received a short course of metyrapone preoperatively to control her cortisol and underwent an uncomplicated right open transabdominal adrenalectomy in July 2019. Intraoperative findings noted a right adrenal gland measuring 3 x 3 cm in size. Histopathological examination of the right adrenal gland revealed a cortical adenoma.

During the postoperative period, she was started on oral hydrocortisone as cortisol replacement. Bisphosphonate (zoledronic acid) and cholecalciferol were also initiated for the severe osteoporosis. Her anti-hypertensive treatment was significantly reduced from 5 agents to only a single agent during her postoperative period.

DISCUSSION

The initial presentation for this case was unique as the patient presented with acute pulmonary oedema and hypertensive crisis during her pregnancy. The suspicion of Cushing's syndrome was strengthened with the presence of typical clinical features such as the purplish striae on the abdomen, facial acne, skin thinning and easy bruising. Her diagnosis was mainly delayed due to logistic issues and not due to difficulty of laboratory results interpretation. However, in the absence of hypertensive crisis and acute pulmonary oedema, the diagnosis of Cushing's syndrome may be missed due to some overlapping clinical features of Cushing's syndrome and normal pregnancy. Hence, the hunt for the diagnosis would require a high index of suspicion.

There is also a concern regarding the interpretation of screening and confirmatory tests for Cushing's syndrome

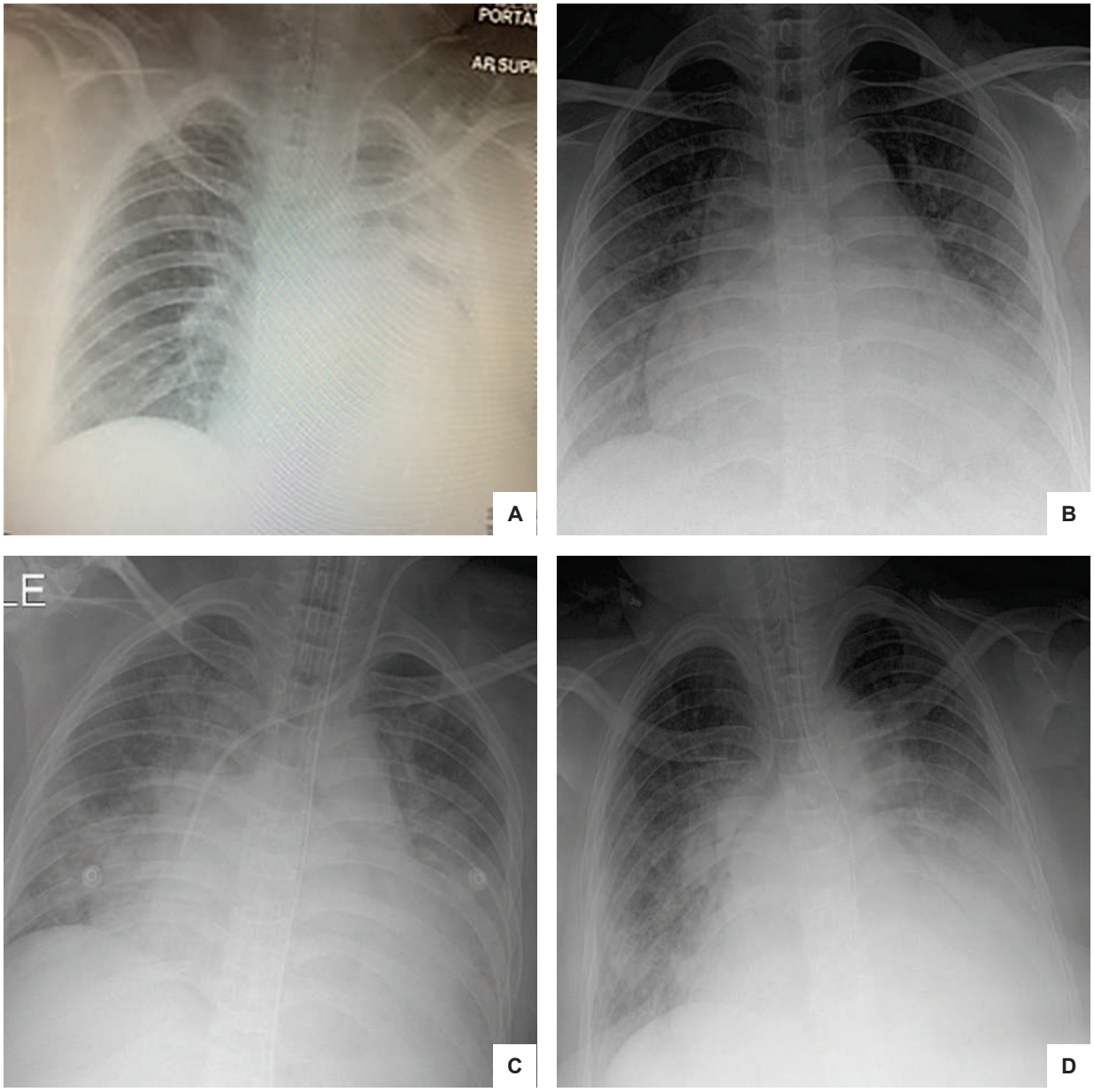

Figure 2. Serial chest radiographs showing acute pulmonary oedema from her previous 4 admissions. **(A)** left pleural effusion with bat's wings appearance and cardiomegaly; **(B)** left pleural effusion with cardiomegaly; **(C)** upper lobe diversion with bat's wings appearance and cardiomegaly; **(D)** left pleural effusion.

during pregnancy. There are physiological changes in cortisol regulation during the normal pregnancy. The rising estrogen level in pregnancy enhances the synthesis of cortisol-binding globulin in the liver. This in turn would increase the total plasma cortisol level during pregnancy.[4] Plasma and urinary free cortisol are also increased during pregnancy due to the up-regulation of the hypothalamic-pituitary-adrenal axis.[4] Hence, the morning cortisol may not be suppressed following an overnight dexamethasone suppression test, leading to a false positive result in normal pregnancy.

The high circulating cortisol in Cushing's syndrome during pregnancy may result in severe maternal and fetal complications. Maternal complications include increased risk of hypertension, diabetes and pre-eclampsia. Fetal complications include increased risk of intrauterine growth restriction and premature delivery.[1] Osteoporosis is also a known complication of Cushing's syndrome like in our patient. Glucocorticoids cause loss of cortical osteocytes and lead to impaired bone healing which leads to osteoporosis.[5]

Heart failure has been previously reported as a presenting symptom of Cushing's syndrome.[6] The occurrence of heart failure in a pregnant mother with Cushing's syndrome is rare and there are no reported cases of recurrent acute pulmonary oedema in pregnancy. Acute pulmonary oedema has only been previously reported once and it was attributed to pre-eclampsia.[7] Kamenicky et al., has shown that excess steroid production in Cushing's syndrome resulted in decreased left ventricular stroke volume index, a lower ejection fraction and an increase in left ventricular mass compared to healthy controls.[8] The causes of recurrent acute pulmonary oedema in this patient are multifactorial. The patient had poorly controlled hypertension due to poor compliance to antihypertensive

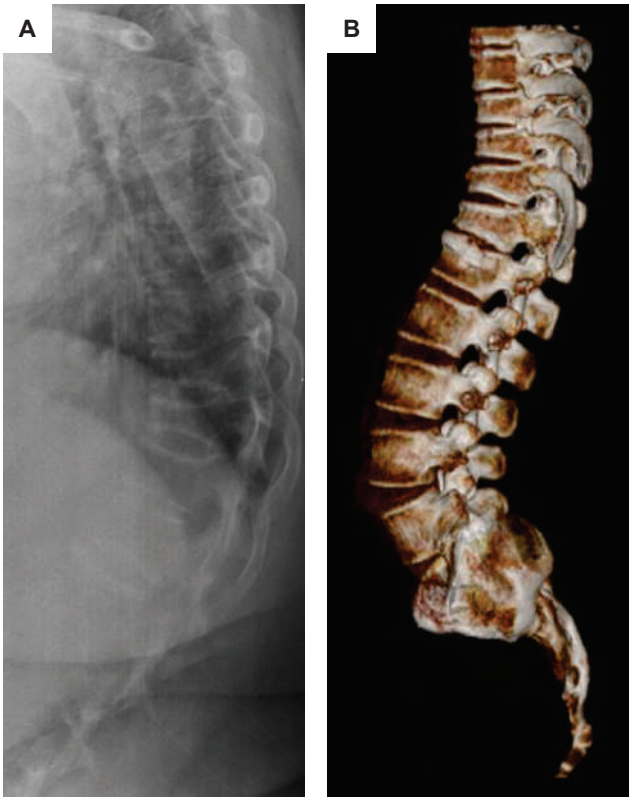

Figure 3. (A) Lateral view of thoracolumbar X-ray showing the compression fracture at T9 to L1 spine with osteopenic bone; **(B)** Volumetric 3D reconstruction of the thoracolumbar spine from CT images showing compression fracture.

medications and a persistently high circulating serum cortisol. Her management became extremely difficult as she frequently defaulted follow-up and had been seeking medical treatment from different centres. She was reviewed mainly in the acute setting during the acute pulmonary oedema admissions during her pregnancy.

During her admission for acute pulmonary oedema, echocardiogram assessment revealed presence of pericardial effusion and regional wall hypokinesia but her ejection fraction was mainly preserved. This observation is peculiar and would suggest possible association of Cushing's syndrome with diastolic dysfunction or heart failure with preserved ejection fraction. Prior study has also shown that patients with successful normalization of cortisol had improvement in their ejection fraction and reduction in left ventricle mass.[8] In our patient, she had normal ejection fraction and had no regional wall abnormalities after her right adrenalectomy.

In our patient, her diagnosis of cortisol-producing right adrenal adenoma was only confirmed after delivery and imaging was done very much later. This is reflective of the cases of Cushing's syndrome in pregnancy reported in literature. Almost half of the cases of Cushing's syndrome in pregnancy were due to adrenal adenomas compared to only 15% in non-pregnant women.[4] In our case, our management during pregnancy was centered on managing her acute pulmonary oedema, hypertensive crisis and determining her timing for delivery as she came for evaluation mainly in an emergency setting. Her acute pulmonary oedema management during pregnancy required treatment with intravenous diuretics and magnesium sulphate infusion.

In cases where Cushing's syndrome secondary to cortisol-producing adrenal adenoma was detected earlier in pregnancy without acute complications, medical and surgical treatment can be offered. Surgical unilateral adrenalectomy can safely be performed between 6 to 28 weeks of gestation.[9] Medical therapy option in pregnancy is limited and indeed challenging. The use of metyrapone has been suggested but safety of medical therapy in pregnancy remains doubtful.[1-3] Hence, management requires a multi-disciplinary discussion among the endocrinologist, endocrine surgeon and obstetrician to achieve management goals in pregnancy.

CONCLUSION

This case highlights the rare occurrence of recurrent acute pulmonary oedema and consequential premature birth

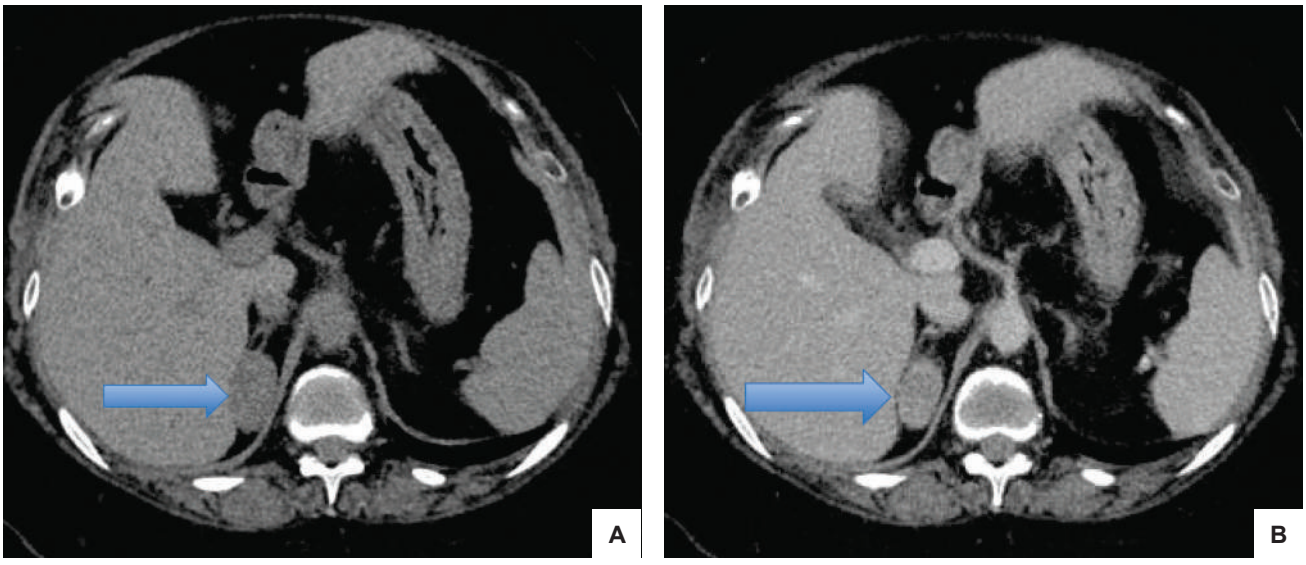

Figure 4. (A) CT adrenal pre-contrast scan showing the right adrenal adenoma (blue arrow); **(B)** CT adrenal post-contrast scan showing the well-defined hypodense lesion at the medial limb of the right adrenal gland.

in a mother with Cushing's syndrome. Management of Cushing's syndrome in pregnancy is complicated and would definitely require a compliant patient and a coordinated endocrinologist-surgeon-obstetrician team.

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

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

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CASE REPORT

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Pediatric Adrenocortical Oncocytoma presenting as Cushing's Syndrome and Peripheral Precocious Puberty: A Case Report and Review of Literature*

Niya Narayanan,[1] Sadishkumar Kamalanathan,[1] Jayaprakash Sahoo,[1] Dukhabandhu Naik,[1] Sambandan Kumaravel,[2] Rajesh Nachiappa Ganesh[3]

[1]*Department of Endocrinology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India*
[2]*Department of Pediatric Surgery, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India*
[3]*Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India*

Abstract

Oncocytic adrenocortical tumours (OATs) or oncocytomas are extremely rare and are usually benign and nonfunctional. We report the case of a 4-year-old male with a right-sided, functional oncocytic adrenocortical adenoma, who presented with precocious puberty and Cushing's syndrome. After work-up, the patient underwent laparoscopic adrenalectomy. The excised adrenal mass weighed 21 g and measured 3.5 cm in maximum dimension. Histological examination demonstrated no features suggestive of aggressive biological behaviour. The patient had no features of recurrent or metastatic disease and had prepubertal testosterone levels with suppressed hypothalamic-pituitary-adrenal axis twelve months after the surgery. A discussion of this case and a review of the literature on functional OATs in the pediatric population are presented.

Key words: adrenal oncocytoma, functioning adrenal adenoma, pediatric adrenal tumours

INTRODUCTION

Oncocytic adrenocortical tumours (OATs) or neoplasms are extremely rare. Most of the cases are nonfunctional and benign, predominantly affecting middle-aged women. About 183 cases have been reported globally according to a systematic review by Costanzo et al., with most patients in the age group of 40 to 60 years.[1,2] In the pediatric age group, only 9 cases have been reported so far.

CASE

A 4-year-old male presented with penile enlargement, deepening of voice and excessive body hair growth for over six months. He had recently gained 6 kg in over 6 months with no evidence of growth spurt. The mother also noticed the patient's excess body odour, aggressive behaviour and irritability.

On physical examination, he had Cushingoid facies and prehypertensive blood pressure (BP) at 108/70 (50th percentile for age and height, 95 mm Hg for systolic BP and 51 mm Hg for diastolic BP). His weight was in the 75th percentile for age, while his height was in the 10th percentile of the combined Indian Academy of Pediatrics (2015) and WHO (2006) height chart for boys 0 to 18 years. His mid-parental height corresponded to the 10th percentile. Examination of the external genitalia revealed a stretched penile length of 10 cm, prepubertal testes (testicular size 3 cc) and Tanner stage 3 pubic hair with no concomitant axillary or facial hair. Abdominal examination was normal, with no palpable mass. There was no history of similar clinical presentation or malignancy in the family.

Hormonal studies showed a basal cortisol level of 19.8 μg/dL (reference range 4.3 to 22.4 μg/dL) and a plasma adrenocorticotropic hormone (ACTH) level <10 pg/mL (reference range 10 to 50 pg/mL). Additional tests indicated disruption of diurnal cortisol rhythm (midnight cortisol 21.3 μg/dL) and non-suppression of cortisol after intake of dexamethasone 1 mg (19 μg/dL). Levels of total serum testosterone (231 ng/dL, reference range for age <20 ng/dL), and dehydroepiandrosterone sulfate (DHEAS) (1261 μg/dL, reference rage 32 to 276 μg/dL) were also elevated. Serum follicle-stimulating hormone (FSH) (0.37 mIU/mL) and luteinising hormone (LH) (<0.07 mIU/mL) were normal and below detection limit, respectively.

The patient's bone age by Tanner Whitehouse III method was advanced by three years compared to his chronological age. Contrast-enhanced computerized tomography (CECT) of the abdomen revealed a 3.3 cm x 3.0 cm x 3.7 cm heterogeneously enhancing mass lesion with a baseline density of 43 HU in the right suprarenal region arising

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Corresponding author: Prof. Sadishkumar Kamalanathan, MD, DM
Deparment of Endocrinology,
Jawaharlal Institute of Postgraduate Medical Education and Research,
JIPMER Campus Road, Dhanvantri Nagar
Puducherry, 605006, India
Tel. No.: +919629528518
E-mail: sadishkk@gmail.com
ORCiD: https://orcid.org/0000-0002-2371-0625

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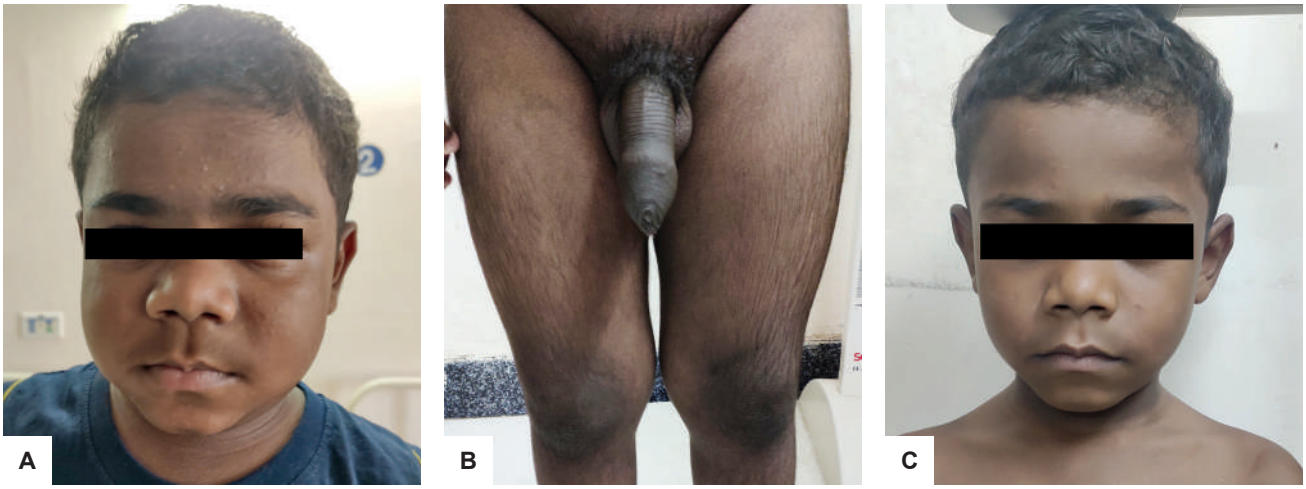

Figure 1. Clinical presentation of the patient showing facial fullness and plethora **(A)**, enlarged penile shaft and appearance of pubic hair **(B)**. There was a decrease in facial fullness and plethora three months postoperatively **(C)**.

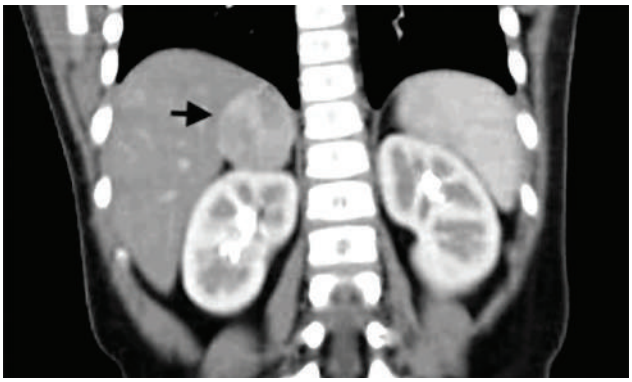

Figure 2. Computed tomography scan of the abdomen in coronal view showed a solid, rounded, well-defined tumour in the right adrenal gland.

from the medial limb of the right adrenal gland. The lesion was confined to the adrenal gland with no evidence of local invasion or enlarged abdominal lymph nodes.

The patient underwent right laparoscopic adrenalectomy with removal of a well-defined mass weighing 21 g and measuring 3.5 cm in maximum dimension. Gross examination showed a well-circumscribed tumour without any breach in the capsule. Histopathologic examination of the tumour revealed cords, trabeculae and sheets of tumour cells, which were round to polygonal with minimal nuclear pleiomorphism, central nuclei, prominent nucleoli and abundant eosinophilic cytoplasm. Majority of the tumour cells exhibited oncocytic morphology. Mitosis count was 3/50 high power field with no evidence of atypical mitosis. Meticulous examination revealed no evidence of capsular invasion, vascular invasion, necrosis or extra-adrenal extension of the tumour. On immunohistochemistry, the tumour cells were positive for inhibin and negative for S-100, melan-A and chromogranin. The MIB-1 proliferation index was 5%. According to the Lin-Weiss-Bisceglia (LWB) criteria, the tumour did not fulfill any of the major or minor criteria for malignancy; therefore, a diagnosis of oncocytic adrenocortical adenoma was made.[3]

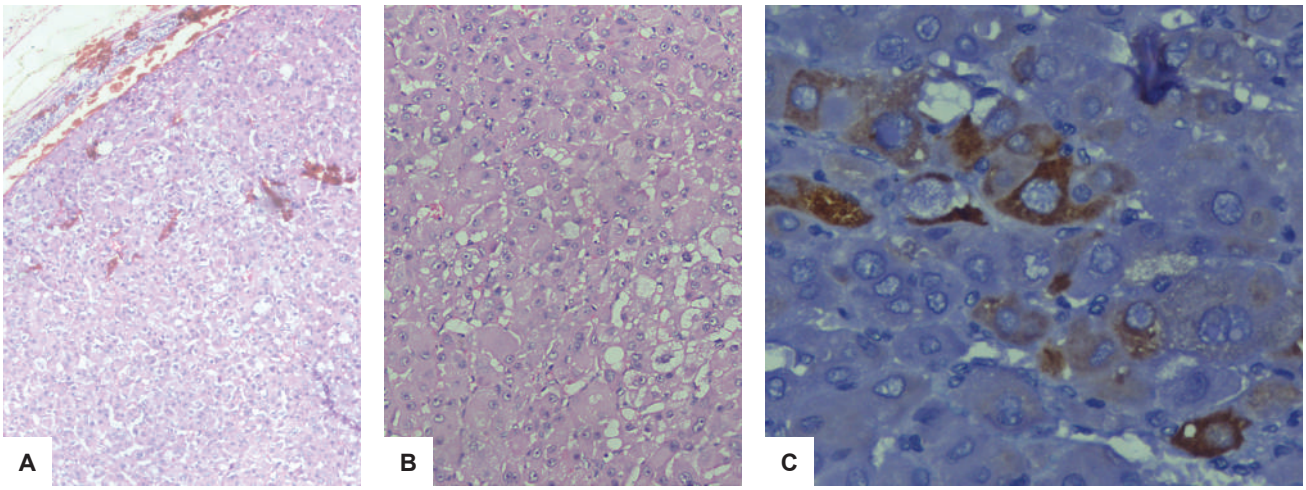

Figure 3. Histopathologic examination showed an capsulated tumour with cells exhibiting abundant granular eosinophilic cytoplasm arranged in cords and trabecular pattern (H&E, 100x) **(A)**. Abundant oncocytic cytoplasm and vesicular nuclei with minimal nuclear pleomorphism and prominent nucleoli were noted. Mitoses are inconspicuous (H&E, 200x) **(B)**. Immunohistochemical examination using diaminobenzidine staining (400x) with DAKO monoclonal antibody showing focal strong expression of inhibin in tumour cells **(C)**.

Table 1. Clinicopathologic characteristics of functional oncocytic adrenocortical tumours in pediatric patients

Pt	Case	Country	Age, year/ Gender	Clinical Presentation	Main Hormone	Tumour Location, Size (cm)	Year	Follow up, Outcome	Hormonal Status on Follow-up	LWB
1	Gumy-Pause et al	Switzerland	12/F	Acne, abdominal pain	A4, TT	L, 5	2008	18 months Remission	Normal	Benign
2	Tahar et al	Tunisia	6/F	Pseudo PP	E2	R, 3.5	2008	12 months Remission	Normal	Benign
3	Lim et al	Korea	14/F	Virilization	DHEAS, TT	R, 17.5	2010	2 weeks Remission	Normal	Borderline
4	Subbiah et al	India	3.5/F	Premature pubarche, Virilization	DHEAS, TT, Cortisol	R, 2.5	2012	1 month Remission	TT DHEAS: normal Cortisol: NA	Benign
5	Sharma et al	India	16/F	Virilization	DHEAS, TT	R, 11.6	2012	3 months Remission	NA	NA
6	Pereira et al	Portugal	5.8/F	Pseudo PP, Cushing's	Cortisol	L, 4.5	2014	64 months Remission	NA	Benign
7	Kawahara et al	Japan	11/F	Fever, Weight loss	IL6	L, 4.5	2014	48 months Remission	Normal	NA
8	Yordanova et al	Bulgaria	9/F	Virilization	A4, TT	L, 2.2	2015	11 months Remission	Normal	Benign
9	Badi et al	Saudi Arabia	5/M	Pseudo PP, Cushing's	Cortisol, TT	R, 3	2018	28 months Remission	TT, cortisol: normal	Benign
10	Our case	India	4/M	Pseudo PP, Cushing's	Cortisol, TT, DHEAS	R, 3.5	2020	12 months Remission	TT: normal on Hydrocortisone	Benign

A4, androstenedione; DHEAS, dehydroepiandrosterone sulfate; E2, estradiol; F, female; IL-6, interleukin-6; L, left; LWB, Lin-Weiss-Bisceglia criteria; M, male; NA, not available; PP, precocious puberty; R, right; TT, total testosterone

The postoperative clinical course was uneventful. The patient was started on hydrocortisone supplementation, which was tapered rapidly to a replacement dose of 7.5 mg given in two divided doses. Serum testosterone levels normalised two weeks post-surgery. On the follow-up visit three months after surgery, the patient had remission of Cushingoid features with no further progression of pubertal development. Regular follow-up was planned.

During his last visit, one year after surgery, he had pre-pubertal testosterone levels with suppressed hypothalamic-pituitary-adrenal axis. Hydrocortisone replacement (7.5 mg) was continued. There was no further progression of puberty. CECT of the abdomen was negative for local remission.

DISCUSSION

OATs are a rare subtype that represents approximately 10% of adrenocortical tumours.[2] As defined by Bisceglia et al., these neoplasms are made up of at least 50% oncocytic cells and can be either pure (>90%) or mixed (50 to 90% oncocytic cells) variant.[3] The spectrum of these tumours includes benign adenomas/oncocytomas, oncocytic carcinomas and oncocytic neoplasms of uncertain malignant potential.[4] Since the first account of OAT in 1986 by Kakimoto et al., 183 cases have been reported.[1,5] Most of these tumours were detected incidentally, with 20% of them demonstrating evidence of malignancy.[1] Approximately 10 to 20% of the OATs were functional; majority were non-functional.[2]

OATs predominantly affect adults, with a mean age at diagnosis of 46 years and a female preponderance by a ratio of 1.8:1.[6] Adrenocortical tumours are particularly rare in children and account for less than 0.2% of all pediatric neoplasms. Nine cases of OATs in the pediatric age population were previously reported.[7-15] All the patients except one were females, with ages between 3.5 and 16 years.[15] Most tumours involved the right adrenal gland, with sizes ranging from 2.5 to 17.5 cm. Six of the cases were diagnosed as adrenocortical adenoma (oncocytoma) on histopathology, while one case was labeled as borderline tumour according to the LWB classification.[3] All these tumours were functional with variable clinical presentations. Four females presented with virilization. Three patients (two females and one male) presented with precocious puberty; two co-presented with Cushing's syndrome. Our case also had similar clinical presentation. All four patients who presented with Cushing's syndrome were younger. Other major presenting symptoms included fatigue, headache, abdominal pain and palpable abdominal mass. Kawahara et al., described a case of interleukin-6-producing oncocytic adrenocortical adenoma in an 11-year-old female, who presented with persistent fever and weight loss.[13] Clinicopathological data of reported cases of OATs in the pediatric population including our patient are summarized in Table 1.

OATs are usually large, rounded, encapsulated and well-circumscribed, with an average diameter of 8 cm (2 to 20 cm). Microscopically, the tumour cells are highly eosinophilic, granular and arranged in solid, trabecular, tubular or papillary patterns. Electron microscopic studies of these tumours have shown the cytoplasm of oncocytes to be rich in mitochondria. The immune profile shows diffuse positivity for vimentin, melan-A, synaptophysin and alpha-inhibin.[2] Wiess score, used for categorizing adrenal tumours, overestimates the potential malignancy risk owing to parameters that are intrinsic to oncocytic cells, such as eosinophilic character, high nuclear grade and diffuse architecture. Hence, the World Health Organization in 2017 recommended the LWB score for categorizing OATs.[4]

Imaging studies such as computerized tomography or magnetic resonance imaging are not useful to differentiate between benign and malignant oncocytic neoplasms. Surgical excision is the definite treatment for both large and functional tumours. Recent advances in laparoscopic techniques have made the application of minimally invasive procedures possible even in the presence of a large adrenal mass. The biological behaviour of OATs differs

from other benign adrenal cortical tumours and carries a better prognosis. Patients with malignant OATs had a median overall survival of 58 months, which is different compared to patients with non-oncocytic adrenocortical carcinoma (31.9 months).[6]

Our patient did not satisfy any of the criteria for high risk stratification and was then classified as having adrenal oncocytic adenoma. Surgical resection of functional OAT normalizes the serum hormonal levels and results in resolution of hormonal overproduction-related clinical symptoms and signs. None of the reported cases of functional OATs, including our patient, had recurrence of disease during the follow-up period ranging from two weeks to 64 months. Seven of the cases had normal hormonal levels appropriate for age and sex at follow-up. None of the cases developed central precocious puberty during follow-up. There are no guidelines for the follow-up of patients with OATs. Considering the possible risk of adrenocortical carcinoma, meticulous follow-up is planned for our patient with hormonal and imaging investigations.

CONCLUSION

OATs are extremely rare in childhood and adolescence. Most pediatric OATs are benign and functional, occurring predominantly in females, with excellent clinical outcomes. In children with adrenal mass and associated features of either virilisation or precocious puberty or Cushing's syndrome, OATs should be considered.

Learning points

1. Oncocytic adrenocortical tumours (OATs) are rare, consisting mostly of benign and functional adrenal tumours in the pediatric population.
2. Clinical, biochemical and radiological investigation cannot differentiate benign oncocytic adenomas from carcinomas, mandating adrenalectomy in most of the cases for histopathological confirmation and definitive treatment of functional tumours.
3. The prognosis of patients with OATs is good when compared to conventional adrenocortical carcinoma, with an excellent rate of remission and higher overall survival.

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

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Acute Suppurative Thyroiditis Secondary to Tuberculosis with Superimposed Bacterial Infection: A Case Report

Siti Sanaa binti Wan Azman and Masni binti Mohamad

Division of Endocrinology, Department of Medicine, Hospital Putrajaya, Federal Territory of Putrajaya, Malaysia

Abstract

Acute suppurative thyroiditis is a rare and potentially fatal condition. We present a case of an 18-year-old Malay female who presented with one-week history of painful right sided neck swelling, fever and odynophagia. Neck CT confirms ruptured multiloculated abscess with posterosuperior extension into prevertebral space. Pus and tissue cultured *Streptococcus anginosus* and *Eikenella corrodens* with positive TB PCR. She responded well to ampicillin/sulbactam and anti-tuberculosis treatment with no evidence of residual collection from ultrasound.

Key words: acute suppurative thyroiditis, thyroid abscess, thyroid tuberculosis, contrast induced thyroiditis

INTRODUCTION

Acute suppurative thyroiditis is a rare potentially life-threatening emergency with reported incidence of only 0.1-0.7% in the literature.[1,2] Due to the scarcity of cases, there are so far no comparative clinical studies, and management has been guided by published case reports and series. Mortality rate ranges from 3.7-12%.[3,4] Here we report a case of a young female with acute suppurative thyroiditis complicated with extensive thyroid abscess resulting from tuberculosis (TB) and secondary bacterial infection.

CASE

An 18-year-old Malay female, previously well, presented with one-week history of right sided painful neck swelling, fever, and odynophagia. Preceding this she denied any acute pharyngitis, constitutional symptoms, night sweats, or TB contacts. There were no hyper or hypothyroid symptoms. She denied any history of trauma to the neck. Clinical examination revealed a blood pressure of 118/72 mm Hg, pulse rate 89 bpm, and temperature 37°C. She was euthyroid, no orbitopathy or other evidence of Grave's disease. There was a right anterolateral neck mass measuring 4 x 5 cm, mild warmth and tender to palpation, however no fluctuant area. There was no cervical lymphadenopathy.

Laboratory investigations showed leucocytosis TWBC 17.6 x 10^9/L with neutrophil predominance and elevated inflammatory markers ESR 98 mm/hour, CRP 105.8 mg/L (<5.0). Negative HIV screening and fasting glucose of 5.1 mmol/L ruled out immunocompromised state. Her baseline thyroid function test (TFT) upon admission was TSH 0.13 mU/L (0.56-4.90) and FT4 21.1 pmol/L (1.5-22.7). Chest X-Ray showed clear lung fields. Neck ultrasound demonstrated heterogenous appearance of both thyroid lobes, with heterogenous hypoechoic mass occupying the right lobe, extending towards the left isthmus-thyroid junction (Figures 1A and 1B). Contrast-enhanced computer tomography (CECT) of the neck showed a multiloculated hypodense rim enhancing collection with the epicentre in the right thyroid lobe measuring collectively 3.5 x 4.6 x 5.4 cm. Posterosuperiorly, there was an extracapsular extension of the collection into the prevertebral space which measures 5.5 cm in craniocaudal length from the level of C2/3 until C6/7 with displacement of trachea to the left. In addition, there were multiple enhancing bilateral cervical lymph nodes in all levels, with the largest measuring 0.9 x 0.6 cm (Figures 2A and 2B). Fibreoptic laryngoscope showed patent airway and no pyriform sinus fistula. A repeat TFT three days after iodinated contrast media (ICM) exposure noted markedly elevated TFT almost three times upper limit with TSH of 0.098 mU/L (0.900 - 3.110) and FT4 36.3 pmol/L (7.8 - 13.2), suggestive of contrast induced thyroiditis. Hence, no anti-thyroid treatment was initiated.

She underwent a bedside fine needle aspiration which aspirated 5 cc of frank pus and a repeat ultrasound guided aspiration which aspirated 25 cc of pus. However, a repeat ultrasound showed persistence of the remaining collection at right thyroid bed thus a decision to proceed with right hemithyroidectomy and incision and drainage of right parapharyngeal abscess. Intra-operatively, the right thyroid gland weighed 12 g, the superior pole was found to be sloughy and adhering to the strap muscles. A total of 5 cc of pus was aspirated from the thyroid gland and parapharyngeal area. A drainage catheter was inserted and kept for six days which drained 10 – 30 mls of pus daily.

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Corresponding author: Siti Sanaa binti Wan Azman, MD
Internal Medicine Specialist, Hospital Putrajaya
Jalan P9, Presint 7, 62250 Putrajaya, Wilayah Persekutuan Putrajaya, Malaysia
Tel. No.: +603-83124200, +603-88880137
E-mail: sitisanaa@yahoo.com
ORCiD: https://orcid.org/0000-0002-3243-3068

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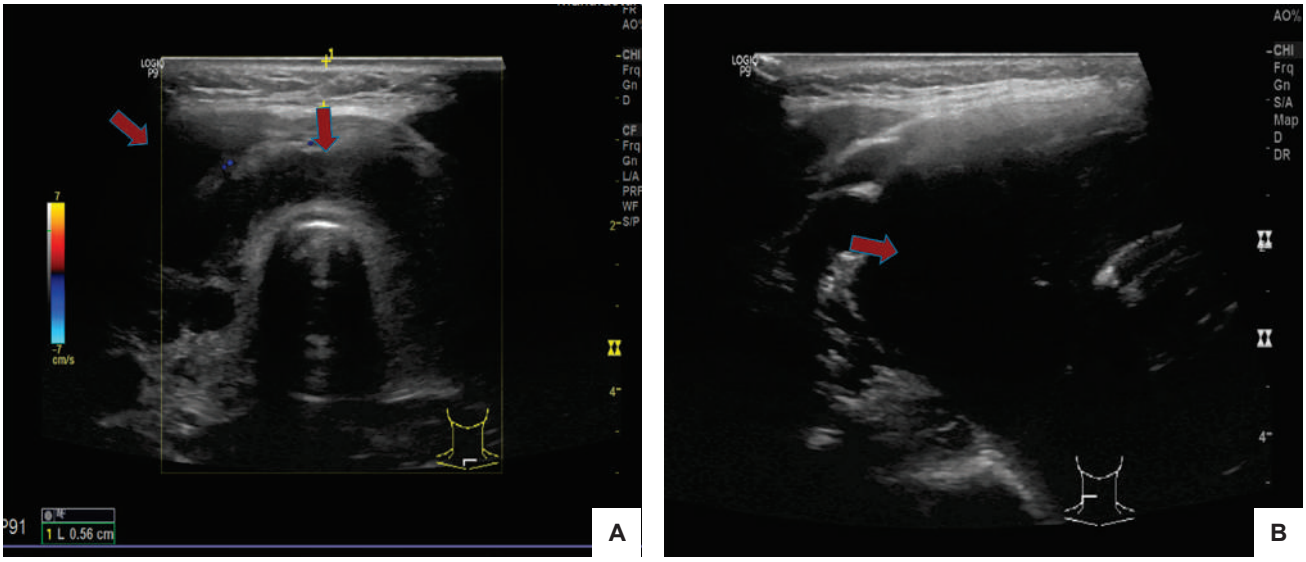

Figure 1. (A) Multi loculated hypoechoic collections arising from right thyroid lobe extending into the isthmus; **(B)** largest hypoechoic collection occupying the right lobe.

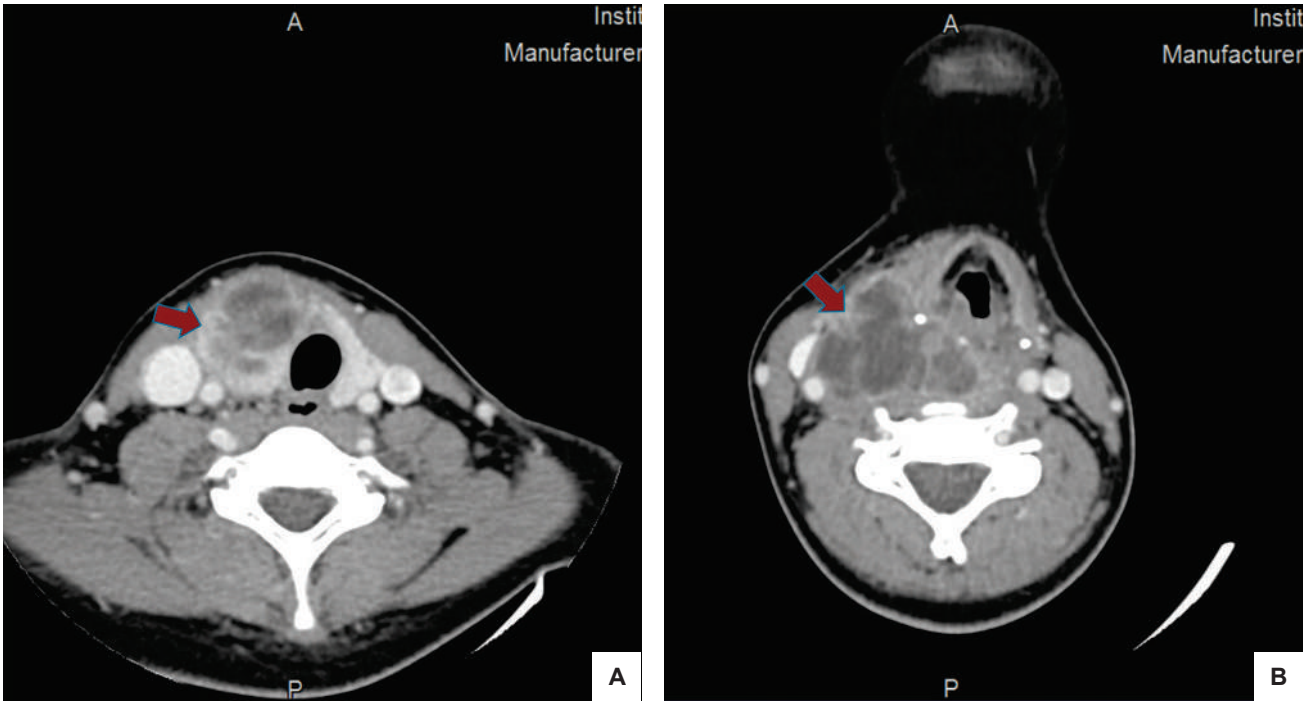

Figure 2. (A) Multi loculated hypodense rim enhancing collection at right thyroid bed, trachea deviated to the left. Left thyroid gland appears normal; **(B)** Collection extends posterosuperiorly into the prevertebral space.

Pus and tissue cultured *Streptococcus anginosus* and *Eikenella corrodens* both sensitive to penicillin G. Polymerase chain reaction (PCR) of the pus was also positive for *Mycobacterium tuberculosis* despite the acid-fast bacilli (AFB) smear being negative. However, pus and tissue culture did not isolate any mycobacterium tuberculosis (MTB). Tissue histopathological examination (HPE) demonstrated xanthogranulomatous inflammation with microabscess formation. No epithelioid histiocytes, granuloma formation nor Langhan's giant cells was seen. Sputum smear for acid fast bacilli sent twice were negative. She was discharged with oral Ampicillin plus Sulbactam 750 mg twice daily for four weeks (total duration six weeks) and combination of Isoniazid 75 mg, Rifampicin 150 mg, Ethambutol 275 mg and Pyrazinamide 400 mg, four tablets once daily based on the initial TB PCR result. A follow-up ultrasound neck five weeks after commencement of antibiotics and 18 days after initiation of anti-TB did not show any residual abscess collection. Outpatient TFT performed four weeks post-surgery indicate recovering TFT with TSH of 0.74 mIU/L (0.46-4.68) and FT4 6.8 pmol/L (10.0-28.2) without any anti-thyroid medication.

DISCUSSION

Acute suppurative thyroiditis (AST) is rare, as the thyroid gland is essentially resistant to infection attributed to its encapsulation, high iodide content, rich vascular supply,

and extensive lymphatic drainage.[5] Common etiological pathogens are staphylococcus and streptococcus with recent reported trend toward more atypical pathogens particularly in the immunocompromised host.[1] TB of the thyroid gland is an extremely rare extrapulmonary manifestation of TB even in areas where TB prevalence is exceedingly high with reported frequency of <1%.[6]

Raman et al., reported a case of primary TB of the thyroid gland presented with thyrotoxicosis symptoms associated with drenching night sweats, high grade fever and neck swelling.[7] Diagnoses was confirmed with fine needle aspiration (FNA) of the left thyroid nodule, which smeared positive for AFB and a subsequent positive TB culture. CT chest, abdomen and pelvis rule out other organ or lymph node involvement. He responded well to TB treatment for six months with complete resolution of symptoms. This case demonstrates that patients with thyroid TB may present with thyrotoxicosis although they are usually euthyroid.

Additionally, Falhammar and collegues published six case series of adult patients with AST.[8] The causative factors were identified as iatrogenic in two patients from FNA of thyroid gland and septicaemia from prostate biopsy in the other. Blood cultures were positive in three (*Streptococcus pneumonia, Streptococcus sanguinis, Pepto streptococci*), deep tissue culture in three (*Escherichia coli, Candida, Hemophilus influenzae*) and no positive culture at all in two. All patients were treated with antibiotics, three of them required drainage and all of them recovered from acute episode without reported recurrence during a mean period of seven years follow up. Our patient isolated *Streptococcus anginosus* and the less common gram-negative aerobes *Eikenella corrodens*. Her pus smear did not visualize any AFB and anti-TB was instituted earlier based on pus TB-PCR positivity. Following this pus and tissue culture failed to isolate MTB with no supporting evidence from tissue HPE. After consultation with infectious diseases physician, we decided to maintain her anti-TB treatment as she responded clinically to treatment.

Distinguishing AST from subacute thyroiditis is crucial as both may present similarly with preceding history of pharyngitis, fever, and painful thyroid swelling.[9] Both these entities are managed differently with an emphasis on early treatment for AST. Typically, ultrasound examination in the acute phase of AST shows a hypoechoic lesion spreading in or around the affected thyroid lobe. However, ultrasound may show an unclear hypoechoic area in the early acute phase which may lead to an erroneous diagnosis of subacute thyroiditis.[10] The most discriminating method for differentiating is FNA of the thyroid to detect pus and in the case of subacute thyroiditis, it is possible to observe multinucleated giant cell, granulomatous inflammation, and mononuclear cell infiltration.[1,9] In our case, the diagnoses was clear as ultrasound demonstrated classical finding of hypoechoic collection, FNA aspirated frank pus enabling prompt treatment with empirical antibiotics.

In AST it is important to consider an anatomical defect such as a pyriform sinus fistula which has a predilection to involve the left thyroid gland due to an atrophic right ultimo branchial body.[11] Means of diagnosing this may be with transnasal flexible fibreoptic laryngoscopy, CT scan with `trumpet manoeuvré and barium oesophagography.[1] Pyriform sinus fistula was not visualized from fibreoptic laryngoscope performed in our case, furthermore, the epicentre of abscess was located at the right thyroid gland instead of the usual typical left side.

Patients with acute thyroiditis are generally euthyroid. However, occasionally, the condition presents as destructive thyroiditis with thyrotoxicosis.[9,12] Serum levels of thyroid hormone can be transiently increased due to release of preformed thyroid hormone into the circulation resulting from the destruction of the thyroid follicles.[9] We deduce that the rapid increase of TFT in our patient from the baseline was partly contributed from exposure to ICM from CECT imaging.

Management of AST primarily focuses on antibiotic therapy and the need for invasive surgery and drainage or correction of a predisposing anatomic defect.[1] There are published cases on less invasive management not requiring open surgical drainage.[13] Ilyin et al., described two cases of successful nonsurgical management of a thyroid abscess with percutaneous 21-gauge needle aspiration under sonographic guidance with intra-thyroidal injection of antibiotic. Both patients recovered well with no recurrence during follow-up periods of 6 months and 5 years, respectively.[13] However, in our case open drainage with hemithyroidectomy was indicated because the thyroid abscess extended to the prevertebral space with tracheal compression and persistent collection post FNA. Paes et al., advocate a treatment duration of two weeks for thyroid abscess with no underlying anatomical defect.[1] We treated our case for a total of six weeks with antibiotics and continued anti-TB medication for six months.

CONCLUSION

This case exemplifies the importance of recognizing the rarer form of thyroiditis, distinguishing AST with other differentials particularly subacute thyroiditis and instituting treatment early to avoid fatal complications.

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

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

Author Disclosure
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CASE REPORT

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Successful Oral Levothyroxine Desensitization in a Patient with Severe Hypothyroidism Post Radioactive Iodine Therapy: A Case Report

Chua Yi Jiang,[1] Bay Shing Shen,[1] Taye Zhi Yun,[2] Carolina Singarayar,[1] Foo Siew Hui[1]

[1]*Endocrinology Unit, Department of Medicine, Selayang Hospital, Selangor, Malaysia*
[2]*Pharmacy Department, Selayang Hospital, Selangor, Malaysia*

Abstract

Levothyroxine remains the standard therapy for patients with hypothyroidism worldwide. Levothyroxine allergy is rarely seen and alternative therapies are less efficacious and scarcely available. The use of liothyronine (LT3) monotherapy is less favoured due to its short half-life and unpredictable pharmacological profile. We report a 59-year-old male with a hypersensitivity reaction to levothyroxine who was successfully desensitized with oral levothyroxine within a day using a 14-step protocol.

Key words: levothyroxine, hypersensitivity, hypothyroidism, desensitization

INTRODUCTION

Hypothyroidism is common post radioactive iodine (RAI) therapy. The incidence of hypothyroidism within a year post RAI therapy in Malaysia is 32.9%.[1] The standard treatment for hypothyroidism is oral levothyroxine (LT4). The majority of patients tolerate levothyroxine well without any adverse effects as it is identical to the molecule produced by the body.[2] Unfortunately, patients who develop an allergy towards levothyroxine have no other substitute compound that is as efficacious to alleviate the hypothyroid symptoms.

The common practice of switching to other commercially available preparations of levothyroxine with different excipients will usually resolve the issue.[2] However, if this strategy fails, desensitization to levothyroxine should be considered.

CASE

A 59-year-old male with Graves' disease who was rendered hypothyroid post radioactive iodine (RAI) therapy, reported he was unwell four days after commencement of levothyroxine 50 mcg daily. Free thyroxine (FT4) level was 3.9 pmol/L (normal range 11.8-23.2 pmol/L) and thyrotropin (TSH) level was 41.26 mU/L (normal range 0.35-5.50 mU/L). His comorbidities include hypertension and diabetes with no history of drug allergies. Within four days of levothyroxine initiation, he developed facial edema, abdominal distension, swelling of distal extremities and dyspnoea. He continued taking the medication but due to worsening symptoms, he withheld it two weeks prior to the clinic consultation. During the clinic review, his previous symptoms had completely resolved but he was clinically hypothyroid. He had weight gain of 9 kg (97 kg to 106 kg) and constipation. He was switched

Table 1. Oral levothyroxine desensitization protocol

Steps	Stock Solution	Cumulative Time (min)	Dose (mcg)	Volume (mL)	Cumulative Dose
1	1	30	0.01	0.1	0.01
2	1	60	0.02	0.2	0.03
3	1	90	0.04	0.4	0.07
4	1	120	0.08	0.8	0.15
5	1	150	0.16	1.6	0.31
6	1	180	0.32	3.2	0.63
7	2	210	0.64	6.4	1.27
8	2	240	1.28	12.8	2.55
9	2	270	2.56	25.6	5.11
10	2	300	5.12	51.2	10.23
11	3	330	10.00	5.0	20.23
12	3	360	20.00	10.0	40.23
13	3	390	30.00	15.0	70.23
14	3	420	40.00	20.0	110.23

adapted from Fevzi et al.[3]

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Corresponding author: Chua Yi Jiang, MD
Medical Physician, Endocrinology Fellow
Selayang Hospital, B21, Lebuhraya Selayang, Kepong
68100 Batu Caves, Selangor, Malaysia
Tel. No.: +(60)3-61263333
Fax No.: +(60)3-61377097
E-mail: chuayijiang@yahoo.com
ORCiD: https://orcid.org/0000-0001-9388-747X

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to another levothyroxine preparation with different excipients. The same symptoms recurred and he presented to the emergency department the next day.

On examination, his vital signs were stable with a blood pressure of 113/74 mm Hg, heart rate of 72 beats per minute, oxygen saturation of 100% on room air. He was afebrile. He had mild facial puffiness and swelling of his fingers. Jugular venous pressure was not elevated and cardiovascular examination was unremarkable. He was not tachypnoeic and his lung examination revealed clear lung fields.

Admission biochemistry revealed a normal full blood count with readings of haemoglobin 13.0 g/dL (normal range 13.2-16.6 g/dL), white blood cells 7.63 x 10^9/L (normal range 4.0-11.0 x 10^9/L), platelets 137 x 10^9/L (normal range 135-317 x 10^9/L) and eosinophils 2.5% (normal range 1-4%). His renal function revealed an acute kidney injury profile where the urea was 6.3 mmol/L (normal range 2.5-10.7 mmol/L) and creatinine 153 μmol/L (normal range 62-106 μmol/L) (baseline 92 μmol/L). His creatine kinase was markedly elevated at 3085 u/L (normal range 34-145 u/L). This coincided with his severe hypothyroidism where his free T4 was <1.3 pmol/L (normal range 11.8-23.2 pmol/L) and thyrotropin (TSH) level was 62.05 mU/L (normal range 0.35-5.50 mU/L).

He was initiated with intravenous levothyroxine at a daily dose of 100 mcg for four consecutive days as he was severely hypothyroid. This was done with an initial test dose of 1 mcg administered as a slow bolus over five minutes, followed by the remaining dose given over another five minutes with continuous cardiac and vital sign monitoring. He had no immediate or delayed hypersensitivity reaction to the intravenous preparation.

Oral levothyroxine desensitization was commenced on the second day of admission. The dosage was designed based on a previously reported protocol (Table 2).[3] After obtaining a written consent from the patient, oral levothyroxine was given at an initial dose of 0.01 mcg and this was doubled every 30 minutes for seven hours until a cumulative dose of 110 mcg was reached (Table 2). He was put on continuous cardiac and vital sign monitoring throughout the desensitization process and emergency medications of parenteral hydrocortisone, chlorpheniramine and adrenaline were prepared at bedside in case he developed any allergic reaction. The desensitization of levothyroxine was successful without signs or symptoms of allergy. He was discharged well five days after admission with 100 mcg of oral levothyroxine.

Table 2. Oral Levothyroxine Stock Solution Preparation

Name of Medication: Levothyroxine			
Stock Solution	**Volume Per Stock Solution (mL)**	**Concentration (mcg/ml)**	**Total Dose Per Stock Solution (mcg)**
1	10	0.1	1
2	100	0.1	10
3	50	2.0	100
Target dose (mcg): 110.23			

DISCUSSION

Hypersensitivity reaction to levothyroxine can present as a type 1 (immediate) or type 4 (delayed) hypersensitivity reaction.[4] The IgE mediated immediate reaction most commonly manifests as urticarial rash within minutes to hours, whereas the T-cell mediated delayed reaction usually occurs several days to weeks after exposure. Other hypersensitivity reactions to levothyroxine include angioedema, eczematiform skin eruptions, and pruritus.[5] To date, there is limited information on whether levothyroxine hypersensitivity reaction is IgE-mediated or non-Ig-E-mediated.[6] It is recommended to perform skin testing but this was only reported in certain cases. Unfortunately, skin testing was not available in our setting. We believe that our patient developed type 1 hypersensitivity reaction as his allergic symptoms occurred on the day where he consumed the oral levothyroxine and similar reactions occurred almost immediately with the change to the other oral levothyroxine preparation.

Most patients with hypersensitivity reaction tolerated an alternative thyroxine preparation without further reaction, supporting the theory that the allergy is likely due to the excipients or fillers rather than the thyroid hormone itself.[5] Thus, a trial of switching the patient to an alternative levothyroxine preparation is usually done. This was not successful with our patient and the gel capsule formulation which has the least excipients was not available locally. However, our patient was able to tolerate the intravenous preparation of levothyroxine, suggesting that it was the excipients or fillers that most likely triggered the atypical hypersensitivity reaction that resolved upon stopping the oral levothyroxine and recurred upon reintroduction.

Therapies such as desiccated thyroid extracts (DTE) from animal thyroid glands and oral liothyronine (T3) are not recommended as substitutes for levothyroxine therapy.[2] The use of these formulations as monotherapy or in combination with levothyroxine remains an ongoing debate. This is due to the short half-life of liothyronine (T3) and the non-standardized doses of the desiccated thyroid hormone.[2]

While compounded thyroid hormone has been suggested as a reasonable alternative for patients with levothyroxine allergy,[2] the cost is high and their formulations are not standardized, resulting in occurrences of both hypothyroidism and hyperthyroidism that are difficult to predict.[7] Thus, if patients are unable to tolerate the alternative preparations of levothyroxine with different excipients, desensitization should be performed in an inpatient setting.

Desensitization is a procedure that alters the immune response to a drug and results in temporary tolerance, allowing the patient with a drug hypersensitivity reaction to receive an uninterrupted course of the medication safely.[8] Once the medication is discontinued or if treatment is interrupted for a sufficient period, the patient's hypersensitivity to the medication returns. Successful levothyroxine desensitization was mostly reported in IgE mediated drug hypersensitivity reactions with only one case involving delayed hypersensitivity reaction.[9]

Successful desensitization was achieved within 1-2 days in most cases.[3,10] These patients remained asymptomatic without further allergic reactions.

CONCLUSION

With the lack of alternative option to treat hypothyroidism, patients who develop hypersensitivity reaction to oral levothyroxine should be desensitized using a step-wise protocol if they are unable to tolerate alternative preparations of levothyroxine. This should be performed as soon as possible to prevent complications of untreated hypothyroidism that can be life threatening.

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

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

Author Disclosure
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CASE REPORT

De Novo Extra-Thyroidal Manifestations of Graves' Disease presenting 16 Years after Total Thyroidectomy for Thyroid Cancer

Ann Kwee,[1] Kai-Ling Yong,[2] Lay Leng Seah,[2] Chiaw-Ling Chng[1]

[1]*Department of Endocrinology, Singapore General Hospital*
[2]*Oculoplastics Department, Singapore National Eye Center*

Abstract

We present a 61-year-old Chinese female who had a history of angioinvasive follicular thyroid cancer (FTC) treated with total thyroidectomy 16 years ago, without radioactive iodine (RAI) treatment who now presents with *de novo* pretibial myxedema (PTM) followed by active severe Graves' ophthalmopathy (GO) requiring pulse steroids and radiotherapy.

Key words: thyroid cancer, Graves' disease, thyroidectomy, radioactive iodine

INTRODUCTION

There have been very few reports of extrathyroidal manifestations of Graves' Disease (GD) after a total thyroidectomy, without radioactive iodine (RAI) treatment. In this case, our patient presented 16 years post total thyroidectomy with extrathyroidal manifestations. This case underscores the occasional difficulty in diagnosis of extrathyroidal manifestations in the absence of hyperthyroidism. Furthermore, it emphasizes the point that presence of thyroid stimulating hormone receptor antibodies (TRAb) are risk factors for extrathyroidal manifestations of GD.

CASE

Our patient is a Chinese female, non-smoker, who presented at age 43 years old with an incidental finding of a non-obstructive anterior neck mass. A fine needle aspiration biopsy was performed on the left thyroid nodule, which showed a follicular neoplasm. She proceeded with a total thyroidectomy and was found to have a 3.0 x 2.5 cm minimally invasive FTC with capsular and possible angioinvasion (TNM staging T2N0M0, Stage 1). There was no histological evidence of hyperplasia or hypertrophy of the remaining thyroid follicular cells to suggest possible Graves' disease (GD). The post-operative recovery was complicated by secondary hypoparathyroidism. No remnant RAI ablation was performed post-operatively.

Her significant medical history included diabetes mellitus, hypertension, and hyperlipidemia on treatment. Notably, her sister had hyperthyroidism, while her brother had hypothyroidism, both likely related to autoimmune thyroid disease. There was no family history of thyroid cancer. Medications after surgery included levothyroxine (LT4) 100 mcg on weekdays and 125 mcg on weekends (total 750 mcg/week), calcitriol 0.25 mcg OD, calcium carbonate 600 mg on weekdays and 1200 mg on weekends. She was subsequently followed up in another institution.

In May 2016, she consulted a dermatologist for bilateral non-resolving, red, swollen, and itchy skin lesions on her lower limbs which had been present for a year. Cutaneous examination revealed presence of multiple skin-colored firm nodules over both shins, ranging in sizes from 1-2 cm in diameter. The underlying area was hyperpigmented up to mid-shin (Figure 1). This was initially diagnosed as eczema by her general practitioner prior to the consult. She was treated with multiple rounds of topical steroids and emollients without improvement. A left shin punch biopsy showed dermal mucinosis, consistent with pre-tibial myxedema (PTM). This was treated with intralesional steroid injections. There were no nail findings.

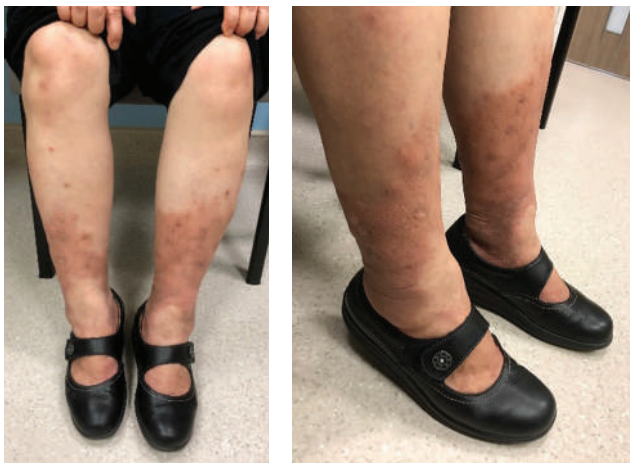

Figure 1. Images of the patient's pre-tibial myxedema (2018). Multiple skin-colored nodules and hyperpigmented plaques with 'peau d'orange appearance' over both shins.

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Corresponding author: Ann K. Kwee, MB BCH BAO, MRCP (UK), MMed (Int Med)
Department of Endocrinology, Singapore General Hospital
Level 3, The Academia, 20 College Road, Singapore 169856
Tel. No.: +65-6222-3322
Fax No.: +65-622-73576
E-mail: ann.kwee.k@singhealth.com.sg
ORCiD: https://orcid.org/0000-0002-5700-2731

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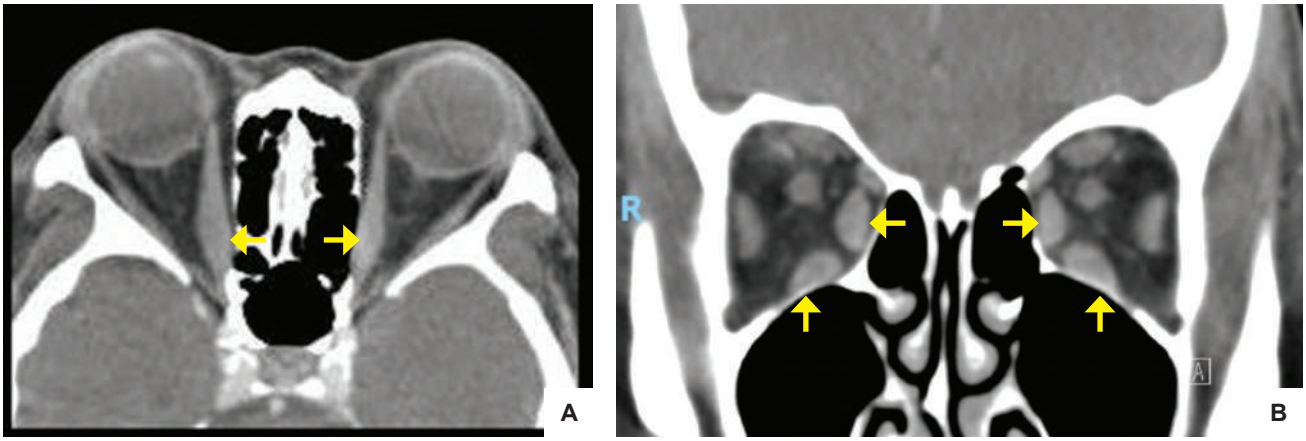

Figure 2. CT scan of the orbits at presentation of GO with **(A)** axial and **(B)** coronal views (2017). Bilateral proptosis, bulky inferior and medial rectus muscles (arrows) with medial deviation of the right eye globe. Optic nerves are stretched without compression.

In August 2017 (a year after diagnosis of PTM), our patient began experiencing intermittent binocular diplopia while driving. She also noticed bilateral eye redness and itchiness. There was no eye pain, tearing, grittiness or photophobia. On examination, she had bilateral periorbital swelling with redness, worse on the left, conjunctival injection, chemosis, exophthalmos, limitation of eye movements in all directions of gaze, especially on abduction and elevation bilaterally but without lagophthalmos. Computed Tomography (CT) imaging of her orbits showed mild bilateral proptosis with medial deviation of the right eye globe, enlarged extraocular muscles, increased fat stranding, and stretched bilateral optic nerves without compression (Figure 2). A diagnosis of active severe GO was made (based on EUGOGO classification).[1] Prior to seeing us, she had been consulting endocrinologists from various institutions and was noticed to have fluctuating thyroid function results requiring adjustments of her thyroxine dosage. During the initial consultation at our institution, she was observed to have an increasing thyroglobulin (Tg) trend and increasingly deranged thyroid function despite reported medication compliance. Her thyroid function results from 2010 till her consultation in our institution in 2017 are summarized in Table 1.

We had a thorough discussion with the patient about undergoing a radioactive iodine whole body scan (RAI WBS) versus a technetium-99 (Tc-99) thyroid scan and ultrasound for detection of possible local thyroid cancer recurrence that might explain the rising Tg levels. We acknowledge that Tc-99 scan is unable to detect distant follicular thyroid carcinoma metastasis, but the patient had stage 1 follicular thyroid carcinoma more than 20 years ago with exceptionally good prognosis and the possibility of distant metastases at this point was quite low. The patient was not keen for RAI WBS despite the rare likelihood of GO activation.

An ovoid, well circumscribed hypoechoic solid lesion (0.9 x 0.5 x 1.1 cm) at the midline anterior neck and superficial to the thyroid cartilage was seen on the Tc-99 thyroid scan and ultrasound. This lesion also corresponded to a focus of intense tracer uptake on scintigraphy (Figure 3). No abnormal cervical lymphadenopathy was seen. An ultrasound guided fine needle aspirate of the thyroid lesion showed cytology of benign nodular goiter. It is interesting that her thyroid stimulating receptor antibody (TRAb) level was also elevated at 35.8 IU/L [Normal Range (NR) 0.0-1.5].

Our patient was treated with pulsed intravenous methylprednisolone (1g for 3 days) followed by fractionated orbital radiation. She showed improvement of her orbital congestion and ocular motility function. Her PTM had resolved after a course of intralesional steroid injections. At her most recent review in 2020, her Tg level had decreased to 1.1Ug/L (NR 1.6-50), FT4 was within normal

Table 1. Thyroglobulin (Tg), Anti-Thyroglobulin Antibody (TgAb), free T4 (fT4), thyroid stimulating hormone (TSH) trends of the patient after thyroidectomy until her presentation to our institution

	Tg (2.0 – 70.0 ug/L)	**TgAb (0 – 60 u/mL)**	**fT4 (8.8 – 14.4 pmol/L)**	**TSH (0.65 – 3.70 mu/L)**	**Oral LT4 cumulative weekly dose (mcg)**
2nd June 2010	<0.17↓	<10	20.9 ↑	0.159 ↓	1050
10th Sep 2012	1.0 ↓	<10	23.4 ↑	0.254 ↓	875
4th Feb 2013	1.4 ↓	<10	21.9 ↑	0.147 ↓	875
20th Mar 2014	1.2 ↓	<10	21.3 ↑	0.710	700
	Tg (1.6 – 61 ug/L)	**TgAb (0 - 40 u/mL)**	**fT4 (12 – 22 pmol/L)**	**TSH (0.27 – 4.20 mu/L)**	**Oral LT4 cumulative weekly dose (mcg)**
8th Jul 2015	2.6	<20	27.3↑	1.11 ↓	725
16th Feb 2016	3.0	<20	24.1↑	5.97 ↑	725
	Tg (2.0 – 70.0 ug/L)	**TgAb (0 – 60 u/mL)**	**fT4 (8.8 – 14.4 pmol/L)**	**TSH (0.65 – 3.70 mu/L)**	**PO LT4 cumulative weekly dose (mcg)**
6th Oct 2017	3.5	<10	18.8 ↑	4.50 ↑	750

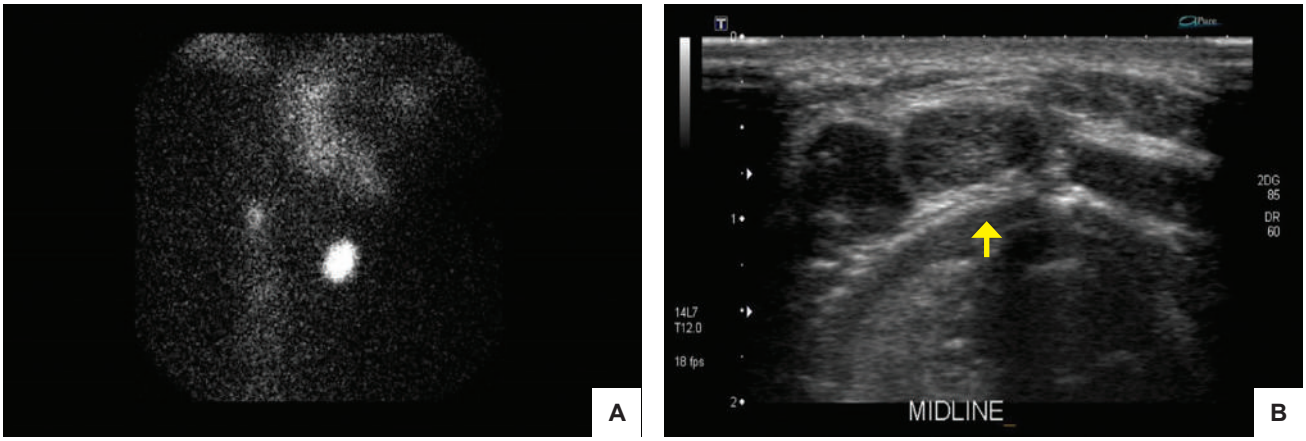

Figure 3. Tc-99 scintigraphy **(A)** and thyroid ultrasound **(B)** in 2017 showed a focus of intense radiotracer uptake at the anterior midline neck corresponding to a solid hypoechoic lesion (arrow) superficial to the thyroid cartilage.

at 19.4 pmol/L (NR 8.8-14.4), TSH was likewise normal at 1.46 (0.65-3.70 mU/L), and TRAb was negative.

DISCUSSION

There are acknowledged links between GD and thyroid cancer, with mechanisms postulated being TSH receptor antibodies stimulating thyroid cancer growth over time and the direct carcinogenic effects of GD.[2–5] In patients with GD, a higher incidence of thyroid nodules and cancer (2.3 – 46%) has been reported, compared to the general population.[6–10] There have been cases of concurrent GD and metastatic thyroid carcinoma implying that TRAb may act as a promoter in the pathogenesis of thyroid cancer.[5] However, a case such as our patient is novel and has not been previously been reported in literature, when thyroid cancer presents before GD.

Despite having undergone a total thyroidectomy, our patient developed extra-thyroidal manifestations of GD. Although there have been case reports of euthyroid patients without a previous history of hyperthyroidism who developed signs of GO,[11–13] our patient presented with a long latency period of 16 years post total thyroidectomy with PTM and GO. There are fewer than 10 cases reported in the literature so far of GD developing after thyroidectomy for nodules or cancer.[14–17] Notably, the occurrence of *de novo* GO in patients with thyroid cancer after total thyroidectomy without RAI such as in our patient's case has not been reported.

Clinical and genetic observations support the concept that GO, PTM and Graves' hyperthyroidism are manifestations of the same autoimmune disease.[3] It follows, therefore, that all components of the clinical triad may stem from an immune reaction directed against the same or a similar autoantigen.[3] The presence of TRAb is central to the pathogenesis of all three related entities. The complete surgical removal of the thyroid gland should theoretically obliterate the risk of development of these manifestations since it avoids worsening of thyroid humoral autoimmunity by removing thyroid antigens and intra-thyroidal autoreactive T lymphocytes.[13] However, our patient still had evidence of a thyroid remnant, most likely arising from the pyramidal lobe that was over-looked at the time of surgery.

Nonetheless, a study by Marcocci et al., has shown that a near-total thyroidectomy does not modify the course of GO.[18] There have been previous case reports of GD being diagnosed biochemically following thyroidectomy, with variable latent time to manifestation (3-120 months, median 48 months).[11,14–17] It has been postulated that the persistence of even minimal residual thyroid can have a role in maintaining orbit autoimmune phenomena since antigen triggers could originate from minuscule amounts of thyroid tissue left behind.[18,19] In addition, even though evidence suggests that the thyroid gland is a major site of TSH receptor antibody synthesis in GD, other sites of TRAb synthesis should be considered.[20,21] TSH receptors are present in both normal and Graves' orbital tissues. Therefore, it is theoretically possible that orbital tissues were the sources of the antigen.[22] There are data to suggest that TSH receptors are likely present in fibroblasts in the anterior tibial region, explaining the genesis of the pretibial myxedema.[23] Some patients with subtotal thyroidectomies have had persistent thyroid antibodies postoperatively, suggesting that other sites of thyroid autoantibody synthesis may also exist.[20,21]

There was no co-occurrence of GD and thyroid cancer prior to thyroidectomy in our patient since there was no biochemical or histological evidence of GD pre-operatively. The presence of functional FTC metastasis contributing to the development of TRAb leading to extra-thyroidal manifestations in our patient is also unlikely since she remained euthyroid on thyroxine replacement and Tg levels were on a declining trend following treatment of her GO. On hindsight, the initial rising Tg trend may be related to development of TRAb and may have been exacerbated by rising TSH levels possibly attributed to the patient occasionally mixing her thyroxine with her meals and calcium supplementation. The elevated TSH was likely due to drug interactions that affected gastrointestinal absorption. The high fT4 could have been due to the erratic intake of thyroxine with respect to timing of the blood investigations.

Hence, we postulate that the development of PTM and GO in our patient was related to the remnant thyroid tissue post total thyroidectomy, which may have triggered thyroid autoimmunity, and led to further perpetuation of the autoimmune cascade over a long latent

period, with eventual presentation of these extrathyroidal manifestations.

CONCLUSION

We describe an unusual case of a patient who presented with severe active GO and PTM 16 years after total thyroidectomy for a minimally invasive follicular thyroid cancer. We postulate that the presence of remnant thyroid tissue post-surgery triggered the development of TRAb which led to the severe extra-thyroidal manifestations in this patient. Clinicians should be aware of the possible occurrence of extra-thyroidal manifestations even after total thyroidectomy.

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

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

Author Disclosure
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CASE REPORT

Diabetes Insipidus Induced by Combination of Short-acting Octreotide and Lanreotide for Recurrent Carcinoid Crisis of Neuroendocrine Tumour: A Case Report

Goh Kian Guan,[1] Subashini Rajoo,[1] Noraini Mohd Dusa,[2]
Nik Hasimah Nik Yahya,[2] Mohamed Badrulnizam Long Bidin[1]

[1]*Department of Medicine, Hospital Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia*
[2]*Histopathology Unit, Department of Pathology, Hospital Kuala Lumpur, Malaysia*

Abstract

Somatostatin analogue is useful in carcinoid crisis for symptom control. Optimal dosing of somatostatin analogues for carcinoid symptoms is not known. This case highlighted management issues using combination short-acting octreotide infusion with long-acting lanreotide during carcinoid crisis. The patient had left lung neuroendocrine tumour that metastasized to his liver and bone, post left lobectomy. Due to extensive metastasis to the liver causing recurrent carcinoid crisis, he required shorter interval long-acting lanreotide with continuous infusion of short-acting octreotide, which led to transient diabetes insipidus. Symptoms resolved with discontinuation of treatment. Somatostatin analogues, especially in combination, may inhibit the posterior pituitary resulting in diabetes insipidus. Prompt withdrawal of short-acting somatostatin analogue and initiation of desmopressin can reverse the complication. It is important to recognize this complication with combination of octreotide and lanreotide injections to avoid serious complications.

Key words: diabetes insipidus, octreotide, lanreotide, neuroendocrine tumors, malignant carcinoid syndrome

INTRODUCTION

Neuroendocrine tumour (NET) is rare malignancy with the potential to secrete bioactive amines resulting in carcinoid syndrome. Pulmonary NET occurred in 0.2 to 2/100,000 population/year in Western countries.[1] Carcinoid syndrome occurred in 19% of NET, which was associated with shorter overall survival.[2] In carcinoid crisis, there is over-secretion of biochemically-active peptides leading to flushing, hypotension, severe hypertension, diarrhoea and acidosis. Somatostatin analogue is used to control carcinoid symptoms in NET. Despite this, some patients still experience breakthrough of carcinoid symptoms, thus requiring a higher dose or alternative strategies. However, there is no optimal dosing recommended so far to overcome carcinoid crisis. Therefore, dose related adverse effects are not frequently sighted or reported in the past. This case highlighted the rare complication of diabetes insipidus in metastatic lung neuroendocrine tumour treated with combination of high-dose somatostatin analogues and understanding the pathophysiology behind it. It is important to recognize this complication, as it is reversible and treatable.

CASE

We present a case of a 62-year-old male who presented with carcinoid syndrome such as recurrent vomiting, diarrhoea, facial flushing, palpitation and unintentional weight loss for two months. Investigation to look for the source of carcinoid syndrome included CT scan of thorax, abdomen and pelvis which showed a heterogeneously-enhancing lobulated mass at the laterobasal segment of left lower lobe of lung (largest diameter 9.5 cm) with multiple large liver lesions (largest diameter 8.2 cm) and bone involvements. Urine homovanillic acid pre-operatively was elevated to 149.94 mg per 24h (0-34.3 mg per 24h). Urine 5-hydroxyindoleacetic acid was similarly raised to 3677.9 mg per 24h (3.6-42.89 mg per 24h). Biopsy of lung was negative for malignancy cells. Baseline Galium-68 DOTANOC scan showed focal uptakes at the area of the lung mass, at left lower lobe and heterogenous uptake in both liver lobes and vertebral body. Ultrasound-guided liver biopsy showed well-differentiated NET.

He underwent left lower lobe lobectomy and histopathology confirmed to be NET with synaptophysin positivity and Ki-67 <2% (Grade 1) (Figures 1 and 2). Intramuscular lanreotide 120 mg was initiated 1-month post lobectomy and continued 4-weekly. Four months post somatostatin analogue therapy, Ga-68 DOTANOC PET CT showed persistent somatostatin-avid lesions in liver and bone. Chromogranin A level was elevated at 1960.78 nmol/L (0.79-2.74 nmol/L) and reduced marginally to 1414.72 nmol/L after surgery. His symptoms persisted requiring multiple admissions, hence, lanreotide injection frequency was shortened to bi-weekly. Despite that, there were multiple carcinoid crises breakthrough requiring monthly admissions. Each time, he received continuous, escalating octreotide infusion during admission of carcinoid crisis

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Corresponding author: Goh Kian Guan, MMed, MRCP (UK)
Internal Medicine Specialist, Department of Medicine,
Hospital Kuala Lumpur, Jalan Pahang, 50586, Kuala Lumpur, Malaysia
Tel. No.: +60326155555
Fax No.: +60326989845
E-mail: eganghoh@gmail.com
ORCiD: https://orcid.org/0000-0001-7784-3530

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to control his symptoms of palpitations, hypotension and flushing. Subsequently, his urine output increased to 300 cc per hour (4.6 ml/kg/hour) (serum osmolarity: 295 mOsm, urine osmolarity: 213 mOsm and serum sodium 146 mmol/L) once octreotide infusion reached 75 mcg per hour. Carcinoid symptoms finally resolved with 150 mcg per hour of octreotide infusion. All other causes of polyuria such as hypercalcaemia, hyperglycaemia and primary polydipsia were excluded. Serum calcium was 2.25 mmol/L (9 mg/dL). He was treated as central diabetes insipidus and was given subcutaneous desmopressin 2 mcg injections, reducing urine output to 0.5 ml/kg/hour. After resolution of carcinoid crisis, octreotide infusion was slowly tapered off and no recurrence of polyuria was observed. These carcinoid crisis episodes were recurrent, and he had a total of 4 admissions for symptoms control. Short-acting octreotide infusion had resulted in carcinoid crisis control but caused recurrent episodes of diabetes insipidus. Repeated Galium scan showed disease progression and extensive metastases (Figure 3). Peptide receptor radionuclide therapy (PRRT) was considered for the patient for disease-control and symptom-control.

DISCUSSION

The posterior pituitary is a neural tissue consisting of distal axons of hypothalamic magnocellular neurons.[3] Control of posterior pituitary hormone synthesis is via messenger RNA (mRNA) transcription in the magnocellular neurons.[4] The major stimulatory pathway of posterior pituitary is through the direct effect of norepinephrine on presynaptic glutamate neurons.[5] The main inhibitory input is via presynaptic gamma aminobutyric acid (GABA) receptors, which can result in decreased secretion of arginine vasopressin (AVP).[6] Vasopressin is the main hormone regulating osmolality and water homeostasis. Diabetes insipidus (DI) is defined as excretion of abnormally large amount of diluted urine (urine osmolality less than 300 mOsm/kg of water). The fundamental aetiology of DI is as follows: decreased AVP secretion (cranial DI, hypothalamic disorder); decreased AVP effects (nephrogenic DI); excessive water intake (dipsogenic or psychogenic polydipsia); and increased AVP metabolism (gestational DI).[7]

Somatostatin is synthesized in parvicellular neurons and found to have overlapped distribution with AVP and somatostatin-like immunoreactive fibres in pituitary and neurohypophysis.[8] This was supported by a study whereby somatostatin administered in increasing doses was able to reduce AVP secretion in haemorrhage-induced sheep.[9] In the distal nephron, somatostatin also inhibits AVP action and increase basal water permeability, leading to diuresis.[10] Octreotide and lanreotide are somatostatin receptor analogues that have multiple inhibitory effects.

The mainstay of treatment in NET is surgical resection of the tumour. Metastatic NET usually requires multimodal approaches such as liver-targeted therapy, cytotoxic chemotherapy, PRRT or medical therapy. Targeted agents such as everolimus and sunitinib had been used to improve progression-free survival.[11] Somatostatin receptor ligands alleviates carcinoid symptoms by blocking multiple hormone release.[12] Both octreotide and lanreotide are equally effective in controlling carcinoid symptoms.[13] However, the patient showed only partial response to high

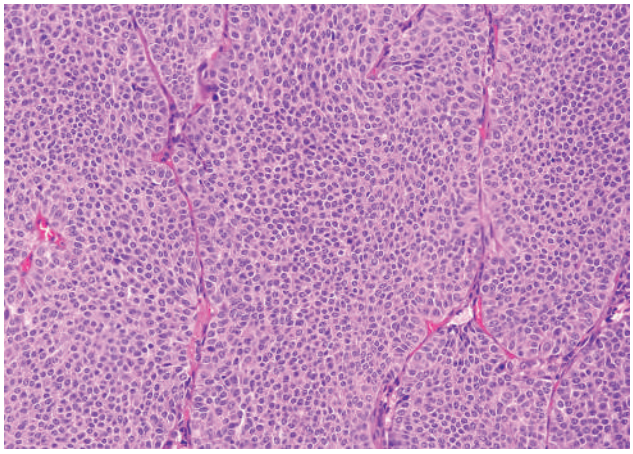

Figure 1. Tumour with uniform population of neoplastic cells with fine granular chromatin pattern and inconspicuous small nucleoli (H&E, 200x).

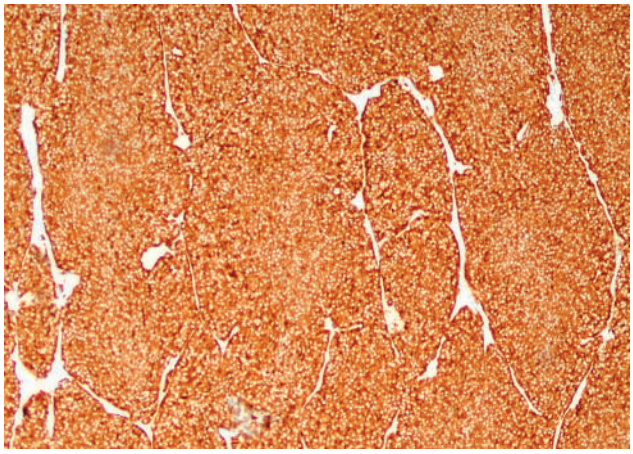

Figure 2. Tumour cells showing diffuse positivity for synaptophysin (SYN, 100x).

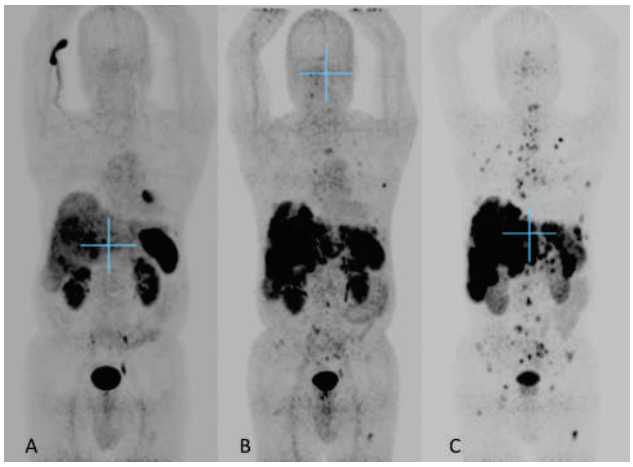

Figure 3. (A) Galium-68 DOTANOC scan showing somatostatin-avid disease in left lower lobe of lung mass and heterogenous uptake in both lobes of liver and vertebra spine; **(B)** Galium-68 DOTANOC imaging post left lung lobectomy and lanreotide therapy showing disease progression with increasing somatostatin-avid lesions in liver, vertebrae, pelvic, ribs and scapula; **(C)** Post PRRT scan showing high tumour burden with increased somatostatin-avid lesions in neck, both lung fields and abdomen.

dose subcutaneous lanreotide (120 mg every 14 days) and required intermittent octreotide infusion (up to 150 mcg per hour) to cover for breakthrough of acute carcinoid crisis. This approach reduced the patient's symptom severity and shortened the length of hospital stay.

In phase I trial of octreotide for NET, carcinoid symptoms were better controlled with a higher dose of octreotide and no dose-limiting adverse effects were observed with doses up to 2000 mcg q 8h (total 6000 mcg per day).[14] Therefore, we propose that escalating doses of octreotide infusion (up to 3600 mcg per day) with concurrent high dose long-acting lanreotide had possibly inhibited AVP release from the pituitary and disrupted AVP action at distal nephrons leading to DI.

From our literature review, this is the first case to report an association of DI with the combination of octreotide and lanreotide. The resolution of DI once octreotide infusion was tapered and stopped also suggests transient effects of somatostatins analogues on the posterior pituitary. Concurrent use of two somatostatin receptor ligands can effectively alleviate carcinoid syndrome. However, the potential complication of DI needs to be monitored and promptly treated.

CONCLUSION

Short-acting somatostatin analogue (octreotide) can be augmented with long-acting somatostatin analogue during breakthrough carcinoid crisis. However, physicians need to practice caution as the combination of somatostatin receptor analogues at high doses can result in iatrogenic DI, though this rare encounter is usually transient and reversible.

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.

Funding Source
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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Recurrent Severe Hypoglycemia Secondary to Benign Phyllodes Tumor of the Breast: A Rare Case of Non-Islet Cell Tumor-induced Hypoglycemia (NICTH)

Hwee Ching Tee and Vijaya Mala Valayatham

Endocrinology Unit, Putrajaya Hospital, Malaysia

Abstract

Non-islet cell tumor-induced hypoglycemia (NICTH) secondary to phyllodes tumor is extremely rare but potentially life threatening if not treated promptly. We report a case of a 46-year-old Indian female without underlying diabetes mellitus who presented with a large breast tumor and recurrent severe symptomatic hypoglycemia. Investigations supported the diagnosis of NICTH. The hypoglycemia only resolved after corticosteroids and mastectomy. This case highlights the importance of considering NICTH in the evaluation of patients with voluminous tumor and hypoglycemia.

Key words: hypoglycemia, insulin-like growth factor II, phyllodes tumor, mastectomy, corticosteroids

INTRODUCTION

Phyllodes tumor is an uncommon fibroepithelial tumor that accounts for less than 1% of all breast neoplasms, with 54 to 64% classified as benign, 12 to 18% borderline and 18 to 35% malignant.[1,2] Non-islet cell tumor-induced hypoglycemia (NICTH) is also a rare but serious paraneoplastic syndrome in which a tumor secretes insulin-like growth factor II (IGF-II), causing hypoglycemia. Although the true incidence of NICTH is unclear, it is generally believed to be much less frequent than hypoglycemia from insulinomas. In most cases, NICTH occurs in patients with solid tumors of mesenchymal and epithelial origin, such as hepatocellular carcinoma, fibrosarcoma or mesothelioma.[3] Only a few cases of NICTH secondary to breast tumors, especially phyllodes tumors, have been previously reported. We present an interesting case of a patient with benign phyllodes tumor presenting with recurrent severe hypoglycemia which only resolved after corticosteroid therapy and mastectomy.

CASE

A 46-year-old Indian female with a six-month history of a rapidly growing left breast mass presented with altered mental status for three days. She was observed to be less responsive and incoherent at times. There were no preceding autonomic symptoms or fever. She was on atenolol for underlying hypertension. She had no previous history of diabetes mellitus. There was no known use of any anti-diabetic medication, insulin or traditional medicine. There was no family history of malignancy.

Upon presentation, she was confused, afebrile and normotensive. She had a Glasgow Coma Scale (GCS) of E4V3M5 and a capillary glucose of 1.9 mmol/L. Her GCS improved after intravenous infusion of 50 mL 50% dextrose, with a capillary glucose of 5.2 mmol/L. Physical examination revealed a large, firm and mobile left breast mass measuring 20 cm x 20 cm, with three ulcerated lesions and *peau d'orange* skin changes (Figure 1). There was no lymphadenopathy or hepatosplenomegaly.

Initial laboratory data showed severe hypoglycemia (random blood glucose 1.7 mmol/L) and hypokalemia (serum potassium 2.8 mmol/L). Otherwise, her full blood count, venous blood gas, and function tests of the kidney, liver and thyroid were normal. Random serum cortisol taken before initiation of hydrocortisone was inappropriately low (166 nmol/L) when her random blood

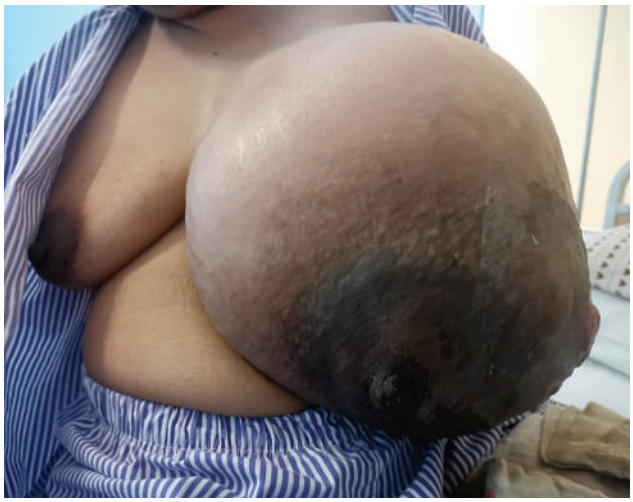

Figure 1. Physical findings showed a giant left breast mass measuring 20 cm × 20 cm in diameter with ulceration of the overlying skin.

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Corresponding author: Hwee Ching Tee, MD
General Physician/Endocrinology Trainee
Endocrinology Unit, Putrajaya Hospital
Jalan 9, Presint 7, 62250 Putrajaya, Malaysia
Tel. No.: +603-83124200
Fax No.: +603-88880137
E-mail: hweeching_718@yahoo.com
ORCiD: https://orcid.org/0000-0002-1111-8229

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glucose was 1.7 mmol/L. During the same hypoglycemic episode, the serum levels of insulin (<0.5 mU/mL) and C-peptide (35 pmol/L) were suppressed, suggesting that the hypoglycemia was not linked to either endogenous or exogenous hyper-insulinism. Plasma insulin-like growth factor I (IGF-I) (67.4 ng/mL, reference range 53 to 192 ng/mL) and IGF-II (481 ng/mL, reference range 333 to 967 ng/mL) were within normal, but the elevated IGF-II/IGF-I ratio (7:1, normal <3:1) supported the diagnosis of NICTH. Computed tomography (CT) of the brain, chest, abdomen and pelvis showed a large, heterogenous left breast mass with no obvious infiltration of the chest wall and no evidence of lymphadenopathy or metastasis. Bone scan was not done as the patient did not have bone pain and alkaline phosphatase level was normal.

During hospitalization, she experienced recurrent daily hypoglycemia, ranging from 1.7 to 3.2 mmol/L. This resulted in recurring confusion and seizures despite multiple 50% dextrose injections and continuous 20% dextrose infusion at 62.5 mL/hour. She also required large amount of potassium supplementation of up to 150 mmol/day to maintain a normal serum level. Intravenous hydrocortisone at 100 mg three times daily was started on day 3 of admission. This was subsequently converted to oral prednisolone 40 mg daily on day 5. After steroid initiation, she was able to achieve euglycemia, ranging from 4.5 to 7.1 mmol/L within two days, with concurrent continuous 5% dextrose infusion at 62.5 mL/hour. There were also resolution of confusion, seizure and hypokalemia.

Core needle biopsy of the breast lesion showed spindle cell neoplasm. A simple mastectomy was then performed to remove the tumor. On cut section, the 6.3 kg mastectomy specimen showed a well-circumscribed tumor measuring 30 cm x 24 cm x 14 cm with a 2 cm clear resection margin. The tumor contained abundant stromal and epithelial components. The hypercellular stroma was composed of spindle-shaped cells with mild nuclear atypia. Mild epithelial hyperplasia and a few cystically dilated ducts were also seen. There was no evidence of malignancy. Hormone receptor tests were positive for both estrogen and progesterone. All these histological features were consistent with a benign phyllodes tumor (Figure 2).

Infusion with 5% dextrose was continued in the immediate postoperative period until the patient was able to tolerate oral intake. There were no more hypoglycemic episodes subsequently. Prednisolone was converted to hydrocortisone replacement dose in view of possible adrenal insufficiency. After one week, a short Synacthen® test showed adequate cortisol response (baseline, 197 nmol/L; after 30 minutes, 544 nmol/L; after 60 minutes, 587 nmol/L) prompting discontinuation of hydrocortisone. There has been no recurrence of hypoglycemia, confusion or seizure during the subsequent four-month follow-up.

DISCUSSION

Fourteen cases of phyllodes tumor of the breast with NICTH have been described in literature, with only

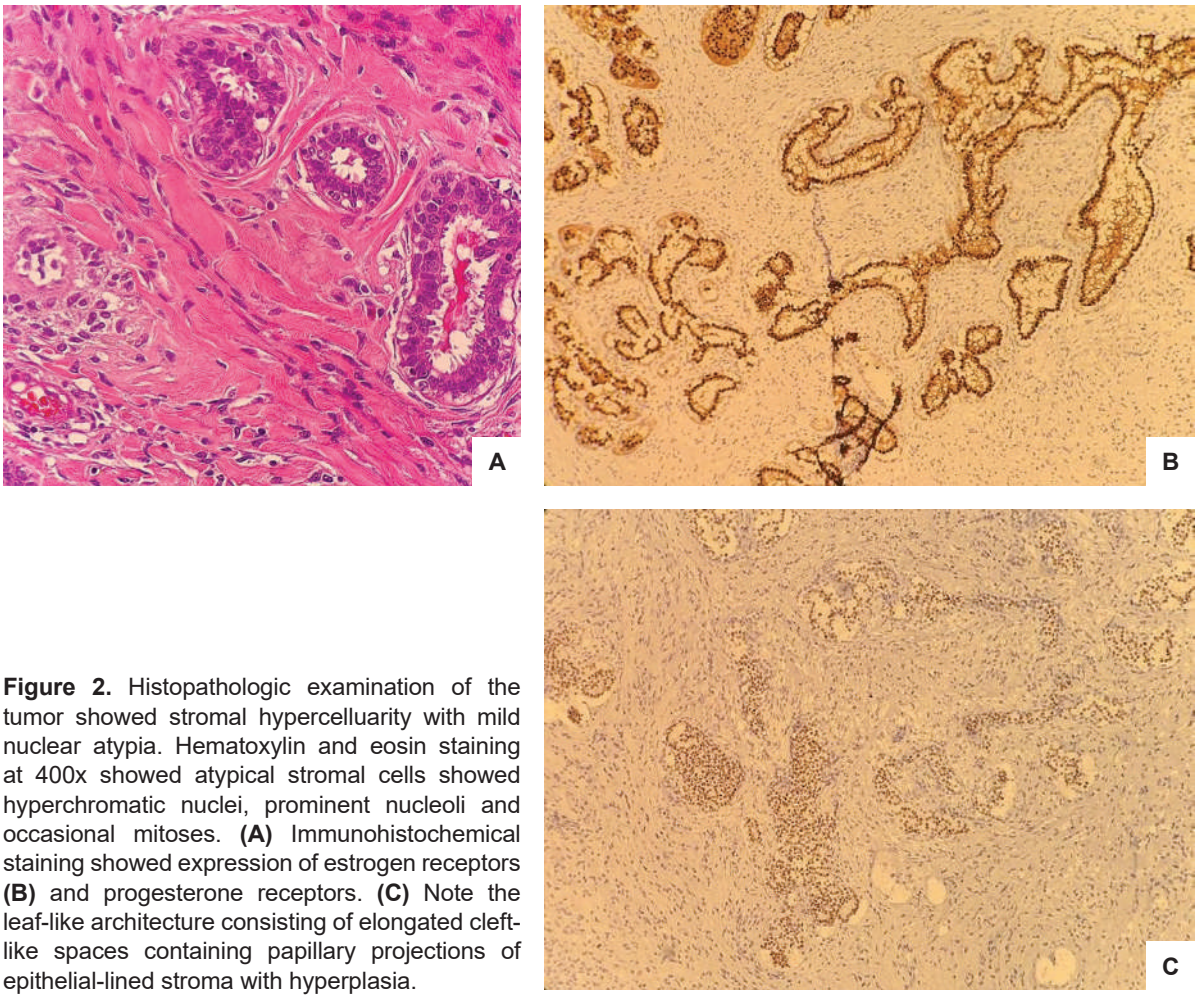

Figure 2. Histopathologic examination of the tumor showed stromal hypercelluarity with mild nuclear atypia. Hematoxylin and eosin staining at 400x showed atypical stromal cells showed hyperchromatic nuclei, prominent nucleoli and occasional mitoses. **(A)** Immunohistochemical staining showed expression of estrogen receptors **(B)** and progesterone receptors. **(C)** Note the leaf-like architecture consisting of elongated cleft-like spaces containing papillary projections of epithelial-lined stroma with hyperplasia.

Table 1. Summary of 14 cases of phyllodes tumor of the breast with NICTH reported from 1983 to 2021

Authors	Year	Tumor size (cm)	Tumor weight (kg)	Histological subtypes	Serum potassium	Serum IGF-II	Serum IGF-I	IGF-II: IGF-I ratio	Big IGF-II[a]	Tissue
Li et al[4]	1983	28	4.2	Benign	Low	High	NA	NA	NA	NA
Tanaka et al[5]	1986	25	4.0	Malignant	NA	NA	NA	NA	NA	NA
Bleau et al[6]	1991	NA	6.0	NA	NA	Normal	NA	NA	NA	Expression of IGF-II[b]
Ishido et al[7]	1992	NA	3.0	Benign	NA	High	NA	NA	NA	NA
Miura et al[8]	1992	26	3.1	NA	NA	Normal	NA	NA	NA	NA
Katoka et al[9]	1998	35	9.0	Malignant	Normal	Low	Normal	2.0	NA	Expression of IGF-II[b]
Bujanda et al[10]	2007	33	10.0	Malignant	NA	NA	Low	NA	High	NA
Hino et al[11]	2008	25	4.2	Benign	Low	Normal	Normal	5.7	High	NA
Renard et al[12]	2012	27	5.8	Malignant	Low	NA	Low	NA	High	High IGF-II mRNA
Argawal et al[13]	2012	34	NA	Benign	NA	NA	NA	NA	NA	NA
Pacioles et al[14]	2014	29	NA	Malignant	Low	Normal	Low	16.9	NA	NA
Saito et al[15]	2016	25	5.0	Borderline	Low	High	Normal	6.3	NA	High IGF-II in tissue extract
Hikichi et al[16]	2018	27	4.5	Borderline	Normal	NA	NA	NA	High	Expression of IGF-II[b] High big IGF-II in tissue extract
Zhao et al[17]	2021	20	NA	Borderline	NA	NA	NA	NA	NA	Expression of IGF-II[b]

[a] Big IGF-II measurement was done by western immunoblotting of the serum with identification of abnormal IGF-II peptide in excess in its precursor form, pro-IGF-II or big IGF-II (10-20 kDa)
[b] Expression of IGF-II was demonstrated by immunohistochemical examination of frozen sections of the tumor
IGF, insulin-like growth factor; NA, not available; mRNA, messenger ribonucleuc acid

four being benign (Table 1).[4-17] Our patient had a similar presentation of a large breast mass compared to previous case reports, describing sizes from 23 to 35 cm in maximal diameter. The median size at diagnosis of phyllodes tumors without NICTH seems considerably smaller (3 cm) compared to those with NICTH, supporting the idea that a large tumor size is necessary to reach a sufficient level of IGF-II secretion to promote hypoglycemia.[18] Similar to findings in insulinoma, hypoglycemia associated with an IGF-II-producing tumor typically presents in the fasting state. Neuroglycopenic symptoms are more commonly seen than autonomic symptoms as in our patient, due to repeated hypoglycemic events and insidious progression. Hypokalemia, frequently observed in NICTH, is attributed to the insulin-like activity of IGF-II, which acutely decreases serum potassium by moving extracellular potassium into cells.[19]

The cause of NICTH is the overproduction of IGF-II or incompletely processed IGF-II from tumor cells. This immature form of IGF-II precursor, also known as high-molecular-weight or big IGF-II (10 to 20 kDa fraction), has higher bioactivity than mature IGF-II (7.5 kDa fraction).[4,20] IGF-II binds to insulin receptor isoform (IR)-A with a higher affinity, about 35 to 40% that of insulin. In contrast, IGF-II binds with IR-B with an affinity of roughly 5% that of insulin.[4] With markedly elevated IGF-II levels and higher bioavailability of big IGF-II found in NICTH, hypoglycemia can occur via activation of insulin receptors. This results to inhibition of hepatic glycogenolysis and gluconeogenesis as well as lipolysis in adipose tissue.

IGF-II levels may or may not be elevated in NICTH. Even if IGF-II levels are normal, IGF-I levels are usually less than 100 ng/mL.[20] This is due to suppression of growth hormone at the level of the pituitary gland by negative feedback mechanisms, leading to suppressed IGF-I levels. While elevated big IGF-II is helpful in diagnosing NICTH, testing is not always readily available.

A clinical review by Bodnar et al., recommended that the diagnosis of NICTH can be established by fulfilling the following criteria: (1) hypoglycemia fulfilling Whipple's triad; (2) low insulin/pro-insulin/C-peptide levels; (3) rapid response to glucocorticoid therapy; (4) IGF-I level less than 100 ng/mL, normal/high IGF-II, IGF-II:IGF-I ratio more than 3 (if feasible, measurement of high molecular weight IGF-II); and (5) identification of culprit tumor.[20]

Our patient fulfilled all these criteria for the diagnosis of NICTH. While an IGF-II:IGF-I ratio more than 10 is frequently found in NICTH, the biggest series of NICTH patients (n=44) showed that 7 out of 13 patients with NICTH without big IGF-II had IGF-II:IGF-I ratios between 3 and 10. The IGF-II:IGF-I ratio is higher in patients with big IGF-II, ranging from 16.4 to 64.2, and lower in normal subjects (3.0 ± 0.2).[21]

Two cases of phyllodes tumor with NICTH reported normal IGF-II levels with elevated IGF-II:IGF-I ratios (5.7 and 16.9, respectively).[11,14] As phyllodes tumors arise principally from mammary fibroblast and epithelial cells known to produce high amounts of IGF, overexpression of IGF-II within the tumor cells had also been observed in four previous case reports of NICTH mainly related to borderline or malignant phyllodes tumor.[6,9,16,17]

Our patient's serum cortisol was inappropriately low during hypoglycemia. A subsequent short Synacthen® test excluded the possibility of hypocortisolism. Repeated hypoglycemia induces attenuation of counter-regulatory hormonal responses to hypoglycemia in patients with insulinomas or in patients with diabetes on intensive insulin therapy. Hence, low plasma cortisol during hypoglycemia is not sufficient evidence of cortisol deficiency.[22] There is a possibility that the same mechanism, specifically a shift in glycemic thresholds for cortisol release in response to lower plasma glucose concentrations, may occur in some patients with IGF-II-producing NICTH.

Complete resection of the IGF-producing tumor is the most effective treatment for NICTH. However, if surgery cannot be readily performed, management of hypoglycemia may include increasing caloric intake, infusion of intravenous glucose and administration of glucocorticoids. Glucocorticoids can prevent hypoglycemia

through several mechanisms, including augmentation of hepatic gluconeogenesis, inhibition of peripheral glucose uptake, mobilization of amino acids from extrahepatic sites, stimulation of lipolysis with fatty acid release from adipose tissue and reduction in IGF-II levels.[3] In our patient, the operation was put on hold while waiting for the CT scan and Tru-cut biopsy results. Systemic steroid was started in view of recurrent severe hypoglycemia despite intravenous glucose.

There are some limitations in our case report. We were not able to perform of serum pro-IGF-II measurement and immunohistochemical analysis to search for IGF-II in the tumor tissue as these tests are commercially unavailable. However, we showed that suppressed insulin and C-peptide levels with elevated IGF-II/IGF-I ratio are sufficient to support the diagnosis of NICTH. The excellent response with resolution of hypoglycemia from glucocorticoids and tumor removal further supports the diagnosis.

CONCLUSION

Despite its rarity, NICTH must be considered in any patient with a large phyllodes tumor and hypoglycemia. Early recognition of symptoms of hypoglycemia is essential in those patients to avoid irreversible neurological sequelae. Whenever possible, excision of the tumor must be attempted. Glucocorticoids can be given to aid hypoglycemia if surgery may not be done immediately.

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

Celiac Disease as a Cause of Anemia and Brittle Diabetes in Type 1 Diabetes Mellitus

Yotsapon Thewjitcharoen,[1] Vichai Viriyautsahakul,[2] Natthaporn Sasijaroenrat,[3] Surat Komindr,[4] Phawinpon Chotwanvirat,[1] Chadaporn Nongkhunsarn,[1] Soontaree Nakasatien,[1] Thep Himathongkam[1]

[1]*Diabetes and Thyroid Center, Theptarin Hospital, Bangkok, Thailand*
[2]*Division of Gastroenterology, Theptarin Hospital, Bangkok, Thailand*
[3]*Division of Hematology, Theptarin Hospital, Bangkok, Thailand*
[4]*Division of Clinical Nutrition, Theptarin Hospital, Bangkok, Thailand*

Abstract

Untreated celiac disease (CD) leads to an increased risk for hypoglycemia and diabetic complications. However, the diagnosis of CD can be challenging and some extra-gastrointestinal tract manifestations could be a presenting symptom. We report a case of a 29-year-old Indian male with brittle T1DM whose underlying CD was discovered from a work-up for anemia. After an introduction of a gluten-free diet, he gained 5 kgs in two months, was responsive to oral iron supplement, and had stable glycemic control with much less hypoglycemia. Even though this disease is rare in Asian populations, the diagnosis of celiac disease should always be kept in mind when people with T1DM present with unexplained microcytic anemia and/or unexplained hypoglycemia.

Key words: Celiac disease, Type 1 diabetes, Brittle diabetes

INTRODUCTION

Celiac disease (CD) is a disorder of gluten-sensitive enteropathy that occurs in genetically susceptible individuals after dietary exposure to gluten.[1] The alcohol-soluble component of gluten called "*gliadin*" does not degrade in the intestinal lumen and causes inflammation in the small intestine. The prevalence rates of CD vary considerably by geographic location and genetic predisposition, with higher rates found in northern latitudes compared with southern latitudes.[2] Moreover, the frequency of those presenting with non-classic features which are commonly associated with malabsorption has increased. There is also a strong familial component to this disease with the prevalence of CD among first-degree relatives being up to 5 times than the general population.[3]

The association of CD and type 1 diabetes mellitus (T1DM) has been known for more than 40 years with prevalence varying from 1% to 8% (contrasted with only less than 1% in the general population). Both diseases have a common genetic basis in the major histocompatibility complex class II antigen DQ2 and DQ8 alleles together with shared non-human leucocyte antigen (HLA) loci.[4] Undiagnosed CD in T1DM patients lead to an increased risk for hypoglycemia and diabetic complications. The diagnosis of CD can be challenging and some extra-gastrointestinal tract manifestations could be a presenting symptom. We report a case of a 29-year-old Indian male with brittle T1DM whose underlying CD discovered was discovered from work-up of anemia. Elimination of gluten from the patient's diet allowed all symptoms including frequent hypoglycemia to improve substantially.

CASE

A 29-year-old Indian male with a 20-year history of T1DM presented with intermittent headache in the emergency room (ER). He reported fatigue, headaches, and 5-kilogram weight loss over a few months. He denied any gastrointestinal symptoms, palpitation, sweating, hematemesis, hematochezia, or hemorrhoids. The patient had moved from Rajasthan, a state in northern India to Bangkok, Thailand 2 years ago to work as a marketing technology developer. He was using a multiple daily insulin injection regimen with no other medications. His insulin regimen consisted of 12 units of insulin glargine at bedtime and regular insulin 10-12 units before meal. The last glycated hemoglobin (A1C) was 6.7% (50 mmol/mol) in India before moving to Thailand. No diabetic complications were reported.

Apart from T1DM, he had no pertinent past medical history. He had been breastfed for 1 year and had normal development. He had never smoked or used illicit drugs. After relocating to Thailand, he self-titrated insulin and did self-monitoring blood glucose (SMBG) 1-2 times per day but never attended regular follow-up in the hospital.

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Corresponding author: Yotsapon Thewjitcharoen, MD
Diabetes and Thyroid Center, Theptarin Hospital
3858 Rama IV Rd., Long Toey, Bangkok 10110, Thailand
Tel. No: 066-02-348-7000
Fax No.: 066-02-2498774
E-mail: kamijoa@hotmail.com
ORCiD: https://orcid.org/0000-0002-2317-4041

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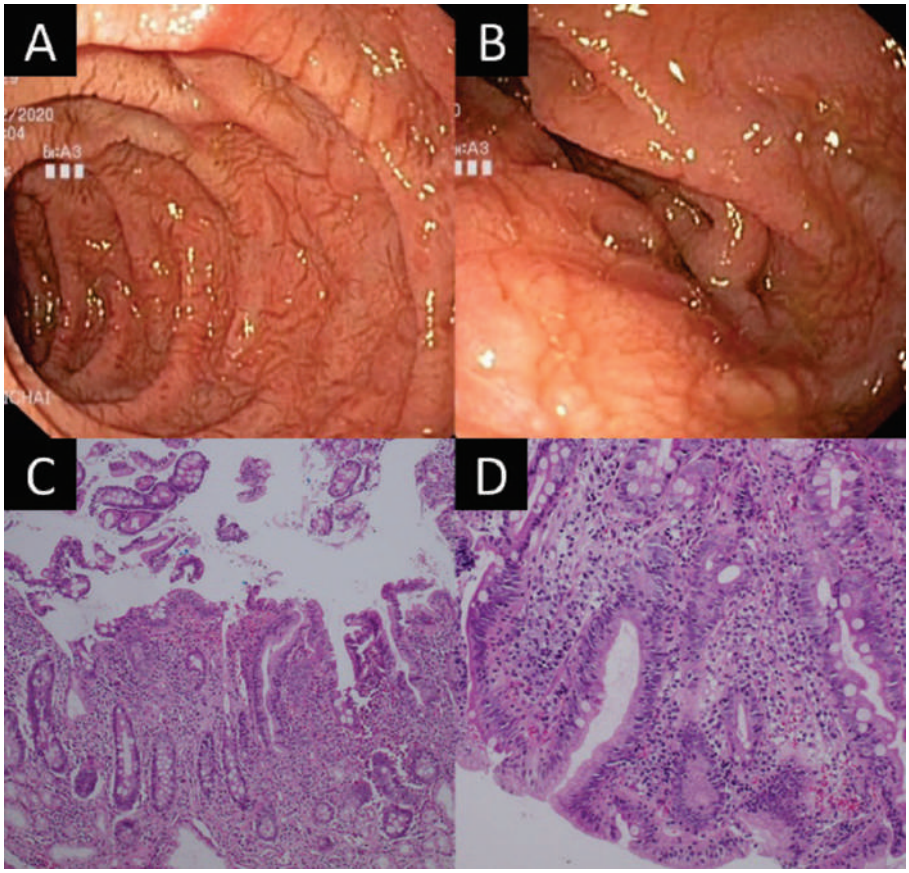

Figure 1. Endoscopic and pathologic findings in duodenum. **(A)** Endoscopy shows loss of mucosal folds. **(B)** Severe atrophic duodenitis. **(C)** Duodenal biopsy specimen showing subtotal villous atrophy and crypt hyperplasia (H&E, 100x). **(D)** Histologic changes in the duodenum characteristic of increased intraepithelial lymphocytosis and a chronic inflammatory infiltrate in the lamina propria (H&E, 200x).

The initial assessment in the ER showed a thin and pale Indian male without dysmorphic features. Upon physical examination, his height was 168 cm and weight was 45 kgs (BMI 16.1 kg/m^2). His blood pressure is 105/75 mm Hg. The rest of his examination findings were normal. He did not have subcutaneuous lipohypertrophy at insulin injection sites. Point-of-care testing (POCT) glucose 3 hours after lunch showed capillary glucose value at 54 mg/dL (3.0 mmol/L). Hypoglycemic unawareness was diagnosed and he had been given oral glucose to correct hypoglycemia. The initial laboratory data revealed A1C 5.7% (39 mmol/mol), hemoglobin 9.2 g/dL, MCV 65 fL, very low serum iron and ferritin levels. Oral iron supplement was given and further investigations were planned.

However, he was lost to follow-up for 9 months and came back with uncontrolled A1C at 8.0% (64 mmol/mol). At an outpatient follow-up, the patient described a 1-month history of feeling more tired and intermittent headache and increased frequency of nocturnal hypoglycemic episodes. He reported unstable glycemic values from 33-467 mg/dL (1.8-25.9 mmol/L) over a few months. He denied severe hypoglycemia requiring assistance. Additional history revealed that his mother in India had a recent diagnosis with celiac disease in the last month. The patient denied any abdominal pain, nausea, vomiting, or changes in weight or appetite. However, on further questioning, he noted occasionally irritable bowel syndrome-like symptoms and abdominal bloating in the past year. Therefore, celiac disease was suspected and further investigations were performed.

Tissue transglutaminase IgA antibody (IgA anti-tTgA) was positive at more than 200 RU/mL (reference range, <20 RU/mL). Other laboratory tests including thyroid function tests were normal. Upper gastrointestinal endoscopy was done and revealed severe atrophic duodenitis with scalloped duodenal folds. The results of histopathologic findings from random duodenal biopsies revealed subtotal villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, shown in Figure 1. A diagnosis of celiac disease was confirmed and additional malabsorption-related problems were investigated.

Severe vitamin D deficiency (25-OH vitamin D 4.8 ng/mL, 12 nmol/L) with osteopenia (T-score -1.8 at lumbar spine) were found. Elevated serum aspartate transaminase (AST) at 68 U/L (normal <40 U/L), alanine transaminase (ALT) at 109 U/L (normal <41 U/L), and alkaline phosphatase 157 U/L (normal <129 U/L) were also noted. Abdominal ultrasonography was unremarkable except for diffuse heterogeneous echogenicity of liver parenchyma. Viral hepatitis and autoimmune hepatitis profiles revealed negative results. Liver biopsy showed mild non-specific change of hepatocytes without evidences of autoimmune hepatitis. Reactive hepatitis-associated CD was diagnosed.

The patient was referred to a dietitian for a strict gluten-free diet (GFD) and also was prescribed oral iron supplementation, calcium, vitamin D, and multivitamins. He was also advised to do SMBG frequently at least 3-6 times per day after initiation of GFD. After its introduction, the patient gained 5 kgs in 2 months and had stable glycemic control at 6.6% (49 mmol/mol) with much less hypoglycemia. His total insulin dose per day was reduced from 48 units per day to 40 units per day. Improvements of headaches and fatigue were also noted within the first month after the GFD initiation and completely relieved at 3 months. Laboratory follow-up revealed a hemoglobin of 15.7 g/dL and MCV of 83 fL at 3 months, then oral iron supplement was stopped.

The patient switched the approach of monitoring his daily glycemic control from SMBG to intermittently scanned continuous glucose monitoring (isCGM, FreeStyle Libre) at 3 months. As shown in Figure 2, the time-in-range (70–180 mg/dL, 3.9-10.0 mmol/L) was achieved at 69% and time spent in hypoglycemia (less than 70 mg/dL, 3.9 mmol/L) was at only 3%. His follow-up A1C varied from 5.9% to 7.3% (41 to 56 mmol/mol) during the period of 18 months after the confirmed diagnosis of celiac disease. The follow-up liver function tests were returned to normal values at 6 months. The follow-up IgA anti-tTgA at 6 months and 12 months revealed results at 54 RU/mL and less than 20 RU/mL respectively, confirming dietary adherence with GFD.

DISCUSSION

Our case highlights several important points about associated CD in patients with T1DM especially in extra-gastrointestinal tract manifestations. First, a high degree of clinical suspicion including awareness of geographic and ethnic data in expatriates is needed in evaluation of T1DM patients. The prevalence of CD from the northern part of India (Punjab, Haryana, Delhi, Rajasthan, Uttar Pradesh) where wheat rather than rice is the staple food is nearly the same as that reported from Western countries.[5] Recent data suggest that asymptomatic or non-classic presentations of CD are common in patients with T1DM and could affect unstable glycemic control from malabsorption problems.[6] Therefore, a low screening threshold for serologic testing is warranted in these patients.

Second, the presence of iron deficiency anemia in the absence of known etiologies should be screened for celiac disease in high-risk CD patients including first-degree relatives of CD patients, patients with T1DM, autoimmune thyroid disease, Down's syndrome, and Turner syndrome.[1]

Third, when celiac disease and T1DM are both diagnosed together, a referral to professional dietitians is required to ensure GFD adherence without substitute dietary options of high glycemic index food choices. The effect of GFD on the quality of life had been demonstrated to improve after initiation in T1DM patients with symptomatic CD.[4]

Brittle diabetes or unstable diabetes control should be thoroughly investigated for co-existing medical conditions.[7] Even though routine serologic screening test for CD in adult patients with T1DM yield no clinical benefits,[8] the possible co-existence of CD in T1DM patients must be kept in mind in unexplained hypoglycemia or other non-specific symptoms such as anemia, fatigue, paresthesia, infertility, amenorrhea, male impotence, and osteopenic bone disease. T1DM patients with undiagnosed CD have poor glycemic control and higher chance of diabetic complications. The mechanism of unexplained hypo- or hyperglycemia in T1DM patients with CD is believed to be due to disordered food absorption from immune-medicated enteropathy and inadequate food intake due to gastrointestinal symptoms.

The development of unstable blood glucose patterns tends to occur in the postprandial period due to food

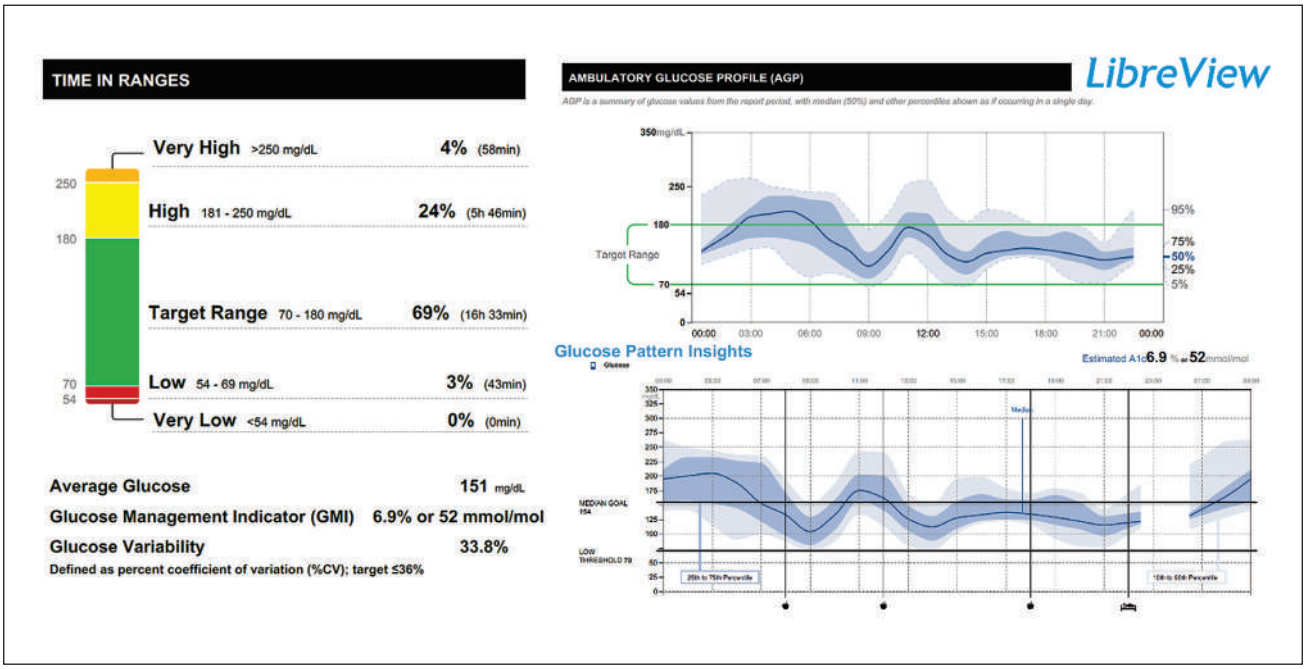

Figure 2. Intermittently scanned continuous glucose monitoring (isCGM) recorded through 14-day showed time-in-range (70–180 mg/dL) at 69% after a strict gluten-free diet for 3 months.

malabsorption.[4] Clinical manifestations of CD are determined by the severity and the extent of the intestinal lesions. Due to its protean clinical manifestations, it is an easy to miss diagnosis or misdiagnosis. Available evidence suggests that young age at onset of T1DM increases the risk of CD.[4] However, one needs to be aware that CD is not only a disease of children. The majority of cases were asymptomatic and identified only by screening tests. A high index of suspicion in a patient with a confounding presentation is required to diagnose CD. If diagnosed early, completely reversible complications from CD might be achieved with initiation of a GFD as shown in our present case.

Anemia is the most common hematological manifestation of CD due to impaired iron absorption in the upper part of the small intestine and could be the sole presenting symptom.[9] The suggestive feature of anemia-associated with CD in patients without obvious evidence of gastrointestinal bleeding is its refractoriness to oral iron supplement due to iron malabsorption. Up to 50% of CD patients could show positive fecal occult blood tests from villous atrophy in the small bowel. Moreover, untreated patients are at higher risk of developing a rare enteropathy-associated T-cell lymphoma.[1] Celiac screening should be considered in the diagnostic algorithm of high-risk patients with anemia.

The only current treatment for CD once discovered is a strict lifelong GFD. A strong commitment is warranted to eliminate any possible contaminated gluten in food and also over-the-counter medications. In patients with T1DM, the co-existence of CD could limit food choices and can be a burdensome in affected patients especially patients who do not prepare food in their homes. Carefully checking the food labels for ingredients in packaged food and encourage patients to join a peer support group for CD should be recommended in all newly diagnosed patients.

Periodic serologic testing for IgA anti-tTgA could allow for quantitative measurement of the severity of mucosal damage and monitoring dietary adherence in some patients who still have symptoms after treatment. Excessive weight gain as a consequence of fat ingestion, commonly present in GFD is also another challenge in CD patients.[10] Mindful eating and regular follow-up with professional dietitians or nutritionists is important to prevent this unintended consequence of GFD. It cannot be overemphasized that the management of these patients requires experience and expertise of a dedicated clinical team.

CONCLUSION

Our case highlights the importance of CD awareness in T1DM patients with unstable glycemic control due to erratic absorption of digested food and also in patients with iron deficiency anemia. The multifaceted clinical presentation of CD leads to several manifestations that physicians, other than gastroenterologists might encounter. Clinical vigilance is needed to promptly diagnose these patients and start lifelong treatment with GFD.

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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IMAGES IN ENDOCRINOLOGY

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Rare Presentation of Subclinical Hypothyroidism from a Lingual Thyroid

Choirina Windradi,[1] Soebagijo Adi Soelistijo,[1] Sony Wibisono Mudjanarko,[1] Muhtarum Yusuf[2]

[1]*Department of Internal Medicine, Airlangga University, Faculty of Medicine, Airlangga University Hospital*
[2]*Department of Otolaryngology, Airlangga University, Faculty of Medicine, Airlangga University Hospital*

Key words: subclinical hypothyroidism, ectopic thyroid, lingual thyroid, levothyroxine

A 25-year-old female, presented with a posterior lingual mass, without pain nor bleeding (Figure 1). She became more prone to shortness of breath upon exercise and felt uncomfortable swallowing solid food but denied snoring, cold intolerance, or unintentional weight gain. Examination revealed a mass posterior to her tongue and no palpable thyroid gland at the thyroid fossa. Investigations revealed thyroid function tests (TFTs): FT4 1.29 µg/dl (0.89-1.76); TSH 17,049 IU/ml (0.55-4.78); T3 total 1.27 µg/dl (0.6-1.81). Fiber optic laryngoscopy showed a smooth, slippery, unilocular mass attached to the base of tongue. CT cervical-head showed a high-density 2.6 x 2.2 x 2 cm^3 soft tissue mass posterior to the tongue, which narrowed the airway to a diameter of 0.4 cm (Figure 2). The mass was likely to be thyroid tissue. To reduce the obstructive symptoms from the mass we did excisional surgery followed by the administration of levothyroxine 25 µg once daily. She had no complaints after surgery. A follow-up thyroid function profile showed FT4 1.46; TSH 6.467; T3 1.59. Histopathology of the tissue revealed multiple thyroid follicles consistent with ectopic thyroid (Figure 3).

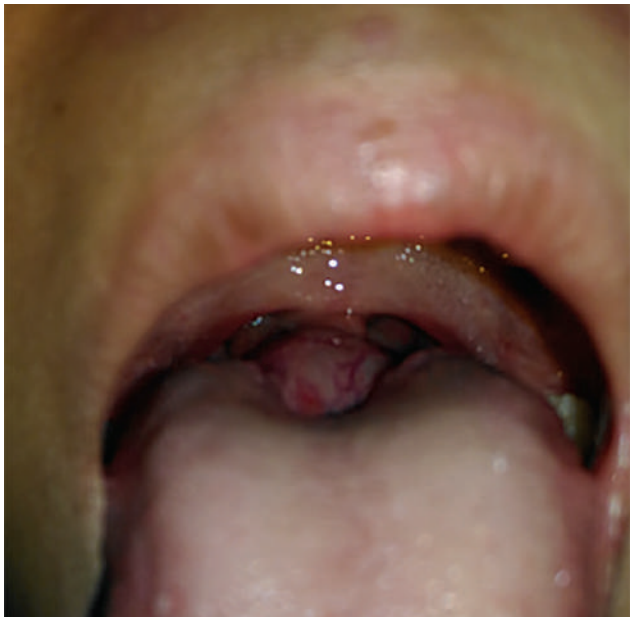

Figure 1. Lingual thyroid in the oropharynx.

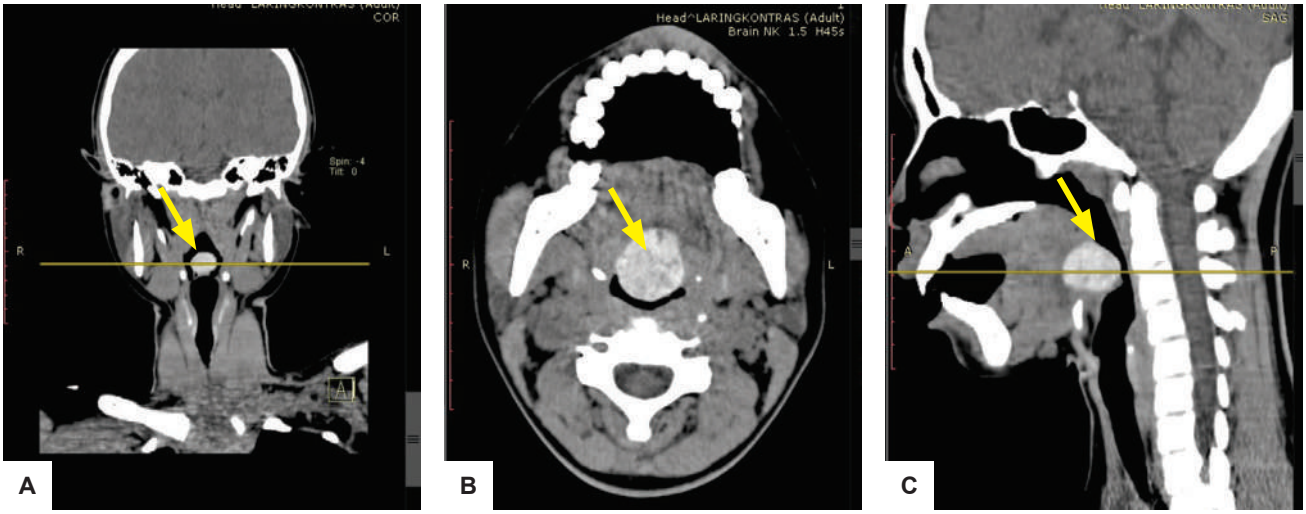

Figure 2. Head and neck CT scan examination. **(A)** Coronal and **(B)** axial enhanced neck CT scan demonstrates well-defined homogeneous enhancing mass without calcification (yellow arrows); **(C)** A sagittal enhanced CT scan of the neck demonstrates enlargement of the thyroid gland. It shows the location of the thyroid gland above the normal thyroid (sublingual position) (yellow arrow).

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Corresponding author: Choirina Windradi, MD
Department of Internal Medicine, Faculty of Medicine,
Airlangga University, General Teaching Hospital Dr. Soetomo
Jl. Mayjen Prof. Dr. Moestopo No. 6-8, Airlangga, Kec. Gubeng,
Surabaya, East Java, 60115, Indonesia
Tel. No.: (031) 5501078
E-mail: chylonly@gmail.com
ORCiD: https://orcid.org/0000-0002-3394-400

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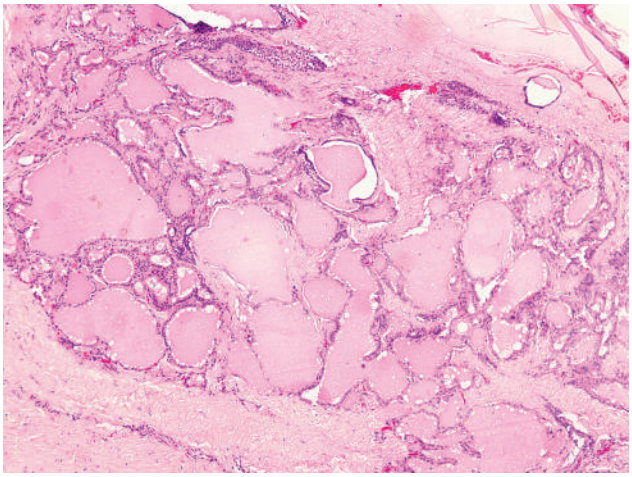

Figure 3. Microscopic examination shows various sized thyroid follicles with hyperplastic change (H&E, 400x).

The ectopic thyroid is a rare congenital disorder with incidence between 1:3000 – 1:300000 although it could present with thyroid dysfunction. Most ectopic thyroid cases are euthyroid, only a few patients are subclinically hypothyroid.[1] It is usually aysmptomatic but as the mass increases it can cause obstructive symptoms.[2] At the age of puberty, thyroid hormone deficiency causes hypertrophic glands and results in obstructive symptoms. Asymptomatic cases can be monitored with serial exams or receive hormonal therapy with levothyroxine. However, such treatment does not have a good success rate. The reduction in size occurs very slowly, without significant decreases in volume.[1] Therefore, the decision to excise the mass was made for this patient. After surgery, monitoring of symptoms and thyroid hormone levels should be done regularly. Levothyroxine supplementation is recommended to prevent overt hypothyroidism and to suppress production of TSH.[3,4]

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

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

Author Disclosure
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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 UPDATE

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. Include PMID, PMCID and DOI of the references.
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 Philipp. 1990; 26(2):81-5.

One to Six Authors (Commentary, Online)

Krause RM. The origin of plagues: Old and new. Science. 1992;257:1073-8. PMID: 1509258. https://doi.org/10.1126/science.257.5073.1073.

Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. J Translational 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): 1195-200. PMID: 11559264. https://doi.org/10.1001/jama.286.10.1195.

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. 2003;348(26):2635-45. PMID: 12826639. https://doi.org/10.1056/NEJMsa022615.

Jasul Jr. GV, Paz-Pacheco E, Jimeno CA, et al. AFES A.S.-O.N.E.: ASEAN Survey Of Needs in Endocrinology in the time of the COVID-19 pandemic. J AFES Fed Endocr Soc.2020;35(1):5-13. PMID: 33790494. PMCID: PMC7992306. https://doi.org/10.15605/jafes.035.01.10.

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): 1987-91. PMID: 11308435. https://doi.org/jama.285.15.1987.

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 .tif, .jpeg, or .png files) of high resolution (at least 300 dpi).
3. Editable figures or graphs can also be created using Microsoft Word.
4. Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
5. All identifying data of the subject/s or patient/s under study such as name or case numbers should be removed.
6. 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 .tif, .jpeg, or .png files).
   1.1 There should be minimal processing of digital images submitted with a manuscript for review to the JAFES. A certain degree of image processing (lighting, color, contrast, size, orientation, cropping, placement of identifying markers and labels) is deemed acceptable only if the final image correctly and accurately represents the original information or data. Thus, JAFES requires all unprocessed, unaltered, and raw image files to be submitted with the manuscript to facilitate evaluation and review. These shall serve also as JAFES' records for issues that may arise after publication of the manuscript.
   1.2 Adjustments in brightness, color balance, or contrast should be applied equally to the whole image and should not result in the exclusion, hiding, obscuring, or deletion of any information that is present in the original image, enhancement of any particular portion of the image. Manipulations such as grouping of images for comparison should be indicated with image margins or clear demarcations, and must be described in the caption. Other types of manipulation such as copying and pasting of images and passing them off as multiple figures is not acceptable. Appropriate re-orientation of the whole image, as well as, superimposition of arrows, markers, or other figures and labels is acceptable.
2. For photomicrographs, the stain used and the resolution at which the image was acquired (e.g., H&E, 100x) should be included in the description.
   2.1 All image adjustment and processing tools/software used should be disclosed in the methodology section of original articles or described in the caption or description if in article types without a separate section on methods.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn and digitized (preferably as .tif, .jpeg, or .png files) at least 800 x 600 dpi. All letterings for illustrations should be done professionally and be of adequate size to remain readable ever after size reduction during layout.
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 on the specific item stating that such has been adapted or lifted from the original publication and referenced in the **References** portion. Appropriate copyrights and permissions should be secured from the original author/publisher.

PROCESS

1. Upon receipt of the manuscript, the Editor shall review the submission, check if it has met aforementioned criteria and consult with members of the Editorial Board to decide whether it shall be considered for publication or not.
2. Within one (1) week of submission, authors shall be notified through e-mail that their manuscript either (a) has been sent to referees for peer-review or (b) has been declined without review.
3. The JAFES implements a strict double blind peer review policy. For manuscripts that are reviewed, authors can expect an initial decision within forty five (45) days after submission. There may be instances when decisions can take longer than 45 days, in such cases, the editorial assistant shall inform the authors. The editorial decision for such manuscripts shall be one of the following: (a) acceptance without further revision, (b) acceptance with minor revisions, or (c) major manuscript revision and resubmission.
4. Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal.

EDITORIAL OFFICE CONTACT INFORMATION:

Journal of the ASEAN Federation of Endocrine Societies
Unit 2005, 20th Floor, Medical Plaza Ortigas,
San Miguel Avenue, Ortigas Center,
Pasig City, Philippines 1605
Editorial Assistant: Amado O. Tandoc III, MD, FPSP
Telefax number: (+632) 8637-3162
E-mail: JAFES@asia.com; jafes.editor@gmail.com
Website: https://www.asean-endocrinejournal.org

ARTICLE TYPES

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

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

Case Reports / Case Series
The abstract should be from 50 to 75 words and should not be structured. A manuscript for case reports or case series 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.

Endocrine Perspectives
JAFES may invite topic experts to publish viewpoints, opinions, and commentaries on relevant topics. A manuscript for endocrine perspectives should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words. *Not peer reviewed.

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.

Images in Endocrinology
Images may include photographs of clinical cases encountered and documented during practice. They may also include diagnostic images (e.g., photomicrographs of histopathologic diagnosis, radiographs) or special studies performed (e.g., spectral karyotype imaging, fluorescent microscope images, immunostains) that aided in diagnosis. A 250-word text should accompany the images. Submissions to this category should comply with the journal's image integrity guidelines.

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, and (5) the Conversion to Visual Abstract (*optional for original articles) ☐ 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
Tables, Figures, Illustrations and Photographs	☐ All tables, figures, illustrations and photographs should be cited in the text, in numerical order per type ☐ Provide separate files for tables, figures and illustrations ☐ Provide a title and legend (if appropriate) for each table ☐ Provide a title, legend (if appropriate), and caption for each figure and illustration (caption should be no longer than 15-20 words) ☐ If table, figure, or illustration is adapted, state so and include the reference.

Journal of the
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Cover Letter

(Date)

To: **The Editor-in-Chief**
Journal of the ASEAN Federation of Endocrine Societies (JAFES)

Subject: **SUBMISSION OF MANUSCRIPT FOR PUBLICATION**

We intend to publish the manuscript/, entitled "_____," under the Section *[Original Article, Review Article, Feature Article, Case Report, Case Series, Interhospital Grand Rounds, Brief Communications, Letter-to-the-Editor, Special Announcements]* in the Journal of the ASEAN Federation of Endocrine Societies.

LIST OF AUTHORS

Complete Name	Position/ Designation	Institutional Affiliation	Role in writing the manuscript	Email address	ORCID iD

On behalf of all the authors, I shall act as the corresponding author with the journal from this point onward.

Attached herewith are the following: the completely accomplished **Author Form with author contribution disclosure** and **author publishing agreement**, in which all the authors certified authorship criteria was satisfactorily met and the specific contributions of the authors are listed and the author copyright is retained granting publishing and distribution rights to the JAFES; the **Author Declaration** that the work is original and is not under simultaneous consideration in other journals and the **ICMJE Disclosure forms** of ALL the authors (*where all conflicts of interest have been declared/there are no conflicts of interest*).

For original articles, we submit a scanned copy of our Ethics Review Approval/registration in trial registries (as appropriate) and the appropriate EQUATOR Network checklist used in writing the manuscript.

For case reports/series, patient consent forms have been secured for the publication of information.

For animal studies, a scanned copy of the Institutional Animal Care and Use Committee approval was obtained.

Furthermore, we respectfully suggest the following **reviewer**(s) for our manuscript.

Name and Salutation (e.g., Prof., Dr., etc)	Position/Designation	Institutional Affiliation and specialization	Email address

Sincerely,
Corresponding Author
Name: (Salutation, First Name, Middle Initial, Last Name, Title)
Position/Designation
Name of Institution:
Complete Address of Institution **with zip code**
Tel. No. of Institution:
Fax No. of Institution:
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Full Name:
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Author Form

COMPLETE TITLE OF MANUSCRIPT

AUTHOR LISTING (in the order agreed upon by all authors; use an additional sheet if necessary)

Author Name [Last name/First name]	**Institutional Affiliation**
1.	
2.	
3.	
4.	
5.	

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

1. AUTHORSHIP CERTIFICATION

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.

2. AUTHOR DECLARATIONS

☐ The undersigned author(s) of the manuscript hereby certify, that the submitted manuscript represents original, exclusive and unpublished material. It is not under simultaneous consideration for publication elsewhere. Furthermore, it will not be submitted for publication in another journal, until a decision is conveyed regarding its acceptability for publication in the JAFES.
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***NOTE: 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.**

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.

3. AUTHOR CONTRIBUTION DISCLOSURE (Place an "x" mark where an author made the contribution)
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					
Investigation Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection					
Resources Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools					
Data Curation Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse					
Writing – original draft preparation Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation)					
Writing – review and editing Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages					
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Supervision Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team					
Project administration Management and coordination responsibility for the research activity planning and execution					
Funding acquisition Acquisition of the financial support for the project leading to this publication					

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.

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- ☐ **The undersigned author(s) shall retain the copyright for the Article.** No rights in patent, trademark, and other intellectual property rights (to include all research data on which the published manuscript are based) are transferred to the Journal.
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- ☐ **The undersigned author(s) understand and agree that all rights granted under this agreement shall revert to the undersigned author(s)** should the submitted manuscript be withdrawn or rejected, or the published manuscript be retracted.

5. CONVERSION TO VISUAL ABSTRACT (for Original Articles only) **OPTIONAL**

- ☐ **The undersigned author(s) agree to have the published work converted as visual abstract** to improve dissemination to practitioners and lay readers.

SIGNED:*

Author Name [Last name/First name]	**Signature**	**Date** [MM/DD/YY]
1.		
2.		
3.		
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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.

ICMJE Form for Disclosure of Potential Conflicts of Interest

Date: _____

Your Name: _____

Manuscript Title: _____

Manuscript number (if known): _____

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the **current manuscript only.**

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In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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7	Support for attending meetings and/or travel	____None	
8	Patents planned, issued or pending	____None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	____None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	____None	
11	Stock or stock options	____None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	____None	
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Please place an “X” next to the following statement to indicate your agreement:

____ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal of the
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Patient Consent Form

For a patient's consent to publication of information about them in the Journal of the ASEAN Federation of Endocrine Societies (JAFES).

Name of person described in article or shown in photograph: _____

Subject matter of photograph or article: _____

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(The Subject matter of the photograph or article is hereafter termed as the "INFORMATION.")

JAFES manuscript number: _____

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Corresponding author: _____

I, _____, give my consent for this information
[please insert your full name]

about MYSELF / MY CHILD OR WARD / MY RELATIVE relating to the subject matter above
[please encircle correct description]

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JAFES Office
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Telefax: (+632) 86373162

Prof. Lorna R. Abad, MD, MSc, FPPS, FPSPME
Department of Pediatrics
University of the Philippines Manila College of Medicine

Prof. Than Than Aye, MBBS, MMed Sc (Int Med), MRCP (UK), FRCP (Edin), FRCP (London), DTM&H (London), Dr Med Sc (Gen Med)
Professor Emeritus, University of Medicine (2),
Yangon, Myanmar

Assoc. Prof. Pia D. Bagamasbad, PhD
National Institutes of Molecular Biology and Biotechnology
University of the Philippines, Diliman

Johann Fabrian Q. Bolinao, MS
Asian Hospital and Medical Center,
Alabang, Muntinlupa, Philippines

Assoc. Prof. Elizabeth L. Chua, MBBS, FRACP, PhD
Faculty of Medicine & Health, University of Sydney, Australia
Royal Prince Alfred Hospital, New South Wales, Australia

Kim L. Cochon, MSc
JC School of Public Health and Primary Care,
Faculty of Medicine
The Chinese University of Hong Kong

Prof. David S. Cooper, MD, MACP
Division of Endocrinology, Diabetes and Metabolism
Johns Hopkins University School of Medicine,
Baltimore, Maryland, USA

Sylvia B. Capistrano-Estrada, MD, FPPS, FPSPME
Institute of Human Genetics, National Institutes of Health
University of the Philippines Manila College of Medicine

Andres V. Ebison Jr., MD, FPCP, FPSEDM
Westlake Medical Center, Inc.,
San Pedro, Laguna, Philippines

Ethel M. Estanislao

Mia C. Fojas, MD, FPCP, FPSEDM
Department of Biochemistry and Molecular Biology
University of the Philippines Manila College of Medicine

Raphael C. Francisco, MD, FACE
Absentee Shawnee Tribal Health System,
Shawnee, Oklahama, USA

Manish Gutch, MD Medicine, DM Endocrinology
Department of Endocrinology and Diabetes,
Medanta Hospital, Lucknow, Uttar Pradesh, India

Maria Antonia E. Habana, MD, MSc, FPOGS, FPSRM, FPSGE
Department of Obstetrics and Gynecology
University of the Philippines Manila College of Manila

Tien-Shang Huang, MD
Department of Internal Medicine
National Taiwan University & Cathay General Hospital,
Taipei, Taiwan

Prof. Dr. Mohammad Yazid Jalaludin, MD
Department of Paediatrics, Faculty of Medicine
University of Malaya, Kuala Lumpur, Malaysia

Jundelle Romulo K. Jalique, RN, MSPH (Biostatistics) (c)
Veterans Memorial Medical Center,
Diliman, Quezon City, Philippines

Prof. Ko Ko, MBBS, MMedSc (Int Med), MRCP, FRCP (Edin), Dr Med Sc, Diploma in Medical Education
Department of Diabetes and Endocrinology
University of Medicine (2), Yangon, Myanmar

Leslie Charles Chin Loy Lai, MBBS (London, UK), MSc (London, UK), MD (London, UK), FRCP (Edin), FRCPath, FFSc (RCPA), FAMM
Gleaneagles Hospital, Kuala Lumpur, Malaysia

Catherine Jessica M. Lazaro, MD
Department of Radiology, University of the Philippines-Philippine General Hospital

Kim Piow Lim, MD, MRCP (UK)
Department of Medicine,
Sunway Medical Centre Velocity, Malaysia

Chng Chiaw Ling, MBBS (Singapore), MRCP (UK)
Department of Endocrinology, Division of Medicine,
Singapore General Hospital

Anna Angelica P. Macalalad-Josue, MD, FPCP, FPSEDM
Taguig Pateros District Hospital,
Metro Manila, Philippines

Manuelito Madrid, MD, FPSP
Institute of Pathology, St. Luke's Medical Center-Quezon City, Philippines

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Division of Nuclear Medicine
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Cherie Ocampo-Cervantes, MD
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University of the Philippines-Philippine General Hospital

Timothy Joseph S. Orillaza, MD, FPCR, FPSVIR, FCTMRI
Department of Radiology
The Medical City, Pasig City, Philippines

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Metro Davao Medical and Research Center, Philippines

Paul Matthew D. Pasco, MD, MSc
Department of Neurosciences
University of the Philippines Manila College of Medicine

Tjokorda Gde Dalem Pemayun, MD, PhD
Department of Internal Medicine,
Division of Endocrinology and Metabolism,
Faculty of Medicine, University of Diponegoro,
Semarang, Indonesia

Hazizi Abu Saad, BSc, PhD
Department of Nutrition & Dietetics
Faculty of Medicine & Health Sciences
Universiti Putra Malaysia, Selangor, Malaysia

Jesus N. Sarol Jr., PhD
Interdisciplinary Health Sciences Institute,
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Hospital Sultan Haji Ahmad Shah, Pahang, Malaysia

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Grand Hantha International Hospital, Yangon, Myanmar

Aaron Tong Kian Ti, MBBS, MRCP (UK), MMed, FAMS
Department of Nuclear Medicine and Molecular Imaging
Singapore General Hospital

Assoc. Prof. Roberto C. Tanchanco, MD, FPCP, FPSN, MBA
Ateneo School of Medicine and Public Health,
Ateneo de Manila University, Metro Manila, Philippines

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Universiti Sains Malaysia

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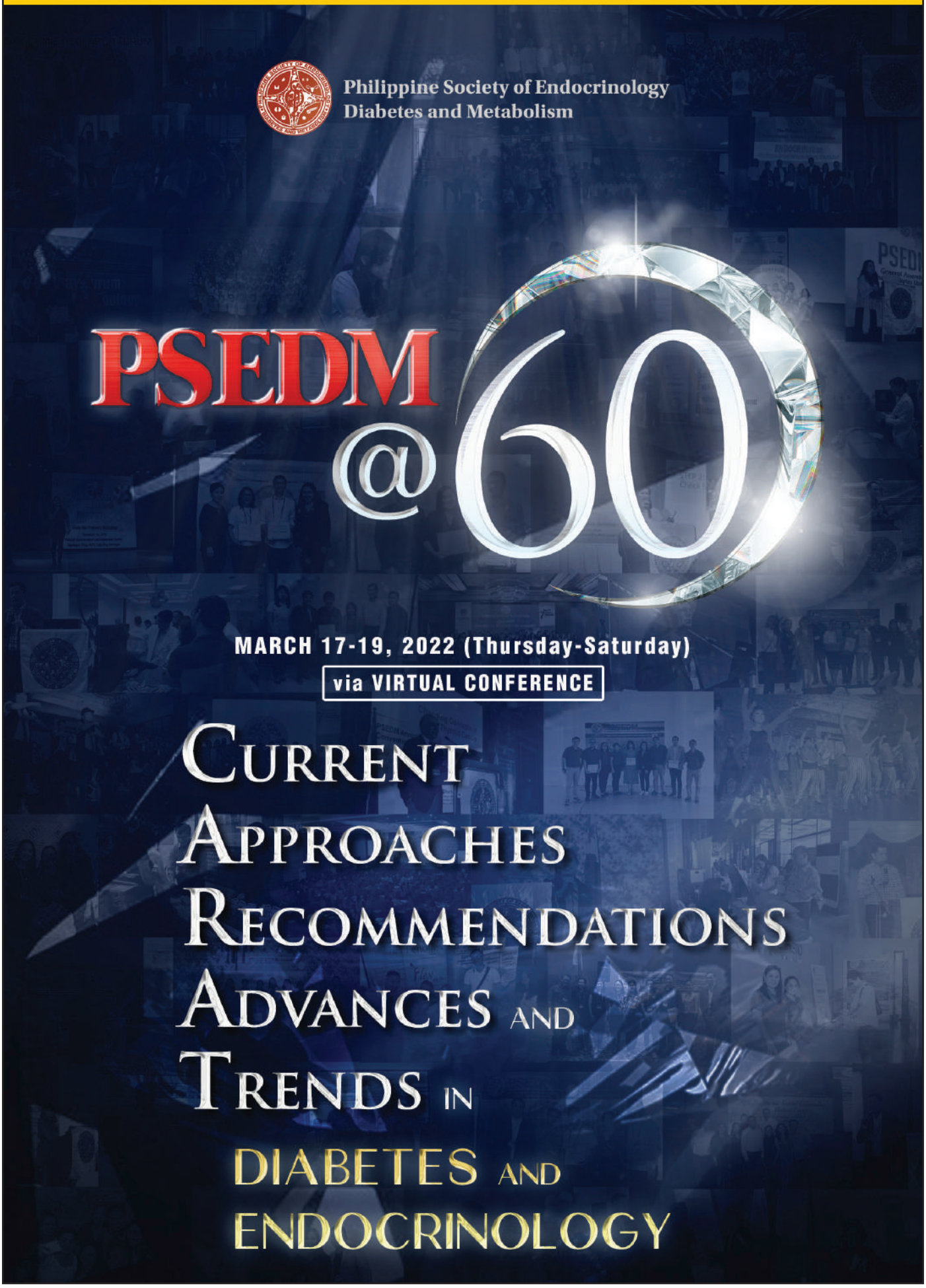

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