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Journal of the ASEAN Federation of Endocrine Societies

Vol. 37 No. 2 November 2022 | ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)

www.asean-endocrinejournal.org

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ASEAN Federation of
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Vol. 37 No. 2 November 2022 | ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)

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Preprinting and Data Sharing in a New Normal?

Even as JAFES evolves to keep abreast with good publication practices, the landscape of research and publication is changing fast.

JAFES, though, is no stranger to innovation and change. A few years from its revival in 2010, the journal established its own website, invested in an editorial management system, and transitioned from print to full digital editions. Back in 2019, JAFES revisited its editorial policies, introduced standardized author forms and author declarations, and endorsed the use of EQuaTOR Network checklists to ensure completeness and promote transparency of information reporting in journal articles. We likewise began screening references for citations sourced from possibly predatory journals. Doing our part to keep our authors' trust, we also updated the journal's publishing agreement by retaining copyright for published articles to the authors and providing JAFES publishing rights. JAFES has also enhanced the communication and promotion of scientific findings through the creation of visual abstracts. This year, JAFES has begun providing information on specific author contributions based on CREDIT [Contributor Roles Taxonomy (https://credit.niso.org)], as well as disclosing editors' potential conflicts of interest.

Editorial board meetings are opportunities for discussion on emerging policies. In some international journals, authors are being asked to participate in "data sharing," to provide public access to de-identified datasets, protocols, and study materials in acceptable repositories. This discussion is timely, as next year, major funding bodies, such as the National Institutes of Health (NIH) will begin requiring researchers and its institutions to include data management plans in their grant applications, and to make the data from these funded researches publicly available. Towards this end, NIH launched the Generalist Repository Ecosystem Initiative (GREI)—a group of established data repositories (Dataverse Project, Dryad, figshare, Mendeley Data, OSF, Vivli, and Zenodo) that shall not only preserve data, but also facilitate data sharing for reuse, reproducibility, quality assurance, and, more importantly, for building new knowledge.

JAFES should carefully consider the details in adopting data sharing as a policy. What will be the form and format of the data to be archived and shared? How will it impact or change a participant's informed consent? How do these policies relate with the prevailing regulations on Data Privacy? How should data be organized, presented, and framed, to prevent misinterpretation or misanalysis?

Another development is the emergence of preprints, which may become the norm in future publications. Preprints are scientific articles that are already published online despite not having undergone or completed full peer review–a seemingly unusual concept in a research world where peer review is the most critical requirement and standard for scholarly publications. What preprints make up for despite the lack of peer review, is the swiftness of publication, which may be particularly helpful in the setting of a novel disease or public health emergency, such as the COVID-19 pandemic. Issues such as article quality, ethics, citations and retractions need to be considered. JAFES will need to weigh the value of preprints as a platform for sharing knowledge, or for sharing of data for that matter.

Sharing data and using preprints are two new publication trends. JAFES continues to thoroughly review these strategies to determine how these will be useful for our journal and its readers. We expect more innovations to come. Indeed, the learning continues.

Elizabeth Paz-Pacheco
Editor-in-Chief

https://doi.org/10.15605/jafes.037.02.01

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Prevalence of Bacterial Urinary Tract Infection Among Patients With Type 2 Diabetes Mellitus on Sodium-Glucose Cotransporter-2 Inhibitors: A Prospective Real-World Setting Study

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Abstract

Background. Genitourinary tract infections, mycotic as well as bacterial, as defined by clinical symptoms, are one of the common adverse effects associated with the use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in type 2 diabetes mellitus (T2DM) patients in clinical trials. However, Indian data in terms of the prevalence of culture-proven bacterial type of urinary tract infection (UTI), and the causative organism is limited.

Objective. This study aimed to determine the prevalence and causative agents of bacterial UTI among patients with T2DM on SGLT2i.

Methodology. This was a prospective longitudinal study involving all patients with T2DM who were prescribed with SGLT2i, uncontrolled on other oral anti-diabetic medications, from June 2019 to February 2020. Prevalence of bacterial UTI was evaluated at baseline and 12 weeks after initiation of SGLT2i.

Results. A total of 80 patients were started on SGLT2i. One female patient on canagliflozin had significant asymptomatic bacteriuria and the causative agent was *Acinetobacter baumannii*. One male patient on dapagliflozin had symptomatic UTI with negative urine culture study. Four patients developed genital mycotic infection.

Conclusion. In this real-world study, SGLT2i as a class, was well tolerated with favorable safety profile, and risk of developing significant bacteriuria and/or symptomatic UTI was minimal.

Key words: SGLT2i, type 2 diabetes mellitus, UTI, significant bacteriuria

INTRODUCTION

Diabetes mellitus is the most common endocrine disease of the century. It is discouraging to contemplate the burden Type 2 diabetes may impose on India in the future.

The significant morbidity and mortality, high rates of complications and the cost of therapy can have a huge socio-economic impact on individuals and families.[1,2] The treatment of T2DM in India has been traditionally based on metformin, sulfonylureas, voglibose and insulin. However, newer agents such as dipeptidyl peptidase 4 inhibitors (DPP4i), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and glucagon-like peptide-1 (GLP1) receptor agonists promise a substantial benefit in the treatment of naive, as well as uncontrolled diabetes patients.[3,4] Inhibition of SGLT-2 offers potential add-on benefits of weight loss, blood pressure (BP) reduction, and cardiovascular-renal benefits, with a low risk of hypoglycemia.[5,6]

Dapagliflozin, canagliflozin, empagliflozin and remogliflozin are currently available in India. They have been approved for the treatment of T2DM as monotherapy and as second- or third-line agents in combination with other therapeutic options for diabetes. This drug class may be used at any stage of T2DM owing to its novel insulin-independent mechanism of action, provided the renal function is above a certain threshold.[7,8] Genitourinary tract (GUT) infections are the most common adverse effect of SGLT2i use in clinical trials.[9-11] People with diabetes are at increased risk for GUT infections due to glucosuria, bacterial adherence to uroepithelium and immune dysfunction.[12]

The prevalence of bacterial urinary tract infections (UTI), defined by clinical symptoms, among patients with T2DM on SGLT2i is 9%.[10] There is limited Indian data on the prevalence of culture-proven bacterial UTI, type of UTI, and the causative organism in T2DM patients on SGLT2i.[13] Real-world data will help ascertain if the safety results

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: November 16, 2021. Accepted: February 8, 2022.
Published online first: June 25, 2022.
https://doi.org/10.15605/jafes.037.02.04

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of SGLT2i seen in clinical trials can be extrapolated to clinical practice. No prospective studies have specifically addressed this issue in India.

Hence, we performed this study to assess the prevalence of bacterial UTI in patients with T2DM on SGLT2i in Indian patients in the ambulatory setting.

METHODOLOGY

This was a prospective longitudinal study conducted in a tertiary care center among patients with T2DM who were started on SGLT2i uncontrolled on other oral antidiabetic medications [glycosylated hemoglobin (HbA1c) >7% and/or fasting venous plasma glucose (FPG) >120 mg/dL]. Patients less than 18 years of age, with estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m^2, pregnant/ lactating women, and evidence of UTI within the past 3 months were excluded. Patients were included after giving them complete relevant information and obtaining a written consent.

The baseline FPG, post-lunch venous plasma glucose (PPG) and HbA1c were recorded. Urine sample for bacterial culture was collected at baseline prior to initiation of SGLT2i. Patients were prescribed any one of the 4 available SGLT2i – dapagliflozin, empagliflozin, canagliflozin or remogliflozin.

Patients were educated about maintaining genital and perineal hygiene. Instructions were given about washing of genital organs with clean water after urination and defecation and routine use of hygienic wipes. Women were advised to wash from front to back, while uncircumcised males were counseled to retract the prepuce before cleaning. Patients were advised to use mild soap if required and avoid alcohol-based disinfectants for washing.

Patients who developed symptoms of UTI at any time during the 12-week period were advised to report to the clinic immediately and a midstream urine sample for bacterial culture was collected as necessary. After 12 weeks on SGLT2i, information regarding symptoms of UTI such as dysuria, fever, frequency, urgency and a midstream urine sample for bacterial culture were collected. A detailed physical examination with special emphasis on temperature, pulse rate, blood pressure, suprapubic tenderness, costovertebral angle tenderness and mass on deep abdominal palpation were carried out. A genital examination was also done. Patients with symptoms and/or signs suggestive of genital mycotic infections and had a positive response to antifungal treatment were considered to have genital mycotic infections.

For collection of midstream urine: Patients were asked to clean the genital region before micturition. Men were asked to clean the glans penis with swabs soaked in clean tap water, pass about 50 ml of urine into a toilet or bowl, and collect the next portion (10 to 20 ml) into a clean sterile bottle. In women, labia were separated by the patient or nurse and the vulva was wiped twice in an antero-posterior direction with swabs soaked in clean tap water and then cleaned with a dry swab before collection of urine. Urine was then collected with the labia held apart. Urine samples were immediately sent to the laboratory for bacterial culture.

For urine culture, samples were incubated at 37 degrees Celsius for 24 to 48 hours in a Blood/ Chocolate agar and MacConkey agar plate. Organisms identified were based on colony characteristics, lactose fermentation and biochemical tests.

The diagnosis was based on symptoms of UTI regardless of urine culture results, or a positive urine culture regardless of symptoms. Urinalysis was not done at baseline or at 12 weeks. The outcome measured was the proportion of patients having symptoms of UTI, or positive urine culture, i.e., significant bacteriuria (>10^5 cfu/mL) at 12 weeks of SGLT2i therapy. Analysis of adverse effect profile (bacterial UTI) was done as a class effect, rather than an individual drug effect.

Statistical analysis was done using "R software 3.5.1." Continuous variables were expressed as mean ± standard deviation (SD). Results of qualitative variables such as fever, frequency, urgency, dysuria, significant bacteriuria and genital mycotic infection symptoms were expressed as frequency and percentages.

The study was approved by the Institutional Ethics Committee. All the patients' details were kept confidential and participants' identity was coded for further analysis.

RESULTS

A total of 80 T2DM patients (47 males and 33 females) were initiated on SGLT2i over a period of 3 months. Four patients discontinued the drug (1 patient underwent prostate surgery, 1 patient had inguinal hernia surgery and 2 patients had subjective non-specific weakness) and 1 patient could not be contacted. At 12 weeks, 75 patients were evaluated.

The baseline characteristics of patients is shown in Table 1. Majority (50 out of 80, 62.5%) of participants were 46-65 years (mean 52.44 ± 10.24 years). The duration of diabetes was more than 5 years in 52 (69.3 %) participants (mean 8.71 ± 0.99 %). The body mass index (BMI) was >25 kg/m^2 in 62 (82.7%) participants, none had BMI > 35 kg/m^2 (mean 26.99 ± 2.24 kg/m^2).

Table 1. Baseline characteristics

Characteristic	Value
Mean age (years) ± SD	52.44 ± 10.24
Gender (Male: Female)	47:33
Mean duration of T2DM (years) ± SD	8.95 ± 4.84
Mean HbA1c (%) ± SD	8.71 ± 0.99
Mean BMI (kg/m^2) ± SD	26.99 ± 2.24

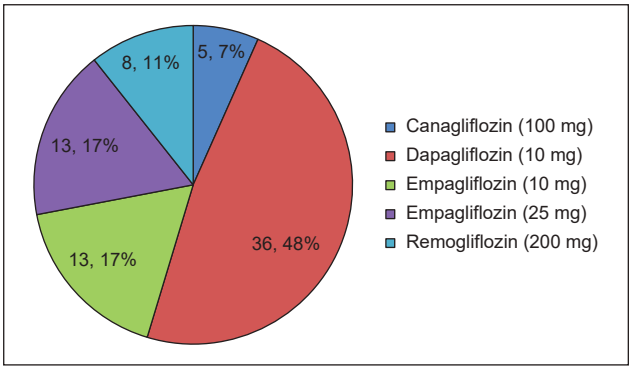

Figure 1. Distribution as per specific SGLT2i taken.

Table 2. Distribution as per significant bacteriuria and symptoms of UTI at 12 weeks

		Total (%)
Significant bacteriuria	Absent	74 (98.7)
	Present	1 (1.3)
Symptoms of UTI	Absent	74 (98.7)
	Present	1 (1.3)

Table 3. Distribution as per genital mycotic infection at 12 weeks

Genital mycotic infection at 12 weeks	Gender		
	Total	Female (n=30) Number (%)	Male (n=45) Number (%)
Absent	71	29 (96.7)	42 (93.3)
Present	4	1 (3.3)	3 (6.7)

Of the 75 participants who completed the study, 36 (48%) were on dapagliflozin 10 mg daily; 13 (17.3%) on empagliflozin 10 mg daily; 13 (17.3%) on empagliflozin 25 mg daily; 8 (10.6%) on remogliflozin 100 mg twice a day; and 5 (6.6%) were on canagliflozin 100 mg daily (Figure 1).

One (1.3%) female patient who received canagliflozin had significant asymptomatic bacteriuria at 12 weeks. The causative organism identified was *Acinetobacter baumannii* (Table 2). One (1.3%) male patient had symptomatic UTI with dysuria 4 weeks after starting dapagliflozin. Urine culture of the patient was negative. (Table 2). One (3.3%) female who received empagliflozin 25 mg and 3 (6.7%) male patients on dapagliflozin had genital mycotic infection as shown in Table 3.

DISCUSSION

The post-hoc power of our study to calculate the prevalence of bacterial UTI and symptomatic UTI was ~80%. The reported prevalence of significant bacteriuria in T2DM patients at baseline, and in control groups ranged from 7.7% to 26%.[10,14,15] In our study, the overall prevalence of significant asymptomatic bacteriuria at 12 weeks of SGLT2i treatment was 1.3%. The patient was on canagliflozin. The prevalence of significant bacteriuria reported in the study conducted by Nicolle et al. was 7.7% at baseline and 6.4% at 12 weeks after taking canagliflozin with no dose dependency.[14] The lack of association of bacteriuria or symptomatic UTI with SGLT2i therapy may be because glucosuria is not the only risk factor for symptomatic UTIs or bacteriuria, and other factors such as hyperglycemia, presence of bladder autonomic neuropathy and urinary tract abnormalities can influence development of symptomatic UTIs or bacteriuria.[9,12]

The prevalence of symptomatic UTI was 1.3% in our study. The patient was taking dapagliflozin 10 mg daily. The prevalence of symptomatic UTI we report was lower than studies conducted by List,[16] Bode[17] and Rosenstock[18] where it was found in 5 to 12%, 5.8 to 8.1%, and 4% patients respectively. The prevalence was similar to the study conducted by Mathieu,[19] (1%), and was higher than in the studies from India by Sosale[20] and Ghosh,[21] where it was 0% and 0.01% respectively.

In our study, the prevalence of genital mycotic infection was 5.3%. The same prevalence was observed in the study of Wan Seman et al.[22] The prevalence was less than the studies conducted by Bode[17] and Aggarwal,[23] where it was 18.6% and 26% respectively; and was more than the study conducted by Kohler,[24] where it was 1% amongst the canagliflozin treated patients.

The likely explanation for the low rate of genital mycotic infections among our patient population may be good genital hygiene, knowledge of side effects and precautions taken while on SGLT2i.

The strengths of our study are that it is a real-world prospective study done in a heterogeneous urban population and the diagnosis of bacterial UTI was based on urine culture done on all patients, regardless of symptoms. We acknowledge that the study period of 12 weeks was relatively short, and UTI as an outcome with more prolonged therapy require further assessment. Lack of a control group and lack of routine urinalysis and microscopy were the limitations of our study. Also, due to small number of outcomes in our study, it is not possible to comment on the choice of specific drug from the SGLT2i drug class.

CONCLUSIONS

In this real-world study, the risk of developing significant bacteriuria and/or symptomatic UTI was minimal in patients with T2DM on SGLT2i. Furthermore, the risk of clinically diagnosed genital mycotic infection was also low. SGLT2i was well tolerated with a favorable safety profile. Additional adequately powered longitudinal randomized real-world studies using urine culture and urine routine analysis may be undertaken to confirm the safety of SGLT2i with regards to the development of significant bacteriuria and/or UTI.

The genital mycotic infections and bacterial UTI may be preventable if patients are diligently educated about maintaining good genital hygiene.

As there was only one patient with asymptomatic bacteriuria, and another patient with dysuria with a negative urine-culture, it is not possible to comment on the choice of specific drug from the SGLT2i drug class.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Contributions Statement

PF conceived the study, developed the methodology, applied statistical techniques to synthesize the study data, conducted investigation, curated the data, prepared the original draft of the manuscript, prepared data presentation; AM validated research outputs, helped in the formal analysis of the study data, curated the data, wrote the original draft, helped in creating data presentation; NFS conceived the study, developed the methodology, validated research outputs, analyzed study data, provided study materials, wrote, reviewed and edited the manuscript, supervised, managed and coordinated the research activity; PC and MC provided study materials, wrote, reviewed and edited the manuscript, supervised the research activity.

Author Disclosure

The authors declared no conflict of interest.

Funding Source

The study was funded by National Education Society (Medical Research Centre) of P. D. Hinduja National Hospital.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Comparison of Maternal and Neonatal Outcomes Among High-Risk Filipino Women With Gestational Diabetes Diagnosed Before and After 24 Weeks of Gestation

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Abstract

Objectives. This study determined the prevalence, clinical characteristics and pregnancy outcomes of high-risk women diagnosed with gestational diabetes mellitus (GDM) before and after 24 weeks of gestation.

Methodology. This retrospective study included all singleton deliveries with GDM at the Pasig City General Hospital from January 2018 to December 2019. Subjects were grouped into those who were diagnosed with GDM before 24 weeks of gestation (<24 weeks, n=61) and thereafter (≥24 weeks, n=219). Outcomes examined were preeclampsia, cesarean delivery, preterm birth, macrosomia, large-for-gestational age, small-for-gestational age, neonatal hypoglycemia, neonatal ICU admission, congenital malformations and perinatal mortality.

Results. The group diagnosed with GDM before 24 weeks was significantly older (33.0 ± 5.7 years versus 29.4 ± 5.9 years, p<0.001), had higher 2-hour 75 g oral glucose tolerance test (OGTT) results (158.2 ± 20.0 mg/dL versus 150.0 ± 23.7 mg/dL, p=0.014), and had more pregnancies with preeclampsia (23.0% versus 9.6%, p=0.005).

Conclusion. High-risk women diagnosed with GDM before 24 weeks of gestation had a higher incidence of preeclampsia compared with high-risk women diagnosed with GDM after 24 weeks of gestation.

Key words: prenatal screening, diabetes, gestational, pregnancy outcomes

INTRODUCTION

Gestational diabetes mellitus (GDM) is known to be associated with perinatal and maternal morbidity, including excessive fetal size, which leads to operative delivery and birth trauma. In a study done at the Philippine General Hospital in 2013, women diagnosed with GDM had an increased risk for primary caesarean section and infant admission to the neonatal intensive care unit (NICU).[1]

There are still many areas regarding GDM management that lack consensus among different authorities. These include the diagnostic criteria, classification, timing of screening and screening population (universal versus selective screening).

The International Association of Diabetes Pregnancy Study Group (IADPSG) proposed the following diagnostic criteria: fasting plasma glucose value ≥92 mg/dL and/or 1-hour glucose value ≥180 mg/dL and/or 2-hour glucose value ≥153 mg/dL in a 75 g OGTT. It should be noted that the screening criteria given by the IADPSG for the diagnosis of GDM at 24 to 28 weeks age of gestation (AOG) has not been validated in the first or early second trimester.[2]

Screening for GDM is usually performed between 24 to 28 weeks of gestation because insulin resistance increases during the second trimester, and glucose levels increase in women who do not have the ability to produce enough insulin to counter this resistance.[3] Presently, routine screening for GDM in the Philippines is done at 24 to 28 weeks of gestation.

The importance of early identification of dysglycemia in pregnancy arises from the effect of early maternal hyperglycemia on fetal growth and existing literature on early GDM reported poor outcomes.[4] The Philippine UNITE for Diabetes Clinical Practice Guidelines and the Philippine Obstetrical and Gynecological Society 2018 Clinical Practice Guidelines on Diabetes Mellitus in Pregnancy recommend that all pregnant women should be evaluated at the first prenatal visit for risk factors for diabetes. These risk factors include age ≥25 years old, overweight or obese before pregnancy, history of abnormal

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: October 25, 2021. Accepted: April 29, 2022.
Published online first: August 27, 2022.
https://doi.org/10.15605/jafes.037.02.05

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glucose metabolism, history of poor obstetric outcome (prior GDM, macrosomia, congenital malformations, recurrent abortions, unexplained intrauterine death), family history of diabetes among first degree relatives, intake of drugs affecting carbohydrate metabolism and glucosuria.[5] Having any of these risk factors confers a high risk for GDM, and a 75 g OGTT should be done as soon as possible. However, this is not universally followed and screening for GDM before 24 weeks remains at the discretion of the primary healthcare provider.

Looking into the pregnancy outcomes associated with earlier identification of GDM in the local setting can help reinforce the recommendations for earlier screening for high-risk women, especially in primary care.

OBJECTIVES

This study aimed to determine the prevalence, clinical characteristics and pregnancy outcomes among Filipino women who delivered at Pasig City General Hospital from January 2018 to December 2019. Women who were diagnosed with GDM before 24 weeks of gestation were compared with women who were diagnosed after 24 weeks of gestation. Maternal outcomes included incidence of preterm delivery, primary caesarean section and preeclampsia. Neonatal outcomes included incidence of macrosomia, large-for-gestational age (LGA) and small-for-gestational age (SGA), hypoglycemia, neonatal ICU admission, congenital malformations and perinatal mortality.

METHODOLOGY

This was a retrospective cohort study of Filipino women diagnosed with GDM at the Pasig City General Hospital from January 1, 2018 to December 31, 2019. Institutional review board approval was obtained.

Starting 2018, it was mandated that all pregnant women seen at the institution's Outpatient Department (OPD) were to be screened for risk factors for diabetes based on the UNITE CPG during their first prenatal visit. Women who had at least one risk factor were considered high-risk and were advised to undergo 75 g OGTT immediately. If they tested negative, they underwent a repeat 75 g OGTT at 24 to 28 weeks. Patients who did not have any identified risk factors underwent 75 g OGTT at 24 to 28 weeks of gestation. Patients were diagnosed with GDM according to the IADPSG criteria based on their 75 g OGTT results.

High-risk women diagnosed with GDM were immediately referred to a multidisciplinary team comprising a dietician, a nurse educator and an endocrinologist. They received individualized dietary advice and self-monitoring of blood glucose education. On follow up after two weeks, insulin therapy was started if fasting blood glucose levels were more than 95 mg/dL and 2-hour postprandial glucose levels were more than 120 mg/dL.[6] Medications and subsequent blood sugar monitoring were adjusted at the discretion of the attending endocrinologist. Obstetric care was in accordance with local standards of care.

Subjects included were women diagnosed with GDM using the IADPSG criteria with singleton pregnancies seen at the OPD and who delivered at the Pasig City General Hospital with complete prenatal, obstetric and offspring neonatal records. Women diagnosed with and treated for diabetes before pregnancy, diagnosed with overt diabetes (FBS ≥126 mg/dL or 2-hour blood glucose levels ≥200 mg/dL post-glucose intake) and those with twin or multiple pregnancies were excluded.

Maternal data included age, parity, prior caesarean section and indication, gestational age at first prenatal visit, gestational age at diagnosis of GDM, 75 g OGTT results, need for insulin treatment, development of preeclampsia, gestational age at delivery, mode of delivery and indication. Neonatal outcomes included APGAR scores, birth weight, birth length, admission to NICU, neonatal hypoglycemia, congenital malformations and perinatal mortality.

Descriptive statistics were used to summarize the general and clinical characteristics of the patients. Categorical variables were reported as frequency and percentage. Continuous quantitative data that met normality assumption by Shapiro-Wilk test were summarized using mean and standard deviation (SD), while those that did not were described with median and range. The two screening groups were compared in terms of their baseline characteristics, maternal outcomes and neonatal outcomes using the following statistical tests: independent samples t-test for continuous data with normal distribution, Mann-Whitney U test for continuous data that deviates from the normal distribution, chi-square test for ordinal/nominal variables and Fisher's exact test for ordinal/nominal variables with expected frequencies less than 5%. Statistical significance was set at $p \leq 0.05$.

Logistic regression was used to determine the association of timing of screening with maternal and neonatal outcomes. Crude odds ratio (OR) and its corresponding 95% confidence intervals (CI) were reported.

STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

RESULTS

From 2018 to 2019, the institution recorded 5072 deliveries, of which 561 were associated with GDM. This was equivalent to a period prevalence of 11.06 (95% CI, 10.21 to 11.96) per 100 births.

Of the 561 patients with GDM, 280 met the inclusion criteria for this study. Twenty-five patients were excluded as they were diagnosed with GDM not using the IADPSG criteria. Two hundred fifty-six patients were excluded

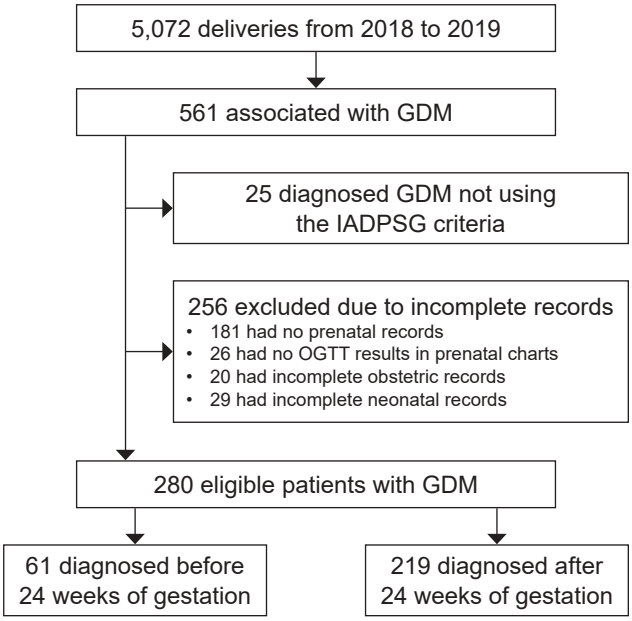

Figure 1. Study design and eligibility of patients.

GDM, gestational diabetes mellitus; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test.

due to incomplete records: 181 delivered at the institution but had no OPD prenatal records, 26 did not have OGTT results in their prenatal charts, 20 had incomplete obstetric records, and 29 had incomplete neonatal records of their offspring (Figure 1).

The 280 eligible patients were reviewed and analyzed: 61 (22%) were diagnosed with GDM before 24 weeks and 219 (78%) were diagnosed with GDM after 24 weeks of gestation (Table 1). Women diagnosed earlier were significantly older (mean 33.0 ± 5.7 years versus 29.4 ± 5.9 years) with 41% older than 35 years of age. They also had higher 2-hour OGTT results (mean 158.2 ± 20.0 mg/dL versus 150.0 ± 23.7 mg/dL) compared to those who were diagnosed after 24 weeks.

On the other hand, FBS, 1-hour OGTT, gravidity, parity and history of prior cesarean section (CS) were comparable between the two patient groups.

There were significantly more women with preeclampsia in the group diagnosed with GDM before 24 weeks (23.0% versus 9.6%, p=0.005) than in the group diagnosed with GDM after 24 weeks gestation. It is notable that there were nearly twice more preterm deliveries among those diagnosed earlier (14.8% versus 7.8%), although this was not statistically significant. The mode of delivery and requirement for insulin was not significantly different between the two groups (Table 2).

Women diagnosed with GDM before 24 weeks had proportionately more neonates born preterm (defined as AOG before 37 weeks) compared with women diagnosed with GDM after 24 weeks (16.4% versus 8.3%) but this did not reach statistical significance. Although the size

Table 1. Maternal baseline characteristics by timing of diagnosis of gestational diabetes mellitus

	Total (N=280)	<24 weeks (n=61)	≥24 weeks (n=219)	p value
Age, years	30.2 ± 6.0	33.0 ± 5.7	29.4 ± 5.9	<0.001*
<35	208 (74.3)	36 (59.02)	172 (78.5)	0.002‡
≥35	72 (25.7)	25 (40.98)	47 (21.5)	
Gravidity				0.252†
G1	86 (30.7)	14 (22.95)	72 (32.9)	
G2 to G5	185 (66.1)	46 (75.41)	139 (63.5)	
≥G6	9 (3.2)	1 (1.64)	8 (3.7)	
Parity				0.543†
P1 to P4	263 (93.9)	56 (91.8)	207 (94.5)	
≥P5	17 (6.1)	5 (8.2)	12 (5.5)	
Previous CS[a]	61 (21.8)	15 (24.6)	46 (21.0)	0.549‡
FBS[b], mg/dL	89.9 ± 12.3	91.0 ± 11.7	89.6 ± 12.4	0.406*
75 g OGTT[c], mg/dL				
1-hour	176.4 ± 30.3	182.2 ± 29.6	174.8 ± 30.3	0.094*
2-hour	151.8 ± 23.1	158.2 ± 20.0	150.0 ± 23.7	0.014*

Data presented are mean ± SD, frequency (%), or median (range)
*Independent samples t-test
‡Chi-square test
†Fisher's exact test
[a]CS, cesarean section
[b]FBS, fasting blood sugar
[c]OGTT, oral glucose tolerance test

Table 2. Maternal outcomes by timing of diagnosis of gestational diabetes mellitus

	Total (N=280)	<24 weeks (n=61)	≥24 weeks (n=219)	*p* value
Preterm delivery	26 (9.3)	9 (14.8)	17 (7.8)	0.096‡
Mode of delivery				0.726‡
NSD[a]	157 (56.1)	33 (54.1)	124 (56.6)	
CS[b]	123 (43.9)	28 (45.9)	95 (43.4)	
Primary	64 (52.0)	15 (53.6)	49 (51.6)	0.853‡
Need for insulin	10 (3.6)	4 (6.6)	6 (2.7)	0.232†
Preeclampsia	35 (12.5)	14 (23.0)	21 (9.6)	0.005‡

Data presented are frequency (%)
‡Chi-square test
†Fisher's exact test
[a]NSD, normal spontaneous delivery
[b]CS, cesarean section

for gestational age appeared to be associated with timing of diagnosis (p=0.038), pairwise comparisons based on Bonferroni adjusted p-values indicated comparable proportions between the two groups (Table 3). Macrosomic babies were delivered by the group diagnosed after 24 weeks (6.0% versus 0.0%). NICU admissions rate was higher in the group diagnosed before 24 weeks (13.3% versus 7.8%, p=0.188), although this did not reach statistical significance. Hypoglycemia was noted in one neonate in the group diagnosed with GDM after 24 weeks of gestation.

Other neonatal outcomes (proportions of live births; congenital anomaly; neonatal hypoglycemia; NICU admission and APGAR scores at 1, 5 and 10 minutes) were not significantly different between the two groups.

There were three neonates with congenital malformations (congenital heart disease, fetal hydrocoele and diaphragmatic hernia), all born to mothers diagnosed with GDM after 24 weeks gestation.

Table 3. Neonatal outcomes by timing of diagnosis of gestational diabetes mellitus

	Total (N=280)	<24 weeks (n=61)	≥24 weeks (n=219)	p value
Neonate sex				0.987‡
Male	148 (53.4)	32 (53.3)	116 (53.5)	
Female	129 (46.6)	28 (46.7)	101 (46.5)	
Live birth	277 (98.9)	60 (98.4)	217 (99.1)	0.523†
Gestational age at birth				
Preterm (≥37 weeks)	28 (10.0)	10 (16.4)	18 (8.3)	0.062‡
Term (<37 weeks)	251 (90.0)	51 (83.6)	200 (91.7)	
Birthweight, kg	3 (0.6–4.2)	3 (0.6–3.7)	3 (1.5–4.2)	0.338§
Birth length, cm	50 (31–56)	50 (31–55)	50 (38–56)	0.230§
Macrosomia	3 (1.1)	0	3 (1.4)	0.999†
APGAR score				
1-minute	8 (3–9)	8 (3–9)	8 (3–9)	0.851§
5-minute	9 (4–9)	9 (5–9)	9 (4–9)	0.123§
Size for GA				0.038†a
Small	6 (2.17)	3 (5.0)	3 (1.4)	
Appropriate	259 (93.5)	57 (95.0)	202 (93.1)	
Large	12 (4.3)	0	12 (5.5)	
Congenital anomaly	3 (1.1)	0	3 (1.4)	0.999†
Neonatal hypoglycemia	1 (0.4)	0	1 (0.5)	0.999†
NICU admission	25 (9.0)	8 (13.3)	17 (7.8)	0.188†

Data presented are frequency (%) or median (range)
‡Chi-square test
†Fisher's exact test
§Mann-Whitney U test
[a]Non-significant on pairwise comparisons using Bonferroni adjusted *p* values.
[b]NICU, neonatal intensive care unit

There were three stillbirths: one born to a woman screened early for GDM, and two from pregnancies diagnosed with GDM after 24 weeks.

To explore the impact of timing of screening on the maternal and neonatal outcomes, logistic regression analysis was performed.

We compared the maternal and neonatal composite outcomes between screening time groups. The maternal composite outcome included preterm delivery and primary caesarean section, while the neonatal composite outcome included macrosomia, SGA/LGA, hypoglycemia, NICU admission, congenital malformations and perinatal mortality.

After stratifying according to timing of screening, univariate analysis showed that timing of screening was not associated with the composite of poor maternal outcomes and the composite of adverse neonatal outcomes (Table 4).

On individual outcome analysis, timing of screening was statistically significant in predicting preeclampsia and low birth weight among those screened before 24 weeks of gestation. The crude OR of preeclampsia and low birth weight is 0.356 and 0.375 times, respectively, lower for those screened after 24 weeks of gestation (Table 4).

Table 4. Effect of timing of screening on maternal outcomes and neonatal outcomes

Outcome	n	Crude OR[a] (95% CI[b])	*p* value
Composite			
Poor maternal outcomes		0.769 (0.42–1.41)	0.394
Adverse neonatal outcomes		0.806 (0.38–1.71)	0.574
Individual			
Preterm delivery	26	0.486 (0.21-1.15)	0.102
Primary CS[c]	64	0.884 (0.46-1.72)	0.716
Need for insulin	10	0.401 (0.11-1.47)	0.168
Preeclampsia	35	0.356 (0.17-0.75)	0.007
Birthweight <2500 g	36	0.375 (0.18-0.79)	0.010
SGA[d] or LGA[e]	18	1.411 (0.39-5.04)	0.596
NICU[f] admission	25	0.558 (0.23-1.36)	0.200

[a]OR, odds ratio
[b]CI, confidence interval
[c]CS, Caesarean section
[d]SGA, small for gestational age
[e]LGA, large for gestational age
[f]NICU, neonatal intensive care unit

DISCUSSION

The period prevalence of GDM in this two-year study was 11.06%, similar to those reported by other local studies.[7,8]

The mean age of women diagnosed with GDM before 24 weeks was significantly higher. Studies have shown that increasing maternal age is a risk factor for developing GDM thus older patients are more likely to be screened earlier.[9]

The 2-hour glucose results in the 75 g OGTT were higher in those who were diagnosed with GDM before 24 weeks of gestation. This observation might be considered when screening for glucose intolerance in early pregnancy using 75 g OGTT. The OGTT may be more sensitive than FBS alone to diagnose GDM in early pregnancy. However, there is paucity of data on OGTT values in early pregnancy and the IADPSG criteria are not validated for early pregnancy. Further studies on this topic are needed. Most of the current glucose thresholds for the diagnosis of GDM are derived from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study and are only validated for use between 24 and 32 weeks of gestation.[10-12]

There were more women with preeclampsia in the group diagnosed with GDM before 24 weeks. Several studies noted similar results, even after adjustment for maternal age, ethnicity, parity, weight and blood glucose control.[13,14]

The development of preeclampsia appears to be associated with insulin resistance and may explain its increased risk and incidence among women with GDM. Management of GDM patients diagnosed earlier, includes not only earlier glycemic control but also earlier blood pressure control.

The increased incidence and higher odds of developing preeclampsia among mothers who were diagnosed before 24 weeks of gestation may be attributed not only to GDM but also to other risk factors that predispose patients to developing preeclampsia such as previous history of preeclampsia, nulliparity, higher body mass index (BMI),

preexisting hypertension, advanced age (more than 40 years) and family history.[15] One limitation of our study is that the risk factors that may have prompted earlier screening were not included during the data collection and analysis.

Although there was insufficient evidence to conclude statistical significance, we observed a trend towards more preterm deliveries in the group diagnosed with GDM before 24 weeks of gestation. The subsequent management following the diagnosis of GDM involves increased frequency of prenatal visits, with additional maternal and fetal monitoring.[16] An earlier diagnosis of GDM may have resulted in more obstetric interventions, taking into consideration conditions such as preeclampsia that may be present in the high-risk early screening group. It was noted that in the subgroup of mothers who developed preeclampsia, preterm delivery was more common among those who were diagnosed earlier (5/14 or 36%) compared to those diagnosed after 24 weeks of gestation (4/21 or 19%) (p=0.432).

The use of insulin was comparable between the two groups. Previous studies have observed more frequent and earlier use of insulin with higher daily doses in those diagnosed with early GDM without improved outcomes.[17-19]

The mode of delivery did not differ between groups, which was similar to the study of Hong et al., where early screening was not associated with significant reduction in the risk of caesarean section.[20]

Although not statistically significant, more neonates in the early GDM group had lower age of gestation at delivery. In the study by Hong et al., women who were screened earlier were more likely to deliver preterm. These women had a higher prevalence of increased BMI, previous GDM and chronic hypertension.[20] The risk factors that may have been present in the group diagnosed with GDM before 24 weeks of gestation in this study may have contributed to the preterm births in addition to increased monitoring of these high-risk patients. Studies that reviewed the benefits and harms of early screening showed that the diagnosis of glucose intolerance in early pregnancy led to more monitoring and interventions, including induction of labor, which may have led to preterm deliveries, without improvement in outcomes.[21,22]

The absence of LGA neonates and higher odds of having neonates with low birth weight in the group diagnosed with GDM before 24 weeks may be due to earlier interventions to control diet and hyperglycemia. Similar studies have concluded that timely restrictions and pharmacologic interventions are contributing factors to limited weight gain in the early screening group.[18,19]

In our study, there were three macrosomic neonates in the group diagnosed with GDM after 24 weeks. LGA neonates were observed to be born to younger mothers. The mothers who had LGA offspring had their screening done much later than the recommended 24 to 28 weeks AOG: six out of the 12 had their OGTT beyond 28 weeks age of gestation. This might have led to delayed interventions for GDM control. Two of the three mothers with macrosomic offspring sought first consult for GDM beyond 30 weeks AOG despite having been screened at 24 to 28 weeks AOG. The compliance to diagnostic requests and the health-seeking behavior of the subjects prove to be realistic limitations in the management of GDM in the local setting.

The limitations of this study include its retrospective design and short time frame of only two years. It was conducted in one institution, limited to women who had their prenatal consults and subsequent delivery at the same institution, excluding a significant number of women who delivered at this institution but did not have their prenatal checkups at the OPD. The risk factors that might have been present in our subjects that prompted early screening and may have contributed to pregnancy complications were not determined.

CONCLUSION

The group diagnosed with GDM before 24 weeks was significantly older and had higher 2-hour 75 g OGTT results compared to the group diagnosed with GDM after 24 weeks of gestation. There were more women in whom GDM was diagnosed earlier in pregnancy who developed preeclampsia and delivered preterm neonates compared to women in whom GDM was diagnosed later in pregnancy. Preeclampsia may be from earlier onset of GDM. There may have been other risk factors contributing to these outcomes in these high-risk patients.

Based on this study's results and limitations, we recommend a prospective study comparing differences in pregnancy outcomes in patients screened before 24 weeks AOG, at 24 to 28 weeks AOG and after 28 weeks AOG using the 75 g OGTT. It is also recommended that all risk factors affecting pregnancy outcomes be considered in future studies. Further research is also needed to determine if early screening for GDM should be done in all pregnant women regardless of the presence or absence of risk factors.

Acknowledgments
The authors are grateful to the Pasig City General Hospital and the Institute for Reproductive Health Philippines for the data they provided for this study, and to 101 Health Research for statistical analysis.

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

Author Contribution Statement
KD collected the data and wrote the manuscript. CY contributed to the discussion and reviewed and approved the final version of the manuscript.

Author Disclosure
Both authors declared no conflict of interest.

Funding Source
None.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Neonatal Outcomes of Pregnancies Complicated by Maternal Hyperthyroidism

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Abstract

Objective. This study aimed to determine the proportion, clinical characteristics, hormonal status, median time for normalization of serum thyroxine (FT4) and thyroid-stimulating hormone (TSH) and factors affecting time to thyroid function test (TFT) normalization of neonates born to mothers with maternal hyperthyroidism admitted in our institution.

Methodology. This was a retrospective cohort study that included 170 newborns admitted to the Neonatal Intensive Care Unit (NICU) of Hospital Universiti Sains Malaysia (HUSM) with a history of maternal hyperthyroidism from January 2013 until December 2018. We analyzed their baseline demographic and clinical characteristics, maternal thyroid status and antibody levels. Finally, we analyzed newborn thyroid function and thyroid antibodies.

Results. The proportion of neonates born to mothers with maternal hyperthyroidism was 0.8% (170 of 20,198 neonates within the study period). Seven (4.1%) developed overt hyperthyroidism, while four (2.4%) had thyroid storm. The median time for thyroid function test normalization was 30 days (95% CI: 27.1 to 32.8). The median time for TFT normalization was longer among neonates of mothers with positive thyroid antibodies [46.6 days (95% CI, 20.6 to 39.4)] and of mothers who received anti-thyroid treatment [31.7 days (95% CI, 23.5 to 39.9)].

Conclusion. Neonates born to mothers with hyperthyroidism is uncommon. These babies were observed to have a longer time for normalization of thyroid function tests if their mothers had thyroid antibodies or received anti-thyroid treatment.

Key words: neonatal thyrotoxicosis, maternal hyperthyroidism, Graves' disease (GD)

INTRODUCTION

Thyroid hormones are important for linear growth, central nervous system myelination and regulation of many metabolic activities in infancy.[1] Routine newborn screening for congenital hypothyroidism was introduced in 1993 by the American Academy of Pediatrics. Newborn screening for congenital hypothyroidism in Malaysia was started in October 1998.[2]

There is a lack of consensus in identifying neonates who are at risk for hyperthyroidism. Neonates born to hyperthyroid mothers, particularly those with Grave's disease (GD), are at risk for significant morbidity and mortality.[3] The prevalence of hyperthyroidism in pregnancy ranges from 0.7 to 2.8% worldwide.[4,5] In Malaysia, studies have shown that the incidence of hyperthyroidism in pregnancy is 0.9 per 1000 deliveries, with GD as the most common etiology.[6] Other etiologies of hyperthyroidism in pregnancy are toxic adenoma, toxic nodular goiter, thyroiditis, gestational hyperthyroidism and mutations in the TSH receptor.[7]

The causative antibodies in GD are thyroid-stimulating hormone receptor antibodies (TRAb) that belong to the immunoglobulin G class. TRAbs cross the placenta freely, particularly during the second half of pregnancy.[8] TRAbs are of two types: TSH-receptor stimulating antibodies that bind to the TSH receptor on thyroid follicular cells and lead to autonomous thyroid hormone production, and TSH-receptor blocking antibodies that bind to the TSH-receptor but do not initiate intracellular signaling, and result in suppression of thyroid hormone synthesis.[9]

Fetal thyroid development is established at seven weeks of gestation. At ten to 12 weeks of gestation, thyroid hormone synthesis begins and becomes functionally mature by 25 weeks. Transfer of these stimulating TRAbs to the fetus can cause *in utero* and/or postnatal hyperthyroidism.[10]

Neonatal thyroid storm is a serious complication of neonates born to mothers with GD. The European Society for Pediatric Endocrinology (ESPE) Consensus Guidelines recommend that babies born to mothers with hyperthyroidism need

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: September 2, 2021. Accepted: February 4, 2022.
Published online first: August 6, 2022.
https://doi.org/10.15605/jafes.037.02.03

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repeat TFT in the first week of life, or on the third to fifth day of life.[11] However, there are no clear guidelines on subsequent management and follow-up of neonates born to mothers with hyperthyroidism. Hence, we sought to study the outcomes of neonates born to mothers with hyperthyroidism, specifically to estimate the median time to normalization of thyroid function and to identify factors that may affect time to normalization of thyroid function.

OBJECTIVES

We aimed to determine the proportion, clinical characteristics, hormonal status, median time for serum FT4 and TSH normalization and factors affecting time to normalization of TFTs of neonates born to mothers with maternal hyperthyroidism admitted to the NICU of Hospital Universiti Sains Malaysia.

METHODOLOGY

Study Design

We conducted a retrospective cohort study covering the period of January 2013 until December 2018. We included neonates born to mothers with hyperthyroidism and admitted to the NICU.

Subjects and Procedures

In HUSM, all neonates born to mothers with hyperthyroidism are routinely admitted at the NICU. Records of neonates of mothers with hyperthyroidism admitted from January 1, 2013 to December 31, 2018 were reviewed.

We excluded subjects with inadequate crucial data, specifically those lacking the date of diagnosis, three or more sociodemographic variables of interest (birth weight, length, head circumference, gestational age, gender, mode of delivery) and follow-up records.

We collected demographic, anthropometric (birth weight, length and head circumference) and clinical data (heart rate, blood pressure, respiratory rate) during initial admission. Maternal demographic characteristics, TFTs, presence of thyroid antibodies and anti-thyroid treatment were also collected.

TFT monitoring was done through cord blood as part of the congenital hypothyroidism screening program and on the third to fifth day of life. Serial TFTs were monitored in babies who had abnormal results, with determinations from cord blood on days 3 to 5, 15, 30, 45, 60, 90 and 180 of life.

Statistical Analysis

Data analysis was done using Statistical Package for Social Science (SPSS) IBM version 26.0. Continuous data were presented as mean (standard deviation, SD) or median (interquartile range, IQR) based on their probability distribution. Categorical data were presented as frequency (percentage). The proportion of neonates born to mothers with hyperthyroidism was calculated by using the total number of newborns admitted to the NICU within the study period as the denominator. The median time for normalization of TFTs was analyzed with Kaplan-Meier survival analysis. Cox proportional hazard regression test was used to calculate associated factors in TFT normalization.

The sample size determination was conducted based on calculation for survival analysis (log-rank test) using G*power software. The median time to normalization among newborns without maternal thyroid antibodies (designated as group *m1*) is four weeks, based on a previous study/expert opinion. The expected time of normalization among newborns with maternal thyroid antibodies (group *m2*) is 12 weeks. Given the accrual time of 312 weeks and additional follow-up time of 52 weeks, the ratio *m2* and *m1* is 0.4. The required sample sizes were 49 for *m1* and 25 for *m2*, for a total of 74 newborns, at 5% type I error and 80% power. Anticipating missing data of 10%, the corrected sample size was 82.

Ethical Approval

This study was approved by the Human Research Ethics Committee USM with reference USM/JEPeM/20100533.

RESULTS

There were 20,198 newborns admitted during the study period. Of these, we identified 186 neonates born to mothers with hyperthyroidism. A total of 170 (0.8%) were included in the study. Sixteen were excluded: three died a few hours after birth due to prematurity and another 13 were born to mothers who had hypothyroidism rather than hyperthyroidism.

Tables 1 and 2 summarize the demographic, clinical and biochemical characteristics of the included neonates. Seventy-seven (45.3 %) were male. The mean gestational age was 38.2 ± 1.5 weeks, and mean birth weight was 2.9 ± 0.5 kg. Majority (81.8%) were delivered via spontaneous vaginal delivery, and had an APGAR score of at least 7 at five minutes (97.1%). Most had normal vital signs: mean heart rate was 131.3 ± 15.9 beats per minute; mean respiratory rate 46.9 ± 8.8 breaths per minute; and mean systolic and diastolic pressures of 73.2 ± 5 mmHg and 44.8 ± 3.3 mmHg, respectively. Median length of stay was 22.3 ± 24.4 days. Mean cord TSH was 15.0 ± 23.1 mIU/L [reference value (RV) 0.001-101 mIU/L], while mean cord FT4 was 25.1 ± 29.6 pmol/L (RV 5.0-85.2 pmol/L). Most (60.0%) had abnormal TFTs at days 3 to 5. These abnormal TFTs were classified into seven categories: subclinical hyperthyroidism; subclinical hypothyroidism; isolated high FT4; overt hyperthyroidism; overt hypothyroidism; high FT4, high TSH; and sick euthyroid (Table 3).

Table 1. Clinical characteristics of newborns with maternal hyperthyroidism

Variable	Mean ± SD[a] / Frequency (%)[b]
Anthropometry	
Birth weight, kg	2.9 ± 0.5
Head circumference, cm	32.3 ± 1.7
Length, cm	49.8 ±3.3
Age of gestation, week	38.2 ± 1.5
Male gender	77 (45.3)
Race	
Malay	162 (95.3)
Others	8 (4.7)
APGAR score	
Poor	5.2 (2.9)
Good	165 (97.1)
Vital signs	
Heart rate, beats per minute	131.3 ± 15.9
Respiratory rate, beats per minute	46.9 ± 8.8
Systolic blood pressure, mmHg	73.2 ± 5.0
Diastolic blood pressure, mmHg	44.8 ± 3.3
Mode of delivery	
Spontaneous vaginal delivery	139 (81.8)
Lower segment Caesarean section	31 (18.2)
Length of stay, day	22.3 ± 24.4

[a]Mean ± SD (standard deviation) for numerical variables
[b]Frequency and percentages for categorical variables

Table 2. Biochemical and clinical characteristics of newborns with maternal hyperthyroidism

Variable	Mean ± SD[a] / Frequency (%)[b]	Reference value
Maternal autoantibodies present	21 (12.4)	
Maternal anti-thyroglobulin, kIU/L	711.7 ± 1299.0	Up to 115 kIU/L
Maternal anti-thyroid peroxidase, kIUL	117.8 ± 173.5	Up to 34 kIU/L
Mother received treatment	105 (61.8)	
Neonatal anti-thyroglobulin, kIU/L	45.88 ± 143.26	Up to 115 kIU/L
Neonatal anti-thyroid peroxidase, kIU/L	25.89 ± 53.54	Up to 34 kIU/L
Cord thyroid function tests		
TSH, mIU/L	15.0 ± 23.0	<20 mIU/L
Free thyroxine, pmol/L	25.1 ± 29.6	15 pmol/L
Day 3 to 5 thyroid function tests		
TSH, mIU/L	5.7 ± 10.1	0.5-6.0 mIU/L
Free thyroxine, pmol/L	27.3 ± 18.5	12-15 pmol/L
Day 15 thyroid function tests		
TSH, mIU/L	5.7 ± 9.7	0.5-4.0 mIU/L
Free thyroxine, pmol/L	34.6 ± 33.1	10-24 pmol/L
Neonate diagnosed overt hyperthyroidism	7 (4.1)[c]	
Neonate diagnosed with thyroid storm	4 (2.4)	

[a]Mean ± SD (standard deviation) for numerical variables
[b]Frequency and percentages for categorical variables
[c]Characteristics described in Tables 4 and 5

Eighteen (10.6%) newborns had normal TFTs at days 3 to 5. At day 15 of life, fewer newborns had abnormal TFTs (from 102 to 19, 11.2%). Most were seen in groups with isolated high FT4 (28, 15.5%); overt hyperthyroidism (4, 2.2%) and high FT4, high TSH (7, 3.9%). However, there was an increase in subclinical hyperthyroidism (from 1 to 2, 1.1%), subclinical hypothyroidism (from 7 to 9, 5.0%) and overt hypothyroidism (from 2 to 5, 2.8%). Thirty-nine (22.9%) newborns had normalization of TFTs on day 15. At days 3 to 5, mean TSH was 5.7 ± 10.1 mIU/L, while mean FT4 was 27.3 ± 18.5 pmol/L. At day 15, mean TSH was 5.7 ± 9.7 mIU/L and mean FT4 was 34.6 ± 33.1 pmol/L (Figure 1).

Seven newborns had overt hyperthyroidism. Of these, four had thyroid storm and were started on Lugol's iodine, carbimazole and propranolol. Medications were stopped in all four newborns with subsequent normalization of TFTs from one to four months of life. All seven newborns were born to mothers with GD: three were diagnosed before pregnancy, while four had mothers who were diagnosed during the second trimester. Serum TRAb was not routinely done in all mothers and newborns: only three newborns and 2 mothers had TRAb done, which were positive (Tables 4 and 5).

Majority of the mothers were diagnosed with hyperthyroidism without specific etiology (142, (83%) (Table 4). The rest had GD (7, 4.1%), gestational hyperthyroidism (3, 1.8%), thyroid nodule (1, 0.5%), goiter (15, 8.8%) and post-total thyroidectomy (2, 1%). Most of the mothers were diagnosed with hyperthyroidism before pregnancy. Only four (2.3%) were diagnosed with GD in the second/third trimester. There were 21 (12.4%) mothers who had thyroid antibodies and 149 (87.6%) who did not have thyroid antibodies. TRAb was only measured in one patient whose mother which turned out to be positive. Mean maternal anti-thyroglobulin (anti-Tg) level was 711.7 ± 1299.0 kIU/L, and mean maternal anti-thyroid peroxidase (anti-TPO) was 117.8 ± 173.5 kIU/L. Most of the mothers received treatment (105, 61.8%) for hyperthyroidism, and most received anti-thyroid drugs (ATDs) only (95, 55.8%).

Differences in median time of TFTs to normalize by presence of maternal thyroid autoantibodies and maternal

Table 3. Categories of abnormal thyroid function tests in newborns

Category	TSH	FT4	Total T3[a] or Free T3[a]
Subclinical hyperthyroidism	Low or undetectable, <0.5 mIU/L	Normal, 10-24 pmol/L	Normal
Overt hyperthyroidism	Low, <0.5 mIU/L	High, >24 pmol/L	
Subclinical hypothyroidism	High, First 30 days of life: 6-20 mIU/L After 30 days of life: 6-10 mIU/L	Normal, First 30 days of life: 10-24 pmol/L After 30 days of life: 10-22 pmol/L	
Overt hypothyroidism	High, First 30 days of life: ≥20 mIU/L After 30 days of life: ≥6 mIU/L	Low, First 30 days of life: ≤15 pmol/L After 30 days of life: ≤10 pmol/L	
Isolated elevated FT4	Normal, 0.5-6.0 mIU/L	High, >24 pmol/L	
High FT4, high TSH	High, >6 mIU/L	High, >24 pmol/L	
Sick euthyroid/central hypothyroidism	Low, 6-10 mIU/L or low	Low, ≤10 pmol/L	

[a]T3, triiodothyronine

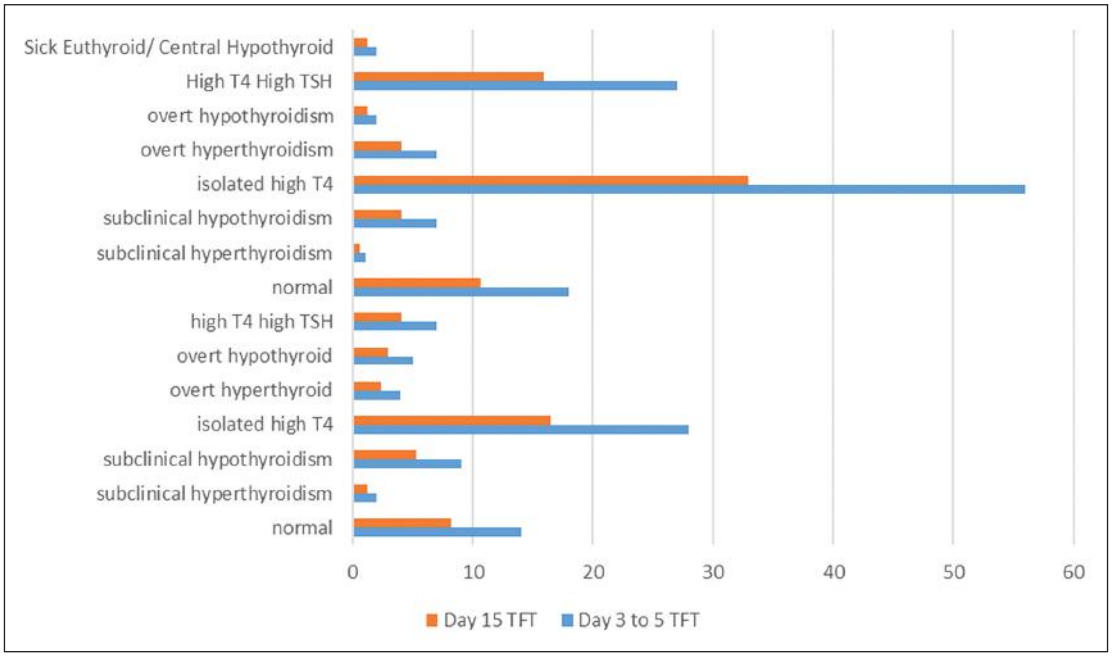

Figure 1. Comparison of categories of abnormal thyroid function tests on day 3 to 5 and day 15 of life. *TFT, thyroid function test.*

treatment are summarized in Table 6. Kaplan-Meier analysis revealed that the overall median time for TFTs to normalize was 30 days (95% CI, 27.1 to 32.8). Among newborns with mothers who had thyroid antibodies, the median time of TFT normalization was longer at 46.6 days (95% CI, 20.6 to 39.4) compared to newborns whose mothers did not have thyroid antibodies [26.2 days (95% CI, 22.0 to 30.4). In terms of maternal thyroid treatment, TFT normalization appeared to be slowest among neonates whose mothers were on thyroxine, at 95.0 days (95% CI, 11.2 to 178.7). Cox proportional hazard regression analysis revealed that none of the variables were significant.

Table 4. Summary of maternal thyroid function tests and antibodies of newborns with overt hyperthyroidism

Case	At diagnosis		At delivery		Antibodies			Treatment
	TSH, mIU/L	FT4, pmol/L	TSH, mIU/L	FT4, pmol/L	Anti-TPO[a], kIU/L	Anti-Tg[b], kIU/L	Anti-TRAb[c], U/L	
1	0.01	23.2	0.01	24.5	156.4	<10	-	Prophylthiuracil, Propanolol
2	0.25	47.4	0.01	29.4	Not done[d]	Not done[d]	Not done[d]	Carbimazole
3	0.01	25.0	28.6	9.5	>600	>4000	-	Thyroxine
4	0.001	52.6	0.01	18.3	22.4	21.1	-	Carbimazole
5	0.67	25.0	0.005	47.0	8.5	<10	-	not mentioned
6	0.01	72.0	0.01	91.0	11.5	88.28	39.8	Carbimazole
7	0.09	59.0	0.01	68.0	-	-	-	Propanolol, Carbimazole

[a]Anti-TPO, thyroid peroxidase antibody
[b]Anti-Tg, thyroglobulin antibody
[c]Anti-TRAb, thyroid receptor antibody
[d]Mother had thyroid storm during pregnancy

Table 5. Summary of thyroid function tests and antibodies of newborns with overt hyperthyroidism

Case	Day 3-5		Day 15		Day 30		Antibodies			Treatment given
	TSH, mIU/L	FT4, pmol/L	TSH, mIU/L	FFT4, pmol/L	TSH, mIU/L	FT4, pmol/L	Anti-TPO[a], kIU/L	Anti-Tg[b], kIU/L	Anti-TRAb[c], U/L	
1	0.01	>100	0.01	21.7	2.6	21.9	7.92	11.73	-	Yes
2	0.04	63.0	0.03	38.2	1.8	16.2	6.1	<10	Not done[d]	Yes
3	-	52.4	2.6	44.7	2.6	26.4	-	356.4	-	No
4	0.01	8.3	0.001	21.9	0.02	27.3	13.5	51.8	-	No
5	0.05	55.0	0.04	25.7	0.01	20.0	<5	<10	28.3	Yes
6	0.02	38.0	0.04	10.3	0.7	3.8	20.25	21.82	37.1	Yes
7	0.03	29.0	0.02	29.0	0.05	23.3	78.9	16	18.6	No

[a]Anti-TPO, thyroid peroxidase antibody
[b]Anti-Tg, thyroglobulin antibody
[c]Anti-TRAb, thyroid receptor antibody
[d]Mother had thyroid storm during pregnancy

Table 6. Analysis of time to normalization of thyroid function tests in newborns with maternal hyperthyroidism

Variable	N (%)	Median, days (95% CI)	Log rank (df)	*p* value
Presence of maternal autoantibodies			4.602 (1)	0.03
Yes	21 (12.4)	46.6 (20.6-39.4)		
No	149 (87.6)	26.2 (22.0-30.4)		
Mother received treatment during pregnancy			3.898 (1)	0.05
Yes	105 (61.8)	31.7 (23.5-39.9)		
No	61 (35.9)	21.4 (16.2-26.5)		
Type of medication received by mother			10.861 (3)	0.01
Carbimazole	49 (28.8)	29.4 (23.7-35.0)		
Propylthyiouracil (PTU)	33 (19.4)	25.8 (18.5-33.0)		
Combined Carbimazole and PTU	13 (76)	21.6 (10.8-32.3)		
Thyroxine	9 (5.3)	95.0 (11.2-178.7)		

[a]Kaplan-Meier analysis
[b]*p* value <0.05 statistically significant
[c]Characteristics described in Tables 5 and 6

DISCUSSION

The proportion of newborns affected by maternal hyperthyroidism at the NICU of HUSM from 2013 until 2018 was 0.8%. This finding is consistent with the study by Laurberg and Andersen where the prevalence of maternal hyperthyroidism was 0.7%.[4] Our finding was slightly lower in comparison to the study by Dulek et al., which reported a prevalence of 2.8%.[5] We found that male and female newborns were equally affected, consistent with other studies.[10,12,13] This implies that TRAbs from mothers are transferred to the fetus regardless of gender. Most of the newborns were born term with normal birth weight, similar to most studies.[12,13] Most of our newborns were delivered via SVD with good APGAR scores. These findings may reflect that majority of the babies born to mothers with hyperthyroidism had stable thyroid disease with or without maternal treatment with anti-thyroid drugs.

Our study had longer mean length of hospital stay (22.3 ± 24.4 days) in contrast to the study by Männistö (10 days).[14] The longer hospital stay may be explained by the delay in the onset of neonatal hyperthyroidism. This may be due to both the effect of maternal transplacental passage of TRAb and maternal transplacental passage of ATD, wherein more than 95% of newborns may develop symptoms anytime between day 1 until day 29 of life, peaking in the first 2 weeks of life.[15] Because TRAb measurement is not routinely performed in mothers with hyperthyroidism in our hospital, it becomes a challenge to foresee who would eventually develop neonatal hyperthyroidism.

Among seven newborns who had overt hyperthyroidism, four had thyroid storm and were started on Lugol's iodine, carbimazole and propranolol. All four had mothers diagnosed with GD. Though TRAb levels are not routinely measured at our institution, most mothers were screened for anti-TPO and anti-Tg. The presence of anti-TPO/anti-Tg is suggestive of autoimmune thyroiditis, but it is not specific for GD. About 10% of GD may also test positive for anti-TPO/anti-Tg.

Thyroid storm or thyrotoxic crisis is an acute, life threatening, hypermetabolic state induced by excessive release of thyroid hormone.[16] The hypermetabolic state is characterized by hemodynamic instability, manifesting as tachycardia, tachypnea, fever and hypertension. Neurologically, babies appear irritable with wide open eyes, jitteriness and difficulty in sleeping.[17] Babies with thyroid storm may also exhibit increased appetite, diarrhea and vomiting. Severe thyroid storm may result in heart failure, pulmonary hypertension and convulsions.[18] All four babies who were treated as thyroid storm had not only overt hyperthyroidism biochemically, but also had systemic manifestations characterized by tachycardia (heart rate 160 to 200 beats per minute), respiratory distress, irritability, jitteriness, increased appetite and diarrhea. Three of the babies had onset of thyrotoxicosis at day 3 to 4 of life; while one was first diagnosed at day five. Anti-thyroid drugs were stopped between day 60 to 90 of life with the resolution of the symptoms and normalization of thyroid function tests. Long-term outcomes associated with suboptimal or delayed diagnosis and treatment are intellectual impairment; central hypothyroidism; craniosynostosis; and neuropsychological, emotional and behavioral problems.[17] Three of our patients who were initially treated for thyroid storm had defaulted long-term follow-up. One of the patients with thyroid storm had normal growth and development and was last seen at the age of five years.

For the diagnosis of GD in mothers, three were diagnosed before pregnancy based on clinical manifestations consistent with thyrotoxicosis, thyroid eye signs and biochemical results compatible with overt hyperthyroidism. Four had clinical manifestations, biochemical results compatible with overt hyperthyroidism and positive thyroid autoantibodies (one with TRAb, three with anti-TPO/anti-Tg).

There was a total of three out of seven newborns who had TRAb. Overt neonatal hyperthyroidism can present at birth; however, the onset can be delayed due to maternal ATD or the coexistence of TSH-receptor blocking antibodies. Several studies have demonstrated that in more than 95% of newborns who developed symptoms, the manifestations occur between 1 and 29 days of life, with most patients diagnosed within the first 2 weeks. Although rare, development of hyperthyroidism as late as day 45 of life has been described.[19]

The time of TFTs to normalize in our study was 30 days. Overall, the thyroid disorder is a self-limiting disease, with anticipated clearance of thyroid antibodies in one month's time.[20] Our findings show that newborns with maternal GD are at risk for neonatal hyperthyroidism and thyroid storm even with the small population size.

Mean initial cord TSH was 15.0 ± 23.1 mIU/L, while mean FT4 was 25.1 ± 29.6 pmol/L. Abnormal cord blood results do not predict subsequent neonatal thyroid status. Newborns born to mothers with GD may not manifest immediately after delivery: thyroid functions tests may show isolated high FT4 or other abnormal values, as ATDs from the mother are expected to be cleared only after 72 hours. In the study by Besançon et al., among 33 newborns born to mothers with thyroid antibodies, seven developed hyperthyroidism at day 7 of life. Among these seven newborns, initial cord blood showed subclinical hyperthyroidism in three patients and hypothyroidism in two.[21] In a review of 69 newborns by Polak et al., only six had neonatal hyperthyroidism: two had initial cord TFTs consistent with hyperthyroidism while the rest had hypothyroidism and normal cord blood.[22] These findings demonstrate that cord blood TFTs do not reliably predict the risk of neonatal hyperthyroidism.

There are limited studies on the median time of normalization of TFTs in newborns with maternal hyperthyroidism. Our median time for TFT normalization in newborns with maternal hyperthyroidism was 30 days. Rovelli et al., observed that spontaneous normalization of TFTs in newborns with autoimmune thyroid antibodies occurred mostly within 15 days of life (93.3%) and a few within one month (0.1%).[23] The resolution of abnormal TFTs was due to disappearance of maternal stimulating TSH receptor antibodies in transient neonatal hyperthyroidism.[24]

High levels of maternal thyroid antibodies were observed. The median time of TFT normalization was longer among newborns with mothers who have thyroid antibodies compared to those without maternal thyroid antibodies.

Antithyroid antibodies, including TRAb, anti-TPO and anti-Tg, have established associations with thyroid autoimmune diseases.[25] Thyroid receptor antibodies can be subdivided into TSH receptor-stimulating (TSAbs), TSH receptor-blocking (TBAbs) and neutral thyroid receptor (N-TRAbs). TSAbs are typical antibodies in GD which can bind and activate TSH receptors, causing increased thyroid hormone production. TBAbs bind to TSH receptors without causing activation and prevent TSH binding to the TSH receptor, resulting in hypothyroidism. N-TRABs do not block the binding of TSH to the TSH receptor, but they are able to induce local infiltration of inflammatory cells into the thyroid gland and eyes.[8] TRAbs can cross the placental barrier freely to disturb thyroid function of both the pregnant woman and the fetus.[26] Thyroid peroxidase (TPO) serves as the core enzyme during the synthesis of thyroid hormones. Elevated TPOAb level is essential in diagnosing Hashimoto's thyroiditis and supportive in the work-up of GD. Anti-Tg is mainly composed of IgG and mainly attacks different antigenic determinants of thyroglobulin. Anti-TPO and anti-Tg are frequently present in the same individual.[27] The pregnant women included in this study were all hyperthyroid. Those with positive thyroid antibodies showed delayed normalization of TFT, which may be due to passage of thyroid antibodies to newborns impairing neonatal TFTs. TFT normalization was also longer among those with maternal ATDs compared to those who were not on ATDs.

Carbimazole and propylthiouracil (PTU) were used in the treatment of maternal hyperthyroidism. Carbimazole and PTU are all thought to be equally effective in controlling hyperthyroidism.[28] PTU is associated with increased risk of severe liver injury, while carbimazole is linked to embryopathy.[3] Management strategies to reduce these risks using PTU in the first trimester and carbimazole thereafter. Of the 61.8% of mothers who received treatment, 95% received ATDs and 5% received L-thyroxine. The delayed time for TFT to normalize may indicate active thyroid disease. We were unable to explain why some of the mothers with hyperthyroidism were not treated in this study.

Many of these newborns exhibited different types of TFT status. There were similar studies that identified different TFT abnormalities in newborn with maternal GD. Levy-Shraga et al., identified 83 out of 96 newborns with maternal GD that had subclinical hyperthyroidism; all were otherwise well and asymptomatic.[13] Lee et al. noted in their case series that some of the newborns showed TFT abnormalities mimicking central hypothyroidism.[29] The variation of TFT status is most likely related to TRAbs which can be either thyroid receptor-stimulating or -blocking antibodies. In some newborns, both antibodies could either co-exist or vary from time to time contributing to the different TFT abnormalities.

Measurement of TRAb levels have been incorporated in guidelines on the management of maternal hyperthyroidism in some countries. However, it is not yet offered as a routine investigation in Malaysia and other countries due to its high cost. TRAbs should be checked in a pregnant woman with a history of GD, active GD or maternal hyperthyroidism secondary to suspected GD. If TRAb levels are low or undetectable in early pregnancy, no further TRAb testing is recommended. If maternal TRAb is positive or patient is being treated with ATD, TRAb should be measured again between 18 and 22 weeks of gestation.[11] In those with levels near three to four times above upper limit of normal, TRAb should be repeated during 30 to 34 weeks of gestation. Maternal TRAb serum concentration greater than two to three times the upper limit of the reference range in the third trimester is a risk factor for neonatal hyperthyroidism.[11] If TRAb testing is not available, all infants born with maternal hyperthyroidism should be considered at risk of acquiring TSH receptor antibodies,

especially those born to mothers who developed clinical thyrotoxicosis during the second and third trimester or with babies who have a history of neonatal GD, and those with fetal signs of thyrotoxicosis during prenatal screening.[3] Besançon et al., studied 68 newborns with maternal GD which were divided into three groups based on TRAb and ATD status in the mother. None of the infants born to TRAb negative mothers with GD developed neonatal thyrotoxicosis. Of the 33 TRAb positive and ATD positive, 24 (72%) had positive TRAb on cord blood assays, and seven of them developed neonatal thyrotoxicosis.[21]

Our results were very reassuring since most often the abnormal thyroid function tests would normalize at a median time of 30 days. None had abnormal thyroid status beyond six months of life. Infants who are completely asymptomatic at three months of life can be safely discharged.

Limitation of study

Our study had a few limitations as it was retrospective in nature. Because TRAb was not routinely done in all mothers and newborns with hyperthyroidism, we could not explore its usefulness in managing infants with maternal hyperthyroidism. Finally, most of the medical records showed a short follow-up which might miss persistent thyroid dysfunction in newborns who were initially treated for overt hyperthyroidism or thyroid storm.

CONCLUSION

The proportion of neonates born to mothers with hyperthyroidism is rare at 0.8%, consistent with international studies. Neonates whose mothers had positive thyroid antibodies and received anti-thyroid treatment had longer time for normalization of thyroid function tests.

Acknowledgments
The authors would like to thank their supervisors, fellow lecturers, colleagues, supporting staff, family and the team of authors used as references.

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

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Prevalence of Diabetes Among Community-Living Older Persons in the Philippines: The FITforFrail Study

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Abstract

Objective. To estimate the prevalence of diabetes among Filipino older persons living in the community.

Methodology. A cross-sectional analysis was done on a random sample of persons 60 years and older from the Focused Interventions for Frail Older Adults Research and Development Program (2018-2019). A diagnosis of diabetes was established by self-reported physician's diagnosis or if the person was on any antihyperglycemic drugs.

Results. The prevalence of self-reported diabetes was 20.5%, with no difference in age, sex, education, or body mass index between older persons with and without diabetes. The presence of 2 or more comorbidities was significantly more common among older persons with diabetes (p<0.001). Visual impairment (p<0.01), hypertension (p<0.001) and hyperlipidemia (p<0.001) were more frequent among those with diabetes.

Conclusion. Diabetes is prevalent among community-living older Filipinos. Therefore, effective public health measures for diabetes prevention and management are needed for the ever-growing older population, who are at the highest risk for morbidity and mortality.

Key words: diabetes, older persons, comorbidities

INTRODUCTION

The International Diabetes Federation reports that there is an estimated 536.6 million (10.5%) persons with diabetes between the ages of 20 to 79 in 2021.[1] This is projected to increase to 783.2 million (12.2%) in 2045 with the greatest increase coming from low-and middle-income countries (LMIC). The prevalence increased with age, with the highest seen in the 75 to 79 age group (24%). For those between the ages of 65 to 99 years, the number of persons with diabetes was reported to be 135.6 million (19.3%) in 2019, mostly coming from LMIC and is projected to increase to 276.2 million in 2045.[2]

Diabetes is a significant contributor to death and disability. The 2019 World Health Organization Global Health Estimates ranked diabetes as the 9th cause of death and 8th cause of disability worldwide.[3] Risk of death increases with age, the pathophysiologic damage of the disease itself and its complications, presence of comorbidities, polypharmacy and even antihyperglycemic drugs.[4-7] Multimorbidity, the presence of two or more diseases in the same person, is commonly seen with diabetes.[8] As much as 97.6% of community-living older persons with diabetes have at least one comorbid disease and about 46% have 3 or more.[9-11] Persons with diabetes are at high risk for cardiovascular complications, such as hypertension, heart disease, stroke and geriatric syndromes, including falls, cognitive impairment or urinary incontinence.[12,13]

Diabetes impairs an older person's ability to carry out activities important for independent living and social interaction. Disability, in terms of dependence in activities of daily living (ADL), instrumental ADL and physical immobility influence one's quality of life.[14,15] This becomes an added complication to the health-related changes of aging and coexisting health conditions. Furthermore, this also implies an increase in the number of drugs prescribed in a setting with limited financial and social capabilities.

The Philippine population is aging. In 2020, the 60 and older age group accounted for 8.6% of the population and is projected to almost double to 16.5% in 2050.[16] The Philippine Statistics Authority report from January to December 2021 lists diabetes as the 5th leading cause of death in the country.[17] There is a lack of epidemiological studies on older persons in the country. Estimating the prevalence of diabetes is of vital importance to the government and health

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: April 27, 2022. Accepted: July 21, 2022.
Published online first: August 23, 2022.
https://doi.org/10.15605/jafes.037.02.15

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professionals for planning, allocation of resources and care of older persons with diabetes in the country.

METHODOLOGY

Study source and population

This study utilized data collected from the Focused Interventions for Frail Older Adults Research and Development Program (FITforFrail) project. This was a cross-sectional survey conducted in 2018-2019, which aimed to determine the health and frailty status of community-living older persons in the Philippines.[18] Briefly, four communities from four provinces representing four regions in the country – National Capital Region (NCR), Laguna, Cebu and Davao, were included in the study. Selection criteria were as follows: proportion of older persons, number of geriatricians, support from the local government and health department, ease of transportation and communication and safety of the research team. The sample size was computed based on the number of older persons in each region. Oversampling was done to compensate for nonresponse. Eligible subjects included individuals 60 years and older, who lived in the selected community of each province and can communicate and respond to questions. A list of older persons was acquired from the Office of the Senior Citizen Association of each community and field listing was conducted to obtain a wider coverage in the study. The study was approved by the University of the Philippines Manila Research Ethics Board.

Data collection

The Comprehensive Geriatric Assessment (CGA), which was used in the FITforFrail study, includes an interview phase and a clinical phase consisting of physical, neurological and laboratory examinations. The CGA is a multidisciplinary evaluation program that uncovers, describes and explains multiple problems of older persons while identifying their needs, resources and strengths. The CGA was applied to create a coordinated care plan that focuses interventions on these identified issues.[19] The CGA was translated, pretested and pilot-tested in *Filipino* for use in NCR and Laguna, and in *Bisaya* for Cebu and Davao.

Trained researchers interviewed the participants regarding sociodemographic variables, such as age, sex, marital status, education, physical and psychosocial health, lifestyle behavior, comorbidity, functional status, physical activity and drug use. Body mass index (BMI) was classified as underweight (<18.5 kg/m^2), normal (18.5 to 22.9 kg/m^2), overweight (23 to 24.9 kg/m^2) and obese (≥25 kg/m^2).[20] History of smoking and alcohol intake were obtained. For self-rated health, participants were asked, *"How would you rate your current state of health?: poor, fair, good, very good, excellent."* Sleeping problems were assessed by asking the participant, *"Have you experienced problems with sleeping such as difficulty falling asleep, waking up frequently at night or waking up early?"* Comorbidity was defined as the presence of two or more chronic diseases, classified according to the International Classification of Diseases (ICD) 10. Drug use was defined as the use of either a prescription drug, over-the-counter drug, herbal preparations or food supplements in the preceding two weeks. The participant or reliable informant was asked to bring the medications and doctor's prescription for verification. Drugs were categorized according to the WHO Anatomic Therapeutic and Chemical (ATC) classification.

Criteria for the diagnosis of diabetes

Participants were diagnosed with diabetes either through self-reporting or the use of insulin or oral antihyperglycemic agents. Self-report was elicited by asking the older person whether they have been told to have diabetes by a physician in the past. The type of diabetes was not taken into account. Other health conditions were also identified.

Statistical analysis

Descriptive statistics were used to summarize the sociodemographic and clinical profile of the study participants. Normally distributed variables were expressed as mean ± standard deviation (*SD*) while variables with non-normal distribution were expressed as median and interquartile range (IQR). Categorical variables were expressed as percentages. Point and 95% confidence interval estimates of the prevalence of diabetes among community-living older persons in the Philippines were computed. Pearson's chi-square test or Fisher's exact test was used to test for differences between proportions, while Student's t test or Mann-Whitney U test was used to compare means or medians. The statistical significance was set at p <0.05. Statistical analyses were performed using STATA v15.1.

RESULTS

Out of 424 eligible older persons in the target communities, 405 completed the CGA, which translated to a response rate of 95.5%. The ages ranged from 60 to 99 years, with a median of 68 years. Majority were female (63.9%). There was no significant difference in terms of age (p=0.866), sex (p=0.798) and education (p=0.124) between persons with self-reported diabetes diagnosis and those who were identified to have diabetes based on antihyperglycemic drug use.

Table 1 describes the sociodemographic characteristics of the participants. The prevalence of diabetes was 20.5%, 95% *CI* [16.7, 24.8], and was highest in the 60 to 69 age group (63.9%). No statistical differences were noted between older persons with and without diabetes with regards to age (p=0.404), sex (p=0.703), civil status (p=0.064), and education (p=0.109). According to location, there were significantly more older persons with diabetes from Cebu (p<0.01) and Laguna (p<0.01)

Persons with and without diabetes were comparable with regards to smoking (p=0.211), exercise (p=0.852,), BMI (p=0.167), and sleep problem (p=0.389). Majority of persons with and without diabetes reported poor

Table 1. Sociodemographic characteristics of community-living Filipino older persons by diabetes status

	With diabetes N=83, % (95% CI)	Without diabetes N=322, % (95% CI)	*p* value
Age			0.404
60-69	63.9 (52.6, 74.1)	56.2 (50.6, 61.7)	
70-79	26.5 (17.4, 37.3)	30.1 (25.2, 35,5)	
80+	9.6 (4.2, 18.1)	13.7 (10.1, 17.9)	
Female	66.3 (55.0,76.3)	64.0 (58.5, 69.2)	0.703
Location			0.005
NCR	21.7 (29.2, 51.1)	29.2 (16.8, 26.0)	
Laguna	28.9 (	33.2 (12.6, 21.0)	
Cebu	39.8 (13.4, 32.1)	29.2 (24.5, 34,5)	
Davao	28.9 (19.5, 39.9)	33.2 (28.1, 38.7)	
Civil status			0.064
Single[a]	38.6 (28.1, 49.9)	50.6 (45.0, 56.2)	
Married	61.4 (50.1, 71.9)	49.4 (43.8, 55.0)	
Education			0.109
Elementary[b]	27.7 (18.4, 38.6)	40.1 (34.7, 45.6)	
High school[c]	34.9 (24.8, 46.2)	28.0 (23.1, 33.2)	
College[d]	37.4 (27.0, 48.7)	32.0 (26.9, 37.4)	
Pension			0.900
Yes	41.0 (30.3, 50.2)	39.8 (34.4, 45.4)	
No	71.2 (60.1, 80.5)	60.2 (54.7, 65.6)	
Financial support			0.305
Yes	81.9 (72.0, 89.5)	76.1 (69.1, 78.9)	
No	18.1 (10.5, 28.0)	23.9 (19.4, 29.0)	

a – includes separated and widowed; b – includes no education; c – high school and vocational course; d – college and postgraduate

Table 2. Clinical and behavioral characteristics of community-living Filipino older persons by diabetes status

	With diabetes N=83, % (95% CI)	Without diabetes N=322, % (95% CI)	*p* value
Smoking history			0.211
Non-smoker/previous	65.1 (53.8, 75.2)	56.8 (51.2, 62.3)	
Current	34.9 (24.8, 46.2)	43.2 (37.7, 48.8)	
Alcohol consumption			0.035
Non-drinker/previous	53.0 (41.7; 64.1)	40.1 (34.7, 45.6)	
Current	33.7 (35.9; 58.3)	59.9 (54.4, 65.3)	
Exercise			0.852
Yes	85.5 (76.1, 92.3)	86.3 (82.1, 89.9)	
No	4.5 (7.7, 23.9)	13.7 (10.1, 17.9)	
Comorbidities			0.002
0	4.8 (1.3, 11.9)	13.4 (9.8, 17.6)	
1	8.4 (3.5, 16.6)	19.6 (15.4, 24.3)	
2+	86.7 (77.5, 93.2)	67.1 (61.6, 72.2)	
BMI			0.167
Underweight	7.4 (2.0, 13.5)	15.6 (10.4, 18.4)	
Normal	41.2 (23.7, 45.0)	33.6 (25.2, 35.4)	
Overweight-Obese	51.5 (31.4, 53.5)	50.9 (40.1, 51.3)	
Sleep problem			0.389
Yes	6.6 (45.23, 67.5)	50.6 (45.0, 56.2)	
No	43.4 (32.5, 54.7)	49.4 (43.8, 54.2)	
Self-rated health			0.061
Poor – fair	93.6 (84.5, 98.2)	83.7 (78.1, 88.1)	
Good – excellent	6.4 (1.8, 15.5)	16.3 (11.6, 22.9)	

to fair self-rated health (93.7% and 83.7% respectively) (Table 2). Approximately half the study population were obese (51.5%) while 48.5% were non-obese. For persons with diabetes, the median number of comorbidities was 4, while among those without diabetes, the median number was 2 ($p<0.001$). Those without diabetes were also less likely to drink alcohol ($p<0.05$).

Persons with diabetes were more likely to have visual impairment ($p<0.001$), hypertension ($p<0.01$), and hyperlipidemia ($p<0.001$) than those without diabetes (Table 3). The most common comorbidity was visual impairment (61.5%), which included the following: error of refraction (60.2%), cataract (22.9%), diabetic retinopathy (8.4%), glaucoma (3.6%), and hypertensive retinopathy (1.2%). Sub-analysis of each condition revealed no significant difference between the two groups. Hyperuricemia, cerebrovascular disease and urinary tract infection were also more common among those with diabetes but these findings did not reach statistical significance. The most common coexisting conditions among those with diabetes were hypertension and visual impairment (56.6%), hypertension and hyperlipidemia (45.8%), and hyperlipidemia and visual impairment (42.2%).

Table 3. Most common comorbidities (≥5%) of community-living Filipino older persons by diabetes status

	With diabetes N=83, % (95% CI)	Without diabetes N=322, % (95% CI)	*p* value
Visual impairment	71.1 (60.1, 80.5)	57.4 (51.8, 62.9)	<0.01
Hypertension	73.5 (62.7, 82.6)	52.2 (46.6, 47.7)	<0.001
Hyperlipidemia	53.0 (41.7, 64.1)	16.5 (12.6, 21.0)	<0.001
Hyperuricemia	19.3 (11.4, 29.4)	14.3 (10.6, 18.6)	0.304
Arthritis	16.9 (9.5, 26.7)	17.1 (13.1, 21.64)	0.877
Urinary tract infection	14.5 (7.7, 23.9)	11.2 (8.0, 13.1)	0.446
Cerebrovascular disease	13.3 (6.8, 22.5)	7.5 (4.8, 10.9)	0.122
COPD	6.0 (2.0, 13.5)	8.4 (5.6, 12.0)	0.511
Vertigo	2.4 (0.3, 8.4)	6.5 (4.1, 9.8)	0.189
Anemia	6.0 (2.0, 13.5)	4.4 (2.4, 7.2)	0.560

COPD – asthma and chronic bronchitis; hyperuricemia – includes gout; visual impairment – error of refraction, use of glasses and reading aids, cataract, diabetic and hypertensive retinopathy

DISCUSSION

We aimed to estimate the prevalence and determinants of diabetes among the community-living older persons in the Philippines. This is particularly important because of the continuously increasing prevalence of diabetes and its complications, the increased risk of mortality and disability from diabetes, and the steadily increasing aging population.

Comparison with other studies may be challenging because of methodological differences in diabetes ascertainment and data collection, socioeconomic factors, age distribution and setting.[21,22] In this study, the prevalence of diabetes was 20.5%, which is consistent with the IDF worldwide prevalence of 19.3%.[1] Our result is also well within the range of the report from the 10/66 Dementia Research Group study which showed that the prevalence of diabetes among persons 65 years and older in rural and urban areas ranges from 0.9% in rural China to 32.1% in Puerto Rico.[21] Among neighboring Asian countries, the prevalence of diabetes among those 60 years and older in the Malaysian 2011 National Health and Morbidity Survey was 34.4%, and in the Indonesian Family Life Survey was 6.3%.[23,24] In the UP Wellness Initiative for Seniors and Elders study, which included those 55 years and above, 17.6% of the participants were reported to have diabetes based on diagnoses by geriatricians and fasting blood sugar levels.[25]

In this study, diabetes prevalence increased with age, peaking in the 70 to 79 age group, followed by a decrease in the oldest old (80 years and above). Similar findings were observed in the 10/66 study on the prevalence of diabetes in LMICs and also in the Canadian Study on Health and Aging, showing a similar peak in diabetes among those ages 75 years and above.[21,26]

In a study done on the natural history of prediabetes by Shang et al., most of the older adults with prediabetes reverted to normoglycemia. This was most evident in the oldest age group (81 years and above) and was associated with weight loss and lower systolic blood pressure.[27]

Persons with diabetes had significantly greater comorbidities than those without diabetes, consistent with previous reports.[9,14,28,29] This has been attributed to the effect of longstanding hyperglycemia and insulin resistance on several organ systems, particularly on the microvasculature and immune response.[30,31] Hypertension, hyperlipidemia, hyperuricemia and cerebrovascular disease were more common among those with diabetes consistent with findings from other studies.[28,29,32] These conditions are directly related to the pathophysiology of diabetes. We also found visual impairment to be more common among persons with diabetes. This was consistent with the findings from a nationally representative sample of the 60-year-old and higher age group in the US.[14] It is important to recognize the greater burden these comorbidities place on the person with diabetes as a result of a more complicated treatment regimen, an increased risk of morbidity and mortality, increased health care utilization and cost, and a poor quality of life.[9-11]

Our findings add to existing literature that showed mixed results in terms of sex, education and BMI. Our results found no difference between sexes as reported in other studies.[9,32-34] A review on the association of socioeconomic status and type 2 diabetes risk showed that minimal educational attainment was highly associated with increased risk of diabetes, which was not seen in our study.[35] With regards to BMI, obesity is considered a significant risk factor for type 2 diabetes.[36,37] Consequently, diet and exercise were recommended to aid in controlling diabetes. In this study, we found comparable proportions of obese/overweight and non-obese (normal/underweight) persons with diabetes. A report consistent with our findings was seen in a study in Japan where more than 60% had non-obese diabetes.[38] In the DECODE-DECODA study, ethnicity played a role in diabetes susceptibility. Results showed that the diabetes risk among Asians was higher at a lower BMI.[39]

To our knowledge, this is the first study to estimate the prevalence of diabetes among persons aged 60 years and older in the country. The response rate of 90.5% allows our study findings to be generalized among similar-aged persons living in a community.

Limitations in our study include the cross-sectional study design which may increase survival bias. The use of self-reported doctor's diagnosis to determine diabetes may introduce misclassification bias leading to an incorrect estimate of the prevalence. However, studies have shown that there is substantial agreement when self-report was compared with medical or administrative records.[40,41] Moreover, our findings on the prevalence of diabetes were within the range of estimates from other studies.[21]

The prevalence of diabetes among community-living older persons is 20.4%. There was a higher burden of comorbidities among persons with diabetes and the most common were hypertension, visual impairment and hyperlipidemia. Effective public health measures for diagnosis and prevention are needed to manage diabetes in the older population. Future research may examine the influence of diabetes and its comorbidities and its impact on the use of available resources.

Acknowledgments
The authors express their appreciation to the research team of the FITforFrail study.

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

Author Contribution Statement
MTG and SDV conceived the study, developed the methodology, validated the research outputs, synthesized the study data, conducted the research, provided the study materials, reviewed and edited the manuscript, and supervised the research activity planning. MTG curated and presented the data and prepared the original draft. SDV coordinated the research activity planning and acquired financial support for the study.

Author Disclosure
All authors declared no conflict of interest.

Funding Source
This study was supported by a grant from the Department of Health AHEAD Program, managed by the Philippine Center for Health Research and Development.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Risk Factors for Inpatient Hypoglycemia in a Tertiary Care Hospital in Indonesia

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Abstract

Introduction. Hypoglycemia is an important and harmful complication that often occurs in inpatient and outpatient settings. This study aims to assess the incidence of inpatient hypoglycemia and its related factors. We also assessed mortality and length of hospital stay.

Methodology. We performed a retrospective cohort study among patients with type 2 diabetes mellitus admitted to a tertiary hospital in Indonesia. Using multivariate regression, we analyzed age, sex, body mass index, comorbidities, history of hypoglycemia, hyperglycemia treatment administered, nutritional intake, and medical instruction as the related risk factors for inpatient hypoglycemia.

Results. From 475 subjects, 80 (16.8%) had inpatient hypoglycemia, of which, 7.4% experienced severe hypoglycemia. We found that patients with a history of hypoglycemia (RR: 4.6; 95% CI: 2.8-7.6), insulin and/or sulfonylurea treatment (RR 6.4; 95% CI: 1.6-26.5), and inadequate nutritional intake (RR 2.6; 95% CI: 1.5-4.3) were more likely to have hypoglycemic events compared to those who did not. The length of hospital stay for patients in the hypoglycemic group is significantly longer than those in the non-hypoglycemic group (13 vs 7 days, $p<0.001$), but their mortality rates did not differ (16% vs 10.9%, $p=0.18$).

Conclusion. Inpatient hypoglycemia may be affected by a history of hypoglycemia and inadequate nutritional intake. Patients who had inpatient hypoglycemia tend to have a longer median length of hospital stay.

Key words: hypoglycemia, diabetes mellitus, insulin, mortality, length of stay

INTRODUCTION

Hypoglycemia is an important and harmful complication of diabetes that often occurs in outpatient as well as inpatient settings. According to the American Diabetes Association (ADA), hypoglycemia is defined as a blood glucose level of ≤70 mg/dL.[1]

Hypoglycemia can be divided into two types: primary and secondary. Hypoglycemia is termed primary if it is the indication for hospital admission, whereas secondary hypoglycemia is hypoglycemia that occurred during hospitalization.[2] In 2012, the National Diabetes Inpatient Audit in the UK found that the prevalence of inpatient hypoglycemia was 22%, with 11% being severe.[3] A Spanish study by Gomez et al., found the incidence of secondary hypoglycemia was higher than primary hypoglycemia (2.8% vs 1.7%).[2]

Several risk factors for inpatient hypoglycemia include age, type of diabetes, comorbidities (sepsis, impaired liver and renal function, malignancy,[1,4] heart failure,[5] endocrine disorders[6]), history of hypoglycemia,[1,4] low body mass index (BMI),[5] anti-hyperglycemic agents, lack of blood glucose monitoring, limited healthcare personnel, and the discordance between nutritional intake and anti-hyperglycemic agents administered.[5]

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: February 8, 2022. Accepted: May 11, 2022.
Published online first: August 25, 2022.
https://doi.org/10.15605/jafes.037.02.06

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Inpatient hypoglycemia may cause serious clinical and non-clinical consequences. In terms of clinical trajectory, inpatient hypoglycemia could lead to increased mortality, cardiovascular and cerebrovascular diseases.[1,4,5] A study that involved >100,000 patients with diabetes found that in patients who had hypoglycemic episodes during hospitalization, the length of hospital stay was three days longer and the medical cost was 39% higher than the control group.[7]

It is important to discuss inpatient hypoglycemia because of the serious impact that could occur. A study on the incidence and related risk factors for inpatient hypoglycemia has never been conducted in Indonesia, which has different patient characteristics, hospital policies, and healthcare resources compared to other countries. Therefore, we aimed to determine the incidence of inpatient hypoglycemia and its related risk factors among admitted patients with type 2 diabetes in Fatmawati General Hospital, Jakarta, Indonesia, a tertiary care center with integrated diabetes healthcare services. We also set out to determine whether the mortality rate is higher, and the length of hospital stay longer, in patients who experienced hypoglycemic episodes during hospitalization.

METHODOLOGY

This retrospective cohort study used secondary data from patients with type 2 diabetes mellitus admitted to Fatmawati General Hospital from January 2016 to December 2018. We used the hospital registry and searched entries under the ICD-10 codes E10-E14. We included patients ≥18 years old with type 2 diabetes mellitus hospitalized during the pre-determined periods. Exclusion criteria were patients diagnosed with hypoglycemia or with documented blood glucose levels ≤70 mg/dL upon admission, and patients who had only reactive hyperglycemia and were not proven to have diabetes during hospitalization (medical records were incomplete or could not be found).

The primary outcome of this study was inpatient hypoglycemia. The subjects were followed during hospitalization. Blood glucose levels were regularly checked using a point-of-care glucose meter in accordance with the ADA guidelines.[8] A blood glucose level of ≤70 mg/dL is defined as inpatient hypoglycemia. Hypoglycemia was further classified as either mild-moderate or severe hypoglycemia if the hypoglycemia caused cognitive dysfunction and required external assistance to recover from the hypoglycemia.

The independent variables in this study were age, sex, BMI, comorbidities (chronic kidney disease grade 4-5 according to KDIGO 2012,[9] heart failure, liver failure, malignancy, sepsis or septic shock, and other endocrine disorders), history of hypoglycemia, hyperglycemia therapy administered, and daily nutritional intake (it was considered to be adequate if the subject consumed up to 75% of their daily portion[10]). Older individuals should be regarded as a special population more prone to inpatient hypoglycemia. The ADA and the Endocrine Society Clinical Practice Guidelines defined older patients as those aged >65 years old.[11,12] However in this study, we modified this criterion and classified age as either <60 or ≥60 years old. BMI was classified according to the WHO BMI classification for the Asian population.[13] Hyperglycemia therapy was classified into 2 groups: insulin and/or sulfonylurea vs non-insulin and non-sulfonylurea. We included patients using various insulin regimens (basal only, basal-bolus, basal with correction dose, prandial only, sliding scale, and insulin drip) and patients using either first or second-generation sulfonylureas. We also studied in-hospital mortality and length of hospital stay as secondary outcomes.

The calculated sample size was based on the formula for the comparison of hypoglycemic events between the two groups.[14] Akirov et al., reported that inpatient hypoglycemia occurred in 24.7% of patients using insulin compared to 8.0% of patients using non-insulin treatment.[15] Using this proportion, the minimum sample size required for a 2-tailed analysis was 178 subjects, with a 95% confidence level and 80% statistical power. The samples were selected using proportionate stratified random sampling. The data analysis was performed using SPSS Statistics 20.0 software.[16] Bivariate analysis was done using chi-square test or Fisher's exact test if chi-square was inappropriate. To give a more precise statistical analysis that was suitable for our cohort design, cox regression was used for estimating relative risk (RR) in the multivariate analysis.[17] Multivariate analysis was carried out with a p-value <0.25[18] in the bivariate analysis and other factors that are clinically associated with hypoglycemia to provide complete control of confounding. The related factors were supposed to be statistically significant if the p-value is <0.05. Mortality rates between hypoglycemic and non-hypoglycemic groups were analyzed using chi-square or Fisher's exact test if chi-square was inappropriate. Length of hospital stay was analyzed as numerical data. Normality test was conducted using Kolmogorov-Smirnov and the difference between the two groups was analyzed using independent t-test or Mann-Whitney test if results had a skewed distribution.

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, with Ethical Approval No.0822/UN2.F1/ETIK/2018.

RESULTS

From 9,071 patients with diabetes who were hospitalized from January 2016 to December 2018, a total of 565 subjects met our inclusion criteria. We excluded 90 patients (18 subjects were re-hospitalized during the study period, 19 subjects were admitted due to hypoglycemia, 17 subjects were not diagnosed with type 2 diabetes mellitus, and 36 subjects had incomplete/missing medical records). Our final sample size was 475 subjects.

Table 1. Baseline characteristics of the subjects

Variable	Value N=475
Age, n (%)	
≥60 years old	213 (44.8)
<60 years old	262 (55.2)
Sex, n (%)	
Male	243 (51.2)
Female	232 (48.8)
Body mass index, n (%)	
Underweight (<18.5 kg/m^2)	39 (8.2)
Overweight (23.0 – 27.5 kg/m^2)	84 (17.7)
Obese (>27.5 kg/m^2)	154 (32.4)
Normal weight (18.5 – 22.9 kg/m^2)	198 (41.7)
Comorbidities, n (%)	
Chronic kidney disease	101 (21.3)
Heart failure	52 (10.9)
Liver failure	19 (4.0)
Malignancy	29 (6.1)
Other endocrine disorders	2 (0.4)
Sepsis or septic shock	50 (10.5)
History of hypoglycemia, n (%)	
Yes	36 (7.6)
No	439 (92.4)
Anti-hyperglycemic agents, n (%)	
Insulin and/or sulfonylurea	370 (77.9)
Non-insulin and non-sulfonylurea	105 (22.1)
Nutritional intake, n (%)	
Inadequate	38 (8.0)
Adequate	397 (83.6)
No data	40 (8.4)
Unreadable or unclear medical instruction, n (%)	
Yes	5 (1.1)
No	470 (98.9)
Hypoglycemia, n (%)	
Yes	80 (16.8)
No	395 (83.2)
Mortality, n (%)	
Yes	56 (11.8)
No	419 (88.2)

Table 2. Bivariate analysis of risk factors for inpatient hypoglycemia

Variables	Hypoglycemia		*p*-value
	Yes	No	
Age, n (%)			
≥60 years old	42 (19.7)	171 (80.3)	0.131
<60 years old	38 (14.5)	224 (85.5)	
Sex, n (%)			
Male	37 (15.2)	206 (84.8)	0.336
Female	43 (18.5)	189 (81.5)	
Body mass index, n (%)			
Underweight (<18.5 kg/m^2)	13 (33.3)	26 (66.7)	0.008
Overweight (23.0 – 27.5 kg/m^2)	13 (15.5)	71 (84.5)	
Obese (>27.5 kg/m^2)	17 (11.0)	137 (89.0)	
Normal weight (18.5 – 22.9 kg/m^2)	37 (18.7)	161 (81.3)	
Chronic kidney disease, n (%)			
Yes	23 (22.8)	78 (77.2)	0.073
No	57 (15.2)	317 (84.8)	
Liver failure, n (%)			
Yes	5 (26.3)	14 (73.7)	0.342
No	75 (16.4)	381 (83.6)	
Heart failure, n (%)			
Yes	10 (19.2)	42 (80.8)	0.626
No	70 (16.5)	353 (83.5)	
Sepsis or septic shock, n (%)			
Yes	8 (16.0)	42 (84.0)	0.866
No	72 (16.9)	353 (83.1)	
History of hypoglycemia, n (%)			
Yes	33 (91.7)	3 (8.3)	<0.001
No	47 (10.7)	392 (89.3)	
Anti-hyperglycemic agents, n (%)			
Insulin and/or sulfonylurea	78 (21.1)	292 (78.9)	<0.001
Non-insulin and non-sulfonylurea	2 (1.9)	103 (98.1)	
Nutritional intake (n=435), n (%)			
Inadequate	28 (73.7)	10 (26.3)	<0.001
Adequate	51 (12.8)	346 (87.2)	
Unreadable or unclear medical instruction, n (%)			
Yes	2 (40.0)	3 (60.0)	0.199
No	78 (16.6)	392 (83.4)	
Insulin Therapy, n (%)			
Non-fixed dose	21 (23.6)	68 (76.4)	0.650
Fixed dose	45 (21.2)	167 (78.8)	

In this study, 55.2% of the subjects were <60 years old and 41.7% had normal body mass index. The most common comorbidity was chronic kidney disease (21.3%). A previous history of hypoglycemia was present in 7.6% and 63.4% received insulin therapy. Sixty-nine subjects (14.5%) were on sulfonylurea monotherapy, of which 53.7% were on gliquidone and 2.9% were on glibenclamide. Blood glucose levels were not adequately monitored in 11.8% of subjects, and 1% had unreadable or unclear medical instructions. The mortality rate was 11.8%. The incidence of inpatient hypoglycemia was 16.8%, 7.4% of which were severe cases (Table 1).

Bivariate analysis showed that a previous history of hypoglycemia, hyperglycemia treatment, and nutritional intake were related to inpatient hypoglycemia (Table 2). We decided to include all variables with $p<0.25$ in our multivariate analysis (age, BMI, chronic kidney disease, history of hypoglycemia, hyperglycemia treatment and nutritional intake). We added the type of insulin therapy to the variables because we considered it to have a substantial effect on the incidence of hypoglycemic events.

Our final model (Table 3) showed that patients with a history of hypoglycemia (RR: 4.6; 95% CI: 2.8-7.6), insulin and/or sulfonylurea treatment (RR: 6.4; 95% CI: 1.6-26.5), and inadequate nutritional intake (RR 2.6; 95% CI: 1.5-4.3) have a higher risk for inpatient hypoglycemia.

In our cohort, 13 subjects with hypoglycemia (16%) and 43 subjects without hypoglycemia (10.9%) died (p=0.18).

Table 3. Multivariate analysis for the related risk factors of inpatient hypoglycemia

Variable	RR (95% CI)	*p*
History of hypoglycemia		
No	Reference	-
Yes	4.6 (2.8-7.6)	<0.001
Anti-hyperglycemic agents		
Non-insulin and non-sulfonylurea	Reference	-
Insulin and/or sulfonylurea	6.4 (1.6-26.5)	0.010
Nutritional intake (N=435)		
Adequate	Reference	-
Inadequate	2.6 (1.5-4.3)	<0.001

Variables included in the multivariate analysis were: age, body mass index, history of chronic kidney disease, history of hypoglycemia, anti-hyperglycemic agents, nutritional intake, and insulin therapy.

The median length of hospital stay in subjects with hypoglycemia was 13 days (min-max, 1-58 days), whereas, for subjects without hypoglycemia, the median was seven days (min-max, 1-48 days), $p<0.001$).

DISCUSSION

Our study aimed to evaluate factors affecting the incidence of inpatient hypoglycemia. We found that patients with a history of hypoglycemia, insulin and/or sulfonylurea treatment, and inadequate nutritional intake were more likely to have hypoglycemic events.

The incidence of inpatient hypoglycemia in this study was 17% with 7.4% of them being severe cases. Our findings were similar to the 18% incidence of hypoglycemia reported by the Voluntary Hospitals of America (VHA Inc.) in a cohort study of 15 hospitals in the United States.[19] In the VHA Inc. study, hypoglycemia was defined as a blood glucose level below 60 mg/dL, whereas in our study, we followed the cut-off value of the International Hypoglycemia Study Group (blood glucose level ≤70 mg/dL).[20]

In this study, patients with diabetes who had a history of hypoglycemia were four times more likely to have inpatient hypoglycemia (RR: 4.6; 95% CI: 2.8-7.6). Quilliam et al., stated that previous emergency department hypoglycemia visits (OR = 9.48; 95% CI = 4.95–18.15) and previous outpatient hypoglycemia visits (OR = 7.88; 95% CI = 5.68–10.93) were strongly associated with inpatient hypoglycemia.[21] Patients with diabetes who had recurrent hypoglycemia may have hypoglycemia-associated autonomic failure where the counter-regulatory mechanism mediated by the adrenomedullary catecholamines was blunted and led to recurrent hypoglycemia with more severe manifestations, known as hypoglycemia unawareness.[22]

In this study, inadequate nutritional intake during hospitalization (<75% of daily portion)[10] was also a risk factor for inpatient hypoglycemia. Maynard et al., also showed that compared to the control group, the hypoglycemia group more commonly had nausea, vomiting, or anorexia (18 vs 8, $p=0.05$). They also found that changes in nutritional intake, inappropriate nutritional intake, and inappropriate anti-hyperglycemic therapy were the risk factors for inpatient hypoglycemia (OR 112.09; 95% CI = 1.23-118.05).[5] Reduced caloric intake with an unadjusted anti-hyperglycemic agent dose, particularly in those treated with insulin, or a delay in providing food would increase the incidence of inpatient hypoglycemia.[5]

Insulin and/or sulfonylurea therapy were also risk factors for inpatient hypoglycemia (RR: 6.432; 95% CI: 1.559-26.535). This result was in line with the study of Akirov et al.,[14] that found the proportion of insulin therapy to be higher in the hypoglycemia group (68% vs 37%, $p<0.01$). The use of basal (15% vs 8%) and basal-bolus (19% vs 8%) insulin were found to be higher in the hypoglycemia group. The FADOI-DIAMOND study[23] stated the opposite result: hypoglycemic events were more common in subjects who had sliding scale insulin compared to basal-bolus insulin (19.4% vs 11.4%, $p<0.01$).[24] In their study, Ignaczak et al., stated that 48% of type 1 diabetes and 20% of type 2 diabetes who received continuous intravenous insulin therapy experienced a hypoglycemic event.[24] In our study, we performed a sub-analysis for the method of insulin therapy to determine whether it affects inpatient hypoglycemia. We further grouped the subjects who were on insulin therapy into fixed dose and non-fixed dose, and we found that there was no difference in the incidence of hypoglycemia between the two groups ($p=0.650$).

Sulfonylurea use is widely known to cause hypoglycemic events. The majority of our subjects used gliquidone, a second-generation sulfonylurea with a lower risk for hypoglycemia compared to the first-generation sulfonylureas.[25] However, compared to other oral anti-diabetic drugs, sulfonylureas still contribute to a higher risk for hypoglycemia,[26] especially in patients with older age, lower renal function, lower BMI, and lower triglyceride levels.[27]

In this study, we decided to use 60 years old instead of 65 years old as our cut-off age because a previous study showed that individuals above 60 years of age were significantly more prone to hypoglycemia.[28] Moreover, the National Health Ministry of Indonesia used 60 years old as the age cut-off to classify geriatric patients.[29] Hence, in most national referral hospitals in Indonesia that have a geriatric department, inpatient and outpatient facilities for patients above 60 years old are separated from those below 60 years old. We expected this delineation to lead to better monitoring and care. However, our study showed no association between age and the risk of hypoglycemia. This finding was consistent with a case-control study by Maynard et al., which did not find a significant age difference between the cases and controls (mean 56 ± 15 vs 58 ± 13; $p=0.309$).[5] On the contrary, Akirov et al., stated that patients with inpatient hypoglycemia tend to be older (74 ± 14 (median 76)) compared to patients without hypoglycemia (72 ± 12 (median 74)) with adjusted OR = 1.01 (95%CI =1.01-1.02)[15] It should be noted that older age did affect hypoglycemic events, yet most of these studies were conducted in an outpatient setting,[30,31] where (glucose monitoring depends merely on the patients' self-monitoring, while our study was conducted in the inpatient setting, where glucose monitoring was scheduled and carefully watched by nurses.

In this study, we found that chronic kidney disease did not increase the risk of inpatient hypoglycemia. This result was similar to the study by Maynard et al., which found that heart failure and chronic kidney disease did not increase the incidence of inpatient hypoglycemia (OR = 6.35; 95% CI = 0.65-61.47; OR = 5.16, 95% CI = 0.61-43.3). Based on the literature, impaired renal function increases the risk of hypoglycemia due to the impairment of renal gluconeogenesis, as well as the impairment in the degradation process and clearance of anti-hyperglycemic

drugs, including exogenous insulin therapy.[32] Our finding may be due to the small number of patients with chronic kidney disease included in our study. The association between impaired renal function and inpatient hypoglycemia is beyond the scope of our study.

The secondary outcomes of this study were mortality and length of hospital stay. The mortality rate of the hypoglycemia group was 16%, whereas in subjects without inpatient hypoglycemia, the mortality rate was 10.9%, a difference that was not statistically significant (p=0.18). This result contradicts the result of the FADOI-DIAMOND study that involved 3,167 subjects.[23] The FADOI-DIAMOND study found that inpatient mortality was higher in the hypoglycemia group (8.8% vs 4.8%, p<0.01).[23] In another prospective cohort study, Hsu et al., also found that patients with diabetes who had hypoglycemia episodes, either in an inpatient or outpatient setting, had a threefold higher mortality risk (HR = 3.49; 95% CI = 3.01-4.05).[33] Our study found most of the hypoglycemic events were mild to moderate (92.6%). Only 7.4% of them were severe which may account for the non-significantly increased mortality rate. In a study involving 5,404 elderly patients, they found that the incidence of hypoglycemia was associated with in-hospital mortality. However, further multivariate analysis adjusting for sepsis, malignancy, and hypoalbuminemia showed that hypoglycemia was not associated with mortality. Hypoglycemia was only considered as a marker of serious disease that can lead to mortality.[1,4]

Another secondary outcome of this study was the length of hospital stay. The subjects that had hypoglycemic episodes during hospitalization had a longer median length of stay (13 days vs 7 days, p<0.001). Our result echoes the FADOI-DIAMOND study which stated that patients with hypoglycemia had a longer length of stay (mean 12.7 ± 10.9 vs 9.6 ± 6.5, p<0.01).[23] Curkendall et al., also found that patients who had inpatient hypoglycemia would be hospitalized longer compared to control (11.7 days vs 5.1 days, p<0.001).[7]

This is the first study on inpatient hypoglycemia and its related factors conducted in Indonesia. It has several weaknesses though. First, this is a retrospective cohort study using medical records with its limitation of incomplete documentation of patients' internal risk factors and other institutional risk factors that might cause inpatient hypoglycemia that were not studied in this research, such as duration of the diseases, A1C level, other drugs that could induce hypoglycemia, prolonged fasting before an invasive procedure, therapy administered by nurses that was not in accordance with medical instructions, limited health personnel resources, and the lack of glucose meters to monitor patients' blood glucose levels. Second, in this study, we used the rule-of-thumb formula to calculate sample size. We did not calculate the minimum sample size for each variable to have a minimum statistical power of 80%. A qualitative study is needed to further assess the risk factors for inpatient hypoglycemia, particularly the institutional risk factors. Last, with our small sample size, our results may not be generalizable to the large population of diabetic patients in Indonesia.

From this study, we have shown that the related risk factors for inpatient hypoglycemia, both patients' internal risk factors (history of hypoglycemia) and institutional risk factors (nutritional intake, hyperglycemia therapy with insulin or insulin combined with sulfonylurea) should guide clinicians to be more cautious in treating patients with diabetes to prevent inpatient hypoglycemia which may increase the length of hospital stay and increase medical cost.

CONCLUSION

Patients with a history of hypoglycemia, insulin and/or sulfonylurea treatment, and inadequate nutritional intake were at higher risk for inpatient hypoglycemia. This can lead to a prolonged hospital stay, resulting in higher healthcare costs. Hence, clinicians need to take these risk factors into account to minimize inpatient hypoglycemia.

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

Author Contribution Statement
CP, MR, IAMK, PS conceived the study; conducted research; reviewed and edited the manuscript. CP, MR, IAMK, PS developed the study design. CP and MR developed the software, curated and synthesized the data. CP verified the research outputs and presented the data. CP and IAMK provided the study materials and prepared the original draft. MR, IAMK, and PS supervised the research activity planning. CP, IAMK, and PS coordinated the research activity planning. CP and PS acquired financial support for the study.

Author Disclosure
All authors declared no conflict of interest.

Funding Source
This work was supported by Universitas Indonesia International Indexed Publication Grants for Student's Final Projects (PITTA) number NKB-0547/UN2.R3.1/HKO.05.00/2019.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

A Comparison of Statin Treatment Algorithms Based on the ACC/AHA and Philippine Guidelines for Primary Prevention of Dyslipidemia in Statin-Naive Filipino Patients

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Abstract

Objectives. This cross-sectional study evaluates the degree of agreement between the 2018 American College of Cardiology/American Heart Association (ACC/AHA2018) and 2020 Philippine Guideline (PG2020) treatment algorithms for the primary prevention of dyslipidemia among Filipinos.

Methodology. This review included 159 charts of statin-naive Filipinos who are 45-79 years old. Using risk profile and lipid measurements, statin treatment recommendation was determined through the PG2020 algorithm and ACC/AHA-ASCVD Risk Estimator Plus web application. The degree of agreement was measured by Cohen's kappa statistic with the two algorithms as independent raters.

Results. A total of 159 patients were included in the final analysis. There was a slight agreement with a kappa coefficient of 0.209 or 4.4% (95% CI 0.078-0.340, p=0.003). Statin treatment was recommended in 69 out of 159 patients (43.4%) by the PG2020 overlapping with ACC/AHA2018 in 56 cases (81.2%). On the other hand, 109 cases (68.6%) were recommended for statin treatment by ACC/AHA2018 overlapping with PG2020 in only 51.4%.

Conclusions. The low degree of agreement between the two treatment algorithms highlights the key demographic and ethnic variations in dyslipidemia management necessitating outcome-based studies to translate these differences. Overestimation of ASCVD risk calculation in the ACC/AHA2018 and consideration of important, unique risk factors among Filipinos favors the applicability of the Philippine guideline.

Key words: dyslipidemia, hypercholesterolemia, algorithms, statins, primary prevention

INTRODUCTION

The Asia-Pacific region is afflicted with approximately half of the burden of cardiovascular disease worldwide.[1] Among its Asian neighbors, the Philippines is leading with 46.9% in terms of total cholesterolemia greater than 200 mg/dL. With regards to low high-density lipoprotein cholesterol (HDL-C), the Philippines is also among those with the highest prevalence, with 71.8% having HDL-C of less than 40 mg/dL. The Philippines similarly has the highest prevalence of high low-density lipoprotein cholesterol (LDL-C) at 47.2%. Hypertriglyceridemia is likewise notable with 38.6% among those surveyed having levels above 150 mg/dL.[2]

Since the majority of events leading to the development of atherosclerotic cardiovascular disease (ASCVD) are clinically silent, much of the early phase of the disease process remains undetected until the development of end-point events. This highlights the pivotal role of risk assessment in the management of dyslipidemia.[3,4]

Despite the availability of local guidelines and equivocal evidence for the use of other risk estimators based on international guidelines, practitioners in the Philippines still predominantly use the ASCVD risk calculator.[3] No head-to-head comparisons have been made between the Philippine Guidelines for the Management of Dyslipidemia in the Philippines (PG2020) and the American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on the Management of Blood Cholesterol (ACC/AHA2018) notwithstanding the prevalence of use. Therefore, the applicability of these guidelines in the selection of appropriate treatment groups in the local setting remains unclear.

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: April 1, 2022. Accepted: August 2, 2022.
Published online first: September 15, 2022.
https://doi.org/10.15605/jafes.037.02.16

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This study was aimed at determining the degree of agreement between PG2020[4] and the ACC/AHA2018[5] based on the eligibility for statin therapy of Filipino patients.

METHODOLOGY

Design and Population

In this cross-sectional chart review study, we screened and reviewed a total of 297 charts of individual patients from the outpatient department of Cebu Velez General Hospital and Velez Medical Arts clinic from January 25 to March 18, 2022. The protocol was subjected to technical review and approved by the Research Committee of the Department of Internal Medicine of Cebu Velez General Hospital. The protocol was also approved by the Institutional Review Board of the same institution.

Personal information was not collected and each chart was identified by a coded chart number. Included patients were Filipinos between 45 to 79 years of age. All participants were either statin naive or have been off statins for at least 6 months before blood collection. The parameters taken for the chart review are all disclosed in the chart including the following details: gender, menstrual status, history of diabetes mellitus and medications, history of hypertension and medications, weight, height and BMI, family history of coronary heart disease, urinalysis and either a 2D-echocardiogram and/or a 12-lead electrocardiogram. All individuals that have the following characteristics were excluded from the study: patients younger than 45 or older than 79 years old, non-Filipino patients, patients with documented chronic kidney disease (CKD), and those who have had documented primary ASCVD. Charts with missing data essential for proper risk stratification as mentioned above were excluded from the final analysis.

Comparison

Eligibility for starting statin therapy was determined through algorithms derived from the PG2020 and ACC/AHA2018 algorithms, respectively. Details for risk profiling and lipid panel were taken solely from each chart review form.

The algorithm in Figure 1 is based on the recommendations and algorithm of the 2020 Philippine Guidelines for the Management of Dyslipidemia in the Philippines. Note however that in the absence of complete clinical data to rule familial hypercholesterolemia by the Dutch lipid network criteria, the algorithm cannot be followed to the letter. Meanwhile, ACC/AHA algorithm was applied using

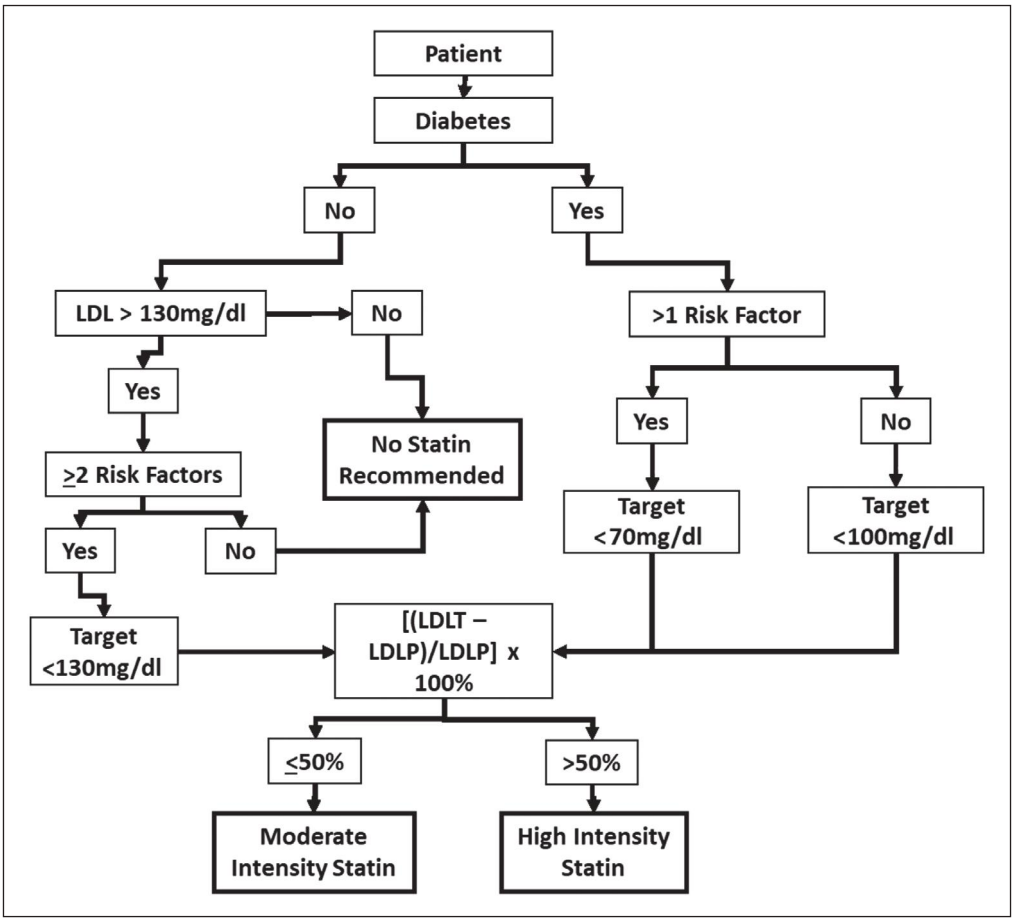

Figure 1. Algorithm based on the 2020 Clinical Practice Guidelines for the management of dyslipidemia in the Philippines.[4] LDLT is the LDL target as recommended by the guideline; LDLP is the patient's LDL level on assessment of lipid profile.

the ASCVD risk calculator plus webapp (accessed thru ASCVD Risk Estimator + (acc.org)) following the 2018 ACC/AHA/AACVPR/AAPA/ABC/ACP Guideline for the management of blood cholesterol.[5] The PG2020 algorithm and ACC/AHA2018 were applied to each case using logic function in Microsoft Excel and the webapp respectively. The application of both algorithms was automated and standardized to avoid operator bias.

Statistical Analysis

The two guideline algorithms were applied to facilitate decision-making on whether to start statin therapy for each of the included patients. The degree of agreement between the two guidelines was analyzed using Cohen's kappa statistic. A minimum of 133 charts was needed to achieve a power of 80% at 0.05 margin of error for a 2x2 cross-tabulation. The study by Bujang et al.,[6] was used as the basis for sample size calculation as well epidemiologic data from the 8th FNRI National Nutrition Survey.[7] Descriptive statistics were measured to summarize demographic characteristics. T-test for independent samples and Chi-Square analyses were used to compare diabetic and non-diabetic subsets for parametric and categorical data, respectively. All statistical analyses were performed using IBM SPSS version 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armok, NY: IBM Corp).

RESULTS

A total of 297 charts were screened. To reconcile the age restrictions of both guidelines (>45 years old for PG2020 and <80 for ACC/AHA2018), patients outside these age groups were excluded. Patients on statin therapy, those with lacking risk data and those with chronic kidney disease were all excluded. One hundred fifty-nine (159) patients were included in the final analysis.

The mean age was 58.4 years old (SD=8.7 years) with a slight female predominance at 51.6%. The risk characteristics are detailed below in Table 1. Majority of the patients were hypertensive (62.3%) but most of them were already on treatment (67.7%). Diabetes was seen in only 19.5% of included patients. Of the 82 female patients included, most (63.4%) were post-menopausal. Only 17.6% of patients were smokers. Only 1 of the 159 patients screened disclosed a family history of premature ASCVD. Laboratory risk parameters such as left ventricular hypertrophy on electrocardiography and/or echocardiography and proteinuria on urinalysis were seen in a minority of patients, in 6.9% and 8.2% respectively. The average systolic BP on the first consult was 141.9 mmHg (SD=20.8) and the mean BMI was 27.4 kg/m^2 (SD=4.2) among included patients.

Also summarized in Table 1 is a comparison of demographic and risk profiles between patients with and without diabetes. There was no significant difference between the two subsets across parameters except for 10-year ASCVD risk score and systolic blood pressure. Patients without diabetes had significantly higher systolic blood pressure than those with diabetes (142.5 SD=19.4 mmHg vs 139.4 SD=26.1 mmHg; p=0.038). On the other hand, patients with diabetes had significantly higher computed 10-year ASCVD risk (21.1% vs 10.9%; p=0.002).

The lipid parameters of patients included are further summarized in Table 2. The average total cholesterol of study participants was 203.1 (SD=42.4) mg/dL. The mean LDL-C and HDL-C were 122.6 (SD=36.6) mg/dL and 51.4 (SD=20.2) mg/dL, respectively. The lipid profiles of

Table 1. Patient demographics and risk characteristics (n=193)

Variable	Overall (n=159)	With diabetes (n=31)	Without diabetes (n=128)	*p*
Age (years) Mean (SD)	58.4 (8.7)	59.8 (8.4)	58.1 (8.8)	0.595
Sex, Male, N (%)	77 (48.4)	16 (51.6)	61 (47.7)	0.692
Hypertension, N (%)	99 (62.3)	18 (58.1)	81 (63.3)	0.591
Treated	67 (67.7)	13 (72.2)	54 (66.7)	
Untreated	32 (32.3)	5 (27.8)	27 (33.3)	
Diabetes, N (%)	31 (19.5)	-	-	-
Smoking, N (%)	28 (17.6)	5 (16.1)	23 (18.0)	0.809
Post-menopausal, N (%)	52 (63.4% of 100 Female)	9 (29.0)	44 (34.4)	0.571
Proteinuria on UA, N (%)	13 (8.2)	3 (9.7)	10 (7.8)	0.734
LVH, N (%)	11 (6.9)	2 (6.5)	9 (7.0)	0.909
Family history of premature ASCVD, N (%)	1 (0.6)	0 (0.0)	1 (0.8)	0.622
SBP, mmHg, Mean (SD)	141.9 (20.8)	139.4 (26.1)	142.5 (19.4)	0.038
BMI, kg/m^2 Mean (SD)	27.4 (4.2)	27.6 (3.4)	27.4 (4.4)	0.054
10-Year ASCVD Risk, %, Mean (SD)	12.9 (12.2)	21.1 (17.3)	10.9 (9.6)	0.002

UA urinalysis, LVH left ventricular hypertrophy, ASCVD atherosclerotic cardiovascular disease, SBP systolic blood pressure, BMI body mass index

Table 2. Patient lipid profile (n=159)

Parameter	Overall (n=193)	With diabetes (n=35)	Without diabetes (n=163)	*p*
Total cholesterol (mg/dL) Mean (SD)	203.1 (42.4)	207.6 (43.4)	202.0 (40.2)	0.033
LDL cholesterol (mg/dL) Mean (SD)	121.4 (36.9)	125.0 (51.2)	120.5 (35.2)	0.027
HDL cholesterol (mg/dL) Mean (SD)	51.0 (17.1)	50.8 (13.0)	51.0 (18.0)	0.508
Triglycerides (mg/dL) Mean (SD)	150.3 (77.8)	154.4 (69.2)	149.3 (79.9)	0.989

LDL low density lipoprotein, HDL high density lipoprotein

Table 3A. Cross tabulation of best recommended statin from Philippine Guideline Algorithm vs ACC/AHA Guideline Algorithm

		Philippine Guidelines 2020			
		No Statin Recommended	Moderate Intensity Statin	High Intensity Statin	Total
ACC/AHA 2018	No statin recommended	37	13	0	50
	Moderate intensity statin	50	28	1	79
	High intensity statin	3	21	6	30
	Total	90	62	7	159

Table 3B. Correlation of treatment recommendation and best recommended statin from Philippine Guideline Algorithm vs ACC/AHA Guideline Algorithm

	Kappa	CI	V^2	*p*
Treatment recommendation	0.209	0.078 – 0.340	4.4%	0.003
Specific statin recommendation – PG2020 vs ACC/AHA2018	0.107	-0.0.011 – 0.225	1.1%	0.057

Table 3C. Cross tabulation of treatment recommendation between the Philippine Guideline Algorithm vs ACC/AHA Guideline Algorithm

		Philippine Guidelines 2020		
		Statin not recommended	Statin recommended	Total
ACC/AHA2018	Statin not recommended	37	13	50
	Statin recommended	53	56	109
	Total	90	69	159

patients with and without diabetes were also compared in Table 2. Patients with diabetes mellitus had significantly higher total cholesterol (207.6 vs 202.0 mg/dL, *p*=0.033) and LDL-cholesterol (125.0 vs 120.5 mg/dL, *p*=0.027).

The Kappa agreement coefficient is tabulated in Table 3A. Cohen's κ statistic was run to determine if there was agreement between the two guidelines as to whether or not to start statin therapy. There was slight agreement between the two algorithms, κ = 0.209 or 4.4% (95% CI, 0.078 to 0.340), *p*=0.003. Agreement on the specific type of statin recommended was likewise attempted but the correlation did not reach statistical significance.

The per-patient recommendations of each algorithm are crosstabulated in Table 3B and 3C. Statin treatment was recommended in 69 cases (43.4%) by the PG2020 algorithm. This overlapped with the ACC/AHA2018 by 81.2% with 13 discrepant cases. On the other hand, the ACC/AHA2018 recommended treatment in 109 cases, overlapping with the PG2020 by only 51.4%, with 53 discrepant cases (Table 4). The clinical and laboratory profile of these discrepant cases are tabulated in Table 5. In the subset of 13 patients recommended for treatment by PG2020 but not by ACC/AHA2018, the median age was 55 years, all were females and mostly post-menopausal, 5 (38.5%) were hypertensive, and none were smokers. The median SBP in this subgroup was lower (140 vs 150 mmHg), higher median lipid panel values (TG 236.9 mg/dL, LDL-C 145.1 mg/dL). The computed median 10-year ASCVD risk was significantly lower in this subset with 2.8%.

For the 53 patients recommended for statin therapy by the ACC/AHA2018 but not by the PG2020, the median age was higher at 62 years, and the majority were male (62.3%) and hypertensive (75.5%). Smoking was noted in 30.2%. The lipid panel values were comparatively lower in this subset with median total cholesterol of 179.1 mg/dL and LDL-C of 95.3 mg/dL.

Three patients noted to have an extreme discrepancy in terms of statin recommendation, i.e., high intensity statin is recommended by ACC/AHA 2018 but no statin was recommended by PG2020, are detailed in Table 5. Of note, none of these patients had an LDL-C of 130 mg/dL or more, none had diabetes, all had hypertension and were smokers.

DISCUSSION

The benefit of lowering LDL-C for the primary prevention of ASCVD is largely established. However, there is still much debate as to what levels in a patient's profile constitute dyslipidemia and the threshold levels for treatment. Population-based analysis has largely been inconsistent and determinations of treatment thresholds and targets are mostly individualized.[8–10]

Risk assessment is the cornerstone for the primary prevention of cardiovascular diseases.[11] Several recently published guidelines for the management of dyslipidemia are available. Large studies in the United States and Europe have yielded the creation of risk estimators, such as the ASCVD risk calculator based on pooled cohort equations or PCE used in the ACC/AHA guideline. Similarly, other guidelines make use of other risk calculators such as the Framingham risk calculator (FRC) and the systemic coronary risk evaluation (SCORE) in the Canadian Cardiovascular Society (CCS) and the European Society of Cardiology/

Table 4. Cross tabulation and clinical characteristics of discrepancies in statin treatment recommendations by the Philippine Guidelines vs ACC/AHA Guidelines

	Discrepancies, No. (%), PG2020 and ACC/AHA2018	
	PG2020 Recommended but not by ACC/AHA2018	ACC/AHA2018 recommended but not by PG2020
Overall, No. (%)	13 (18.8)	53 (48.6)
Clinical Characteristics		
Age (years) Median (Min-Max)	55.0 (51-62)	62.0 (45-77)
Sex, Male, N (%)	0 (0.0)	33 (62.3)
Hypertension, N (%)	5 (38.5)	40 (75.5)
Diabetes, N (%)	0 (0.0)	0 (0.0)
Smoking, N (%)	0 (0.0)	16 (30.2)
Post-menopausal, N (%)	12 (92.3)	15 (28.3)
Proteinuria on UA, N (%)	0 (0.0)	6 (11.3)
LVH, N (%)	0 (0.0)	5 (9.4)
Family history of premature ASCVD, N (%)	0 (0.0)	1 (1.9)
SBP (mmHg) Median (Min-Max)	140 (110-160)	150 (100-200)
BMI (kg/m^2) Median (Min-Max)	28.9 (26.7-36.4)	24.9 (16.8-37.6)
Total cholesterol (mg/dL) Median (Min-Max)	236.9 (204.7-282.0)	179.1 (109.5-303.9)
LDL cholesterol (mg/dL) Median (Min-Max)	145.1 (130.7-189.4)	95.3 (76.5-181.0)
HDL cholesterol (mg/dL) Median (Min-Max)	54.4 (45.0-60.0)	46.3 (19.5-73.3)
Triglycerides (mg/dL) Median (Min-Max)	131.2 (37.9-223.5)	135.7 (96.8-482.9)
10-year ASCVD risk	2.8 (1.4-4.8)	12.4 (10.7-43.3)

Table 5. Demographic and risk profile of three patients with extreme discrepancy in statin recommendation (n=3)

Variable	Case 11	Case 138	Case 175
Age, years	57	69	55
Sex	Female	Female	Male
Hypertension	Yes	Yes	Yes
Treated	Yes	Yes	Yes
Diabetes	No	No	No
Smoking	Yes	Yes	Yes
Post-menopausal	Yes	Yes	-
Proteinuria on UA	Yes	Yes	No
LVH	Yes	No	No
Family history of premature ASCVD	No	No	No
SBP (mmHg)	180	150	140
BMI (kg/m^2)	27.1	26.7	24.4
Total cholesterol (mg/dL)	189.2	200.5	242.0
LDL cholesterol (mg/dL)	106.6	117.8	129.1
HDL cholesterol (mg/dL)	21.6	39.3	41.3
Triglycerides (mg/dL)	180.0	217.0	135.7
10-year ASCVD risk (%)	20.7	26.2	20.3

UA urinalysis, LVH left ventricular hypertrophy, ASCVD atherosclerotic cardiovascular disease, SBP systolic blood pressure, BMI body mass index, LDL low density lipoprotein, HDL high density lipoprotein

Table 6. Comparison of ACC/AHA Guideline and Philippine Guideline Algorithms for the primary prevention of dyslipidemia

Parameters	ACC/AHA Guidelines	Philippine Guidelines
Modality of risk estimation	ACC/AHA pooled cohort risk equations	Risk factor counting
Risk parameters	Age, sex, race, SBP, Total cholesterol, HDL cholesterol, LDL cholesterol, diabetes mellitus, smoking, hypertension treatment	Sex, post-menopausal status, smoking, hypertension, BMI, family history, proteinuria, left ventricular hypertrophy
Threshold for treatment	Diabetes without diabetes: • LDL-C ≥70 - <190 mg/dL and • ASCVD risk 5 - <7.5% + risk enhancers or • ASCVD risk > 7.5 - ≤20% or • ASCVD risk >20%	Diabetes without diabetes: • LDL-C ≥130 mg/dL AND • 2 risk factors

European Atherosclerosis Society (ESC/EAS), respectively. These risk estimators facilitated the use of step-by-step algorithms in guiding therapeutic decision-making with, of course, the risk estimators as the pivot point.[12]

The paucity of local data among Asians has limited the availability of risk estimators based on this ethnic population. An extensive literature review of these risk calculators showed that only 2 out of 25 tools were developed for an Asian population.[13] It is for this reason that different countries in Asia utilize different risk estimators. Indonesia, Malaysia, and United Arab Emirates use the ESC/EAS SCORE. Thailand is by far, the only country that uses its very own Thai CV risk score which can estimate risk in the absence of cholesterol measurements. Taiwan and the Philippines employ the use of risk factor counting— duly considering the quantity of risk factors without regard for the relative contribution and interactions between these risk factors. Unlike Thailand, there are no risk estimators available or developed for the Filipino population to date.[3] Additionally, the ASCVD risk score is still used by the majority of Filipino care providers despite the availability of a local guideline since 2015 and an update in 2020.

Several studies have already raised issues as to the applicability of the 10-year ASCVD risk score, particularly the use of these PCEs in populations where they are not based on.[10,14-17] Similar studies have assessed their applicability to other ethnicities. For instance, a study among Malaysians showed that the FRS and SCORE are more suitable alternative risk estimators than the World Health Organization/International Society of Hypertension calculator.[18] Another study among a multi-ethnic Asian cohort showed an overestimation of risk using the FRS.[19]

The ACC/AHA guidelines and the Philippine guidelines are compared in detail in Table 6. The ASCVD risk score

PCE is based on a US-derived pool to estimate a 10-year risk of adverse cardiovascular outcomes. As such, this tool is by design and evidence, specific to race, i.e., for whites and blacks.[20]

In a study involving the use of the ASCVD risk calculator among Asians and Hispanic Americans, 17.6% of whom are Filipinos, the comparison of the predicted incidence of ASCVD by way of PCE and observed major adverse cardiovascular events during a follow-up period showed that the PCE overestimated the risk for Asians. Despite having a disproportionately higher observed event rate than whites and blacks, the Filipino-American predicted event rate was still higher than observed by 0.5%.[10] Additionally, a study on Filipino-American women showed that the ASCVD risk score in its current state tends to overestimate the risk and results in overtreatment of patients unnecessarily. Moreover, it was shown that the addition of measures of central obesity improved clinical discrimination in this cohort of patients.[15]

Several factors play an important role in the estimation of ASCVD risk,[20] especially in a diverse racial population. A systematic review of studies among different minority ethnic groups in Canada including Arabs, Chinese, Hispanic, and Filipinos have shown significant variability of CVD risk factors. Filipinos were found to have higher LDL-C and triglycerides than white cohorts. Moreover, hypertension and diabetes were more prevalent in the Filipino cohort.

When combined, these non-minority factors tend to mask unique CVD risk factors of minority groups such as relatively higher triglycerides and central obesity. Additionally, this would minimize the contribution of these risk factors prevalent in minority groups but are uncommon in the majority group. This can skew the outcomes of risk estimators in favor of the majority.[16,21]

Overall, this study has shown only a slight correlation between the two algorithms compared considering that both algorithms overlapped in only 56 cases to concordantly recommend statin treatment and in only 37 cases to concordantly recommend against statin therapy in our sample of 159 patients. This finding is corroborated by another comparison of dyslipidemia algorithms where in the ESC and ACC/AHA did not align in terms of primary prevention on an individual patient basis.[23] A closer examination of the clinical and laboratory characteristics of the discrepant cases may shed light on this discordance.

The results of this study have shown that among 109 patients recommended for statin therapy by the ACC/AHA2018, 53 (48.6%) were recommended not to start statin by the PG2020. In the analysis of this subset proposed to be started on statin therapy by the ACC/AHA2018 guideline, of note was a significantly lower median total cholesterol (179.1 mg/dL) and LDL-C (95.3 mg/dL) when compared to the PG2020 discrepant subset with 236.9 mg/dL and 145.1 mg/dL, respectively. None of these cases had diabetes.

If we compare the individual algorithms, it is important to consider that for the primary prevention in the non-diabetic subset, the Philippine guidelines will consider treatment if the LDL-C is at least 130 mg/dL with the presence of at least 2 risk factors. In contrast, the ACC/AHA algorithm recommends initiating statins in patients between 40-75 years old and with LDL-C between 70 to 190 mg/dL depending on the percentage of ASCVD risk.[5] The discrepancy is most likely explained by this difference in treatment threshold. It must be acknowledged that, overall, the mean total cholesterol and LDL-C for this study appear to be lower than those seen in national surveys[2,7] which may limit generalizations. Nonetheless, analysis of the discrepant subset of ACC/AHA2018 showed a median 10-year ASCVD risk of 12.4% with a maximum of 43.3%, compared to the PG2020 discrepant subset with a risk score of only 2.8%, hence considered low risk. This is consistent with similar literature previously cited showing overestimation of risk using PCE.[10,14] Although overtreatment would prompt additional cost and unnecessary exposure to potential side effects such as statin-associated muscle symptoms and elevated transaminases,[23] it is also important to recognize the consequences of undertreatment.

A limitation is that this study does not reflect outcomes, and thus may be interpreted in favor of the ACC/AHA guideline. The implications of undertreatment may be more consequential, such as a missed opportunity to start statins amidst the potential risk of future adverse cardiovascular outcomes. This effect may be reflected in the three cases presented in Table 5, showing an extreme discrepancy where high-intensity statin was recommended by the ACC/AHA2018 and otherwise not recommended by the PG2020.

On the other hand, of the 69 patients considered for statin therapy by the PG2020, a discrepant subset of 13 patients (18.8%) is noted. The Philippine guidelines and that of the ACC/AHA differ in terms of parameters included in risk estimation. Unique to the Philippine guidelines are consideration of BMI, postmenopausal status, proteinuria, and left ventricular hypertrophy as additional risk factors. The 2018 update of the ACC/AHA guideline did add the ASCVD risk enhancers such as ethnicity, gender-specific risk factors, and inflammatory conditions. The inclusion of BMI in the assessment of risk is important, considering population-based studies on Filipino-American women have identified that an increased BMI even as low as >23-24.9 kg/m^2 is associated with adverse cardiovascular outcomes.[16,19] In our study, the PG2020 discrepant subset showed a higher proportion of post-menopausal women at 92.3% and a significantly higher median BMI of 28.9 kg/m^2. This strongly supports the iteration that unique peculiarities of population groups contribute significantly to the applicability of the guideline to its target population.

Analysis of both discrepant subsets revealed that the difference in treatment threshold reflected in the two guidelines augments the discordance. Note again that among non-diabetics, the threshold for statin treatment

recommended by the Philippine guideline is 130 mg/dL versus that of 70 mg/dL by the ACC/AHA. The combination of a relatively higher treatment threshold (Philippine guideline) and overestimation of risk (ACC/AHA) skewed the treatment recommendations in opposite directions, portending a lack of overall concordance between the two treatment algorithms.

Both guidelines are concordant on the role of diabetes mellitus, hypertension and smoking in the development of atherogenesis and adverse cardiovascular outcomes as elucidated in the Framingham heart study.[24,25] This is corroborated by the findings of the Five Risks Algorithm study showing diabetes, hypertension, and smoking as independent risk factors in addition to male gender and hypertriglyceridemia.[26]

The results of this study should be interpreted in light of the several limitations which conjointly diminish its generalizability. First, the cross-sectional design limits the detection of differences between the two treatment algorithms in terms of measurable outcomes, particularly, actual cardiovascular events. This limitation highlights the need for longitudinal studies to determine how these differences affect the occurrence of adverse cardiovascular outcomes. Second, the best recommended statin was determined by an algorithm devised from the guideline as released and as interpreted by the authors. Third, it should be reiterated that the mean lipid panel results in this study were lower compared to those found in national surveys. The use of larger research data and standardization of laboratory measurements may improve correlation. Lastly, this study was based on patient and laboratory data taken for clinical purposes and not originally intended for research and as such present inherent limitations. Data concerning the screening for familial hypercholesterolemia (FH) using criteria such as the Dutch lipid network criteria could not be obtained in full and as such could not be included. This study was done in a resource-limited setting, thus may introduce selection bias of included patients. The study, in terms of an analysis of specific statin recommendations, is likewise limited by the sample size.

CONCLUSION

We found that despite the prevalent use of the ACC/AHA guideline in the Filipino population, its agreement with the local guideline was poor overall, highlighting the impact of demographic and ethnic differences in dyslipidemia management. Overestimation of the PCE in this population and the consideration of unique risk factors by the Philippine guidelines favor the applicability of the local guideline. Because of the lack of longitudinal outcome-based studies, whether or not the application of the guideline results to overtreatment or undertreatment, has yet to be elucidated.

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

Author Contribution Statement
BPM, AJ and JR conceived the study, designed the methodology;, conducted the research, verified research outputs, and reviewed and edited the manuscript. BPM synthesized, curated and presented the study data and prepared the original draft. AJ and JR provided the study materials and supervised the research activity planning. AJ coordinated the research activity planning.

Author Disclosure
All the authors declared no conflict of interest.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Detection of Hemostasis Abnormalities in Type 2 Diabetes Mellitus Using Thromboelastography

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Abstract

Introduction. Type 2 DM (T2DM) is associated with inflammation and vascular dysfunction which impact hemostasis. Thromboelastography (TEG) as a hemostasis assessment method, is not routinely applied in T2DM. We aimed to detect hemostasis abnormalities by using the TEG method in association with glycemic levels and type of therapy among T2DM patients.

Methodology. A cross-sectional study was conducted among T2DM patients attending the Endocrinology Clinic of Saiful Anwar Hospital, Indonesia. Glycemic profiles were determined using fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPPG), and glycosylated hemoglobin (HbA1c). Therapy for T2DM was classified into insulin and non-insulin regimens. The primary and secondary hemostasis profile were examined using TEG and was classified as hypo- hyper- and normo-coagulable states.

Result. A total of 57 T2DM patients were included. Kruskal-Wallis test did not reveal a significant association between glycemic profiles and groups of hemostasis. However, the median HbA1c was higher in the hypercoagulable group of primary hemostasis and fibrinolysis. The median FPG and 2hPPG were higher in the normo-coagulable group of secondary hemostasis. Logistic regression did not indicate a significant association between type of therapy for diabetes and hemostasis profile.

Conclusion. This study did not find significant associations between glycemic levels and type of DM therapy with hemostasis profiles using the TEG method in patients with T2DM.

Key words: diabetes mellitus, thromboelastography, hemostasis

INTRODUCTION

Type 2 DM (T2DM) is characterized by inflammation, vascular dysfunction, and thrombosis, all of which could impact hemostasis. The mechanisms leading to hemostasis dysfunction in T2DM include endothelial dysfunction, activation of coagulation factors and platelet hyperreactivity. These are hypothesized to be related to hyperglycemia and insulin resistance.[1,2] The latter also increases fibrinolytic inhibitor, plasminogen activator inhibitor-1 (PAI-1) activity and levels of fibrinogen and coagulation factors.[1]

The prothrombotic condition in T2DM can be classified as abnormalities in platelet and fibrinolystic activity, and coagulation factor levels. In vitro thrombin formation from platelet-rich plasma was found to be higher in patients with T2DM than in normal individuals. Furthermore, T2DM with poor metabolic control have significantly higher thrombin levels than those who have good metabolic control.[3] While complications of DM are determined by disease duration and the average level of chronic hyperglycemia,[4] studies show that glycemic control was the only significant predictor for decreasing blood thrombogenicity in T2DM, irrespective of the type of therapy.[5,6]

Thromboelastography (TEG) is one of the hemostasis assessment methods which was first developed in 1948.[7] TEG is used for optimizing coagulation management because it can holistically identify the hemostasis process and results are faster than the standard coagulation tests namely, prothrombin time and activated partial thromboplastin time.[8] TEG principally measures the viscoelasticity of blood during the hemostasis process.[9] It provides an examination of the entire process of hemostasis from the initial fibrin formation, platelet aggregation, amplification and propagation of the coagulation process

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: October 22, 2021. Accepted: March 29, 2022.
Published online first: August 13, 2022.
https://doi.org/10.15605/jafes.037.02.12

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to fibrinolysis.[10] TEG presents a comprehensive insight into the entire cell-based coagulation process. On the other hand, standard coagulation tests only measure initial fibrin strand formation and does not always reflect minor hypercoagulable states.[11]

With faster and more comprehensive results, TEG may be considered as a point-of-care test.[12] Clinical studies using TEG were mostly performed in the setting of acute conditions such as organ transplantations, perioperative setting of coronary artery bypass grafting, liver surgery and management of trauma, obstetric procedures and massive transfusion.[10,13,14] It has also been studied as an early predictor of disseminated intravascular coagulopathy in patients with septic shock.[15] However, TEG has not been routinely applied to patients with T2DM. Several studies of TEG in T2DM compared the diabetes group with a healthy control group and only a few studies analyzed the correlation between hemostasis and glycemic profile and the type of therapy for diabetes.[7,12,16]

Therefore, the current study aimed to detect hemostasis abnormalities in association with glycemic levels and type of therapy among patients with T2DM by using TEG.

METHODOLOGY

In this cross-sectional study, we recruited all T2DM patients with ages between 40-80 years in the Endocrinology Outpatient Clinic of Saiful Anwar General Hospital Indonesia, from January until March 2021, using a consecutive sampling method. The sample size was calculated using the cross-sectional sample formula using G power software version 9 (G Power, Dusseldorf, Germany). A total of 54 patients was required as the minimum sample with 95% power based on the prevalence of T2DM at 6%[17] and the prevalence of coagulation abnormality in these patients at 58%.[18] The exclusion criteria were use of the antiplatelets, anti-thrombin, and anti-coagulants 10 days before sampling; acute infections; chronic kidney disease; acute and chronic liver failure; congenital hemostasis abnormalities; active malignancy; and pregnancy. All subjects were informed about the study and written consent was obtained. The study was approved by the Ethical Committee of the Medical Faculty, Universitas Brawijaya. Data regarding disease progression and therapy were obtained through history taking and review of medical records.

Glycemic control assessment

Glycemic profile was determined using fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPPG), and glycosylated hemoglobin (HbA1c). Plasma glucose examination was carried out with auto-analyzer Cobas c6000 using the hexokinase enzymatic method. HbA1c measurement was performed appropriately according to National Glycohemoglobin Standardization Program using HPLC (high-performance liquid chromatography) method (Biorad D10).

Hemostasis profile assessment

Assessment of hemostasis profile utilized whole blood sample in a citrated tube (about 4 mL for each procedure). A comprehensive analysis was performed by using Thromboelastography Analyzer 5000 (Haemonetics Corp, USA). TEG simulates venous blood flow using a rotational cup. About 360-µl citrated whole blood sample is placed inside the cup and mixed with kaolin. A pin on a torsion wire is then put inside the blood which is connected to an electromagnetic transducer. The cup is rotated alternately (rotation angle 4°45, 10 seconds for each cycle). The rotation process will induce fibrin clot formation between cup and pin. A fibrin clot creates a torque on the pin and the torque force will be read by an electromagnetic transducer from the platelet aggregation and initial fibrin formation until maximum clot strength is reached. The reading curve will reach the maximum until it decreases as fibrinolysis begins.[8] TEG examination was performed according to the manufacturer's instructions.

There were several thromboelastogram parameters analyzed in this study. The maximum amplitude (MA) represents primary hemostasis, the maximum strength of clot which is determined 80% by platelet level and function and 20% by fibrinogen activities. The normal range of MA is between 50-70% and a value below this is considered hypo-coagulable for primary hemostasis and vice versa. The second parameter, R-value, represents initial fibrin formation and correlates with enzymatic coagulation with a normal range between 5'-10'. The third parameter was the α-angle which depicts dynamic clot strengthening through amplification and propagation processes which are determined by the activities of thrombin that catalyze fibrin formation from fibrinogen. The normal range is between 53-72°. Both R-value and α-angle represent secondary hemostasis. R-value below the normal range and α-angle above the normal range reflect hypercoagulability for secondary hemostasis. Finally, LY30 reflects percentages of lysed thrombin in 30 minutes after MA which was determined by activities of fibrinolysis. The normal range is between 0-8% and a value below the normal range represents hypercoagulability for fibrinolysis and vice versa. All subjects were then classified into hypocoagulable, normocoagulable, and hypercoagulable for each of the hemostasis groups.

Statistical analysis

Data analysis was performed using Statistical Package for Social Sciences (IBM Corp, USA) version 26.0 software. The normality of continuous variables was measured using the Kolmogorov-Smirnov test, while the homogeneity of variances was determined using the Levene test. Continuous variables were presented in median and interquartile range (IQR) because of skewed distribution, whereas categorical variables were presented in numbers (%). Kruskal Wallis test was performed to compare the median HbA1c, FPG, and 2hPPG in each group of hemostasis profiles. The

association between the type of therapy and hemostasis categories were analyzed using logistic regression. Data results were presented as a descriptive table and odds ratio. A *p*-value <0.05 was considered significant.

RESULTS

A total of 80 patients were enrolled in this study, but due to the pandemic restrictions of movement, only 57 patients were able to fulfill all study requirements. Table 1 shows the baseline characteristic of the study subjects. Most participants were female (63.2%; n = 36) and the median age was 55 (51-62.5) years. The median duration of T2DM was 3 (0.83 – 10) years with more patients receiving insulin therapy (59.6%).

Table 1. Baseline Characteristics of Participants

Variables	N (%)
Sex	
Male	21 (36.8%)
Female	36 (63.2%)
Type of Therapy	
Insulin	34 (59.6%)
Non-Insulin	23 (40.4%)
History of CVD	
Yes	8 (14%)
No	49 (86%)
Hypertension	
Yes	29 (50.9%)
No	28 (49.1%)
History of PAD	
Yes	19 (33.3%)
No	38 (66.7%)
Hemostasis profiles	**N (%)**
Primary hemostasis	
Hypocoagulable	12 (20.3%)
Normocoagulable	41 (69.5%)
Hypercoagulable	4 (6.8%)
Secondary hemostasis	
Hypocoagulable	7 (11.9%)
Normocoagulable	50 (84.7%)
Fibrinolysis	
Hypocoagulable	2 (3.4%)
Normocoagulable	55 (93.2%)
	Median (IQR)
Age (years)	55 (51 – 62.5)
BMI	24 (22 – 28)
DM duration (years)	3 (0.83 – 10)
Laboratory Parameters	
Platelet count (/L)	302.000 (256.500 – 368.000)
PT (second)	10.3 (10.0 – 10.6)
aPTT (second)	26.8 (24.4 – 28.5)
INR	0.99 (0.96 – 1.02)
HbA1c (%)	8.40 (7.70 – 10.15)
FPG (mg/dL)	161 (116 – 197)
2hPPG (mg/dL)	204 (173.5 – 281)

Continuous data were presented as median (IQR); categorical data were presented as number (%); BMI: body mass index; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; CVD: cardiovascular disease; PAD: peripheral artery disease.

All subjects were classified into hypocoagulable, normocoagulable, and hypercoagulable for each group of hemostasis (Table 1). Most subjects were normocoagulable for primary hemostasis (69.5%, n=41), secondary hemostasis (84.7%, n=50), and fibrinolysis (93.2%, n=55). The median value and IQR of laboratory parameters were presented in Table 1.

Primary Hemostasis

Overall, there were no significant differences between glycemic levels in each group of primary hemostasis as presented in Table 2. The median level of HbA1c was higher in the hypercoagulable group but the median levels of FPG and 2hPPG were higher in the hypocoagulable group.

Secondary Hemostasis

Analysis of secondary hemostasis only yielded hypocoagulable and normocoagulable groups and there were no significant differences between the glycemic levels in these 2 groups. FBS and 2hPPG were higher in the normocoagulable group but HbA1c was higher in hypocoagulable group (Table 2).

Fibrinolysis

Analysis of fibrinolysis only yielded hypocoagulable and normocoagulable groups (Table 2). The median level of HbA1c was higher in normocoagulable groups but the median level of FPG and 2hPPG were higher in the hypocoagulable group. However, these differences were not statistically significant.

Therapy of DM

Logistic regression analysis showed no significant association between the type of therapy for T2DM and hemostasis profile (primary, secondary, and fibrinolysis) as shown in Table 3.

Table 2. Median comparisons between glycemic parameters in each group of hemostasis profiles

Variables	Primary Hemostasis			*p*	Secondary Hemostasis		*p*	Fibrinolysis		*p*
	Hypo-coagulable	Normo-coagulable	Hyper-coagulable		Hypo-coagulable	Normo-coagulable		Hypo-coagulable	Normo-coagulable	
HbA1c	8.65 (7.28 – 11.25)	8.3 (7.70 – 9.55)	10.9 (7.90 – 13.48)	0.368	8.60 (7.80 – 9.10)	8.35 (7.58 – 10.33)	0.990	7.85 (5.60 – 7.85)	8.4 (7.70 – 10.2)	0.573
FPG	205 (128.8 – 268.3)	150 (116 – 180.5)	192 (126 – 206.3)	0.082	126 (102 – 166)	169 (118.3 – 200.3)	0.193	171.5 (101 – 171.5)	161 (116 – 196.0)	0.931
2hPPG	257.5 (183 – 381.5)	199 (163.5 – 252)	224 (155 – 281.8)	0.162	161 (99 – 207)	204.5 (180 – 288.5)	0.126	266 (245 – 266)	203 (171 – 275)	0.269

Continuous data were presented as median (IQR); p was significant if <0.05. HbA1c: hemoglobin A1c; FPG: fasting plasma glucose. 2hPPG: 2-hour postprandial plasma glucose.

Table 3. Analysis between type of therapy and hemostasis profile

Variables	Insulin	Non-Insulin	OR (95% CI)	*p*
Primary hemostasis				
Hypocoagulable	7 (12.3)	5 (8.8)	0.933 (0.256 – 3.402)	0.917
Normocoagulable	25 (43.9)	16 (28.0)	0.823 (0.255 – 2.652)	0.744
Hypercoagulable	2 (3.5)	2 (3.5)	1.524 (0.199 – 11.670)	0.685
Secondary hemostasis				
Hypocoagulable	5 (8.8)	2 (3.5)	0.552 (0.098 – 3.126)	0.502
Normocoagulable	29 (50.9)	21 (36.8)	1.810 (0.320 – 10.246)	0.502
Fibrinolysis				
Hypocoagulable	0 (0.0)	2 (3.5)	NA	0.999
Normocoagulable	34 (59.6)	21 (36.8)	NA	0.999

Categorical data were presented as number (%); p significant if <0.05.

To our knowledge, this is the first study to examine hemostasis disorders using TEG among T2DM from the outpatient clinic without any acute or critical disorders. Our study showed a non-significant difference in median and IQR of glycemic profiles among categories of primary hemostasis. HbA1c was higher in the hypercoagulable group than in the other two groups. This result is consistent with previous study which showed that poor glycemic control increased prothrombotic conditions.[1] Primary hemostasis implicates complex interaction between thrombocyte, vascular wall and adhesion protein to form a platelet plug.[19] Hyperglycemia increases oxidative stress to endothelial dysfunction. formation of advanced glycosylation end products (AGEP). The latter inhibits nitric oxide expression and increases the expression of adhesion molecules, tissue factors, proinflammatory cytokines and monocyte chemoattractant protein-1.[5] Insulin resistance leads to platelet over-activation due to the reduction of receptors and insulin sensitivity on the platelet surface. Hyperinsulinemia also induces the formation of tissue factors and thrombus generation.[20–22]

The current study revealed a higher median value of FPG and 2hPPG in the hypocoagulable group of primary hemostasis than in the other two groups. This is in contrast to other studies where prothrombotic conditions such as myocardial infarction, stroke, and venous thromboembolism in the setting of acute hyperglycemia were observed.[3] Several studies have shown that acute hyperglycemia is characterized by increased formation of thrombin-antithrombin (TAT) complexes, soluble tissue factors. induced platelet hyperreactivity and acute oxidative stress.[5,23-25] Hyperglycemia also disrupts the glycocalyx of the vascular endothelial layer which eventually increases adhesion between platelet and endothelial cells.[26]

In a study by Lam et al.,[27] the specificity of TEG for platelet abnormalities was low. Thus, the TEG result had to be confirmed by other platelet function tests. Assessment of primary hemostasis abnormalities due to poor glycemic control cannot simply be concluded by the MA as a parameter of primary hemostasis in TEG. A study by Maatman et al.,[20] did not reveal any significant difference in MA value between patients with and without diabetes. Higher glycemic levels in the hypocoagulable group might also be related to the paradoxical effect of insulin therapy, especially in patients with long duration of T2DM.[28] Insulin therapy potentially increases platelet reactivity in the condition of insulin resistance.[29] Hence, patients with long-standing T2DM on insulin therapy often show a hypercoagulable state even with lower glycemic levels.

Our study also observed a statistically non-significant difference in the median value of glycemic profile among groups of secondary hemostasis. Previous studies showed that glycemic control was a significant predictor for improvement in blood thrombogenicity.[5] Poor glycemic control is associated with increased activation of tissue factor and coagulation factors.[3,24] These factors such as fibrinogen, FVII, FVIII, FXI, FXII, kallikrein, and von Willebrand are increased in patients with diabetes compared to healthy individuals.[7] Hyperglycemia also leads to protein glycation which eventually causes dysfunction of proteins in the coagulation cascade.[30]

Our analysis indicated contradictory results between HbA1c and FPG and 2hPPG in secondary hemostasis. HbA1c was higher in the hypocoagulable group, whereas FPG and 2hPPG were higher in the normocoagulable group. Chronic hyperglycemia as evidenced by high HbA1c is related to hypocoagulability of secondary hemostasis. On the other hand, acute hyperglycemia as manifested by high FPG or 2hPPG, is associated with hypercoagulability. Several studies showed that acute hyperglycemia could induce coagulation disorder and eventually lead to thrombosis.[31-33] A study by Xie et al.,[34] revealed a decrease in R-value among patients with gestational diabetes mellitus which was not observed in normal pregnancy. Wang et al.,[16] also obtained a lower R-value in acute stress after surgery among patients with DM compared to non-DM. Hyperglycemic condition combined with hyperinsulinemia may activate the coagulation system by increasing the activation of TF, FVII, FVIII, and platelet.[35] Furthermore, acute hyperglycemia may decrease the protective effect of endothelial glycocalyx which results in faster clot formation.[36] Several studies correlated acute hyperglycemia with thrombotic events such as myocardial infarction, stroke and venous thromboembolism.[3,26] These conditions, in addition to acute hyperglycemia, are risk factors for secondary hemostasis hypercoagulability in TEG.

Chronic hyperglycemia may increase fibrinogen and other coagulation factors such as FVII, FVIII, FIX, FXII, and vWF.[7,25] Higher coagulation factors may render stronger, denser and structurally different clot in patients with chronic hyperglycemia compared to healthy control requiring a longer time for fibrinolysis.[35] However, our study showed higher HbA1c in the hypocoagulable group.

Our study showed higher HbA1c in the normocoagulable group of fibrinolysis. By considering that fibrinolysis only yielded hypo and normo-coagulable groups, this result is consistent with several previous studies which revealed that uncontrolled DM leads to a hypercoagulable condition due to the increase in the levels of fibrinogen, t-PA, PAI-1, and D-dimer.[37] In vitro study using endothelial cells also pointed to an increase in PAI-1 secretion in the setting of high glucose levels.[38] Bryk et al.,[39] showed that intensive glycemic control would improve the fibrinolysis system as measured by PAI-1. Other studies about fibrinolysis compared T2DM patients with healthy control and found that those who have diabetes tended to have hypofibrinolytic conditions.[3,40]

The hypocoagulable group of fibrinolysis, in this study, had a higher FPG and 2hPPG. Several previous studies, on the other hand, showed contradictory results regarding acute hyperglycemia and fibrinolysis. Acute hyperglycemia may inhibit fibrinolysis due to decrease in tissue plasminogen activator and increase in PAI-1 level.[26,41] Hyperglycemia also disrupts fibrin clot lysis due to increase in beta-thromboglobulin.[4] On the contrary, another study by Wang et al.,[16] in DM patients undergoing CABG, showed no significant difference in LY30 between DM and non-DM patients.

Analysis between the therapy for DM and hemostasis profile also revealed a non-significant association in all three hemostasis groups (primary, secondary, and fibrinolysis). In this study, more than 50% of subjects were on insulin therapy. Insulin has prothrombotic activities and insulin resistance condition in T2DM may induce increase in PAI-1 and fibrinogen.[42] In contrast, oral hypoglycemic agents such as metformin, sulfonylurea and thiazolidinediones could ameliorate coagulation dysfunction in diabetes by decreasing the level of FVII, PAI-1, fibrinogen concentration, and in vivo FXIII activity. Newer therapy such as gliptins and GLP-1 agonists exhibited in vitro anti-inflammatory activities by decreasing TNF-α and PAI-1.[43-45] Nevertheless, overall glycemic control rather than type of therapy is the significant predictor for improvement in blood thrombogenicity.[5,6]

Several factors may explain the contradicting results of our study with previous studies on TEG in T2DM. Our study subjects were different from previous studies since we included T2DM subjects without acute illness or critical comorbidities. Published data on TEG revealed the sensitivity and specificity of TEG in hemostasis monitoring of acute conditions.[11,16-19] Therefore, TEG might be less sensitive and less specific in detecting hemostasis abnormalities in subjects without acute critical comorbidities. Although several studies indicated significant associations between acute and chronic hyperglycemia with hemostasis abnormalities, those associations were not consistently found in all parameters of hemostasis and all subsets of T2DM patients.[16,20,27,34]

The TEG method has several shortcomings. It is less specific in detecting platelet abnormalities.[27] Primary hemostasis is represented in TEG as MA value, where MA value is influenced by both platelet function and fibrinogen activities. TEG also does not measure several factors in hemostasis such as endothelial function, tissue factor and microparticles. Therefore, the TEG method may be less reliable in detecting hemostasis abnormalities in association with glycemic profile and type of therapy, especially in T2DM patients without any acute and critical comorbidities.

There were some limitations in the current study. Assessment of FPG and 2hPPG were only done once, thus, our study did not reflect glycemic variability. Our study also did not perform multivariate analysis to observe the association between the therapy for T2DM and glycemic profile towards hemostasis profile. Because of the pandemic restrictions, our study could only recruit the aforementioned sample size. A future study might be needed to confirm the results of the current study. The current study only included T2DM patients without any acute diseases, thus our study results might not be applicable to acute clinical settings.

CONCLUSION

This study did not find a significant association between glycemic levels and hemostasis profiles using the TEG method in patients with T2DM. Chronic hyperglycemia was poorly associated with hypercoagulability of primary hemostasis and fibrinolysis. Acute hyperglycemia was associated with hypercoagulability in secondary hemostasis, although the association was not significant. The type of DM therapy was also not significantly associated with the hemostasis profile. Further research is still needed to evaluate the role of TEG in analyzing the hemostasis profile of T2DM patients to stratify the risk and consider anticoagulation therapy. Further research might also require healthy control and T2DM patients with acute conditions to evaluate the effect of acute glycemic fluctuations on hemostasis profile using the TEG method.

Acknowledgment
The research team would like to acknowledge Badan Penelitian dan Pengabdian Masyarakat, Faculty of Medicine, Universitas Brawijaya for the funding of this study.

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

Author Contribution Statement

PMA, NKF, SF, AKW, ADN conceived the study; conducted the research; provided the study materials; prepared the original draft; reviewed and edited the manuscript and managed the research activity planning. PMA, NKF, SF designed the methodology; verified the research outputs and supervised the research activity. NKF, SF, AKW, ADN programmed the software. NKF, AKW, ADN synthesized and curated the study data and prepared the data presentation. PMA and NKF acquired financial support.

Author Disclosure

The authors declared no conflict of interest.

Funding Source

The study was funded by the Badan Penelitian dan Pengabdian Masyarakat, Faculty of Medicine, Universitas Brawijaya.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Glycaemic Changes Among Children and Adolescents With Type 1 Diabetes Mellitus Before and During Ramadan Fasting Using Continuous Glucose Monitoring

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Abstract

Objectives. This study described and compared glycaemic changes with the use of the following Continuous Glucose Monitoring (CGM) metrics: time in range, time in hyperglycaemia and time in hypoglycaemia from retrospective CGM data among children and adolescents with Type 1 Diabetes Mellitus (T1DM), before and during Ramadan to better understand the impact of fasting during this season.

Methodology. This study was conducted in 2 tertiary centres: Hospital Putrajaya (HPJ) and Hospital Universiti Sains Malaysia (HUSM) from February to May 2020. Muslim T1DM patients between ages 8 to18 who intended to fast during Ramadan were given Ramadan-focused education. CGM iPro2® (Medtronic) was used before and during Ramadan, complemented by finger-prick glucose monitoring or self-monitoring of blood glucose (SMBG).

Results. Of the 32 patients, only 24 (12 female) were analysed. Mean age was 13.6 ± 3.1 years old, mean HbAlc was 9.6 ± 1.9% and mean duration of illness was 5.4 ± 3.4 years. Majority (91.7%) were on multiple dose injections (MDI) while only 8.3% were on continuous subcutaneous insulin infusion (CSII). All fasted in Ramadan without acute complications. Retrospective CGM analysis revealed similar results in time in range (TIR), time in hyperglycaemia and time in hypoglycaemia before and during Ramadan, indicating no increased hypoglycaemic or hyperglycaemic events related to fasting. Glycaemic variability before Ramadan as measured by the LBGI, HBGI and MAG, were similar to values during Ramadan.

Conclusion. Ramadan fasting among T1DM children and adolescents, by itself, is not associated with short-term glycaemic deterioration. T1DM youths can fast safely in Ramadan with the provision of focused education and regular SMBG.

Key words: paediatric, T1DM, CGM, Ramadan fasting

INTRODUCTION

Fasting from dawn (*Sahur*) until sunset (*Iftar*) in Ramadan, the 9th month of the Islamic Calendar, is one of the five pillars of Islam and is obligatory for all healthy Muslim adults, adolescents, and children from the time of puberty.[1] This one-month-long fasting is a period of spiritual contemplation and seeking nearness to God when the followers strictly refrain from eating or drinking during daylight and practice abstinence. For patients with T1DM, Ramadan fasting is even more demanding as their body's glucose homeostasis is dependent on exogenous insulin and has been associated with higher risks of hypoglycaemia, hyperglycaemia, diabetic ketoacidosis (DKA), dehydration, and venous thrombosis.[2–6]

Despite exemption by religious authorities for medical concerns[3–5] and alternatives like *Fidya*, which is a form of donation of food or money to the poor to compensate for the missed fasting days, most T1DM patients still insist on fasting during Ramadan.[2–8] The Epidemiology of Diabetes and Ramadan study (EPIDIAR) in 2001 reported that 42.8% of T1DM patients fasted for at least 15 days during Ramadan.[6] More recently, the DaR (Diabetes and Ramadan) Global Survey in 2020[8] by the International Diabetes Federation - Diabetes and Ramadan alliance (IDF-DaR) looked at profiles of T1DM youths from 13 major Islamic countries, 75% of them fasted for a mean duration of 22 days, despite the COVID-19 pandemic. More than half (55.6%) had at least one daytime hypoglycaemia and only 71.2% performed regular SMBG.[8] To better assess and

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: February 11, 2022. Accepted: May 4, 2022.
Published online first: September 9, 2022.
https://doi.org/10.15605/jafes.037.02.08

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manage risks associated with fasting, IDF-DaR in their updated guidelines 2021,[5] introduced a risk calculator to determine the risk of a person with diabetes prior to fasting for Ramadan. The calculator, which included T1DM as one of the risks, provides a convenient way to determine risk but it is still advisable for diabetes care in Ramadan to be highly individualised. In addition, knowledge gaps regarding the true glycaemic impact of Ramadan fasting still remain.[5]

The International Society of Paediatric and Adolescent Diabetes (ISPAD) in their 2018 guidelines, recommended that Muslim T1DM youths may fast, provided they have reasonable glycaemic control, good hypoglycaemic awareness and willingness to frequently monitor blood glucose.[2] Both the IDF and the ISPAD have emphasized the importance of glucose monitoring during Ramadan, either through SMBG or via advanced technology, such as intermittent flash CGM (iCGM) or real-time CGM (rt-CGM).

Before the era of CGM, most of the glycaemic data from previous Ramadan studies[9-11] in T1DM children and adolescents were from SMBG records. Unlike CGM which provides continuous glucose data for the entire day, SMBG only provides single-point glucose readings and is unable to reflect the overall glycaemic picture. Following the increasing use of CGM in clinical and research settings, more Ramadan studies using CGM were conducted among paediatric T1DM in recent years.[12–18] Instead of retrospective CGM, most of these authors[12,14–18] utilized personal or real-time CGM (rt-CGM), which has the benefit of immediate glucose visualisation and intervention, as well as "communication," or coupling with the insulin infusion pump, also referred to as the sensor-augmented pump (SAP). However, with retrospective or professional CGMs, patients wearing the devices are not aware of their glucose values until their care provider downloads and reviews data during an office visit. Despite being "blinded," they provide important information to both patients and clinicians, especially in resource-limited countries. As opposed to rt-CGM, these "unaltered" glycaemic profiles from retrospective CGM could provide insights, as well as promote self-learning for Muslim T1DM patients who rely mostly on SMBG.

As one of the developing Islamic countries in Southeast Asia with 61.3% of its population comprising of Muslim population, Malaysia has a growing number of Muslim T1DM youths. Referring to the local diabetes registry or DICARE,[19] 70% of the diabetic population less than 18 years old were T1DM and the majority of them were Muslims. Despite the existing knowledge gap of Ramadan fasting, there is still a lack of local T1DM Ramadan studies specifically looking at CGM outcomes. Also, most previous Ramadan CGM fasting studies were conducted in either the Middle East or Central Asia countries, where fasting practices and local cultures may not be entirely similar to the Muslim countries in Southeast Asia.

For these reasons, we decided to investigate the CGM profiles of our Muslim T1DM youths during Ramadan fasting. Our study aimed to describe and compare the glycaemic changes among children and adolescents with T1DM before and during fasting in Ramadan month. These glycaemic changes were measured using CGM metrics, which include time in range, time in hypoglycaemia and time in hyperglycaemia. We hypothesized that Ramadan fasting is not associated with increased or worsened glycaemic risks. We also analyzed the impact of optimal HbA1c level and younger age on glycaemic changes.

We hope to support and empower Muslim T1DM youths for a safer Ramadan fasting experience though the conduct of this study.

METHODOLOGY

Patient and study design

This was a prospective study involving two tertiary centres in West and East Peninsular Malaysia, namely Hospital Putrajaya (HPJ) and Hospital Universiti Sains Malaysia (HUSM), respectively. It was conducted from February until May 2020 and included Ramadan 2020 (Hijri 1441) which was from 23rd April to 24th May 2020. Inclusion criteria were Muslim T1DM children and adolescents aged 8-18 years old, under follow-up care by paediatric endocrinologists and had expressed intentions to fast. Participants with all types of insulin delivery were included. Exclusion criteria were history of severe hypoglycaemia, recurrent hypoglycaemia episodes, hypoglycaemia unawareness, diabetic ketoacidosis (DKA) three months prior, intervening acute illnesses, pregnancy or chronic dialysis, in accordance to the Malaysia Paediatric T1DM Management Guideline.[20] Stratified sampling proportionate to sample size was applied in recruitment from both centres.

Ramadan-focused education and regular clinic visits

Ramadan-focused education and single-day workshop were conducted for both patients and their caregivers before Ramadan, involving paediatric endocrinologists, diabetes educator nurses, and dieticians. A total of 4 clinic visits were performed throughout the study period: 2 clinic visits before and another 2 during Ramadan. Standardized diabetes assessment and Ramadan-focused education were provided during clinic visits. Individual insulin adjustment and dietary advice were provided according to published international guidelines.[3–5]

Retrospective CGM

Retrospective CGM data analysis was performed twice for all the participants, using the *i*Pro2 device (Medtronic, 18000 Devonshire Street, Northridge, CA 91325, USA), before and during Ramadan fasting. The coin-sized glucose sensor was inserted into the participants' abdominal subcutaneous tissue together with the iPro2 recorder for 6

to 7 days (according to manufacturer's recommendation), this was then removed the subsequent week. Both the insertion and removal procedures were performed by skilled diabetes nurse educators (DNE). All participants were also given emergency contact information for support, in case of any medical or technical problems arising during the CGM periods.

Self-Monitoring of Blood Glucose (SMBG)

Standardised glucometers (Contour Plus One, Ascensia Diabetes Care, 600 North Bridge Road) with blue-tooth connectivity were provided to every participant together with an ample supply of glucose strips for use for SMBG throughout the study period, including the entire Ramadan month. Participants were advised to perform SMBG at least 4 times per day and more frequently during Ramadan fasting (pre-*sahur*, 2-hour post-*sahur*, pre-*iftar*, 2-hour post *iftar,* or when symptomatic). SMBG readings were recorded by participants into individual diabetes logbooks with other relevant details such as amount and type of food, physical activities, and insulin doses. During Ramadan, the participants could discontinue fasting, if they experience any symptoms of being unwell, hypoglycaemia, severe hyperglycaemia, or sudden change of decision for any personal reasons.

Ethical approval

This study received ethical approval from the Medical Research & Ethics Committee (MREC), Ministry of Health, Malaysia and the Human Research Ethics Committee of Universiti Sains Malaysia (USM). It had also received a research grant from the National Institute of Health (NIH) under the Ministry of Health, Malaysia.

Sample Size Estimation

For the specific objective of comparing the CGM glycaemic parameters (time in range, time in hyperglycemia and time in hypoglycemia) before and during fasting in Ramadan, sample size calculation was done using PS software (paired t-test). Alpha (α) was set at 0.05, power at 0.8.

With reference to earlier findings by Nader Lessan et al.,[13] for time in range (TIR), the smallest difference that is of clinical significance was pre-determined at 4 hours. International consensus[21,22] and experts have recommended targeting the TIR for 70% of the day (16.8 hours of the 24 hour-day), but no data have reported the smallest deviation that could result in unfavorable clinical outcomes, hence, we have set the smallest difference at 4 hours.

For hyperglycemia duration, the smallest difference that is of clinical significance was also predetermined at 4 hours based on clinical assumption.

For hypoglycemia duration, the smallest difference that is of clinical significance was set at the lowest, and for safety reasons, we predetermined the value to be 15 minutes or an equivalent of 0.25 hours. Prolonged hypoglycemia of more than 15 minutes may result in severe neuroglycopenic symptoms that would necessitate medical care. Table 1 summarizes sample size considerations for each of the prespecified CGM outcomes.

Taking into consideration a drop-out rate of 10%, the initial sample size required for this study is estimated to be 33 subjects. This sample size is however, was limited by the short duration of Ramadan month and the unexpected COVID-19 pandemic.

Statistical methods

SPSS version 22 statistical analysis software (SPSS Inc., Chicago, IL, USA) was used. CGM data were downloaded from Medtronic Care-link Pro to Microsoft Excel (2010) and transcribed into SPSS. Descriptive statistics were used to characterise demographics (Table 2). Normality was tested by Shapiro–Wilk test and graphical assessment of normality. Continuous variables were presented as mean (SD) or median (IQR) based on their normality distribution; categorical data were presented as frequency (percentage). Glycaemic variability (GV) were calculated using EasyGV Excel version 9.0.R2 (https://www.phc.ox.ac.uk/research/resources/easygv) that was developed by Nathan R Hill, (©University of Oxford 2010-2016).[23] All CGM metrics were compared by paired t-test or Wilcoxon Signed Rank test, as appropriate, whereas Chi-Squared test and Fisher Exact test were used to assess for differences in the categorical variables, as appropriate. A value of $P<0.05$ was considered statistically significant.

Glossary of CGM outcomes

Time in Range (TIR): The percentage of time a person spends with their blood glucose levels in a target range which varies depending on the person, but as a general guideline, it is suggested to start with a range of 3.8 to 10 mmol/L.

Mean absolute relative difference (MARD): Computed using temporally matched glucose data from CGM systems and comparison glucose measurements (most often obtained by capillary blood glucose (BG) measurements)

Table 1. Summary of sample size considerations per CGM outcome

	α	β (power)	δ	σ	Sample size
Time in range (hr)	0.05	0.8	4	6.98	26 pairs
Hyperglycaemia duration (hr)	0.05	0.8	4	7.49	30 pairs
Hypoglycemia duration (hr)	0.05	0.8	0.25	0.38	20 pairs

Table 2. Demographics

Baseline characteristics		Centres		*p*-value	Total (n=24)
		HPJ (n=10)	HUSM (n=14)		
Age* (years)		12.8 ± 3.0	14.1 ± 3.1	0.30[a]	13.6 ± 3.1
Duration of diabetes* (years)		5.3 ± 3.6	5.4 ± 3.4	0.94[a]	5.4 ± 3.4
Baseline HbA1c* (%)		9.2 ± 1.5	10.0 ± 2.0	0.28[a]	9.6 ± 1.9
Anthropometry*	Weight (kg)	45.1 ± 14.9	42.8 ± 15.0	0.72[a]	43.7 ± 14.7
	Weight SD	-0.1 ± 0.9	-1.0 ± 1.4	0.09[a]	-0.6 ± 1.3
	Height (m)	1.5 ± 0.2	1.5 ± 0.1	0.74[a]	1.5 ± 0.2
	Height SD	-0.3 ± 1.0	-1.3 ± 1.5	0.07[a]	-0.9 ± 1.4
	BMI* (kg/m^2)	19.1± 2.7	18.6 ± 4.4	0.74[a]	18.7 ± 3.7
	BMI SD	0.2 ± 0.8	-0.5 ± 1.7	0.28[a]	-0.2 ± 1.4
Gender[+]	Male	5 (50)	7 (50)	1.00[b]	12 (50)
	Female	5 (50)	7 (50)		4 (16.7)
Puberty[+]	Tanner 1-2	1 (10)	3 (21.4)	0.39[c]	20 (83.3)
	Tanner 3-5	9 (90)	11 (78.6)		22 (91.7)
Insulin delivery[+]	MDI	9 (90)	13 (92.9)	1.00[c]	2 (8.3)
	CSII	1 (10)	1 (7.1)		1.2 (0.2)
Daily insulin dose* (unit/kg/day)	Before Ramadan	1.1 ± 0.13	1.25 (0.24)	0.11[a]	1.0 ± 0.2
	During Ramadan	1.0 ± 0.14	1.01 (0.22)	0.45[a]	23 ± 95.8
Ramadan experience[+]	Yes	9 (90)	14 (100)	0.42[c]	1 (4.2)
	No	1 (10)	0 (0)		12 (50)
Socio-economic[+]	B40	1 (10)	10 (71.4)	0.003[c]	11 (45.8)
	M40	6 (60)	4 (28.6)		10 (41.7)
	T20	3 (30)	0 (0)		3 (12.5)
HbA1c subgroups[+]	HbA1c level <7.5%	3 (30)	1 (7.2)	0.24[c]	4 (16.6)
	HbA1c level 7.5-9.0 %	0 (0)	3 (21.4)		3 (12.5)
	HbA1c level >9.0%	7 (70)	10 (71.4)		17 (70.9)

* Numerical data, presented in means ± SD
[+] Categorical data, presented in number (%)
[a] Independent t-test
[b] Chi-square test
[c] Fisher-exact test
[‡] B40: Household income below RM 4850 per month
[‡] M40: Household income RM 4851 – RM 10,970 per month
[‡] T20: Household income above RM 10,971 per month
(Laporan Kaji Selidik Pendapatan dan Gaji 2019, Jabatan Statistik, Malaysia)[38]

of all subjects from a clinical study. For paediatric population the acceptable MARD is 12.2%.

Estimated A1C (eA1C): A measure converting the mean glucose derived from CGM or self-monitored blood glucose readings, using a formula obtained from glucose readings from a population into an estimate of a simultaneously measured laboratory A1C.

Standard Deviation (SD): A measure of the spread in glucose readings around the average – some call this the variation. If there are many highs and/or many lows on a given day, they will have a larger SD whereas a lower SD reflects a pretty stable glucose readings throughout a day.

Coefficient variant (CV): A term derived by dividing the SD by the mean glucose and multiplying by 100 to get a percentage. An acceptable CV is within or < 36%.

Glycaemic varialbility (GV): Refers to oscillations in blood glucose level or fluctuation of glucose over a given period of time.

Mean amplitude of glycemic excursion (MAGE): The mean of blood glucose values exceeding one SD from 24 hour mean blood glucose. This can be used to gauge the degree of glucose fluctuation or glycemic variability.

High blood glucose index (HBGI) and low blood glucose index (LBGI): Indexes designed based on symmetrisation of blood glucose ranges to summarize the number and extent of extreme blood glucose fluctuations into single number. LBGI accounts for hypoglycemic episodes and HBGI for hyperglycemic episodes.

Time in Hypoglycaemia:
Level 1: <54–70 mg/dL (3.0–3.9 mmol/l)
Level 2: <54 mg/dL (<3.0 mmol/l)

Time in Hyperglycaemia:
Level 1: >180 mg/dL (>10 mmol/l)
Level 2: >250 mg/dL (>13.9 mmol/l)

RESULTS

Clinical and demographic characteristics

A total of 32 participants were initially recruited (14 from HPJ and 18 from HUSM). Due to the escalating COVID-19 pandemic and implementation of Movement Control Order (MCO) by the Government of Malaysia (Phase 1; 16th March 2020),[24] 8 participants defaulted their follow-up visits in Ramadan. Only 24 participants (n=24), 10 from HPJ and 14 from HUSM, were eventually included for analysis. Their mean age was 13.6 ± 3.1 years old with 83.3% at either

Table 3. CGM Glycaemic outcome (before and during Ramadan)

		Before Ramadan (n=24)	During Ramadan (n=24)	*p*-value
Adherence and Sensor Accuracy	Sensor readings* (per CGM cycle)	1739.8 ± 366.9	1613.9 ± 416.1	0.14[a]
	MARD* (%)	14.3 ± 7.7	15.0 ± 9.5	0.61[a]
	Calibrations* (per CGM cycle)	23.7 ± 6.7	21.9 ± 8.2	0.29[a]
Sensor Glucose (SG) data	Mean SG* (mmol/L)	9.7 ± 2.2	10.6 ± 2.9	0.04[a]
	Coefficient of variation*, CV (%)	42.91 ± 8.1	40.76 ± 9.1	0.31[a]
	Estimated A1c* (%)	7.7 ± 1.4	8.3 ± 1.8	0.03[a]
	Time in range_level 1* (%)	51.1 ± 14.6	42.4 ± 20.9	0.05[a]
	Time in range_level 2* (%)	34.6 ± 16.0	27.3 ± 17.4	0.02[a]
	Time in hyperglycemia_level 1* (%)	21.2 ± 9.2	24.5 ± 12.0	0.12[a]
	Time in hyperglycemia_level 2* (%)	19.5 ± 14.0	25.6 ± 18.6	0.10[a]
	Time in hypoglycemia_level 1* (%)	4.0 ± 4.9	4.0 ± 6.2	0.96[a]
	Time in hypoglycemia_level 2* (%)	4.2 ± 7.1	3.5 ± 5.3	0.54[a]
Glycaemic Variability (GV)	MAGE* (mmol/L)	8.2 ± 3.0	8.7 ± 2.3	0.48[a]
	HBGI*	14.3 ± 6.5	17.1 ± 8.0	0.07[a]
	LBGI*	5.6 ± 4.2	6.2 ± 4.9	0.62[a]

* Numerical data, presented in means ± SD
[a] Paired sample t-test
Time in range_level 1, SG readings between 3.9-10 mmo/L
Time in range_level 2, SG readings between 3.9-7.8 mmol/L
Time in hyperglycemia_level 1, SG readings 10-13.9 mmol/L
Time in hyperglycemia_level 2, SG readings >13.9 mmol/L
Time in hypoglycemia_level 1, SG readings 3.0-3.9 mmol/L
Time in hypoglycemia_level 2, SG readings <3.0 mmol/L
MAGE, mean amplitude glycaemic excursion
HBGI, high blood glucose index
LBGI, low blood glucose index
(Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range)[22]

mid- or late-puberty and were of equal gender distribution. The baseline mean HbA1c was 9.6 ± 1.9% and the mean duration of diabetes was 5.4 ± 3.4 years. Anthropometry or BMI SDS was -0.2 ± 1.4. Insulin administration were though multiple daily injections (MDI) for 91.7% while 8.3% were through continuous subcutaneous insulin infusion (CSII). The mean daily insulin requirement was 1.2 ± 0.2 unit/kg/day and 1.0 ± 0.2 unit/kg/day before and during Ramadan, respectively. Majority (95.2%) had past fasting experiences and 4.8% were attempting to fast for the first time. Most (87.5%) came from either the middle- or lower-income groups (M40 and B40, respectively), while 12.5% were from the upper-income group (T20). For the HbA1c subgroups, 16.6% had HbA1c <7.5%, 12.5% were within the HbA1c range of 7.5-9.0% and 70.9% had HbA1c >9%.

No significant differences were seen between participants from HPJ and HUSM, apart from socio-economic status. All participants fasted in Ramadan for at least 7 days while on CGM. None experienced complications of severe hyperglycaemia, DKA, or hypoglycaemia episodes requiring assistance or emergency visits.

Adherence of CGM data

As indicated in Table 3, total sensor glucose (SG) readings (per CGM-cycle) were 1739.8 (SD 366.9) and 1613.9 (SD 416.1) before and during Ramadan, respectively. This amounted to 41,755 and 38,734 SG readings before and during Ramadan, respectively. In addition, 23.7 ± 6.7 and 21.9 ± 8.2 valid calibrations (per CGM-cycle) were reported before and during Ramadan, respectively. The mean absolute relative difference (MARD) was 14.3 ± 7.7% and 15.0 ± 9.5% before and during Ramadan, respectively.

Outcomes from CGM data

As indicated in Table 4, the mean SG was 9.7 ± 2.2 mmol/L before Ramadan and increased to 10.6 ± 2.9 mmol/L during Ramadan (p=0.04). Estimated A1c similarly increased from 7.7 ± 1.4% before to 8.3 ± 1.8% during Ramadan (p=0.03). However, the coefficient of variation (CV) showed no difference with 42.9 ± 8.1% and 40.8 ± 9.1% before and during Ramadan, respectively (p=0.31).

Other important clinical CGM metrics, such as time in range level 1(SG 3.9-10 mmol/L), time in hypoglycaemia level (SG 3.0-3.9 mmol/L), time in hypoglycaemia level 2 (SG <3.0 mmol/L), time in hyperglycaemia level 1 (SG 10-13.9mmol/L) and time in hyperglycaemia level 2 (SG >13.9 mmol/L) showed no difference before and during Ramadan fasting. Only TIR level 2 (SG 3.9-7.8 mmol/L) demonstrated a difference but this was not applicable for paediatric patients.

Breaking down each CGM metric for the periods before and during Ramadan, TIR level 1 (SG 3.9-10 mmol/L) was 51.1 ± 14.6% and 42.2 ± 20.9%, respectively (p=0.05); time in hypoglycaemia level 1 (SG 3.0-3.9 mmol/L) was 4.0 ± 4.9% and 4.0 ± 6.2%, respectively (p=0.96); time in hypoglycaemia level 2 (SG <3.0 mmol/L) was 4.2 ± 7.1% and 3.5 ± 5.3%, respectively (p=0.54); time in hyperglycaemia level 1 (SG 10-13.9 mmol/L) was 21.2 ± 9.2 and 24.5 ± 12.0%, respectively (p=0.12); time in hyperglycaemia level 2 (SG >13.9 mmol/L) was 19.5 ± 14.0% and 25.6 ± 18.6%, respectively (p=0.10). These are shown in Figure 1.

For glycaemic variability (GV), represented by mean amplitude glycaemic excursion (MAGE), high blood glucose

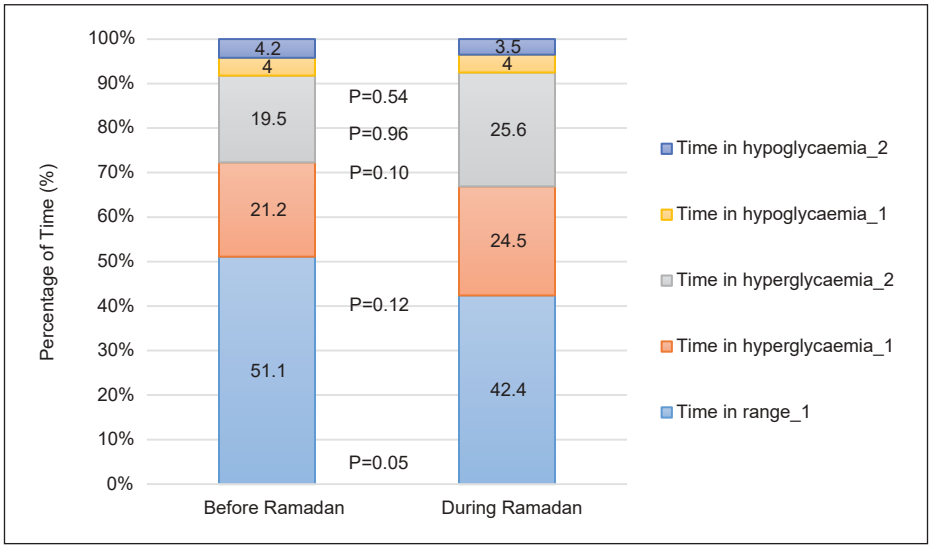

Figure 1. CGM metrics before and during Ramadan.

index (HBGI) and low blood glucose index (LBGI), there were no differences across both periods. Results before and during Ramadan were: MAGE 8.2 ± 3.0 mmol/L and 8.7 ± 2.3 mmol/L (p=0.48); HBGI 14.3 ± 4.5 and 17.1 ± 8.0 (p=0.07); LBGI 5.6 ± 4.2 and 6.2 ± 4.9 (p=0.62).

Comparing effect of HbA1c over Ramadan fasting

Analysis of CGM data for participants within optimal HbA1c group (HbA1c <7.5%; n =4), indicated higher mean SG (10.4 ± 3.2 mmol/L vs. 8.6 ± 2.6 mmol/L; p=0.03) and estimated A1c (8.2 ± 2.0% vs. 7.1 ± 1.7%; p=0.03) during Ramadan (Table 4). TIR level 2 (SG 3.9-7.8 mmol/L) was also reduced in Ramadan (27.0 ± 18.9% vs. 38.3 ± 20.5%; p=0.04).

Other important CGM metrics, such as TIR level 1 (SG 3.9-10 mmol/L), time in hypoglycaemia level 1 (SG 3.0-3.9 mmol/L), time in hypoglycaemia level 2 (SG <3.0 mmol/L), time in hyperglycaemia level 1 (SG 10-13.9 mmol/L) and time in hyperglycaemia level 2 (SG >13.9 mmol/L) showed no difference between the two periods. GV (MAGE, HBGI, and LBGI) also did not show a significant difference.

On the other hand, among participants with suboptimal HbA1c (HbA1c >7.5%; n =20), there was no difference across the two periods for all the above CGM metrics and for GV.

Comparing effect of age over Ramadan fasting

Sub-analysis of CGM data among the younger age group (10 years old and less, n=6) showed differences for TIR

Table 4. Comparing the effect of HbA1c

	HbA1c <7.5% (n=4)			HbA1c ≥7.5% (n=20)		
	Before Ramadan	During Ramadan	*p*-value	Before Ramadan	During Ramadan	*p*-value
Mean SG* (mmol/L)	8.6 ± 2.6	10.4 ± 3.2	0.03[a]	9.9 ± 2.2	10.6 ± 2.9	0.15[a]
Estimated A1c* (%)	7.1 ± 1.7	8.2 ± 2.0	0.03[a]	7.8 ± 1.4	8.3 ± 1.8	0.12[a]
Time in range_level 1* (%)	51.8 ± 7.9	39.3 ± 19.4	0.23[a]	51.0 ± 15.7	43.0 ± 21.6	0.12[a]
Time in range_level 2* (%)	38.3 ± 20.5	27.0 ± 18.9	0.04[a]	33.9 ± 15.5	27.3 ± 17.6	0.06[a]
Time in hyper_level 1*(%)	35.3 ± 23.0	52.3 ± 30.9	0.05[a]	41.8 ± 18.3	49.8 ± 25.4	0.10[a]
Time in hyper_level 2* (%)	10.8 ± 10.7	24.8 ± 18.5	0.08[a]	21.2 ± 14.1	25.8 ± 19.0	0.28[a]
Time in hypo_level 1* (%)	13.0 ± 19.5	8.5 ± 12.6	0.29[a]	7.3 ± 8.4	7.2 ± 10.4	0.97[a]
Time in hypo_level 2* (%)	6.5 ± 10.5	2.8 ± 2.6	0.46[a]	3.8 ± 6.5	3.6 ± 5.8	0.90[a]
MAGE* (mmol/L)	6.6 ± 1.3	8.1 ± 1.5	0.09[a]	8.5 ± 3.2	8.8 ± 2.5	0.74[a]
HBGI*	10.0 ± 5.4	15.4 ± 7.7	0.09[a]	15.1 ± 6.5	17.4 ± 8.3	0.19[a]
LGBI*	6.3 ± 4.7	7.0 ± 4.8	0.80[a]	5.5 ± 4.2	6.1 ± 5.0	0.68[a]

* Numerical data presented in means (SD)
[a] Paired sample t-test
[b] Wilcoxon Sign Ranked test
Time in range_level 1, SG readings between 3.9-10 mmo/L
Time in range_level 2, SG readings between 3.9-7.8 mmol/L
Time in hyperglycemia_level 1, SG readings 10-13.9 mmol/L
Time in hyperglycemia_level 2, SG readings >13.9 mmol/L
Time in hypoglycemia_level 1, SG readings 3.0-3.9 mmol/L
Time in hypoglycemia_level 2, SG readings <3.0 mmol/L
MAGE, mean amplitude glycaemic excursion
HBGI, high blood glucose index
LBGI, low blood glucose index
(Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range)[22]

Table 5. Comparing the effect of age

	Age ≤10 years old (n=6)			Age >10 years old (n=18)		
	Before Ramadan	During Ramadan	*p*-value	Before Ramadan	During Ramadan	*p*-value
Mean SG* (mmol/L)	10.3 ± 1.1	12.4 ± 1.8	0.02	9.5 ± 2.5	10.0 ± 2.9	0.33
Estimated A1c* (%)	8.1 ± 0.7	9.4 ± 1.1	0.02	7.6 ± 1.6	7.9 ± 1.8	0.28
Time in range_level 1* (%)	48.5 ± 6.7	30.5 ± 12.5	0.00	51.9 ± 16.4	46.3 ± 21.9	0.32
Time in range_level 2* (%)	30.2 ± 5.5	16.2 ± 10.9	0.01	36.1 ± 18.1	30.9 ± 17.8	0.16
Time in hyperglycaemia_level 1*(%)	24.7 ± 9.0	30.7 ± 7.4	0.24	20.1 ± 9.2	22.5 ± 12.7	0.31
Time in hyperglycaemia_level 2* (%)	22.5 ± 5.5	37.5 ± 16.1	0.07	18.4 ± 15.8	21.7 ± 18.0	0.45
Time in hypoglycaemia_level 1* (%)	3.7 ± 4.3	0.8 ± 1.3	0.11	4.1 ± 5.1	5.0 ± 6.9	0.29
Time in hypoglycaemia_level 2* (%)	0.7 ± 1.2	0.5 ± 0.8	0.61	5.4 ± 7.9	4.4 ± 5.8	0.57
MAGE* (mmol/L)	9.2 ± 1.8	8.6 ± 1.5	0.52	7.9 ± 3.3	8.7 ± 2.6	0.34
HBGI*	15.3 ± 3.4	20.2 ± 5.5	0.08	13.9 ± 7.3	16.0 ± 8.6	0.25
LGBI*	3.9 ± 2.0	3.1 ± 2.9	0.47	6.2 ± 4.6	7.2 ± 5.1	0.50

* Numerical data presented in means (SD)
[a] Paired sample t-test
Time in range_level 1, SG readings between 3.9-10 mmo/L
Time in range_level 2, SG readings between 3.9-7.8 mmol/L
Time in hyperglycemia_level 1, SG readings 10-13.9 mmol/L
Time in hyperglycemia_level 2, SG readings >13.9 mmol/L
Time in hypoglycemia_level 1, SG readings 3.0-3.9 mmol/L
Time in hypoglycemia_level 2, SG readings <3.0 mmol/L
MAGE, mean amplitude glycaemic excursion
HBGI, high blood glucose index
LBGI, low blood glucose index
(Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range)[22]

level 1 (SG 3.9-10mmol/L), TIR level 2 (SG 3.9-7.8 mmol/L), mean SG, and estimated A1c across both periods (Table 5).

Values before and during Ramadan were: TIR level 1 was 48.5 ± 6.7% and 30.5 ± 12.5% (p=0.00); TIR level 2 was 30.2 ± 5.5% and 16.2 ± 10.9% (p=0.01); mean SG was 10.3 ± 1.1 mmol/L and 12.4 ± 1.8 mmol/L (p=0.02); and estimated A1c was 8.1 ± 0.7% and 9.4 ± 1.1%, (p=0.02). There were no differences demonstrated for time in hyperglycaemia level 1 (SG 10-13.9 mmol/), time in hyperglycaemia level 2 (SG >13.9 mmol/L), time in hypoglycaemia level 1 (SG 3.0-3.9 mmol/L) and time in hypoglycaemia level 2 (SG <3.0 mmol/L). There were also no differences in GV metrics (MAGE, HBGI, and LBGI) across both periods.

On the other hand, for those in the older age groups (more than 10 years old, n=18), all CGM metrics and GV show no difference across the two periods.

DISCUSSION

To the best of our knowledge, this is the only other study after Lessan et al.,[13] that utilised retrospective CGM to investigate the glycaemic effect of Ramadan fasting among diabetes patients before and during Ramadan. Of the studies among T1DM children and adolescents, this is the first that selected retrospective CGM over rt-CGM, with its advantage of analysis of "unaltered" glycaemic data. This may be more reflective of the true glycemic profile of patients and is helpful for Muslim T1DM youths in this part of the world who have less access to rt-CGM technology.

Our demographic findings were generally similar with the global trend of Ramadan fasting among T1DM children and adolescents, evidenced by the younger age, shorter duration of diabetes, higher percentage of past experiences and the less optimal HbA1c. This is similar to the recent DaR Global Survey 2020,[8] that had reported 75% of T1DM youths attempted Ramadan fasting with HbA1c of 9.5 ± 2.0%. Apart from religious inclination, this trend could be driven by our local socio-cultural background and preferences.[4,5,25] In Malaysia, despite the reportedly growing prevalence of obesity,[26] the prevalence of diagnosed T1DM youths in our cohort were not affected.

In terms of access to advanced diabetes technology, compared to the DaR Global Survey 2020 which had reported 93.8% of T1DM on MDI, 4.8% on CSII, and rest 1.5% on pre-mixed insulin,[8] our cohort also showed lesser access to more advanced technology.

The Malaysia Health Technology Assessment Section (MaHTAS) in 2015 stated that the switch from MDI to CSII in T1DM would cost the public health care system an increased estimate of USD 1230 to USD 1900 per annum that would translate to an incremental cost-effectiveness ratio (ICER) of USD 12,930.[27] At the time of writing of this report, CSII is yet to be included as part of public health care for T1DM children in Malaysia and is limited only to those who could afford it. That said, the existing public health care system that provides near-fully subsidised health care services to its citizens regardless of socio-economic class has effectively nearly eliminated the impact of financial gaps. T1DM youths from both West and East Peninsular Malaysia in our cohort were comparable, in terms of the diabetes care and insulin treatment they received, despite differences in socio-economic profiles. To further illustrate these socioeconomic differences, the Malaysia National Census 2019[28] reported that the Federal Territories of Putrajaya, Kuala Lumpur, and the state of Selangor (West peninsular Malaysia) had a higher median monthly income (USD 1,959 to RM 2,517), compared to the state of Kelantan

(East peninsular Malaysia) with a reported median monthly income of USD 850.

The reported MARD was close to the data published by Medtronic®, which quoted 12.2% for paediatric populations.[29] According to the latest CGM consensus guidelines by Advanced Technologies and Treatments for Diabetes (ATTD),[21,22] recommended clinical targets for paediatric T1DM are as described: TIR level 1 (SG 3.9-10.0 mmol/L) of >60%; time in hyperglycaemia level 1 (SG 10-13.9 mmol/L) of <25%; time in hyperglycaemia level 2 (SG >13.9 mmol/L) of <5%; time in hypoglycaemia level 1 (SG 3.0-3.9 mmol/L) of <4%; and time in hypoglycaemia level 2 (SG <3.0 mmol/L) of <1%.

For ease of discussion, we used the term "rate" to refer to the percentage of time spent in a certain glycaemic range, e.g., mild hypoglycaemia rate as referring to the time in hypoglycaemia level 1 (SG 3.0-3.9 mmol/L), severe hypoglycaemia rate as referring to time in hypoglycaemia level 2 (SG <3.0 mmol/L), and as appropriate for the others.

When applying these recommended clinical targets, it is evident that the glycaemic profiles in our cohort were suboptimal even before Ramadan month, as seen in the lower TIR level 1, higher severe hyperglycaemia rate and higher severe hypoglycaemia rate. Both the mild hyperglycaemia rate and mild hypoglycaemia rate were within normal limits. During fasting, similar CGM profiles were observed with no further difference across both the periods for TIR level 1, mild hypoglycaemia rate, severe hypoglycaemia rate, mild hyperglycaemia rate, and severe hyperglycaemia rate. The mean SG and estimated A1c, referred to as glucose management indicator (GMI) to avoid confusion with the laboratory obtained HbA1c, even though different for before and during Ramadan, have limited clinical values reflecting glycaemic outcome by themselves.[21,22]

In contrast the CGM metric TIR correlates well with HbA1c.[30,31] Specifically, TIR level 1 (SG 3.9-10 mmol/L) of >60%, is associated with a HbA1c level of <7.5%. Furthermore, Beck et al.,[32] in 2019 who used the existing Diabetes Control and Complications Trial (DCCT) SMBG data set to compute TIR for validation, concluded that TIR is strongly associated with the risk of microvascular complications and should be used as another clinical outcome measure apart from HbA1c.[32]

The TIR level 2 (SG 3.9-7.8 mmol/L) despite being worse during Ramadan, carries no clinical implication for the paediatric T1DM population,[21,22] as this CGM metric is specifically applied only for pregnant women with diabetes.

Similar to other authors,[13,17] glycaemic variability (GV) in our cohort showed no difference before and during Ramadan, indicating no worsening of glucose variability during Ramadan. However, it should be noted that acceptable GV should ideally be within or less than 36% according to the ATTD consensus guidelines,[21,22] and this threshold was exceeded by our cohort from the onset. The CGM findings from our cohort indicated that Ramadan fasting, did not negatively impact or worsen glycaemic control.

Considering the confounding effects of different insulin delivery systems and CGM technology (rt-CGM vs. retrospective CGM) over the glycaemic outcome, the comparison of our CGM data with previous authors[12–18] should be adjusted to these differences.

Lessan et al.,[13] who used retrospective CGM, reported similar outcomes of no difference for mean SG, hypoglycaemia rate, as well as MAGE, LBGI, HBGI, before and during fasting. Their study however, included 56 adult patients with unspecified diabetes and 7 of them were healthy volunteers, forming a heterogeneous cohort. The study of Kaplan et al.,[17] with participants consisting of 12 T1DM adolescents with rt-CGM on CSII (85%) and 2 with rt-CGM on MDI (15%), reported no difference in the mean SG, hypoglycaemia rate, hyperglycaemia rate and TIR level 1 before and during Ramadan fasting. Their subanalysis also reported that for HbA1c <8% (n=6), there was a lower hypoglycaemia percentage (6.2% vs. 9.6%) during Ramadan as opposed to before.[17] This was not reproduced in our cohort, (Table 4) and will be discussed later.

Consistent with the baseline HbA1c of 9.6 ± 1.9%, the TIR level 1 in our cohort was 51.1 ± 14.6% and 42.2 ± 20.9% before and during Ramadan, respectively (p=0.05), which were worse than the study of Kaplan et al.,[17] who had used more advanced diabetes technology. However, compared to the study of Alfadhli et al.,[16] whose cohort characteristics were closer to ours, the reported TIR level 1 was 42% during Ramadan.

Nevertheless, it is noteworthy that despite advanced diabetes technology, most TIR during Ramadan fasting still fall short of the clinical targets, implying the importance of other aspects of diabetes care, such as nutritional interventions.

The similar CGM outcomes for before and during Ramadan reassures that fasting *per se*, is not associated with worse glycaemic outcomes during Ramadan. Instead, the differences in diabetes technology used seemed to be affect glycaemic outcomes more, and would be an interesting area of focus for future studies.

On the other hand, the CGM findings of high severe hypoglycaemia rates before and during Ramadan did indicate serious clinical concerns and reflected the extent of subclinical hypoglycaemia or unawareness that escapes clinical evaluation. The reported severe hypoglycaemia rate of 4% before Ramadan was equivalent to the duration of 1 hour per day, when blood glucose levels was below 3.0 mmol/L, far exceeding the clinical target of fewer than 15 minutes or 1%. This hypoglycaemia unawareness due to impaired counter-regulatory hormone response and defective adrenaline drive from hypoglycaemia-

associated-autonomic failure (HAAF)[33] could lead to detrimental and life-threatening complications, if left unrecognised. Hence, compliance to SMBG during fasting among T1DM youths cannot be over-emphasized. Most Ramadan guidelines,[2,4,5] state that doing SMBG should not symptom-based alone, but should be done regularly for 7-points per day to include pre-*suhur,* morning, mid-day, mid-afternoon, pre-*iftar,* 2-hours post *iftar*, and at any time when symptomatic or unwell. This is also important because hypoglycaemia not only occurred during fasting hours but also post *iftar*, due to insulin carbohydrate mismatch or increased physical activites.[12]

On the other hand, the elevated severe hyperglycaemia rate in both periods raise a concern over the risk of DKA, and other long-term metabolic consequences. The severe hyperglycaemia rate of 25.6% during Ramadan in our cohort was equivalent to a duration of 6 hours per day when blood glucose was beyond 13.9 mmol/L. Most of this exposure happened at the post-*iftar* hours.[12,16] Lessan et al.,[13] described the mean CGM curve for diabetes patients during fasting, where the gradual fall of blood glucose during fasting hours was followed with an abrupt and sustained rise of blood glucose after the sunset meal, and this effect was exaggerated for the insulin-dependent. This hyperglycaemia phenomenon could be attributed to the large carbohydrate-rich food or drink with high fat and glycaemic index during *iftar* to compensate for daytime fasting. For the Muslim community in Malaysia, this could also be owing to the widespread culture of food *Bazaars* that commonly flourish during Ramadan, on top of our tradition of serving guests with sweet drinks *(syrup)*, and baked goods (*kuih*) during family gatherings of breaking fast. Ramadan has been viewed as the most important time of the year for the food retail sector in Malaysia, with an increase in retail growth of baking ingredients and non-alcoholic beverages, compared to the non-Ramadan period.[25]

The suboptimal and at-risk CGM profiles among Muslim T1DM youths outside of and during Ramadan as seen in previous studies[13,17] and our cohort, is indicative that work needs to be done to improve Ramadan glycemic outcome. Diabetes technology could potentially be part of the solution. In a meta-analysis and systematic review of 17 observational studies involving 1699 patients[34], the use of CSII in Ramadan was associated with lower severe hyperglycaemia rate but higher mild hyperglycaemia rate when compared to MDI. Alamoudi et al.,[35] similarly concluded that CSII use in Ramadan was associated with less glucose variability, while Khalil et al.,[36] concluded that SAP in Ramadan was associated with more flexibility and reduced the severity and duration of hypoglycaemia.

However, as emphasized by the IDF-DaR guidelines,[3–5] intensive Ramadan-focused education must be given to patients and families before the commencement of Ramadan, covering the aspects of risk quantification, blood glucose monitoring, fluids, and dietary advice, exercise and physical activity patterns, medication adjustments, when to stop fasting and the recognition of complications with self-management strategies. Diabetes-focused education and empowering both caregivers and patients is crucial, together with individualised care by clinicians who have an understanding of the patients' lifestyles and cultures, to enable appropriate advice and suitable insulin titration.

Our study did not demonstrate the beneficial effect of optimal HbA1c, which was seen in the study of Kaplan et al.,[17] which showed that patients below the threshold of HBA1C of 8% had less hypoglycaemia rates during fasting. For the purpose of standardization, we used a HbA1c threshold of <7.5%, in accordance to the latest IDF-DAR guideline 2021,[4] which defines HbA1c risk score as "0" when <7.5%, "1" when HbA1c 7.5-9.0%, and "2" when HbA1c >9.0%. For the subgroup with optimal HbA1c (HbA1c <7.5%, n=4), there was no difference observed for all the CGM metrics across both periods. These findings suggest that among those with optimal HbA1c, Ramadan fasting did not adversely affect their glycaemic outcomes. We therefore surmised that the apparent benefit in Ramadan observed in the Kaplan study[17] may be related to the effect of the diabetes technology used. Similarly, for the subgroup with poorer HbA1c (HbA1c >7.5%, n=20), no differences before and during Ramadan were demonstrated, implying no escalation of glycaemic risks during fasting. This was also been discussed by Zabeen et al.,[37] based on SMBG readings, concluded that T1DM children and adolescents with poorly controlled HbA1 could fast safely in Ramadan, with no differences in glycaemic outcomes observed between the periods before and during Ramadan.

Since the appropriate age of fasting is controversial and could be further complicated by the trend of earlier puberty onset seen worldwide, we did a sub-analysis of our cohort by age, with 10 years old chosen arbitrarily as the cut-off. For those younger (10 years old or less, n=6), there was a seemingly worse glycaemic outcome during Ramadan fasting, evidenced by the reduction of both TIR level 1 and TIR level 2 during Ramadan compared to before.

However, this needs to be re-evaluated in future studies with a greater number of participants. The apparent glycaemic deterioration among younger children could be incidental and confounded by factors such as the "conservative approach" of insulin dosing by the clinicians or the caregivers that administer lower doses, due to concern for hypoglycaemia. Furthermore, reduction of physical activities, which usually occurs to a greater extent among younger children in Ramadan, could also be another reason. According to the IDF-DaR guidelines,[5] there is no lower age limit or age-risk mentioned, except for those >70 years old. And when titrating the insulin dose, HbA1c levels rather than age were used to stratify the risk, in that when it exceeds 7.5%, no basal insulin reduction is required and prandial insulin could be given as per exchange for both *suhur* and *iftar* meals. Lastly, the relatively higher severe hypoglycaemia rate noticed in the older group is also likely to represent the effect of diabetes duration,

which resulted in a higher likelihood of hypoglycaemic unawareness and implying the need for more frequent SMBG, even among older children.

Limitations

Sample size was limited primarily due to travel restrictions from the COVID-19 pandemic through the Movement Control Order (MCO) which made it difficult for some patients to participate in our study.

Future CGM studies with larger sample sizes should be conducted for better generalisability, and include different types of diabetes technology. If feasible, we also recommend that CGM be done for the entire duration of Ramadan for a more complete representation of glycaemic profiles.

CONCLUSION

Our study described and compared CGM outcomes of T1DM children and adolescents before and during Ramadan. We found that fasting by itself, is not associated with short-term glycaemic deterioration. This study had also confirms that with Ramadan-focused education and compliance to SMBG, fasting is feasible and safe.

With knowledge that fasting has a neutral effect on glycaemic profiles, Ramadan month may be viewed as an opportunity for T1DM youths to improve their glycaemic control, in conjunction with spiritual development.

Aside from pursuing advanced diabetes technology that could be helpful in better management of diabetes, efforts should also be focused on pre-Ramadan education and self-care empowerment.

Lastly, Ramadan diabetes care and insulin titration should be highly individualised and guided with an understanding of the individual's background, lifestyle and culture.

Acknowledgments
The authors thank the following: the Director General and Deputy Director General (Research and Technical Support) of the Ministry of Health; Dr. E Puvanesvaran Ramachandran, the Medical Officer of Hospital Universiti Sains; Ms. Nurshazliza Zakaria and Ms. Syahidatun Mardhiah, dietitians from the Dietetics Department of Hospital Putrajaya; Ms. Mumtas Abu Gani and Ms. Ezzatulakma Mohd Nadzri, Diabetes Nurse Educators of the Diabetes Resource Center of Hospital Putrajaya and Dr. Lisa Mohamed Nor from the Clinical Research Centre of Hospital Putrajaya.

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

Author Contribution Statement
STT, SH and JYHH conceived the study; developed the methodology; verified research outputs; reviewed and edited the manuscript and administered the research activity planning and execution. STT and SH synthesized the study data and provided the study materials. STT curated the data; prepared the original draft; prepared the data presentation and acquired financial support for the study. SH and JYHH supervised the research activity planning.

Author Disclosure
All authors declared no conflict of interest.

Funding Source
The study was funded by the National Institute of Health (NIH), Research and Technical Support Unit, Ministry of Health, Malaysia.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Factors Associated With Dietary Behaviour Among Patients With Type 2 Diabetes Mellitus in Rural Indonesia

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Abstract

Background. Type 2 Diabetes Mellitus (T2DM) is one of the fastest-growing diseases and most serious major health problems worldwide. Few studies have focused on the association of social support with diabetes-related dietary behaviour.

Objective. To examine the relationship between social support and dietary behaviour among patients with diabetes in a rural area of Indonesia.

Methodology. This was a descriptive cross-sectional study that included 120 physically healthy patients above 18 years old with T2DM for at least 6 months. Data analysis was done using a stepwise regression model.

Results. The mean age was 61.97 years (SD = 7.85, range = 52-74); 86.7% of the participants were females. Social support (β = 0.272, *p* = <0.001), diabetes medications (β = 0.169, *p* = 0.003), duration of diabetes (β = 0.118, *p* = 0.0047), and presence of diabetes complications (β = 0.197, *p* = 0.008) were significant predictors of dietary behaviour and accounted for 34.2% of the variance.

Conclusions. Social support, diabetes medications, presence of diabetes complications, and duration of diabetes were associated with improved dietary behaviour. Therefore, social support should be considered when designing dietary interventions for patients with type 2 diabetes mellitus.

Key words: critical illness-related corticosteroid insufficiency, shock, corticosteroid, cortisol

INTRODUCTION

Diabetes mellitus type 2 (T2DM) is a chronic metabolic disorder that has affected approximately 463 million adults; it is estimated to increase to 700 million by 2045.[1] It is one of the fastest growing diseases that poses a serious impact on public health worldwide.[1] Globally, there were about 4.2 million diabetes-related deaths and at least US$ 760 billion in diabetes-related healthcare costs.[1]

Approximately 79% of adults with diabetes reside in developing countries. Indonesia ranks 7th among countries with the highest prevalence rates of diabetes mellitus globally. In 2019, the number of people with diabetes in Indonesia was 10.7 million (6.2% of the total population).[2] According to the Basic Health Research in 2018, East Java province ranked 2nd in the number of patients with diabetes in Indonesia. About 151,878 people with an average age of 15-45 years were reported to have diabetes in 2018.[2] Up to 90% of T2DM cases may be preventable if people adopted proper eating habits and lifestyle changes.[3] Approximately 80 to 90% of people with T2DM are overweight or obese. Weight reduction of 5 to 10% from initial body weight will significantly decrease the risk of cardiovascular disease by improving glycemic control.[4]

Medical Nutrition Therapy is a key component in diabetes management. Numerous dietary and lifestyle guidelines promoting healthy eating patterns have been created to achieve optimal levels of blood glucose, blood pressure, and lipids to delay or prevent diabetes complications.[5] In previous observational researches, dietary habits were reflected by data on food intake and involved various diets such as the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet or the alternative Healthy Eating Index (AHEI).[4] These diets are known to lower the risk for chronic diseases.

Previous studies have reported predominant dietary trends in American, European and Asian populations and their

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: April 20, 2021. Accepted: November 11, 2021.
Published online first: June 16, 2022.
https://doi.org/10.15605/jafes.037.02.02

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relationship with diabetes. A balanced diet composed of nutritious food such as fish, meat, vegetables, fruits and whole grains is associated with a decreased risk of T2DM. Results of a systematic review showed that diets based on the Mediterranean diet, DASH and AHEI have great potential for diabetes prevention. However, these diets differ in some specific components and appear to be population-specific.[6] For example, food accessibility and consumption vary significantly in Indonesia compared to other regions due to differences in environment, agriculture, food production, processing and cultural practices. In addition, people consume various combinations of food groups. Studies on population-specific dietary habits have emerged in an attempt to address this issue.

Recent studies have shown that patients with a strong social support system have better glycemic control, improved therapeutic compliance, and enhanced self-care behaviors, making it a significant parameter in diabetes management.[7,8] Social support was identified as a significant predictor of certain self-care behaviors such as diet, exercise, blood glucose monitoring and foot care.[9]

A study done among Turkish patients with diabetes showed that self-care practices increased as perceived social support also increased.[10] Another study among Indonesians found that social support was associated with self-management.[11,12] However, social support also varies by culture, and the role of social support in people with diabetes should be studied in a culture-based context.[8] While some empirical studies have explored the relationship between social support and diabetes management, few have concentrated specifically on the impact of social support on diabetes-related dietary behaviour. Hence, the aim of this study was to examine the relationship between social support and dietary behaviours among patients with diabetes in rural Indonesia.

METHODOLOGY

This cross-sectional study was conducted at one of the community centers in Malang, East Province, Indonesia.

Participants

The study enrolled 120 people with type 2 diabetes between January and July 2019 using convenience sampling. This study was conducted at a community center in Malang, East Province, Indonesia. It was approved by the ethical review board at the authors' institution (No.E.5.a/029/KEPK-UMM/II/2020).

All recruited participants agreed to take part in the study. Patient inclusion criteria were as follows: Type 2 diabetes duration of at least 6 months, age over 18 years old, and absence of any physical disability. Patients were excluded if they were pregnant, had a mental/cognitive problem, or had advanced chronic complications of type 2 diabetes.

The sample size was calculated using a power analysis (G-Power software Version 3.1) for the planned regression analyses, effect size = 0.15, power level = 0.80, effect size = 0.15, and p = 0.05, resulting in a required sample size of 98.

Data Collection

The nurses in the community center helped identify potential participants. Data were gathered through face-to-face interviews. Before the questionnaires were administered, the research coordinator informed the nurses about the process of data collection, as well as the inclusion and exclusion criteria. On the average, completion of the forms took 15 minutes.

Demographic information such as gender, age, level of education, marital status, job and level of income was obtained through self-reports. The patient's clinical diabetic symptoms over the last year were also assessed with self-reports. A 3-month review of the patient's complications, other non-communicable diseases and medications were extracted from medical records in the community health center. Five types of diabetes-related complications were included: hepatic, ophthalmologic, cardiac, cognitive, and peripheral vascular. A patient was labelled as having diabetes complications if he/she had at least one of the above.

Dietary behaviour was measured using the Dietary Behaviours Questionnaire (DBQ), a self-reported dietary behaviour questionnaire developed by Primanda et al. The instrument has been translated into Bahasa The DBQ consisted of four dimensions (33-items): recognition of calorie needs (4-items), selection of healthy food (16-items), arrangement of a meal plan (6-items), and management of challenges in dietary behaviours (7-items). The DBQ rating scale was a four-point Likert scale ("1" = never, "2" = occasionally, "3" = frequently, and "4" = routinely). The total DBQ scores ranged from 33 to 132 and were categorized into three: low (33 to 65), moderate (66 to 98), and high (99 to 132).[13] Cronbach's alpha coefficient was 0.73.

Social support was measured using an instrument developed by Megananda, et al.[14] This questionnaire has 12 items related to social support provided by family, friends, and others (e.g., health workers) including emotional support, appreciation support, information support and instrumental support. This questionnaire used a five-point Likert scale scoring as follows: 1 (strongly disagree), 2 (disagree), 3 (neutral), 4 (agree), and 5 (strongly agree). The total score ranged from 12 to 60. Social support was considered low if patients scored below 22, moderate if the score was 22 to 30, high if the score was 31 to 41, and very high if greater than 41. Reliability using Cronbach's alpha coefficient was 0.76.[14]

Statistical analyses

Data regarding demographic characteristics and clinical information were presented using numbers, percentages,

means and standard deviations. A Kolmogorov-Smirnov test showed that the data were normally distributed (p-value = 0.089). The Pearson product-moment correlation coefficient was used to examine relationships between two variables for continuous data with normal distribution and Spearman's rho test was used for non-normally distributed data. Standardized residuals were examined for variables before the regression model was created, and independent variables were examined for multicollinearity. Variables in the analysis included complications, treatment and nondiabetic complications. In the regression model, the variables significantly associated with dietary behaviors were included in the bivariate correlation analysis. A stepwise linear regression analysis was used to examine the relationship between social support and dietary behaviours after accounting for duration of disease and presence of diabetic complications. The data in the study were analysed using the SPSS 15.0 (Statistical Package for the Social Sciences) package program.

Table 1. Descriptive characteristics of individuals with type 2 diabetes and model variables (N = 120)

Variables	Mean ± SD	n (%)
Age in years	61.97±7.85	
Gender		
Female		104 (86.7)
Male		16 (13.3)
Educational level		
Primary school		14 (11.7)
Secondary school		79 (65.8)
Tertiary school		27 (10.5)
Marital status		
Married		98 (81.7)
Single		22 (18.3)
Employment		
Employed		25 (20.8)
Unemployed		95 (79.2)
Income level		
Income less than expenses		88 (73.3)
Income equal to expenses		23 (19.2)
Income more than expenses		9 (7.5)
Duration of diabetes (months)	26.93±7.65	
Diabetes chronic complications		
Yes		56 (46.7)
No		64 (53.3)
Nondiabetic chronic diseases		
Yes		32 (26.7)
No		88 (73.3)
Medications		
Oral hypoglycaemic agents only		56 (46.7)
Insulin only		30 (25.0)
Oral hypoglycaemic agents + insulin		34 (28.3)
Dietary behaviours questionnaire scores	109.32±13.05	
Recognizing amount of calorie needs	14.19±2.53	
Selecting healthy food	54.92±6.06	
Arranging a meal plan	18.53±2.38	
Managing dietary behaviours challenges	21.68±3.53	
Social support	55.37±6.69	
Emotional support	14.07±1.97	
Information support	13.91±1.62	
Appreciation support	13.55±1.95	
Instrumental support	13.83±1.78	

RESULTS

A total of 120 respondents were included in this study. The mean age was 61.97 years (SD = 7.85, range = 52-74); 86.7% were females; 65.8% graduated from secondary level; 81.7% were married; 79.2% were unemployed, and 64.1% had an income less than basic minimum regional salary. The mean period of diabetes diagnosis was 10.17 years (SD = 7.95, range = 1-60). Almost 50% of participants had diabetes complications while 26.7% had other nondiabetic chronic diseases. Forty-six percent were treated with oral hypoglycaemic agents (Table 1).

There is a positive relationship between dietary behaviour, social support, duration of diabetes, diabetic complications, medications and nondiabetic chronic diseases. (Table 2). There was no identified multicollinearity among the independent variables. Social support and dietary behaviour had a normal distribution. Stepwise regression analysis was performed to determine the contribution of dietary behaviour (Table 3).

Using Pearson's correlation, linear regression used the predictor variables shown to have a strong correlation with the dependent variable of dietary behaviour (Table 3). According to the results of our analysis, social support ($\beta = 0.272$, $p = <0.001$), medications ($\beta = 0.169$, $p = 0.003$), duration of diabetes ($\beta = 0.118$, $p = 0.0047$), and diabetes complications ($\beta = 0.197$, $p = 0.008$) were significant predictors of dietary behaviour and accounted for 34.2% of the variance (Table 3).

DISCUSSION

This study found that among patients in rural Indonesia, dietary behaviours were moderate in all dimensions (acknowledging caloric requirements, choosing nutritious foods, planning a meal schedule and handling the complexities of dietary behaviour). Varying results were observed in previous researches that used the same tool.[13]

Table 2. Correlation between different diabetes predictor variables and dietary behaviour (N = 120)

Variables	1	2	3	4	5	6	7
Years with diabetes	—						
Medications	-0.35*	—					
Diabetic complications	-0.35*	0.42**	—				
Nondiabetic chronic diseases	-0.36*	-0.37*	0.33**	—			
Medications	-0.25*	0.52**	0.44**	0.47**	—		
Social support	0.42**	0.40**	0.47**	0.39*	0.52**	—	
Dietary behaviour	0.44**	0.42**	0.38*	0.32*	0.41**	0.49**	—

Table 3. Predictors of dietary behaviours (N = 120)

Variables	β	SE of B	t	p
Total score of dietary behaviours				
Medications[a]	0.169	0.080	3.045	0.003
Diabetes complications[b]	0.197	0.137	-2.491	0.008
Years with diabetes	0.118	0.104	1.897	0.047
Social Support	0.272	0.141	4.072	<0.001

Model $R^2 = 0.351$, adjusted $R^2 = 0.342$, $F = 17.95$, $p < 0.001$.

[a] Medications (insulin medication use: yes = 1, no = 0) and [b] diabetes complications (yes = 1, no = 0) are dummy variables.

Cultural context can affect the dietary habits of patients with diabetes, (e.g., greater rice consumption, sweets and salt intake), which may be difficult to avoid.[15] In addition, social desirability, comfort, quality and price influence the determinants of food choice. Low income was seen as one barrier to the management of dietary behaviours among patients with type 2 diabetes.[16,17] In particular, there might have been poor-reporting among patients with diabetes and/or obesity in favour of socially appropriate answers. Therefore, nonjudgemental dietary behaviour assessment should be routinely integrated into diabetes management.

Social support is a significant factor that influences dietary behaviour even if its role in diabetes management has previously been underscored.[8,18] However, positive family support has helped individuals with diabetes adjust to their disease.[8] One of the possible reasons is that social support enhances adherence to a restricted diet and greatly impacts self-care and eating behaviours of individuals with diabetes. These studies did not directly measure dietary behavior but it was included as part of the self-management indicators.[10,12] Respondents who had higher scores were found to have very high levels of comfort and affection from family, friends and health workers. Respondents felt support in the form of assistance, if needed, from family, friends and medical personnel as well as affectionate advice on how to lead a healthy life.[19] This relationship can also be explained as a cultural phenomenon.

Most people in Indonesia are Muslims and therefore practice fasting. This custom may have influenced their answers to the questions in the diet domain. This proves that designing a diabetes self-management plan to include enhanced social support leads to improved dietary behaviours among patients.

Diabetes medications also affect dietary behaviour. In this study, we found that the dietary activity of the patients improved when insulin was included in the treatment.

We also found a significant association between the presence of diabetes complications and dietary behaviours, in contrast with the results of other related studies.[7,20] The reason for this inconsistency from previous findings may be due to individual culture-influenced interpretation of disease.[21] Patients have been observed to adjust eating behaviour when they have diabetic complications. Also, the duration of diabetes has been positively correlated with diet adherence. This is interesting because earlier studies did not reveal any association between the duration of diabetes and dietary behaviors.[7,20,22]

Limitations

In this study, the social support instrument we used was meant to evaluate the dimensions of social support in the general population, and was not specific for patients with diabetes. Indonesia has 35 provinces with many islands. This study was conducted in a region where the population had comparably lower income levels, which may have posed limitations on its generalizability. However, given that we conducted this study in one of Indonesia's major rural areas, the results can still be regarded as relevant.

CONCLUSIONS

In conclusion, we found that a good social support system improved dietary behaviours. The use of diabetes medications, presence of diabetes complications, and duration of diabetes were also significantly associated with a healthier dietary behaviour. When designing management strategies to benefit people with type 2 diabetes, it should include social support. Note that patients with diabetes may frequently adjust their diets because medical complications require them to do so. For this reason, individualize each dietary prescription according to the patient's needs. Future studies that investigate eating patterns with longer follow-up are recommended.

Acknowledgments
The authors thank all the patients who participated in this study.

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

Author Contributions Statement
ADK, NLM, NM conceived and designed the study. YBP and HNH helped in the collection, analysis and interpretation of data. ADK and NLM drafted the article. ADK revised the article.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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REVIEW ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Efficacy and Safety of Semaglutide for Weight Loss in Obesity Without Diabetes: A Systematic Review and Meta-Analysis*

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Abstract

Background. The weight loss benefit of semaglutide in patients with diabetes is well-documented, but its clinical utility in treating obesity among patients without diabetes is less described. We therefore assessed the efficacy and safety of subcutaneous semaglutide as treatment for obesity in patients without diabetes.

Methodology. A comprehensive search of PubMed/MEDLINE, Cochrane and Google scholar was performed to identify trials on the efficacy and safety of subcutaneous semaglutide on patients with obesity without diabetes. Primary outcome was expressed as percent mean weight difference. Secondary outcomes including risk for gastrointestinal adverse events, discontinuation of treatment and serious adverse events were expressed as risk ratios. These were calculated using the random effects model.

Results. The study included 4 randomized controlled trials having a total of 3,613 individuals with obesity without diabetes. The mean difference for weight reduction was -11.85%, favoring semaglutide [95% confidence interval (CI) (-12.81,-10.90), p<0.00001]. Secondary outcomes showed that the risk of developing gastrointestinal adverse events was 1.59 times more likely with semaglutide (RR 1.59, 95%CI [1.34, 1.88], p<0.00001). Risk for discontinuation due to adverse events was twice as likely in the semaglutide group (RR 2.19, 95%CI [1.36,3.55], p=0.001) and the risk for serious adverse events was 1.6 times more likely for semaglutide (RR1.60, 95%CI [1.24, 2.07], p=0.0003). Serious events were mostly of gastrointestinal and hepatobiliary disorders such as acute pancreatitis and cholelithiasis.

Conclusion. Among individuals with obesity without type 2 diabetes, subcutaneous semaglutide is effective for weight loss with an 11.85% reduction from baseline compared to placebo. This supports the use of semaglutide for weight management in obesity. However, risk of gastrointestinal adverse events, discontinuation of treatment and serious adverse events were higher in the semaglutide group versus placebo.

Key words: obesity, Glucagon-like Peptide -1, weight loss, semaglutide

INTRODUCTION

Obesity is a chronic relapsing condition,[1] defined as excessive fat accumulation[2] with serious clinical complications such as diabetes mellitus, cardiovascular disease, musculoskeletal disorders and malignancy.[2,3] It is caused by an imbalance between energy intake and expenditure.[4] Obesity has tripled worldwide since 1975. In 2016, more than 1.9 billion adults older than 18 years were overweight and 650 million were obese.[2] Treatment options for obesity include bariatric surgery and nonsurgical treatment such as diet modification, behavioral therapy and pharmacologic therapy.[5]

Liraglutide, a glucagon-like peptide-1 receptor agonist (GLP1-RA), has been approved for the pharmacologic treatment of obesity, and is the only drug in its class approved for this indication.[6,7] GLP-1 RAs were developed for the treatment of diabetes since the incretin GLP-1 was shown to decrease blood glucose by stimulating insulin secretion and decreasing glucagon release. It also promotes weight loss by inducing satiety, leading to decreased caloric intake by delaying gastric emptying. In the brain, it decreases appetite through the stimulation of satiety centers indirectly through neural afferents and directly by crossing the blood brain barrier.[4] GLP-1 RAs available in the market have different duration of action, frequency of administration and dosing.[8] Dosing frequency

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: March 2, 2022. Accepted: June 2, 2022.
Published online first: August 23, 2022.
https://doi.org/10.15605/jafes.037.02.14

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* *Presented in the poster exhibition category of the 9th Seoul International Congress of Endocrinology and Metabolism (SICEM 2021), awarded Best Poster Exhibition Award.*

affects adherence to therapy and studies show that a once weekly dosing was associated with significantly better adherence.[9,10] GLP-1 RAs available for once weekly dosing are exenatide, and the larger molecular weight dulaglutide and albiglutide. In a head-to-head review of GLP-1 RAs, albiglutide and dulaglutide were associated with less weight loss.[11] Large molecular weight GLP-1 RAs do not cross the blood brain barrier, which decreases its effect on stimulating the satiety center and leads to lesser weight loss compared with GLP-1 RAs with smaller molecular weight.[12] Semaglutide is a once weekly GLP-1 RA with smaller molecular weight[12] that is currently used for the treatment of type 2 diabetes mellitus (T2DM) and is associated with dose dependent reduction in glycosylated hemoglobin (HbA1c) as well as body weight in patients with diabetes.[6] It has not been approved for the treatment of obesity but the research study comparing a semaglutide to liraglutide in type 2 diabetics (SUSTAIN 10 trial) has shown that it was superior to liraglutide for weight reduction.[13]

Only a few drugs have been approved for treatment of obesity.[6,7] Some of these drugs include phentermine, bupropion/naltrexone and phentermine/topiramate. Safety has been a major concern since these drugs cause adverse psychological and physical effects.[7] It is therefore necessary to have an overall efficacy and safety evaluation of semaglutide as a promising option for the pharmacologic treatment of obesity. We conducted this systematic review and meta-analysis to present a comprehensive picture of the efficacy and safety of semaglutide for weight loss in obesity without diabetes.

Research question

Among individuals with obesity without T2DM, how effective and safe is semaglutide for weight loss?

Objectives

The objective of the study was to conduct a systematic review and meta-analysis on randomized controlled trials (RCT) of subcutaneous semaglutide on patients who are obese without T2DM. It aimed to determine the percent weight reduction from baseline after treatment with semaglutide. The study also aimed to determine the risk of gastrointestinal adverse events, risk for discontinuation and serious adverse events after treatment with semaglutide.

METHODOLOGY

Search strategy

This meta-analysis was performed in accordance to the PRISMA 2020 statement. A comprehensive systematic search of PubMed/MEDLINE, Cochrane and Google scholar was performed from inception to June 2021 to identify publications in the English or foreign language with adequate English translations on semaglutide versus placebo and other GLP-1 RAs for weight loss in obesity without T2DM. The search strategy was "semaglutide" AND "obesity." No filter was used. Ongoing trials were also sought in the relevant search. Two reviewers (HCT and MMM) independently searched the databases to identify all potentially eligible studies and reviewed the full articles for inclusion. Selected articles were then compared and the decision to include the article was reached through a consensus. Consult with the third author (OAD) was done when a consensus could not be made.

Types of studies and patient characteristics

RCTs were included in this review. Only published studies on adults with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with at least one weight-related comorbidity were included. Patients with diabetes mellitus were excluded. The inclusion and exclusion criteria of each article were reviewed to confirm the target population.

Interventions/outcome

Studies that measured percent weight loss from baseline after treatment with semaglutide were included. Studies that compared semaglutide with medications other than GLP-1 RA or placebo were excluded.

Selection of studies

Two authors (HCT, MMM) independently screened and reviewed the abstracts and articles for inclusion. Articles were selected based on the inclusion criteria and decision to include the article was made through consensus. After removal of duplicates, the search yielded 945 publications. Based on title and abstract, 895 were either a clinical trial, review, meta-analysis, or cohort study and these were excluded. Full texts of 50 studies were reviewed and 4 were eligible for systematic review. Studies that had comparison groups and outcome not compatible with the goals of this review were excluded.

Data extraction and risk of bias assessment

Selected articles were downloaded and independently reviewed by the reviewers. Discrepancies in the selection process were resolved through discussion and reaching a consensus. Consultation with a third expert investigator was done when a consensus could not be reached. A data collection form was created and was used to extract information from each article. This included author, demographics of study population, inclusion and exclusion criteria, intervention and comparison methods, primary outcome of percent weight reduction and gastrointestinal adverse events. Quality assessment was done using the Cochrane Collaboration's tool for assessing risk of bias. Each article was critically appraised for risk of bias, which includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. These were graded

as high, low, or unclear, and discrepancies were settled through constructive discussion and reaching a consensus.

Data synthesis and analysis

Data synthesis and analysis were performed using Revman 5.4 for Mac. The effect measure was reported as percent mean weight change at 95% confidence interval. A p value < 0.05 was considered as statistically significant. Statistical heterogeneity between trials were assessed using the I^2 statistics. An I^2 value of 30 to 60% indicated moderate heterogeneity, 50 to 90% substantial heterogeneity, and 75 to 100% indicated considerable heterogeneity. Random effects model was used when heterogeneity was identified. When significant heterogeneity was detected even after using random effects model, a sensitivity analysis was performed. This was done by repeating the initial analysis, reviewing the inclusion and exclusion criteria and evaluating the methodology of each trial to see what could have contributed to the heterogeneity.

Registration

This study was registered with Prospero with ID CRD42021251299.

RESULTS

Study selection

The search yielded 1208 articles, of which 263 were duplicates. After removal of duplicates and 895 articles based on title and abstract alone, 50 full text articles were assessed for eligibility, of which 46 were excluded since the studies were either done in patients with diabetes or non-obese population, used an intervention other than semaglutide, or had an outcome that was not compatible with the goals of this review. After careful evaluation, 4 RTCs were included in the review (Figure 1). These trials measured the percent change in body weight after treatment with semaglutide versus placebo and reported the most common adverse effects associated with treatment. No ongoing similar studies were identified in the search.

Study characteristics

Across 4 trials, 3,613 individuals were included in the study (2,350 in the semaglutide group and 1,263 in the placebo group). Baseline characteristics were similar between both groups in the 4 individual trials. The mean weight, BMI, age and sex of the participants included in the trials are shown in Table 2. All were adults ≥18 years old with a BMI of ≥30 kg/m^2 or ≥27 kg/m^2 with at least 1 treated or untreated weight-related comorbidity without diabetes. The most common comorbidities were hypertension and dyslipidemia. The study of Wilding et al., used once weekly semaglutide injected subcutaneously starting at a dose of 0.25 mg and escalated every 4 weeks until the target dose of 2.4 mg was reached. However, unlike the other 2

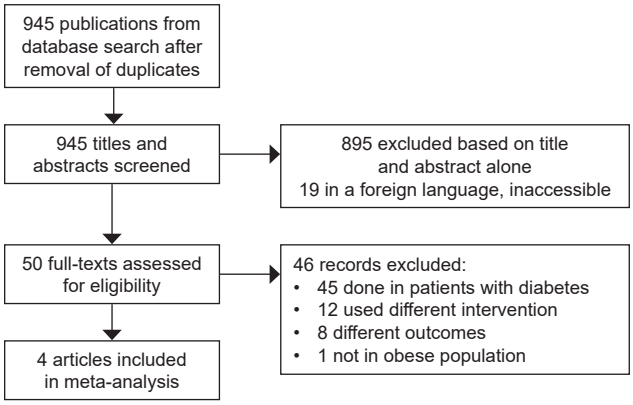

Figure 1. Flow diagram for systematic review and study selection of randomized controlled trials on semaglutide for weight loss in patients who are obese without diabetes.

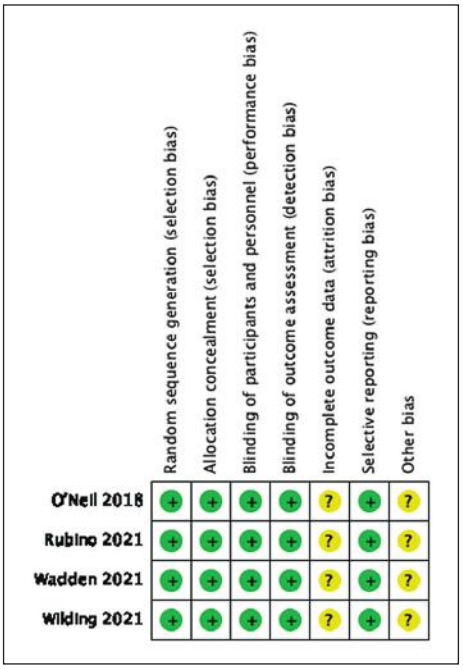

Figure 2. Risk of bias assessment of the included randomized controlled trials.

studies where participants were randomized to receive semaglutide or placebo at the start of study, Rubino's study randomized participants after the target dose was reached to continue with semaglutide or switch to matching placebo. O'Neil et al., used a smaller dose of semaglutide that was given once daily at 0.05 mg to 0.4 mg. The course of treatment was 68 weeks for Wilding, Rubino and Wadden et al., but only 52 weeks for O'Neil et al.'s study. All trials reported percent change in body weight from baseline until the end of study as well as most common adverse events associated with treatment (Table 1).

Risk of bias

Summary of the risk of bias is shown in Figure 2. The risk of bias is generally low for all studies. However, we deemed the risk of attrition bias questionable since in all 4 studies,

Table 1. Characteristics of the studies included in the systematic review and meta-analysis

First author, year	Study design	Study population	Inclusion criteria	Exclusion criteria	Interventions	Outcome
O'Neil, 2018	RCT	≥ 18 yo with BMI ≥30 kg/m^2	BMI ≥30 kg/m^2 with no weight fluctuation more than 5 kg in the 90 days before screening Undergone at least one unsuccessful non- surgical weight-loss attempt Free from major depressive symptoms	Diabetes	Semaglutide injected subQ once daily at one of the following doses (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg) or liraglutide (3.0 mg). Doses started at 0.05 mg and incrementally escalated every 4 weeks to the next level until reaching the final doses vs placebo of equal injection volume.	Percent change in bodyweight from baseline to week 52 most common reported adverse events
Rubino, 2021	RCT	≥ 18 yo with BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with at least 1 treated or untreated weight-related comorbidity	At least 1 self-reported unsuccessful dietary effort to lose weight BMI of 27 kg/m^2 or higher with at least 1 treated or untreated weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)	Diabetes, HbA1c 6.5% or greater More than 5 kg change in body weight within 90 days of screening.	Semaglutide started at 0.25 mg given subQ once weekly, increased every 4 weeks until 2.4 mg by week 16, and continued to week 20, then randomized, to continue semaglutide or switch to matching placebo for 48 weeks plus lifestyle intervention with monthly counseling, reduced calorie diet, increased physical activity	Percent change in body weight from randomization (week 20) to week 68 Most common reported adverse events
Wadden, 2021	RCT	≥ 18 yo with BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with at least 1 treated or untreated weight-related comorbidity	1 or more unsuccessful dietary effort to lose weight BMI of 27 kg/m^2 with at least 1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)	Diabetes, HbA1c 6.5% or greater More than 5 kg change in body weight within 90 days of screening prior or planned obesity treatment with surgery or a weight loss device	Semaglutide started at 0.25 mg given subQ once weekly, with dose escalation every 4 weeks until reaching target dose of 2.4 mg by week 16, continued until week 68 plus diet modification vs placebo	Percent change in body weight by week 68 Most common reported adverse events
Wilding, 2021	RCT	≥ 18 yo with BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 with at least 1 treated or untreated weight-related comorbidity	1 or more unsuccessful dietary effort to lose weight BMI of 27 kg/m^2 with at least 1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)	Diabetes, HbA1c 6.5% or greater history of chronic pancreatitis, acute pancreatitis within 180 days before enrollment, previous surgical obesity treatment, and use of anti-obesity medication within 90 days before enrollment	Semaglutide started at 0.25 mg given subQ once weekly, with dose escalation every 4 weeks until reaching target dose of 2.4 mg by week 16, continued until week 68 plus counseling sessions every 4 weeks on adhering to a reduced calorie diet and increased physical activity vs placebo	Percent change in body weight from baseline to week 68 Most common reported adverse events

yo – year old, BMI – body mass index, subQ – subcutaneously

Table 2. Summary of the trial participants' baseline characteristics

First author, year	Mean weight semaglutide group (kg)	Mean weight placebo group (kg)	Mean BMI semaglutide group (kg/m^2)	Mean BMI placebo group (kg/m^2)	Mean Age semaglutide group (years)	Mean Age placebo group (years)	Female sex – no. (%) semaglutide group	Female sex – no. (%) placebo group
O'Neil, 2018	113.2	114.2	39.9	40.1	48	46	66/102 (65%)	88/136 (65%)
Rubino, 2021	96.5	95.4	34.5	34.1	47	46	429/535 (80.2%)	205/268 (76.5%)
Wadden, 2021	106.9	103.7	38.1	37.8	46	46	315/407 (77.4%)	180/204 (88.2%)
Wilding, 2021	105.4	105.2	37.8	38.0	46	47	955/1306 (73.1%)	498/655 (76%)

data for those who were lost to follow-up were included, which could affect the mean weight difference. As for other bias, it was also deemed questionable since all trials had confounding factors such as diet and exercise adherence that may have significantly affected the magnitude of weight loss.

All trials were double blinded, randomized, using interactive web-based response system with identically looking placebo and semaglutide. Hence, they are at low risk for selection, detection and performance biases.

Outcome of the meta-analysis

There was an 11.85% mean difference for weight reduction between the treatment groups, favoring semaglutide (mean difference -11.85, 95%CI [-12.81,-10.90], p<0.00001, I^2 43%) (Figure 3A). There is heterogeneity in between trials with an I^2 43%, P=0.16%. A sensitivity analysis was then performed, which decreased the heterogeneity to 0% after removing the study by Wadden et al. (Figure 3B). On review of the methodology, a possible cause of the heterogeneity is that in Wadden et al.,'s study, all participants received a very low calorie diet of 1000-1200 kilocalories per day (kcal/day) for the first 8 weeks followed by 1200-1800 kcal/day for the remainder of the study. They were also prescribed physical activity of 100 minutes per week that was slowly increased to reach 200 minutes per week. The other studies also prescribed reduced calorie diet and increased physical activity, but only a 500 kcal deficit per day and 150 minute of physical activity per week. The very low-calorie intake as well as increased minutes of physical activity in Wadden et al.'s study may have resulted in more weight loss especially in the placebo group, causing a smaller mean weight difference compared to the other studies.

Another outcome of this review is the risk for gastrointestinal adverse events (typically nausea, vomiting, diarrhea,

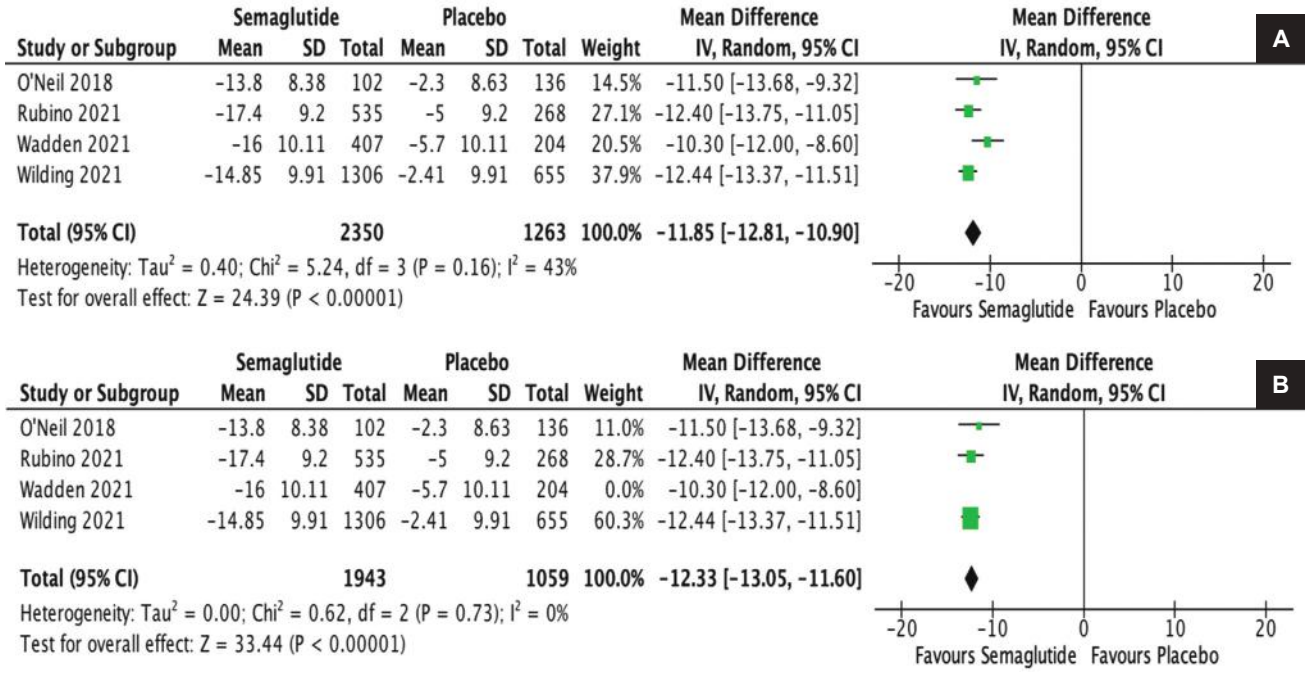

Figure 3. (A) Forest plot showing the effect of semaglutide on mean weight difference versus placebo. **(B)** Sensitivity analysis showing the effect of semaglutide on mean weight difference versus placebo.

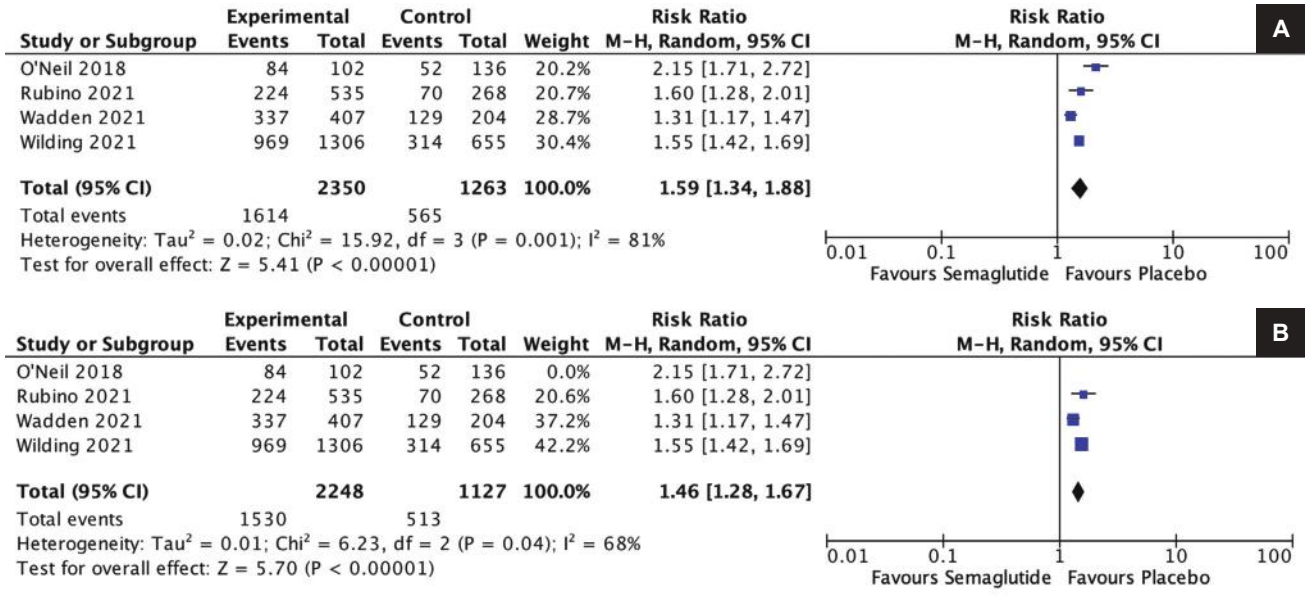

Figure 4. (A) Forest plot showing the risk of gastrointestinal adverse events with semaglutide treatment versus placebo. **(B)** Sensitivity analysis showing the risk of gastrointestinal adverse events with semaglutide treatment versus placebo.

constipation). The review showed that the risk of developing gastrointestinal adverse events was 1.59 times more likely with semaglutide treatment (RR 1.59, 95%CI [1.34, 1.88], p< 0.00001, I^2 81%) (Figure 4A). However, between-trial heterogeneity was high I^2 81%, which prompted a sensitivity analysis that decreased the heterogeneity to 68% (Figure 4B). The major source of heterogeneity was with the dose of semaglutide. Rubino, Wadden, and Wilding et al., all achieved a dose of 2.4 mg once weekly compared to O'Neil et al., where participants received only 0.4 mg once weekly subcutaneous injections.

Even though the risk for gastrointestinal adverse events was statistically significant, the studies of Rubino, Wadden and Wilding et al., reported that the duration of the adverse events was short, transient and resolved without discontinuation of treatment.

The consolidation of the 4 trials also showed that patients given semaglutide were twice as likely to discontinue treatment due to adverse events (RR 2.19, 95%CI [1.36,3.55], p=0.001, I^2 32%) (Figure 5A). Individually, the risk for discontinuation due to adverse events is 6% for semaglutide group and 2.9% for placebo group.

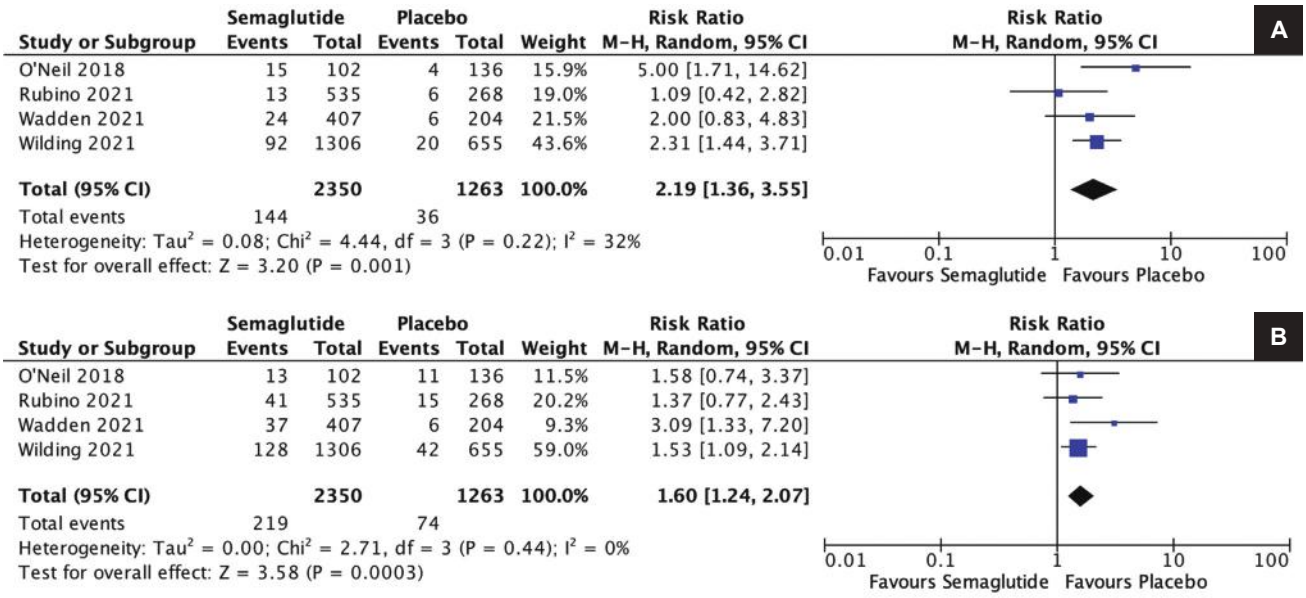

Figure 5. (A) Forest plot showing the risk of adverse events leading to discontinuation of treatment with semaglutide versus placebo. **(B)** Forest plot showing the risk of serious adverse events with semaglutide treatment versus placebo.

Serious adverse events were defined by the study of Rubino, Wadden and O'Neil et al., as life threatening, results in death, requires hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, congenital anomaly/birth defect, important medical event (may jeopardize subject or may require medical/surgical intervention to prevent outcomes listed previously but may not be immediately life-threatening or result in death or hospitalization), as preventing daily activities by Wilding et al. These were reported to be uncommon. The risk for developing serious adverse events was 1.6 times more likely for semaglutide than placebo (RR1.60, 95%CI [1.24, 2.07], p=0.0003, I^2 0%) (Figure 5B). O'Neil, Wilding and Rubino et al.'s studies each mentioned that death was reported during the trial period, but was not considered to be related to semaglutide or placebo treatment. No death was reported in Wadden et al.'s study. Serious events were mostly of gastrointestinal disorders and hepatobiliary disorders such as acute pancreatitis and cholelithiasis.

DISCUSSION

Investigation for the use of semaglutide for obesity has been underway because trials in diabetic patients have shown that it is associated with weight loss. It is currently approved for the treatment of diabetes but not for obesity.[6] Patients with obesity sustain a 46% higher inpatient cost compared to normal weight individuals. They also have 27% more physician visits, outpatient costs and 80% higher expenses on prescription medications.[14]

Guidelines have recommended weight loss of 5 to 10% to improve metabolic function and health outcomes.[15,16] A 5% weight loss improves multi-organ insulin sensitivity[15] whereas, a 5 to 10% weight loss was associated with 0.6 to 1% reduction in HbA1c.[16] This review evaluated 4 double blind RCTs involving 3,613 participants between 2018 to 2021. Combining the results of the trials showed that semaglutide is indeed associated with weight loss with a mean difference of 11.85% compared with placebo. The subjects of the trials all had at least one unsuccessful non-surgical attempt to lose weight, and based on this meta-analysis, a 5 to 10% weight reduction could be achieved with semaglutide. However, it is important to consider that the Rubino study randomized participants to continue with semaglutide treatment or placebo after the target dose was reached. This could have affected the results because participants could have lost weight with initial treatment with semaglutide.

Patient adherence is an important factor in the treatment of obesity, and pharmacologic treatment has been associated with significant adverse events which lead to their discontinuation.[7] This prompted us to evaluate whether semaglutide was also associated with significant adverse events. Consolidating the trials showed nausea, vomiting, constipation and diarrhea to be the most common adverse events. The trials have reported that these were of mild to moderate severity and short duration that resolved without treatment. Moreover, adverse events leading to discontinuation and serious adverse events were uncommon. Dosing frequency is also a factor in adherence to treatment and once weekly dosing was associated with better adherence.[9] With its mild, transient adverse events and once weekly dosing, we can expect good adherence with semaglutide. We observed that aside from the administration of semaglutide, reduced calorie diet and increased physical activity were also part of the intervention. Hence, semaglutide alone probably will not be able to achieve an 11.85% weight loss. Despite these confounding factors, we still believe that semaglutide is a major factor in weight reduction because the subjects all attempted to lose weight prior to starting treatment but were unsuccessful.

Since obesity has been increasing in prevalence worldwide and can cause serious complications like cardiovascular disease and diabetes,[2,3] safe and acceptable treatments for this condition are crucial to prevent further health complications. However, since the trials were all done within a specified follow-up period, it is difficult to predict whether there will be weight gain following discontinuation of treatment, and whether continuous treatment will be necessary.

Strengths and limitations

The study presented a comprehensive systematic review and meta-analysis on semaglutide versus placebo for weight loss in patients who are obese without diabetes. It was able to show the percent mean weight loss after treatment with semaglutide as well as the risks for gastrointestinal adverse effects, discontinuation of treatment and serious adverse events. However, this review is limited to the 4 trials available for this meta-analysis and did not include unpublished literature. Bias may have occurred from these limitations. Furthermore, the studies included the weight for participants who were lost to follow-up and this could have affected the mean percent weight difference. The adherence of the participants to treatment during the trial is also a factor. Each study has their own diet plan and exercise program for the participants in addition to treatment, which could also have affected the magnitude of the effect estimate.

CONCLUSION AND RECOMMENDATIONS

In summary, among individuals with obesity without T2DM, subcutaneous semaglutide is effective for weight loss with an 11.85% reduction from baseline compared to placebo. This supports the use of semaglutide for weight management in obesity. However, risk of gastrointestinal adverse events, discontinuation of treatment, and serious adverse events were higher in the semaglutide group versus placebo. RCTs with longer follow-up are needed to determine long term efficacy, safety and risk for weight gain after treatment discontinuation. Subjects of the trials were also mostly of the white race, hence, future research can focus on its efficacy and safety on the Asian population.

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

Author Contribution Statement
HCT, OAD, MMM conceived the study; developed the methodology; synthesized the data and prepared the original draft. HCT and OAD validated the research; reviewed and edited the manuscript. HCT and MMM conducted the research. HCT presented the data and coordinated the research activity planning. OAD supervised the research.

Author Disclosure
OAD reports receiving consulting fees from Eli Lilly and Novo Nordisk for service outside the submitted work, as well as honoraria for speaking engagements from Astra Zeneca, Novo Nordisk, and Eli Lilly outside the submitted work. HCT and MMM declare no conflict of interest in association with this study.

Funding Source
None.

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CASE REPORT

An Atypical Presentation of Primary Hyperparathyroidism With Multiple Spontaneous Tendon Ruptures: A Case Report and Literature Review on the Management of Primary Hyperparathyroidism

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Abstract

Primary hyperparathyroidism (PHPT) is a common endocrine condition, increasingly presenting asymptomatically and detected on routine laboratory examination in developed countries. Multiple spontaneous tendon ruptures as the initial presentation of PHPT is extremely rare. We present the case of a 28-year-old male diagnosed with severe hypercalcemia secondary to PHPT after presenting with complications of multiple spontaneous tendon ruptures,and discuss the management issues in PHPT for this patient.

Key words: primary hyperparathyroidism, hypercalcemia, tendon rupture

INTRODUCTION

Primary hyperparathyroidism is the most common cause of PTH-mediated hypercalcemia, with an estimated prevalence of one to seven cases per 1000 adults. It occurs three times more often in females and typically in those older than 40 years old.[1] Over the last several decades, there is a changing pattern towards asymptomatic presentation and incidental detection of hypercalcemia, likely due to increased health screening in developed countries.

Symptomatic hyperparathyroidism presenting with osteitis fibrosa cystica has become increasingly uncommon, with its incidence estimated to be under 2%.[2] Multiple spontaneous tendon ruptures as the initial presentation of PHPT is even rarer, with such findings limited to case reports.[3-6]

While PHPT is a common endocrine condition in clinical practice, there are still unanswered questions in the management of severe PHPT which we would address in the discussion of this case.

CASE

A previously well 28-year-old male presented to the emergency department with acute pain and swelling of both knees and left elbow. Prior to this, he was walking on flat ground when both his knees buckled, causing him to fall onto his left side, after which he was unable to weight-bear.

As the initial radiographs did not show any fracture and dislocation, a magnetic resonance imaging (MRI) of bilateral knees and elbows were performed which showed left triceps, right infra-patellar and left quadriceps tendon ruptures as well as subperiosteal bone resorption of bilateral anterior distal femoral metaphysis.

Before this admission, he had no notable past medical history or medication use such as glucocorticoids or fluoroquinolones which may predispose to tendon ruptures. He did not smoke cigarettes or consume any alcoholic beverages. He worked as an office clerk. He did not participate in any high-impact sports. He did not have symptoms suggestive of hypercalcemia. There was no known personal or family history of hypercalcemia, fractures, renal calculi or endocrine tumor to suggest a hereditary cause of PHPT.

Clinical examination revealed signs of dehydration and swelling over his left elbow and bilateral knees, which were immobolised in a brace. No neck mass was appreciated.

Blood investigations revealed elevated serum calcium (3.85 mmol/L, normal range (NR) 2.10 to 2.60) and intact PTH (iPTH) (141.9 pmol/L, NR 1.3 to 7.6), low serum phosphate (0.48 mmol/L, NR 0.65 to 1.65) and concomitant vitamin D deficiency (7.2 μg/L, NR 30 to 100), in the setting of normal renal function (serum creatinine 95 umol/L with eGFR 94.1 ml/min/1.73m^2) (Table 1). This biochemistry was highly suggestive of PHPT. Familial hypocalciuric

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: February 5, 2022. Accepted: April 25, 2022.
Published online first: September 8, 2022.
https://doi.org/10.15605/jafes.037.02.11

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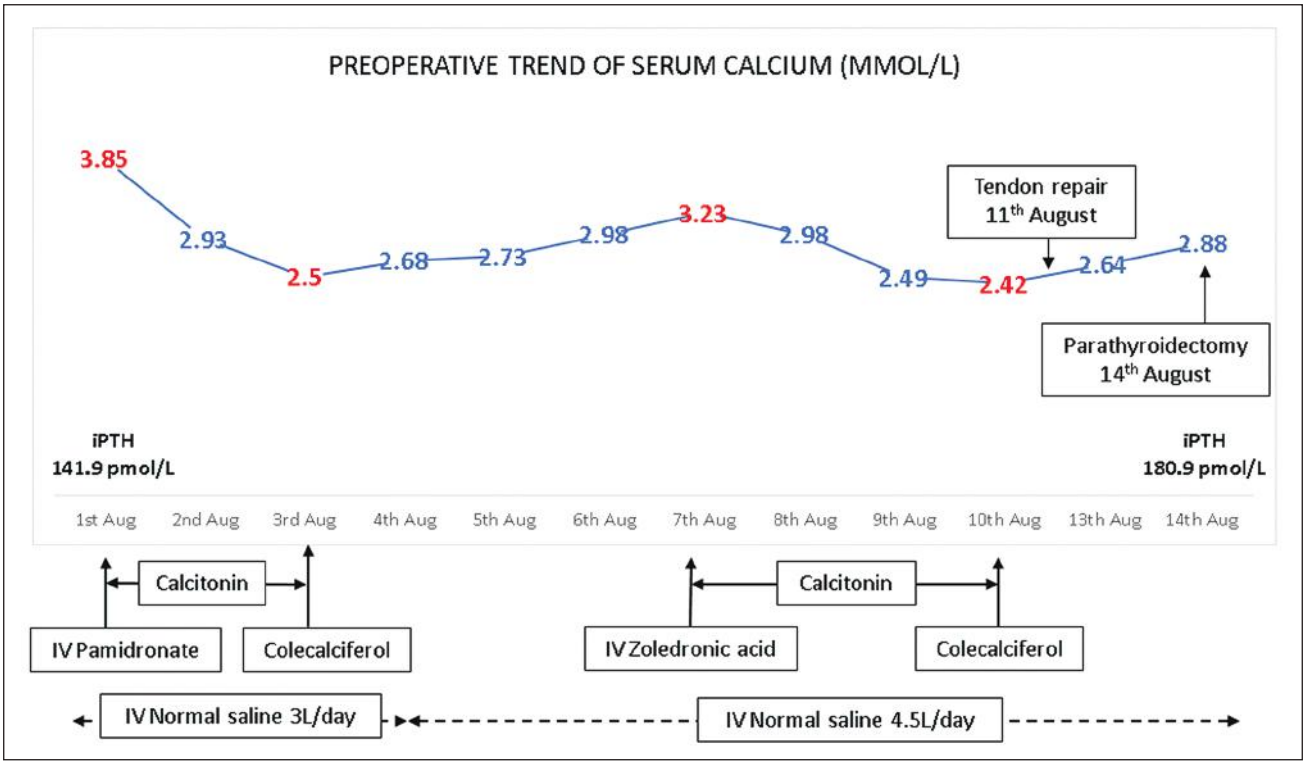

Figure 1. Treatment of hypercalcemia prior to parathyroidectomy.

IV, intravenous

Table 1. Initial laboratory investigations

Parameter	Result	Normal reference range
Calcium (corrected for albumin), mmol/L	3.85	2.10 – 2.60
Phosphate, mmol/L	0.48	0.65 – 1.65
Magnesium, mmol/L	0.67	0.65 – 0.95
Intact parathyroid hormone, pmol/L	141.9	1.30 – 7.60
25-hydroxyvitamin D, µg/L	7.2	30 – 100
Alkaline phosphatase, U/L	1033	32 – 103
Creatinine, µmol/L	95	65 – 125
eGFR	94.1	ml/min/1.73m^2

hypercalcemia (FHH) was unlikely in view of the degree of elevation of both the serum corrected calcium and iPTH levels and there was no family history of hypercalcemia.

The severe hypercalcemia was managed with intravenous (IV) hydration with normal saline at 3 to 4.5 L daily. Subcutaneous calcitonin 300 units every 12 hours and a single dose of IV pamidronate 90 mg were also administered (Figure 1).

Further investigations revealed complications of hyperparathyroidism (Figure 2). Radiographs of hands and MRI of knees showed subperiosteal and subchondral bone resorption. Dual-energy X-ray absorptiometry (DEXA) scan showed low bone mineral density (BMD) for age, worst at the distal third radius with Z-score of -7.6. The Z-scores of left hip and lumbar spine were also low at -2.9 and -3.8, respectively. He also had extra-skeletal complications of bilateral calyceal calculi detected on computed tomography (CT) of the abdomen.

Because of the presence of severe hypercalcemia with extensive complications of PHPT and the need to exclude parathyroid carcinoma, early parathyroidectomy was indicated. He underwent preoperative localization of the lesion with a neck ultrasonography (US) and technetium-99m sestamibi parathyroid scan (Figure 3). Neck US showed a 2.7 cm x 1.8 cm x 1.8 cm right inferior parathyroid gland which demonstrated increased tracer uptake with delayed washout on the technetium-99m Sestamibi scan. These findings were consistent with a hyperfunctioning right inferior parathyroid lesion.

The patient's serum corrected calcium was closely monitored. He required a dose of zoledronate 4 mg IV within one week of pamidronate administration to keep serum corrected calcium <3.0 mmol/L (Figure 1). Vitamin D was judiciously replaced preoperatively to prevent worsening of hypercalcemia.

As hereditary PHPT was still a possibility given his young age of presentation, pheochromocytoma was screened preoperatively (Table 2). Although the 24-hour urine normetanephrines were mildly elevated, this was derived from a urine volume of 8 liters. CT of the abdomen did not detect any adrenal or pancreatic mass suggestive of multiple endocrine neoplasia (MEN) 1 or 2A.

Due to the concern of suboptimal recovery associated with delayed tendon repair, the patient first underwent surgical repair of the right infrapatellar, left quadriceps and left triceps tendons, followed by a focused right inferior parathyroidectomy.

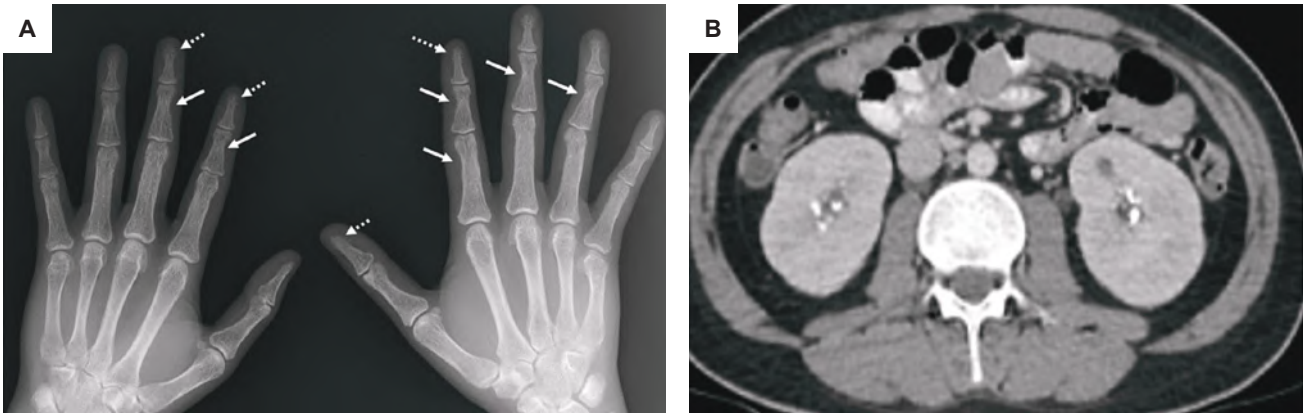

Figure 2. Complications of primary hyperparathyroidism. **(A)** Radiograph of both hands showing subperiosteal bone resorption at the radial aspects of the proximal and middle phalanges *(solid arrows)* and at the tufts of the distal phalanges *(dotted arrows)*. **(B)** Axial contrast-enhanced computerized tomography scan of the kidneys showing bilateral non-obstructing calyceal calculi.

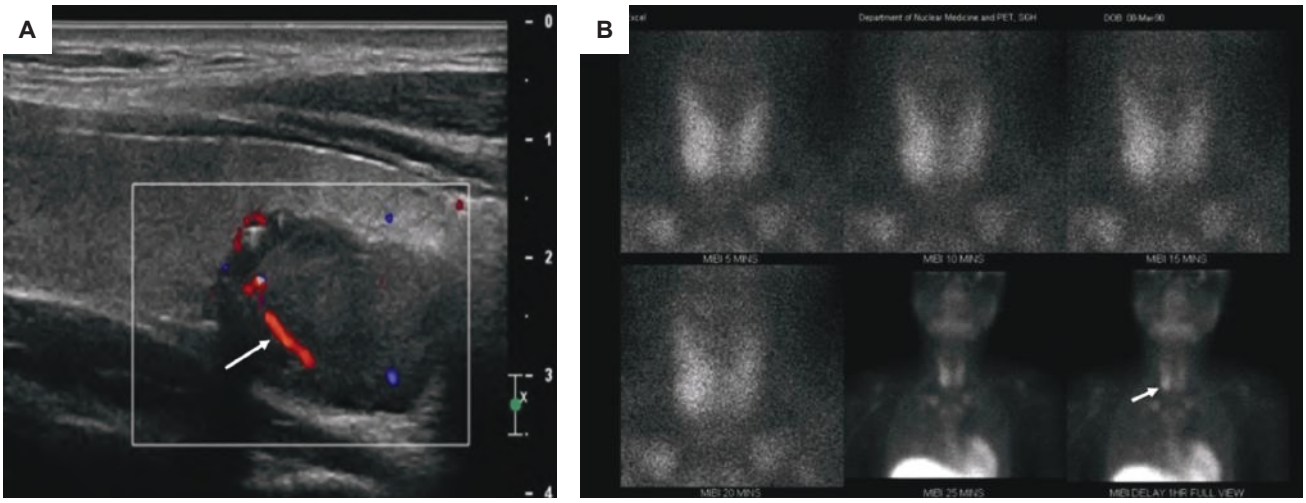

Figure 3. Pre-parathyroidectomy localization studies. **(A)** Ultrasonography of the parathyroid glands demonstrating a 2.7 cm x 1.8 cm x 1.8 cm well-defined hypoechoic nodule located posterior to the right lower pole of the thyroid gland. A characteristic polar vessel is seen *(white arrow)*. **(B)** Parathyroid sestamibi scan demonstrating a focus of intense tracer uptake with delayed washout projected at the lower pole of the right thyroid lobe consistent with a hyperfunctioning right inferior parathyroid nodule *(white arrow)*.

Intraoperative findings during the parathyroidectomy revealed an enlarged right inferior parathyroid gland with no visible invasion of surrounding tissues. The right superior parathyroid gland was normal looking. Intraoperative frozen section confirmed excision of the right inferior parathyroid gland and the intraoperative PTH decreased from 180.9 to 11.26 pmol/L 10 minutes after its excision. Histopathology subsequently reported a 2.0 cm x 1.2 cm x 1.0 cm parathyroid adenoma weighing 4.4 g, with no evidence of vascular or capsular invasion.

In anticipation of hungry bone syndrome (HBS), oral calcium carbonate 2.5 g TDS, calcitriol 0.5 μg BD and cholecalciferol 50,000 units weekly were started postoperatively. Intravenous calcium gluconate infusion was initiated when his serum calcium level dropped to 2.36 mmol/L. This was discontinued on the third postoperative day when he had stable normocalcemia on oral calcium carbonate 2.5 g TDS and calcitriol 1 μg BD (Figure 4). The oral medications

Table 2. Peri-operative screening investigations for MEN-1 and MEN-2A and genetic testing for Hereditary PHPT

Parameter	Result	Normal reference range
24-hour urine volume, mL	8000	700 – 2000
24-hour urine metanephrine, nmol/day	1168	400 – 1500
24-hour urine normetanephrine, nmol/day	2632	600 – 1900
0800H serum cortisol, nmol/L	642	170 – 500
IGF-1, μg/L	115	85 – 236
Gastrin, ng/L	<10	13 – 115
Prolactin, mIU/L	327.3	73 – 407
Genetic Panel	**Result**	**Normal reference range**
MEN 1 gene	Negative	–
RET gene	Negative	–
CDKN1B gene	Negative	–
CDC73 gene	Negative	–
VHL gene	Negative	–

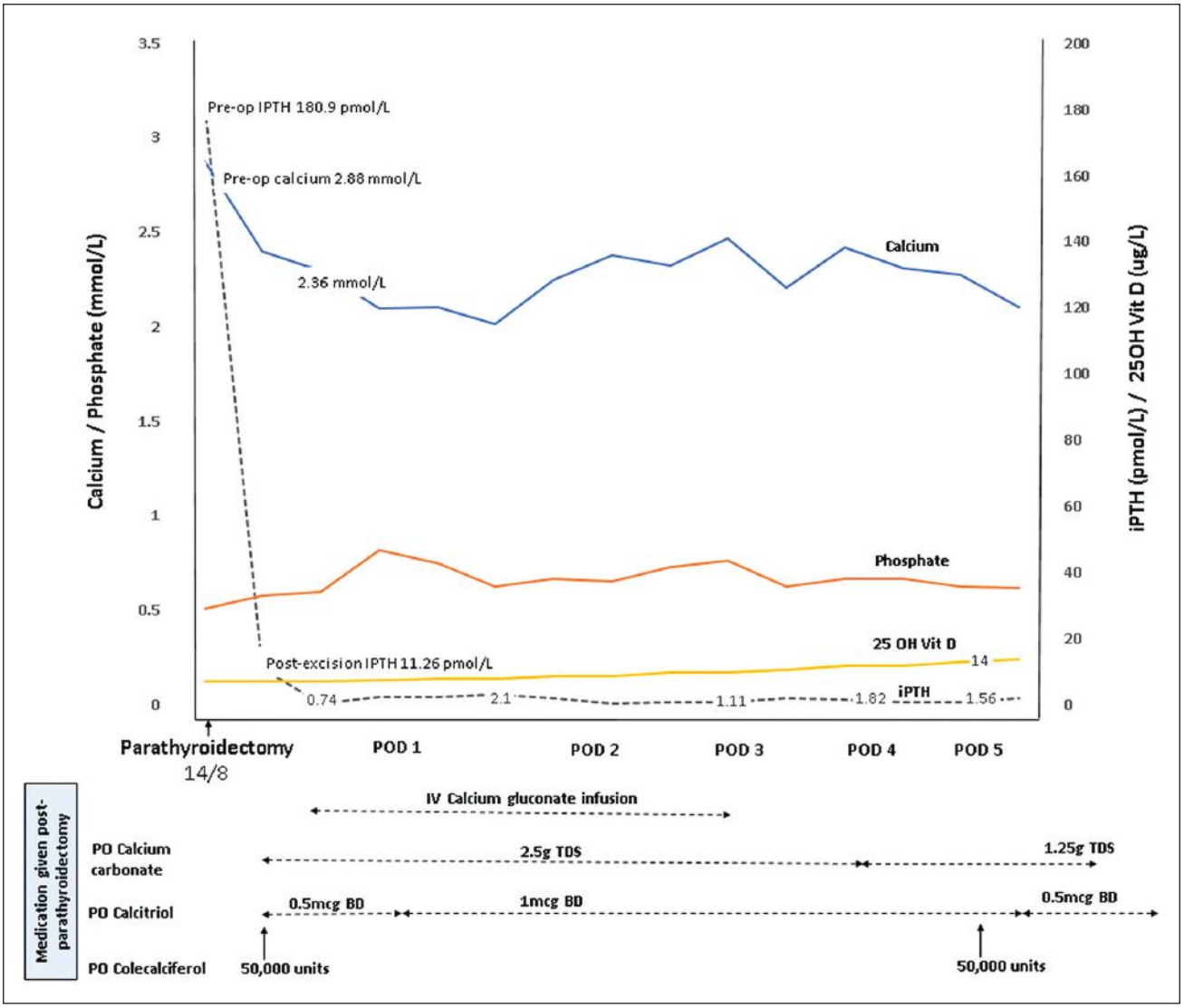

Figure 4. Post-parathyroidectomy management of hypocalcemia.

25OH Vit D, 25-hydroxyvitamin D; BD, twice daily; iPTH, intact parathyroid hormone; IV, intravenous; PO, per orem; POD, postoperative day; TDS, three times daily.

were gradually tapered to calcium carbonate 1.25 g BD and cholecalciferol 1000 units OM over the next three months during his inpatient rehabilitation.

Table 3. Bone mineral density (BMD) trend pre- and post-parathyroidectomy

	Year		
	2017	**2019**	**2021**
Left hip			
BMD, g/cm^2	0.599	0.845	0.866
Z-score	-2.9	-0.9	-0.7
Left femoral Neck			
BMD, g/cm^2	0.443	0.67	0.773
Z-score	-3.5	-1.6	-0.7
Lumbar spine			
BMD, g/cm^2	0.553	0.863	0.852
Z-score	-3.8	-1.0	-1.1
Distal one-third radius			
BMD, g/cm^2	0.41	0.515	0.524
Z-score	-7.6	-5.6	-5.4

Subsequent genetic testing did not detect any pathogenic variant in known susceptibility genes for hereditary PHPT (Table 2). Calcium carbonate and cholecalciferol were completely stopped 17 months after parathyroidectomy. Follow-up DEXA scans at the second and fourth years after parathyroidectomy continued to show improvement in BMD (Table 3).

DISCUSSION

Tendon ruptures are uncommon injuries, usually occurring after trauma in patients older than 50 years. Spontaneous tendon rupture is even more rare, and its occurrence is often associated with chronic renal failure, diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, fluoroquinolone or chronic corticosteroid use.[7-9] Our patient was young and had none of these risk factors.

Although spontaneous tendon ruptures have been reported in hyperparathyroidism, it is usually associated with

secondary or tertiary hyperparathyroidism related to chronic renal failure. Its occurrence in PHPT is extremely rare, with only a few case reports published in the literature.[3-6] In these patients, the tendon ruptures occurred mainly in the lower limbs. Our patient had multiple tendon ruptures affecting both upper and lower limbs. The pathophysiology of spontaneous tendon rupture in PHPT is not clear but postulated to be related to the pathological actions of chronic hyperparathyroidism. Hyperparathyroidism may induce excessive osteoclastic bone resorption at the bony cortex of tendon insertion sites or induce direct damage to tendons via dystrophic calcifications and depolymerization of tendon glycoproteins causing disruption to tensile strength. These mechanisms cumulatively cause weakening at the osteotendinous junction and predispose to tendon rupture following minimal trauma.[4,9,10]

In patients presenting with spontaneous tendon ruptures, it is advisable that clinicians screen for risk factors such as chronic renal failure and diabetes mellitus, to review any history of corticosteroid or fluoroquinolone use and to rule out PHPT due to further implications on its management. The very marked elevation of PTH levels (often 10- to 20-fold increase) illustrating spontaneous tendon ruptures in PHPT in case reports as well as in our patient suggest that this rare complication may be related to the severity of PHPT.[3-6] Hence, in patients with severe PHPT, the potential risk of spontaneous tendon ruptures should be considered. However, due to its rarity, there is insufficient data in the literature to advise on specific PTH, calcium or alkaline phosphatase (ALP) cut-off levels for identifying patients at risk of tendon rupture in PHPT. Nonetheless, with the severity and chronicity of hyperparathyroidism likely contributing to the pathophysiology of tendon ruptures, clinicians should aim to manage PHPT as promptly and optimally as possible.

Parathyroidectomy is the definitive treatment for PHPT. Successful parathyroidectomy has been associated with improvement in BMD, fracture risk, renal calculi formation and quality of life.[11] Our preoperative strategy for this patient consisted of screening for associations with MEN syndrome, optimizing preoperative calcium and vitamin D levels, addressing risk factors for HBS, as well as planning for the surgical approach and extent of parathyroidectomy.

While there are no studies evaluating the safest preoperative serum calcium level, hypercalcemia may interfere with the action of anesthetic agents and increase the risk of cardiac arrhythmias. We opted to maintain preoperative serum calcium at <3.0 mmol/L.

As this patient's pre-parathyroidectomy iPTH and ALP levels were elevated over tenfold, he was at risk of developing HBS. Postoperatively, he was confirmed to have a large right inferior parathyroid adenoma weighing 4.4 g. In literature, parathyroid adenomas >3.5 g have been associated with higher preoperative PTH and calcium levels as well as a greater risk for postoperative hypocalcemia.[12]

A recent dual-center study from Singapore on 164 patients with PHPT who underwent parathyroidectomy showed median preoperative iPTH of 18.8 pmol/L, median corrected calcium of 2.7 mmol/L, median serum 25-hydroxyvitamin D of 20 ng/mL and median adenoma volume of 1 cm^3. The study showed significant correlation between adenoma volume and preoperative iPTH levels and demonstrated that the pre-operative iPTH and ALP levels were significantly associated with the risk of developing HBS.[13] Our patient had significantly higher pre-parathyroidectomy iPTH and corrected calcium levels, lower 25-hydroxyvitamin D levels and larger adenoma size compared to patients from the same population. This further emphasizes the atypical nature of our patient's clinical presentation in a developed country and the risk for development of HBS.

Care was taken to reduce the risk of HBS for this patient by judiciously replacing vitamin D while balancing this with the risk of exacerbating hypercalcemia.

Vitamin D deficiency is common in PHPT. It is associated with higher PTH levels, more severe skeletal manifestations, possibly larger parathyroid adenomas and is also a risk factor for post-parathyroidectomy hypocalcemia.[14] The Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism has recommended preoperative optimization of vitamin D to ≥20 ng/mL.[15] However, there is no consensus on an ideal vitamin D replacement regimen in severe hypercalcemia. There is only one single-center, double-blinded randomized controlled trial with 46 patients addressing this concern. It showed that cholecalciferol 2800 IU daily for six months preceding parathyroidectomy did not significantly increase plasma or urinary calcium.[16] Although there are other studies also supporting the safety of vitamin D replacement in PHPT, the mean serum calcium in these studies before replacement was less than 3.0 mmol/L.[17,18]

A meta-analysis assessing the effect of vitamin D replacement in PHPT showed that although no patient developed hypercalcemic crisis, 2.2% of patients were found to have hypercalcemia exceeding 3.0 mmol/L.[19] The current paucity of evidence on vitamin D replacement in severe hypercalcemia necessitates striking a fine balance between repleting vitamin D and mitigating the risk of aggravating hypercalcemia.

Although IV bisphosphate is used to manage severe hypercalcemia in those with PHPT, its role in the development of post-parathyroidectomy hypocalcemia poses yet another controversy. The evidence assessing the effect of pre-parathyroidectomy bisphosphonate use and the development of HBS has mainly been in the form of observational studies and case reports. While most seem to suggest benefit with IV bisphosphate use and the attenuation of HBS, others implicate it in the exacerbation of hypocalcemia after parathyroidectomy. There are, however, no specific recommendations on the use of bisphosphonates in the prevention of HBS.[20]

Having a randomized controlled trial to evaluate the role of intravenous bisphosphonate administration in the prevention of HBS would be invaluable especially for those at high risk of experiencing this complication.

The ideal surgical approach in parathyroidectomy promotes a balance between achieving surgical cure and normocalcemia while minimizing the risk of persistent or recurrent disease and permanent hypoparathyroidism. The two main surgical approaches are bilateral exploration (BE) to allow four-gland exploration and minimally invasive surgery (MIS) for focused parathyroidectomy.[21] Both approaches have shown good cure rates with few complications. The choice of surgical approach depends on preoperative localization imaging, risk of persistent or recurrent disease and expertise of the surgeon. While BE is more invasive, it is traditionally preferred in patients with hereditary PHPT, multi-gland disease, non-localizing or discordant preoperative imaging and after failure of MIS.[21,22]

Genetic testing for hereditary PHPT has been recommended for patients under 40 years old. As patients with hereditary PHPT have increased risk of having multi-gland disease and recurrence of PHPT, preoperative genetic testing results may guide the patient and the surgeon on the extent of parathyroidectomy.[23] Subtotal parathyroidectomy or total parathyroidectomy with auto-transplantation of parathyroid tissue has been recommended for those with MEN. The risk of permanent hypoparathyroidism, however, may be increased with these approaches compared to MIS. As such, MIS has occasionally been performed in carefully selected cases of hereditary PHPT where preoperative localization studies have confirmed single-gland involvement. This approach may have the benefit of reducing the risk of permanent hypoparathyroidism while preserving the contralateral side to facilitate future parathyroidectomy if PHPT recurs.[21,23]

Nonetheless, prioritization for preoperative genetic testing has to be balanced with the risks of delay to curative parathyroidectomy, especially in severe PHPT. Regardless of intraoperative findings, genetic counseling should still be offered after parathyroidectomy to young patients to prognosticate the risk of recurrent PHPT and to determine the need to screen for other syndromic associations and cascade screening.

The reported recurrence rate of sporadic PHPT after parathyroidectomy may range from 1 to 14.8%, with recurrences occurring up to 20 years after parathyroidectomy.[22,24] A single-center, retrospective study consisting of 196 patients with surgically cured sporadic PHPT were followed up for a median of 9.2 years. Recurrence occurred at a median of 6.3 years at a rate of 14.8%. Notably, 34.5% of recurrences occurred ten or more years after initial parathyroidectomy.[24] A more recent prospective study which included 261 patients with sporadic PHPT were followed up for a median of 60 months post-parathyroidectomy. The recurrence rate was 10.7% with mean time to recurrence of 77 months.[25] Although the risk of recurrence is greater in those with hereditary PHPT, these studies suggest that recurrence is not uncommon in sporadic PHPT and can still occur several years after curative parathyroidectomy.

In a young patient like ours, even though genetic testing did not reveal hereditary PHPT, it may be prudent to pursue long-term follow-up till further evidence advises on an alternative follow-up duration to monitor for the recurrence of PHPT.

CONCLUSION

This case report illustrates a rare and atypical initial presentation of PHPT in a developed country. In those with severe hyperparathyroidism and hypercalcemia, timely treatment is essential, with definitive parathyroidectomy being most ideal because of the likely pathophysiology implicated in spontaneous tendon ruptures in PHPT. Areas in PHPT management that still require clarification include defining a safe regimen of vitamin D replacement pre-parathyroidectomy; the role of pre-parathyroidectomy bisphosphonate use on the development of HBS; and the optimal duration of follow-up for monitoring for recurrence post-parathyroidectomy. Although this patient likely has sporadic PHPT due to a solitary parathyroid adenoma and has attained cure after parathyroidectomy, he will still benefit from continued monitoring for late recurrence.

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

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

Author Contribution Statement
YJ and SSB prepared the original draft, reviewed and edited the manuscript, and prepared the data presentation. SSB supervised the research activity planning.

Author Disclosure
Both authors declared no conflict of interest.

Funding Source
None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Severe Pericardial Effusion Due to Autoimmune Hypothyroidism With Levothyroxine Withdrawal and Systemic Lupus Erythematosus

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Abstract

The presence of autoantibodies is a common link between autoimmune hypothyroidism (AH) and Systemic Lupus Erythematosus (SLE). The coexistence of AH (Hashimoto's Thyroiditis) and SLE is common; however, massive pericardial effusion (PEEF) with signs of tamponade is extremely rare and only a few cases have been reported in literature. We present a case of a 54-year-old female who came in with progressive dyspnea who was found out to have massive PEEF from overt AH and concurrent SLE, which was successfully managed medically. This gave us valuable insight that massive pericardial effusion occurring in overt hypothyroidism may be secondarily caused by other co-existing disease entities such as SLE. The importance of the correct diagnosis cannot be overemphasized, as this largely contributed to the successful management of this case.

Key words: pericardial effusion, pericardial tamponade, autoimmune hypothyroidism, systemic lupus erythematosus, case report

INTRODUCTION

Autoimmunity is a common link between autoimmune hypothyroidism (AH) and Systemic Lupus Erythematosus (SLE) and appears to explain the increase in prevalence of one condition in the presence of the other. Pericardial effusion as a manifestation of each disease is common, but massive pericardial effusion with cardiac tamponade is rare. SLE pericardial effusion has an incidence of 1-2.5%,[1] while there are only about 20 reported cases of AH causing cardiac tamponade in the literature.[2] Pericardial effusion caused by hypothyroidism due to AH (also known as Hashimoto's thyroiditis) can lead to massive pericardial effusion if left untreated. It can be more difficult and challenging to treat. The management of massive pericardial effusion ranges from medical management to life saving surgical procedures. The usual indication for pericardiocentesis, pericardiostomy or creation of a pericardial window is the presence of cardiac tamponade with signs of hemodynamic compromise.[3] Here, we present a rare case of massive pericardial effusion with signs of tamponade caused by both AH and SLE which was successfully managed medically (Figure 1).

CASE

A 54-year-old, hypertensive, Filipino female, non-smoker, was admitted due to difficulty of breathing. Three years prior to admission, she developed hoarseness, cold intolerance and easy fatigability. She consulted an ENT and was assessed with left vocal cord paralysis. No thyroid enlargement was noted both on physical examination and on ultrasound, but thyroid function test showed elevated TSH and levothyroxine 50 mcg 1 tablet once a day was started. Her symptoms improved but she was lost to follow up.

One year prior to admission, she stopped taking levothyroxine because she was in denial about her illness and did not understand the need for levothyroxine maintenance therapy. She then started to have easy fatigability and cold intolerance. Six months prior to admission, she developed increased sleepiness, slowed responses, forgetfulness, blurring of vision, dry skin, weight gain, myalgia and knee arthralgia. No rashes, alopecia and photosensitivity were noted. A week prior to admission, patient had constipation, two pillow orthopnea, and exertional dyspnea when climbing one

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: May 27, 2022. Accepted: July 23, 2022.
Published online first: August 18, 2022.
https://doi.org/10.15605/jafes.037.02.13

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* *Presented at the Endocrine Society Convention 2019, Ernest N. Morial Convention Center New Orleans, March 24, 2019.*

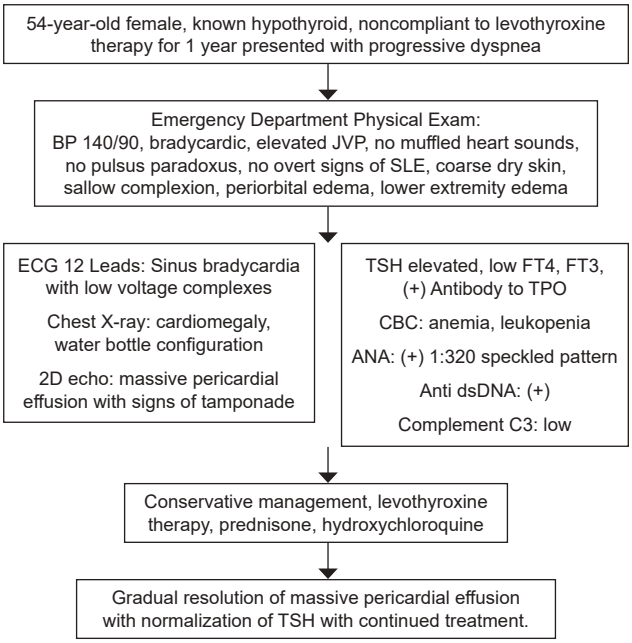


Figure 1. Timeline of pertinent information in the care of this patient.

flight of stairs. A day prior to admission, she experienced difficulty of breathing and consulted at a local hospital. Electrocardiogram revealed sinus bradycardia and 2D-echocardiography showed a large pericardial effusion with signs of tamponade. She was given furosemide 40 mg intravenously and was advised to undergo pericardiostomy. She was referred to our institution and was admitted under the Cardiology service, and co-managed by the Endocrinology service. Pertinent family history includes presence of goiter in the maternal side and sibling (sister).

On physical examination, she was conscious, coherent, in distress. Her blood pressure was 140/90 mm Hg, bradycardic at 57 beats per minute with a regular rate, tachypneic at 22 cycles per minute, afebrile and with body mass index of 28 kg/m^2. She had cold, coarse, dry skin, sallow complexion, no moon facies, no facial plethora, no rashes, no pigmentation. Examination of the eyes revealed pink palpebral conjunctivae, anicteric sclerae, periorbital edema, lid lag, retraction with Queen Anne's sign (thinning of the lateral third of eyebrows) but no exophthalmos. She also had dry lips, macroglossia, distended neck veins, elevated JVP at 5 cm H20 at 30°C. Physical examination of the thyroid showed diffusely enlarged, firm, 4 x 2 x 1 cm right and left thyroid lobes but with no thyroid bruit. She had normal breath sounds with adynamic precordium, apex beat at 5th left intercostal space, no heaves, lifts or thrills. Heart sounds were not muffled. She had full pulses on all extremities with non-pitting edema grade 2 on both lower extremities. No pulsus paradoxus was noted. Her deep tendon reflexes were blunted on all extremities. Neurological examination revealed delayed responses to questions and delayed short term recall, however, long term memory was intact.

At the Emergency Department, 12L ECG showed sinus bradycardia, low voltage limb leads and non-specific ST-T wave changes (Figure 2A). Chest radiograph showed an enlarged heart with water bottle configuration (Figure 2B). There were no pulmonary infiltrates. Thyroid panel was consistent with primary AH: elevated TSH = 95.66 uIU/mL (NV = 0.35-4.94), low FT3 = <1 pg/mL (NV = 1.71-3.71), low FT4 = <0.4 ng/dL (NV = 0.7-1.48) and elevated anti-TPO = 770.9 IU/mL (NV = <9.0). Ultrasound of the thyroid showed non-uniform echo pattern without thyroid enlargement. A 2-dimensional echocardiogram confirmed the presence of massive PEEF with doppler evidence of tamponade (Figure 3). The patient was referred to a cardiothoracic surgeon for possible pericardiostomy.

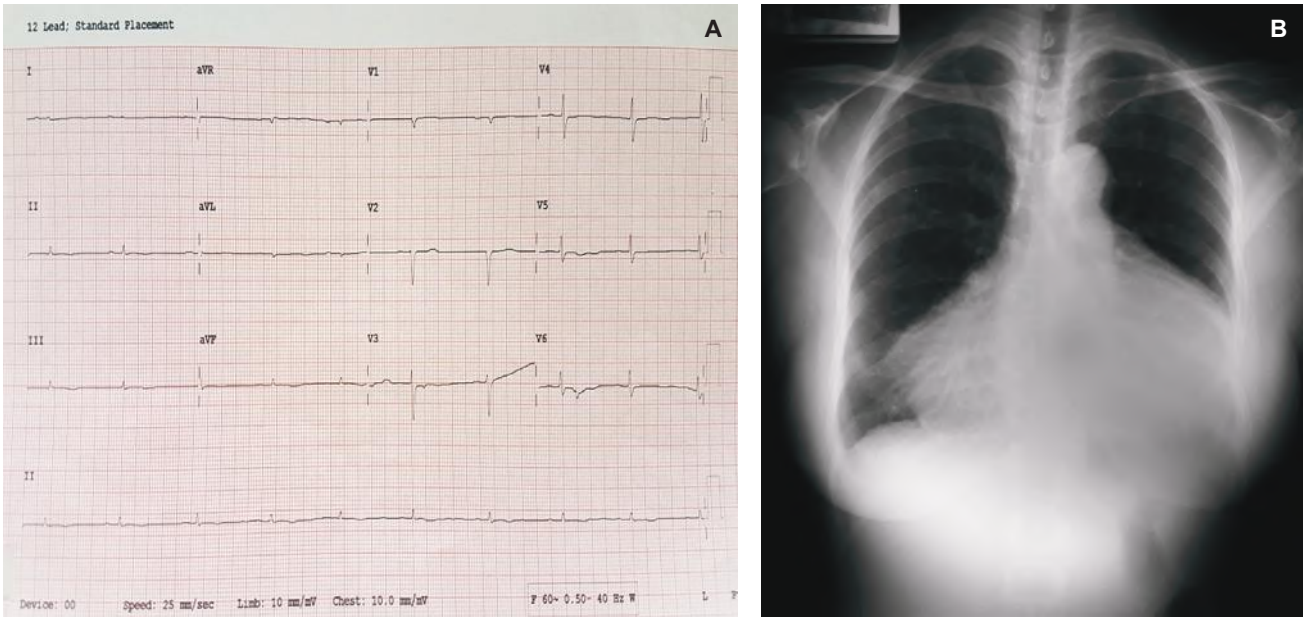
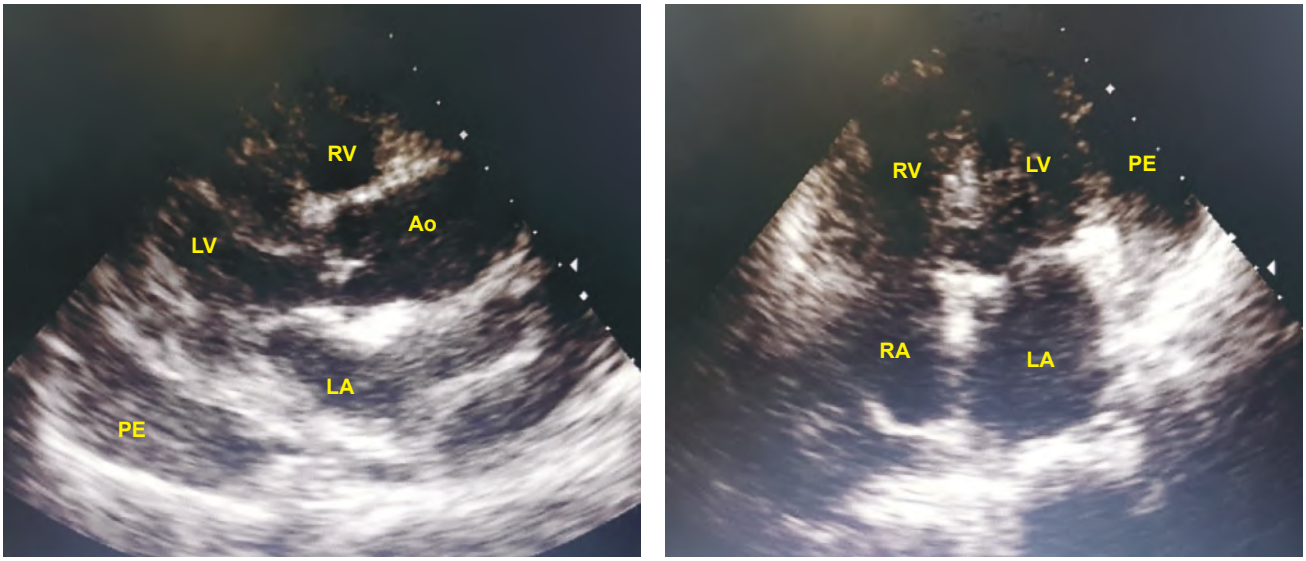


Figure 2. (A) ECG showing sinus bradycardia and low voltage limb leads. **(B)** Chest X-ray showing water bottle configuration.



RV, right ventricle; LV, left ventricle; LA, left atrium; LV, left ventricle; Ao, Aorta; PE, pericardial effusion

Figure 3. 2D echocardiogram with Doppler studies done on admission showed an echo free space posterior to the left ventricle, anterior to the right ventricle and superior to the right atrium with widest diameter of 4.0 cm suggestive of large pericardial effusion. There was an exaggerated respiratory variation of 19.6% at peak mitral inflow and 37.8% at peak tricuspid inflow suggestive of Doppler evidence of tamponade.

A multidisciplinary meeting was held to ensure the best management. As the patient was assessed as having high risk for surgical intervention due to the severe hypothyroidism, the team consensus was to maximize medical management. Since BP continued to be stable, conservative management was continued and patient was monitored closely for worsening cardiac condition.

Patient was started on levothyroxine therapy by the Endocrine service, initially at 50 mcg daily and slowly titrated up to 100 mcg daily. Other laboratory findings were anemia with Hgb of 92 g/L (NV = 11-15), leukopenia of 2.7 x10^9/L (NV = 4-10), albuminuria (+1) and elevated creatinine level of 1.21 mg/dL (NV = 0.51-0.91). With these laboratory results, SLE as a secondary cause of PEEF was entertained, she was referred to rheumatology service and subsequent work up was done. Her ANA was positive at 1:320 dilution with speckled pattern, likewise, her anti-dsDNA was positive at 516.25 IU/ml (NV = <0-200). Her Complement factor 3 (C3) level was low at 0.89 g/L (NV = 0.9-1.8). Summing up both clinical and laboratory results, patient fulfilled six criteria in the Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE. She was then started on prednisone 30 mg once daily and hydroxychloroquine 200 mg once daily.

She was closely monitored. Her vital signs remained stable during the course of hospitalization. Her dyspnea was relieved by diuretics, on top of the levothyroxine and prednisone therapy. Repeat 2D echocardiography after several days of medical management showed a decrease in the pericardial effusion (Figure 4) and patient was subsequently discharged. Outpatient followup showed further resolution of effusion (Figure 5). After a month on levothyroxine 100 mcg daily, her thyroid function test also normalized with TSH of 1.6 uIU/mL (NV = 0.35-4.94), FT4 of 1.7 ng/dL (NV = 0.7-1.48) and FT3 of 2.9 pg/mL (NV = 1.71-3.71). Repeat 2D echocardiography done 9 after months showed further decrease in the pericardial effusion now measuring 0.7 cm widest diameter. Patient continued to take levothyroxine, prednisone and hydroxychloroquine with frequent follow up with cardiology, rheumatology and endocrinology services. A summary of the biochemical parameters and echocardiographic findings from illness to recovery of this patient is shown (Table 1).

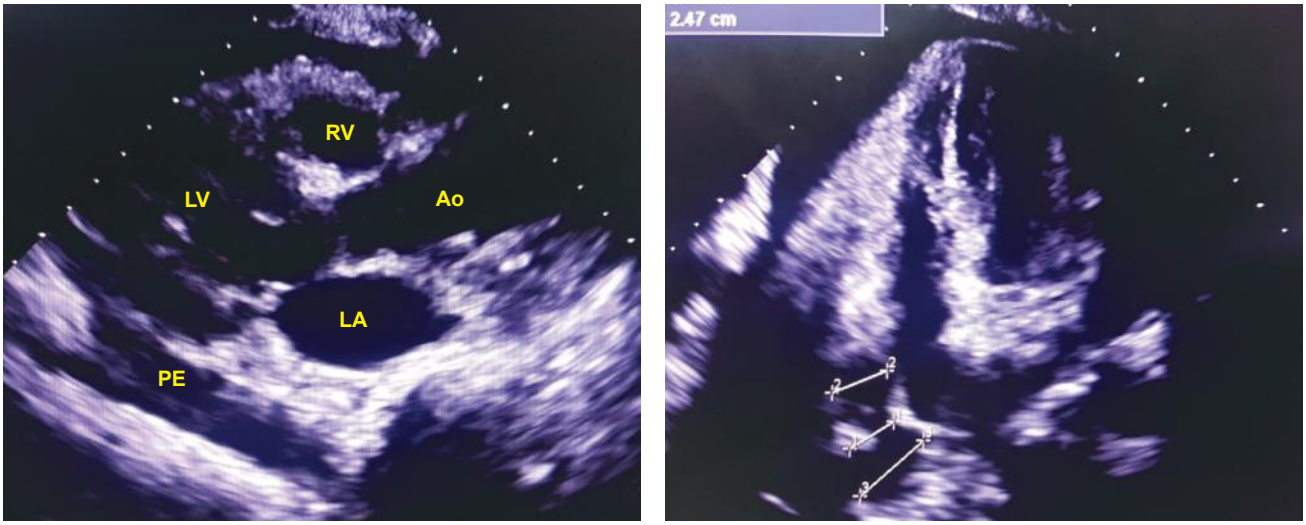
Table 1. Biochemical parameters and echocardiographic findings from illness to recovery

Day	0	4	16	30	270
Biochemical Parameters					
Serum TSH (uIU/mL) NV: 0.35-4.94	95.66			1.6	
Serum FT4 (ng/dL) NV: 0.7-1.48	<0.4			1.7	
Serum FT3 (pg/mL) NV: 1.71-3.71	<1			2.9	
Echocardiographic Findings					
Pericardial Effusion widest diameter on 2D echo (cm)	4	2.1	1.49		0.7
Signs of Tamponade	+	+	+		-

TSH, Thyroid Stimulating Hormone; FT4, free thyroxine; FT3, free triiodothyronine; NV, normal value; 2D echo, 2 dimensional echocardiogram

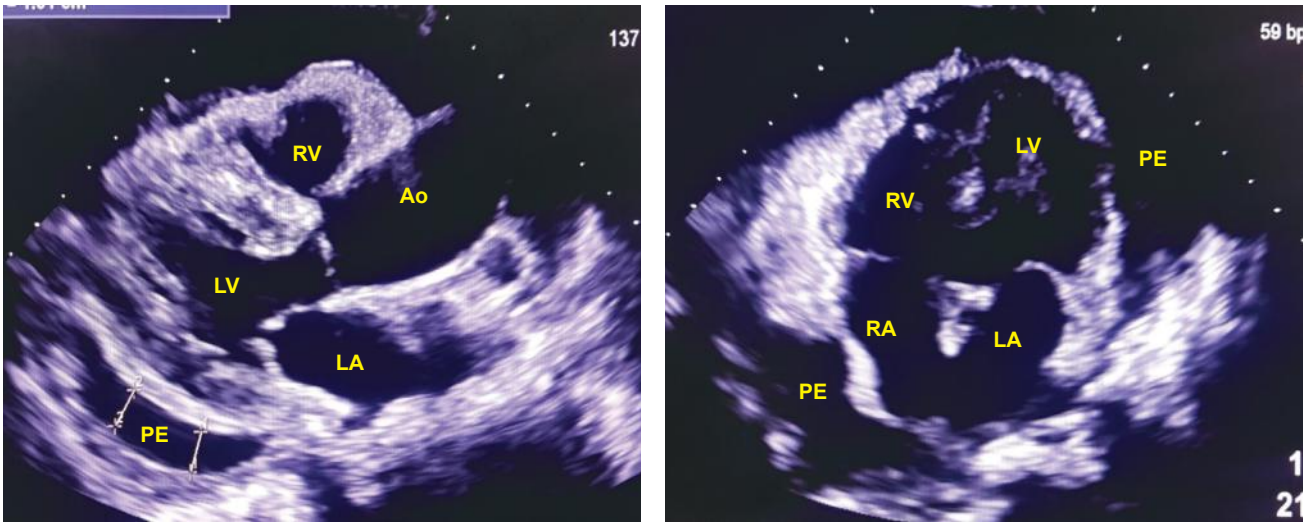
DISCUSSION

Autoimmunity is a common ground for both autoimmune hypothyroidism (AH) and Systemic Lupus Erythematosus (SLE) and appears to explain the increase in prevalence of one condition in the presence of the other. The prevalence of AH reported in the literature among patient with SLE is between 3.9%-21.4%[4] while SLE is observed to



RV, right ventricle; LV, left ventricle; LA, left atrium; LV, left ventricle; Ao, Aorta; PE, pericardial effusion

Figure 4. Follow up plain 2D echocardiogram done 4 days later showed a decrease in amount of pericardial effusion with widest diameter now measuring 2.1 cm from previous 4.0 cm, with noted RA collapse during systole and RV collapse during diastole suggestive of echocardiographic evidence of tamponade.



RV, right ventricle; LV, left ventricle; LA, left atrium; LV, left ventricle; Ao, Aorta; PE, pericardial effusion

Figure 5. 2D echocardiogram with Doppler studies done 16 days after the first study showed a further decrease in amount of pericardial effusion with widest diameter now measuring 1.49 cm from previous 2.1 cm, consistent with moderate pericardial effusion, with echocardiographic evidence of tamponade.

occur in 5.9% of patients with AH.[5] Around one fifth to one half of patients with SLE have positive thyroid autoantibodies[4] while 16% of patients with autoimmune hypothyroidism may present with positive Anti-dsDNA.[5] A potential genetic connection between these two entities is said to involve the human leukocyte antigen (HLA) DR 3,4,5 of the major histocompatibility complex proteins but a complete explanation is still unknown.[6]

Our case presented with signs and symptoms consistent with hypothyroidism and with history of non-compliance to levothyroxine therapy, so autoimmune hypothyroidism as the cause of the effusion was one of the initial considerations. Pericardial effusion in mild AH occurs in 3-6% of cases but can be as high as 30%-80% in severe cases.[7] Although pericardial effusion is a common manifestation, massive PEEF with tamponade is rare. There are roughly 20 cases reported in the literature.[2]

The underlying mechanism of pericardial effusion in AH is said to be caused by the accumulation of glycosaminoglycans and increase capillary permeability leading to protein leakage to interstitial space resulting to water retention causing edema and serous effusion.[8] It is rare to develop massive pericardial effusion in AH, as pericardial fluid accumulates at a slow rate, allowing the pericardial sac to compensate for the increase in volume and intrapericardial pressure.[9] In cases of massive pericardial effusion in AH, other entities should be ruled out including a possible infection, malignancy, systemic diseases and

other metabolic causes. For this case, there were no significant clinical clues that would point to an infection, malignancy, uremia but some findings pointed to a possible concurrent SLE, thus this was further worked up.

Other cardiovascular changes in hypothyroidism would include decrease in cardiac output caused by a decrease in stroke volume and heart rate reflecting the loss of inotropic and chronotropic effects of thyroid hormones[10] which could explain the patient's bradycardia even in the presence of large effusion. It should be noted that bradycardia with low voltage complexes is more consistent with hypothyroidism as opposed to the tachycardia encountered in other conditions.[10] This atypical ECG finding can suggest or enhance the suspicion of hypothyroidism in patients with pericardial effusion.

More than 50% of patients with SLE present with pericardial effusion on echocardiography.[11] However, massive pericardial effusion as an initial presentation is rare and occurs only in 1-2.5% of cases.[1] The underlying mechanism is an immune-mediated inflammation which could be in the form of pericarditis or vasculitis and seen in active SLE.[12] This is more associated with lupus nephritis, Libman-sacks endocarditis and myocardial dysfunction.[13] Our patient manifested signs of lupus nephritis. The rarity of cardiac tamponade in SLE seems to be explained by the same mechanism in AH. Our patient fulfilled six of the Systemic Lupus International Collaborating Clinics criteria (clinical criteria: leukopenia, renal manifestations, serositis; laboratory criteria: (+) ANA speckled pattern, (+) anti-dsDNA and low complement level) and was diagnosed with SLE.

Levothyroxine therapy is the cornerstone for the treatment of pericardial effusion in AH. Different dosing regimens were observed in the different cases reported.[9-18] Average dose was between 50 mcg to 125 mcg daily and delivered through intravenous or oral route. Some started at a small dose with gradual up-titration, while others started with full doses. All of the reports showed resolution of effusion after a few months of levothyroxine therapy. In conjunction with levothyroxine therapy, most of the cases performed surgery for signs of cardiac tamponade (pericardiocentesis or pericardial window) while a few cases showed resolution with only medical management.[9-18] Our case was started with lower levothyroxine dose at 50 mcg considering the patient's age. The dose was gradually titrated up to 100 mcg daily which was well tolerated.

High dose steroid and anti-inflammatory agents are given for SLE pericarditis and pericardial effusion. For life or organ threatening conditions, the administration of IV pulse steroid is even indicated.[19] Although rare, pericardiocentesis is also indicated for cases of massive pericardial effusion with tamponade. Our case was started on prednisone 30 mg once a day and slowly tapered down for months with gradual resolution of pericardial effusion.

We found one similar case where massive pericardial effusion in tamponade was complicated with both AH and SLE. A case report by Chaudhari et al., entitled "SLE or hypothyroidism: Who can triumph in cardiac tamponade?" described a 36-year-old Hispanic female with a history of SLE in remission who presented with progressive dyspnea and massive pericardial effusion in tamponade and subsequently diagnosed with SLE in activity with concommitant autoimmune hypothyroidism. The patient was treated with urgent pericardiocentesis and was given levothyroxine and steroid therapy which resolved the condition.[20] Another case described both AH and SLE causing instead a massive peritoneal effusion (ascites).[21] This case was diagnosed first with AH and later fulfilled criteria for SLE. Patient was treated with levothyroxine replacement and steroid therapy with noted improvement of her condition.

Surgery in pericardial effusion is not indicated unless there is hemodynamic compromise. Pericardiocentesis offers both diagnostic and therapeutic advantages. SLE effusion is usually exudative and filled with fibrinous products, active and/or chronic infiltrates, while AH effusion is more transudative. It effects drainage of the effusion, termination of tamponade and relief of symptoms. This was not done in this case, as the patient's blood pressure remained stable, even in the presence of tamponade physiology on echocardiogram. This may be considered as one of the limitations as we were not able to establish the definite cause of the effusion and remains a diagnostic uncertainty. However, as medical management with levothyroxine and steroid proved to be effective for this case, as manifested by resolution of the large pericardial effusion, it may be concluded that management was appropriate, and that pursuing diagnostic certainty would be a purely academic exercise.

CONCLUSION

In conclusion, this was a rare case of a combination of AH and SLE causing massive pericardial effusion with signs of tamponade which was managed medically. This gave us valuable insight that massive pericardial effusion occurring in overt hypothyroidism may be secondarily caused by other co-existing disease entities such as SLE. It is prudent to always keep the possibility in your differential diagnosis, as the correct consideration largely contributed to the successful management of this case.

Ethical Consideration
Patient consent was obtained prior to submission of the manuscript.

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

Author Contribution Statement
SI, KAT, MFCG, FRG, JUH conceived the study; developed the methodology, applied statistical techniques; provided study materials; reviewed and edited the manuscript; managed the research activity planning. SI, MFCG, FRG, JUH validated the data;

SI and KAT conducted the research, JUH supervised the research activity planning. SI programmed the software; curated the data and acquired financial support for the study.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Collision of Two Tumors: A Case Report of a Lung Adenocarcinoma With Metastasis to a Pituitary Adenoma

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Abstract

A collision tumor involving metastasis to a pituitary adenoma is rare. We describe a case of a 68-year-old Bidayuh woman with underlying treatment-responsive lung adenocarcinoma, who presented with mass effect, panhypopituitarism and polyuria. Her initial imaging study reported pituitary macroadenoma, and she was treated with hormone replacement therapy. She then underwent transsphenoidal tumor debulking surgery with subsequent histopathological findings of a collision tumor of an adenocarcinoma with metastasis to a non-functioning pituitary adenoma.

Key words: collision tumor, pituitary adenoma, pituitary metastasis

INTRODUCTION

Metastatic lesions in the pituitary gland are uncommon, reported to account for <1% of intracranial metastases in a surgical series.[1] Lung and breast cancer are the most common primary malignancies, accounting for 60% of pituitary metastases.[1] Tumor-to-tumor metastasis, also known as a collision tumor, involving metastasis to a pituitary adenoma is rare, with only 35 cases being reported in literature to date.[2] The definitive diagnosis of a collision tumor is determined by histopathological examination, but the clinical presentation, a history of malignancy and imaging findings may provide clues to support the diagnosis. We present a rare case of a lung adenocarcinoma with metastasis to a non-functioning pituitary adenoma, diagnosed after post-operative histopathological and immunohistochemical examination of the excised tissue.

CASE

A 68-year-old Bidayuh woman presented at the emergency department with a 3-week history of confusion, lethargy, blurred vision and polydipsia. Her symptoms deteriorated 2 days before admission. She had been diagnosed with stage 4 epidermal growth factor receptor (EGFR)-positive lung adenocarcinoma 1 year before, with findings of a 1.5 cm x 2.0 cm right perihilar mass and bilateral adrenal masses. She has been receiving the tyrosine kinase inhibitor, gefitinib, as oral chemotherapy. Three months prior to current presentation, a repeat chest computed tomography (CT) performed after six months of oral gefitinib treatment showed a reduction in the size of the right perihilar mass to 1.1 cm x 1.4 cm, suggestive of treatment response.

At the emergency room, the patient appeared confused, with blood pressure ranging from 95 to 100/50 to 60 mmHg. She did not exhibit Cushingoid features, acromegalic appearance or galactorrhea. Eye examination demonstrated reduced visual acuity (VA) limited to finger counting with bitemporal hemianopia. Polyuria was also observed.

The patient had hypernatremia [155 mmol/L, normal value (NV): 135 to 145 mmol/L], low urine osmolality (108 mOsm/kg, NV: 300 to 900 mOsm/kg) and high serum osmolality (331 mOsm/kg), suggestive of diabetes insipidus. Hormonal assays revealed hyperprolactinemia (3665 μIU/mL), with evidence of central hypothyroidism [thyroid stimulating hormone (TSH) 2.62 mIU/L, NV: 0.3 to 3.94 mIU/L; free thyroxine (FT4) 9.24 pmol/L, NV: 12.3 to 20.2 pmol/L], hypogonadism [follicle stimulating hormone (FSH) 2.66 mIU/mL, luteinizing hormone (LH) <0.3 mIU/mL] and hypocortisolism (morning cortisol 19.4 nmol/L). IGF-1 was within normal (57.9 ng/mL, NV: 42.0 to 179.0 ng/mL).

Pituitary magnetic resonance imaging (MRI) revealed a large, solid sellar lesion with suprasellar extension measuring 2.8 cm x 3.6 cm x 3.8 cm, compressing the optic chiasm and abutting the cavernous sinuses (Figure 1). The pituitary gland, pituitary stalk and posterior bright spot were not visualized. There was a blooming artifact at the periphery of the mass with T1 hyperintensity, suggestive of hemorrhage. However, no abnormal meningeal

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: February 2, 2022. Accepted: March 23, 2022.
Published online first: June 16, 2022.
https://doi.org/10.15605/jafes.037.02.09

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enhancement, dural thickening, bony erosion or other suspicious brain parenchymal lesions were present.

Based on the imaging findings and laboratory investigations, the patient was diagnosed with pituitary macroadenoma, complicated by pituitary apoplexy, panhypopituitarism and central diabetes insipidus (CDI). Hydrocortisone and levothyroxine replacement were initiated. Oral desmopressin was also started for CDI. Her blood pressure, urine output and serum sodium levels normalized after hormone replacement and supportive care.

Due to progressive visual decline, she underwent trans-sphenoidal tumor debulking surgery. There was a residual suprasellar mass which was deemed unresectable due to its extension into the third ventricle. Histopathologic examination of the specimen showed fragments of tumor tissue arranged in papillary architecture and some solid clusters. The tumor cells display pleomorphic hyperchromatic to vesicular nuclei with moderate amount of eosinophilic to vacuolated cytoplasm and increased mitosis. These tumor cells stained positive for cytokeratin 7 (CK7) and thyroid transcription factor-1 (TTF-1), suggestive of metastatic lung adenocarcinoma (Figure 2).

In adjacent foci, there were neoplastic pituitary cells with small nucleoli and moderate amounts of granular eosinophilic cytoplasm, with no significant mitotic activity. These neoplastic pituitary cells stained positive for synaptophysin, growth hormone (GH), adrenocorticotropic hormone (ACTH) and prolactin, suggestive of pituitary adenoma (Figure 3). Based on these histopathologic and immunohistochemical findings, the patient was diagnosed with a collision tumor involving a pituitary adenoma and metastatic lung adenocarcinoma.

Postoperatively, the patient was more alert, with improved general well-being. Her VA improved from counting fingers to 6/18 on the right eye and 6/24 on the left. A CT scan of the chest, abdomen and pelvis for further metastatic workup showed a new right upper lung lobe mass measuring 2.4 cm x 1.5 cm, an enlarged right perihilar mass measuring 4.0 cm x 3.1 cm x 2.1 cm, and bilateral adrenal masses which were unchanged in terms of size (Figure 4).

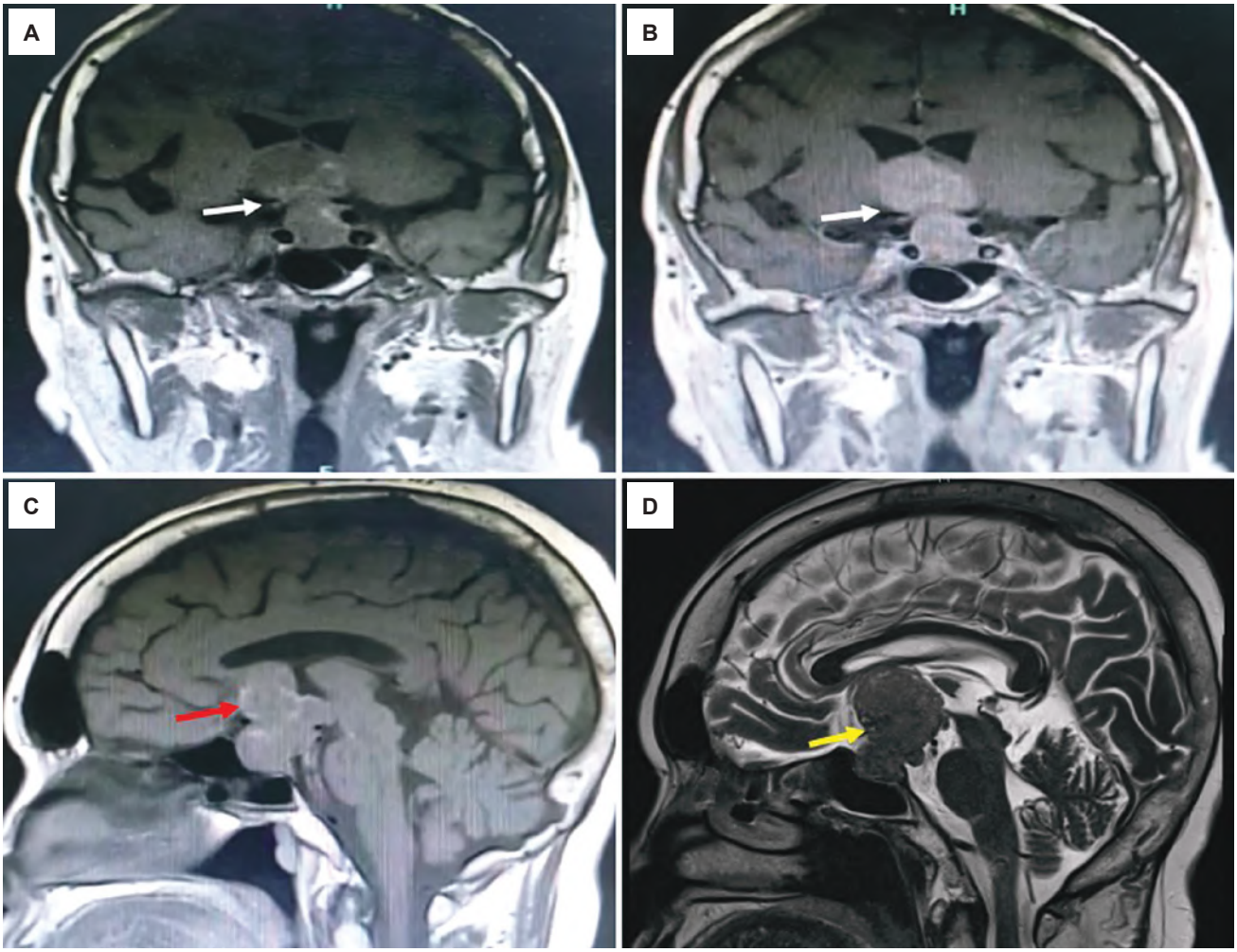

Figure 1. Coronal T1-weighted **(A)** pre-contrast and **(B)** post-contrast magnetic resonance imaging of the pituitary showing a homogenously enhancing dumbbell-shaped sellar mass measuring 2.8 cm x 3.6 cm x 3.8 cm. On non-contrast sagittal view, it is **(C)** T1-hypointense with heterogenous intensity on **(D)** T2. There is T1 hyperintensity *(red arrow)* and T2 hypointensity *(yellow arrow)* at the peripheral aspect of the mass suggestive of hemorrhage. The posterior bright spot is absent.

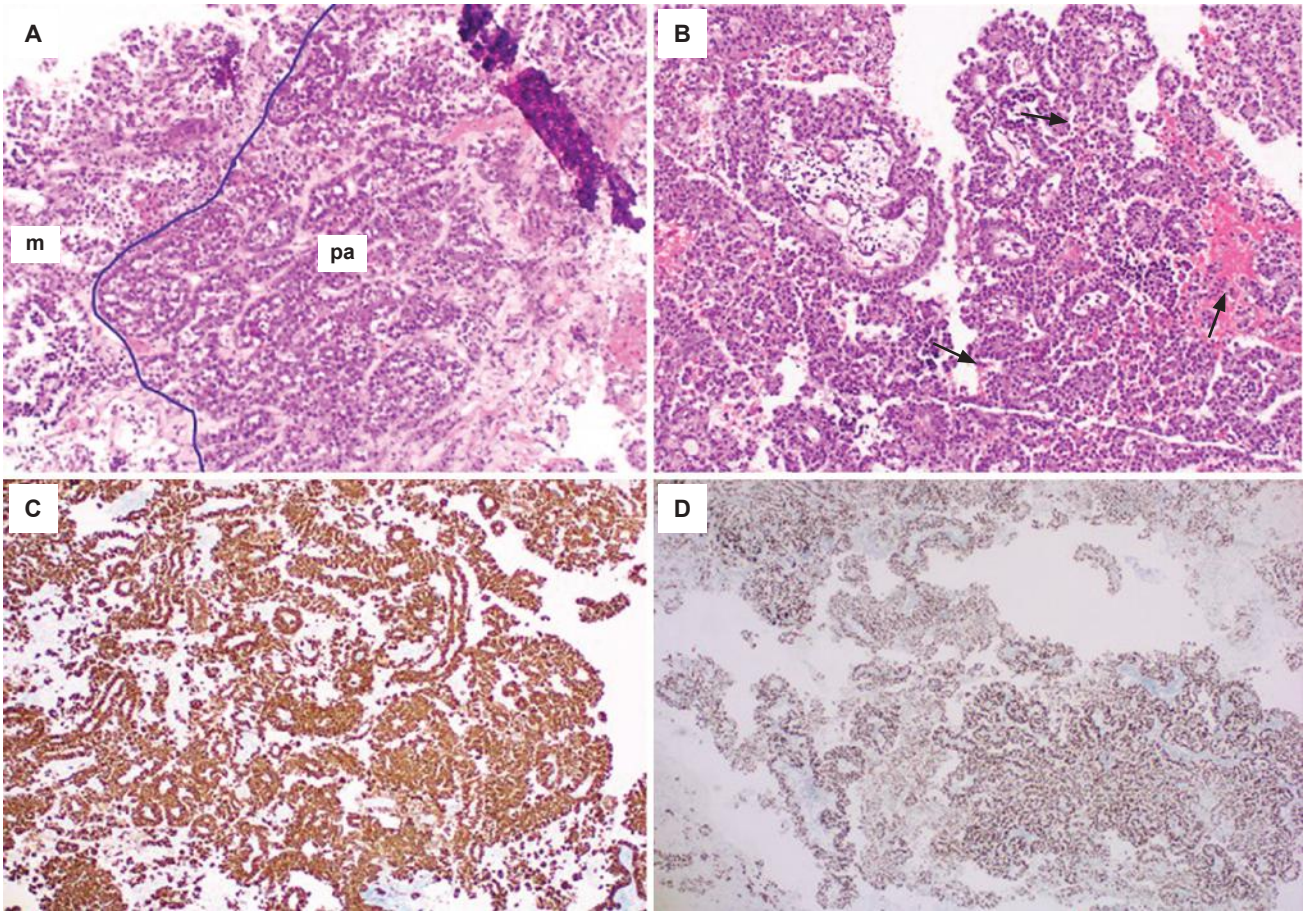

Figure 2. (A) Histopathology of the collision tumor showing a focus of metastatic adenocarcinoma **(m)** adjacent to pituitary adenoma **(pa)** (H&E, 10x). **(B)** The metastatic adenocarcinoma displayed pleomorphic cells arranged in papillary architecture (H&E, 10x). Immunohistochemical staining revealed positive staining for **(C)** cytokeratin 7 (CK7) and **(D)** thyroid transcription factor-1 (TTF-1).

Bone scintigraphy revealed right scapular bone metastasis, indicating progression of the carcinoma. The patient was counseled for radiotherapy by the oncology team; however, the patient refused and opted for palliative care instead.

She was discharged with oral hydrocortisone 10 mg twice a day, oral levothyroxine 75 μg once a day and oral desmopressin 0.05 mg twice a day. On follow-up at the endocrine clinic, she remained well with hormone replacement and reported stable visual acuity. Unfortunately, the patient was subsequently lost to follow-up.

DISCUSSION

Collision tumors represent the coexistence of two morphologically and immunohistochemically distinct tumors within a single organ, that may include neoplastic, vascular, congenital, infectious or inflammatory lesions.[1] Among collision tumors that involve carcinoma metastasizing to sellar tumors, the reported recipient tumors include pituitary adenomas, meningiomas, gliomas, schwannomas and hemangioblastomas, with meningiomas being a more common type of sellar recipient tumor than pituitary adenomas.[1,2] Although pituitary adenomas are the most common sellar lesions comprising 10 to 15% of all intracranial tumors, metastasis to a pituitary adenoma occurs in only 1 to 5% of patients with malignancies.[1] In the 36 reported cases of pituitary adenoma with metastatic carcinoma (including our case), lung cancer was the most common primary malignancy (n=9), with the majority being non-small cell lung carcinoma.[1,3,4] Other primary malignancy sites reported in these case series were the kidney (n=5), breast (n=5), melanoma (n=4), colorectum (n=3), stomach (n=1), pancreas (n=1), mediastinum (n=1) and prostate (n=1); the remaining 5 cases had unknown primary sites.[1-4] With the majority of the reported recipient pituitary tumors as non-functioning pituitary adenomas, most of the patients presented with symptoms of mass effect such as headache, cranial nerve palsies, visual disturbances and anterior pituitary hormone deficiency.[3,4] Compression of the pituitary stalk disrupts delivery of dopamine, the major inhibitory regulator of prolactin secretion, to the pituitary gland. The ensuing hyperprolactinemia is usually less than ten times the upper limit of normal as seen in our case, in contrast to very high levels associated with macroprolactinomas. Patients with metastasis to a pituitary adenoma also had more rapid tumor growth and a higher rate of optic chiasmal compression than patients with pituitary adenoma alone. These differences in clinical presentation are believed to arise from increased

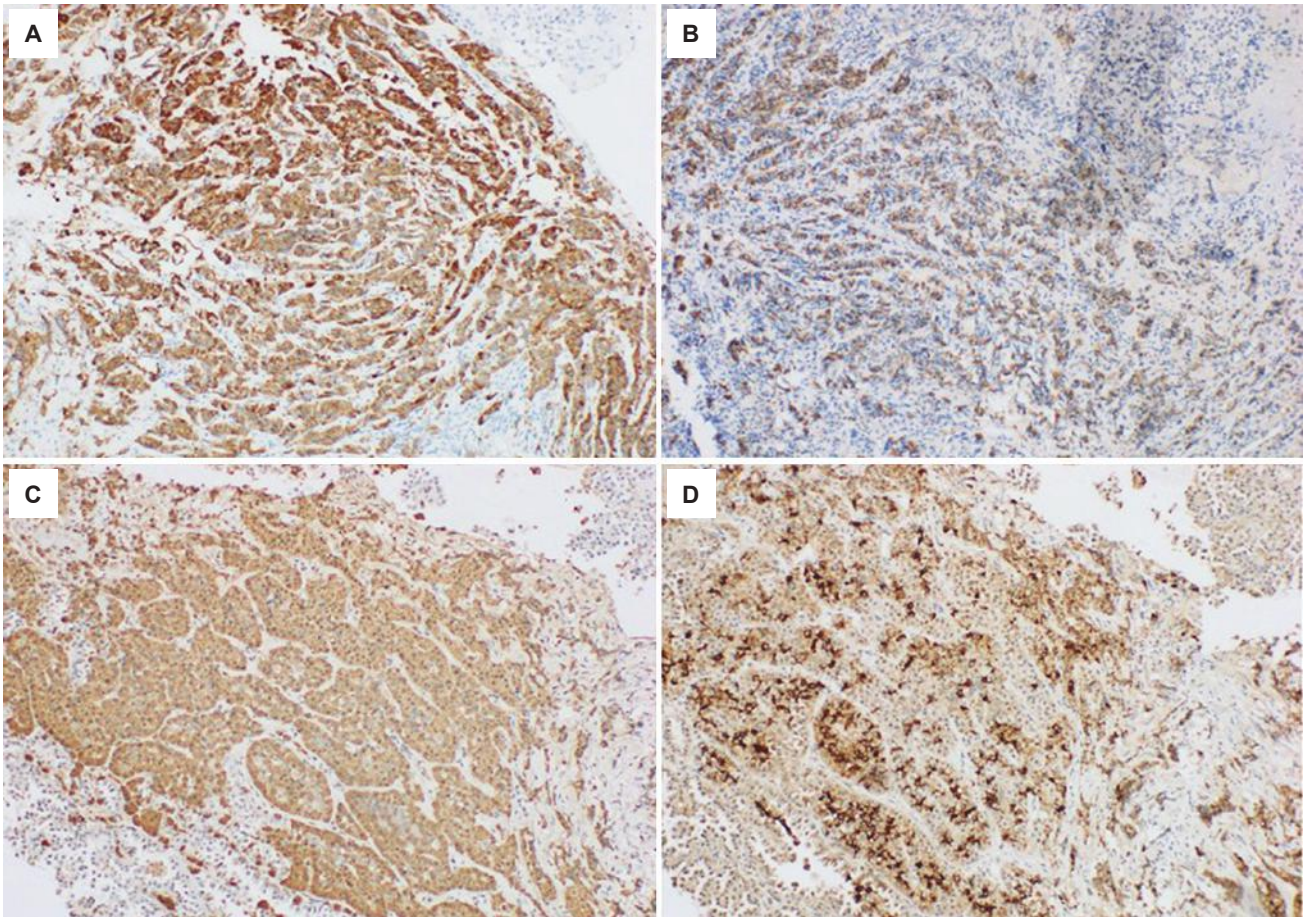

Figure 3. Immunohistochemical staining of the pituitary adenoma at 10x magnification, with positive staining for **(A)** synaptophysin, **(B)** growth hormone (GH), **(C)** adrenocorticotropic hormone (ACTH) and **(D)** prolactin.

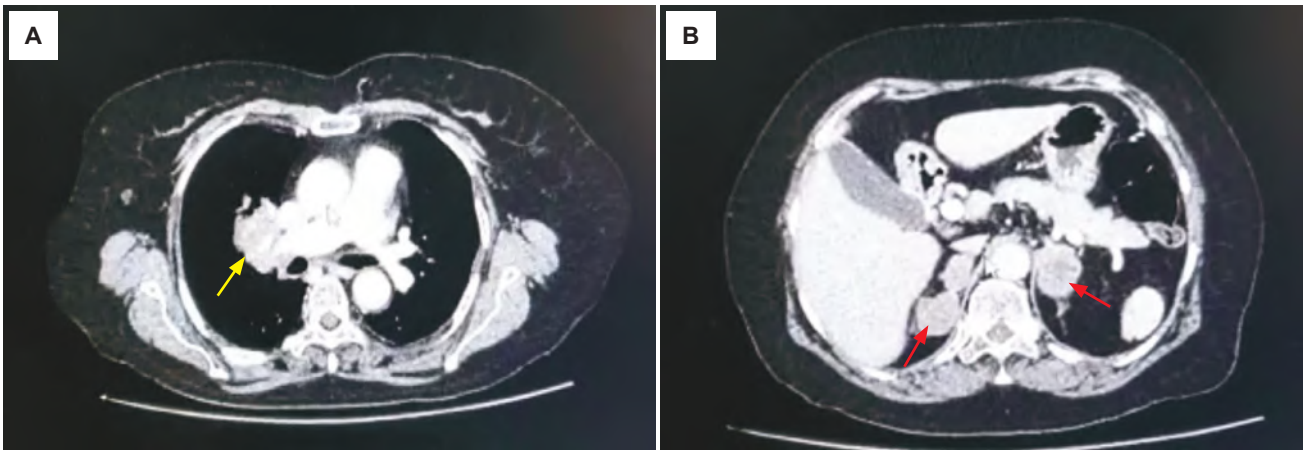

Figure 4. Computed tomography scan with contrast on axial view of the **(A)** thorax and **(B)** abdomen revealing a lobulated lesion at right perihilar area encasing the right pulmonary veins *(yellow arrow)*, bilateral adrenal masses *(red arrows)* and bilobed right adrenal mass.

neoplastic metastatic growth within a pre-existing, benign pituitary adenoma.[4] In our case, the rapid onset of visual disturbances and symptoms of pituitary hypofunction may also be due to pituitary apoplexy. A rare finding in pituitary metastasis, pituitary apoplexy is also attributed to rapid tumor growth that exceeds its own blood supply, as well as underlying vasculopathy causing tumor infarction and hemorrhage.[5]

In addition to the high incidence of visual disturbances and hypopituitarism, central diabetes insipidus is the most common symptom in patients with pituitary metastasis due to the predilection for hematogenous metastatic spread to the posterior pituitary lobe via the neurohypophyseal vessels.[6] Up to 30% of patients with pituitary metastases present with CDI, which rarely occurs with pituitary adenoma alone, as pituitary adenomas typically arise from

the anterior lobe of the gland, which receives systemic arterial blood supply mainly from the capsular and inferior hypophyseal arteries.[2,7] Metastasis to a pituitary adenoma can rarely occur either via the arterial supply of the adenoma itself, via direct extension of an adjacent bone metastasis or via meningeal spread through the suprasellar cistern.[1] Hence, the presence of CDI in our patient should dissuade the diagnosis of pituitary adenoma as the sole cause of the sellar mass.

In our case, differentiating a pituitary adenoma from a collision tumor based on imaging studies alone was challenging: intratumoral hemorrhage and loss of the posterior bright spot on pituitary MRI are also observed in pituitary adenomas and are not specific to pituitary metastases.[8,9] However, metastasis to the pituitary gland should be suspected in the presence of aggressive bony destruction, rapid growth with a relatively normal pituitary fossa, involvement of the infundibulum, the appearance of a dumbbell-shaped tumor with a clear indentation at the level of the diaphragma sellae, or the presence of additional intracerebral metastatic lesions.[10]

The definitive diagnosis of collision tumors, therefore, is made through histopathologic examination of the sellar mass, mostly from tumors resected during pituitary surgery or rarely, from postmortem examination.[1,3,4] The treatment approaches to pituitary adenoma and metastasis differ due to poorer prognosis of the latter. Surgery has no impact on overall survival in patients with pituitary metastasis, but only aims to relieve the mass effect and optic chiasmal compression in patients with cranial nerve palsies and visual disturbances.[11,12]

The prognosis of patients with metastasis to a pituitary adenoma is poor, mainly due to the advanced stage of the primary malignancies at the time of diagnosis of the collision tumor. In a systematic review of 657 patients with pituitary metastases, the median survival rate was 14 months; patients with primary lung cancer (31% of the cohort) had a shorter median survival of 9 months compared to patients with breast and renal cancer.[11] In a review of patients with collision tumors, Hoellig et al., determined the median survival time was 9.8 weeks, but also commented that it was uncertain if the short lifespan was due to concomitant peripheral metastases or additional intracerebral metastases, as the exact cause of death was not mentioned in most cases.[4] In the same review, 56.3% of the patients had multiple peripheral metastases, while 18.8% had coexisting intracerebral metastases, suggestive of advanced stages of malignancy at the time of the presentation of the collision tumor.[4] Due to advanced cancer stage, treatment modalities such as pituitary surgery or sellar radiotherapy are mainly palliative and are unable to improve survival.

The management of collision tumors includes the alleviation of mass effects, replacement of hormone deficiencies, treatment of hormone hypersecretion by functioning adenomas and targeted therapy for metastasis. In recent years, a multimodal treatment approach targeting both the primary malignancy and the metastasis to the pituitary gland, with pituitary surgery, sellar radiotherapy, hormonal replacement and chemotherapy, has been found to improve patient prognosis and extend the median survival time to 16 months.[6] Targeted radiotherapy to the pituitary gland, particularly stereotactic radiotherapy, is associated with a significant improvement in survival time (16 months) compared to that of untreated patients (6 months).[8] Nevertheless, unless effective targeted treatment is available for the primary malignancy, the prognosis is still poor, as survival is determined by the primary malignancy itself rather than the pituitary lesion.

CONCLUSION

Collision tumors are rare and can only be accurately diagnosed by histopathologic examination of the tumor. Although uncommon, the differential diagnosis of collision tumors should be considered in patients with sellar lesions and underlying malignancies, especially when there is rapid tumor growth causing mass effects, apoplexy and/or concurrent diabetes insipidus. Atypical imaging features may also help establish the diagnosis. The management of collision tumors involves treatment of both the pituitary adenoma and associated pituitary dysfunction, as well as the underlying primary malignancy and its metastatic disease. As life expectancy is often limited in patients with advanced primary malignancy, a multidisciplinary approach aimed at palliative care with careful consideration of the risks and benefits of each different therapeutic modality is pragmatic for the improvement of patient care.

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

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

Author Contributions Statement
MKB conceived and wrote the original draft preparation; reviewed and edited the manuscript; created and presented the data of the published work. FHS reviewed and edited the manuscript and supervised the research activity planning and execution. NSAB created and presented the data of the published work.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Adrenocortical Carcinoma With Cushing's Syndrome and Extensive Tumor Thrombosis of the Inferior Vena Cava in a 30-Year-Old Filipino Female

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Abstract

Adrenocortical carcinoma (ACC) is a rare and aggressive neoplasm with poor prognosis. We report a case of a 30-year-old female who presented with profound classic features of an adrenocorticotrophic hormone (ACTH)-independent Cushing's syndrome (CS) and a large adrenal mass with massive venous tumor thrombosis of the entire inferior vena cava (IVC), left renal and adrenal veins confirmed by imaging. Adrenal biopsy histopathology and immunohistochemistry confirmed ACC. Systemic palliative chemotherapy was administered. This rare case presents a unique and atypical presentation of an extensive tumor thrombosis of IVC. With the advanced stage at diagnosis, aggressive nature and poor prognosis of the disease, there is still a need to determine viable therapeutic options for metastatic ACC associated with venous invasion.

Key words: Cushing's syndrome, adrenocortical carcinoma, inferior vena cava thrombosis

INTRODUCTION

ACC is a rare endocrine neoplasm with an incidence of one to two per million of the population.[1] It has a bimodal age distribution with a peak in early childhood and a second peak in the fifth decade of life.[1-3] While patients often present with symptoms of hormone hypersecretion, they may also present with abdominal pain or a palpable mass.[1] Forty to sixty percent of patients manifest with symptoms and signs of excess cortisol (50%), sex hormones (20%), aldosterone (8%) and mixed hormones (15 to 25%).[4] ACC can also present as an incidentally-discovered non-functioning mass (incidentaloma).[1] ACC is an aggressive tumor that may have early-onset metastasis to the lung, lymph nodes, liver and bone.[5] Extension to the adrenal vein, renal vein or IVC occurs in 15-25% of patients.[5] Venous tumor thrombosis in the IVC is rare, usually occurring in right-sided adrenal masses. Surgery is the only curative therapy. The five-year survival of patients with complete resection is 32% to 48%. However, this rate drops to 5 to 10% for metastatic cases.[5] We report the case of a patient with ACC who presented as classic CS complicated by a thrombus extension to the left renal vein, left adrenal vein and IVC, and was treated with an adrenolytic drug and combination chemotherapy.

CASE

A 30-year-old female presented with a one-year history of menstrual irregularity with associated moon facies, acne, easy bruisability, wide, purplish striae and hirsutism. The day before admission, the patient had severe persistent flank pain that prompted admission. The patient is multigravid [G2P2 (2002)], with menarche at age 10 years. She denied any vices or intake of exogenous steroids. She had an unremarkable family history. On admission, she was in pain, with elevated blood pressure (160/100 mm Hg) and normal heart rate (96 beats per minute). She had moon facies, facial plethora, severe hirsutism, acne, and dorsocervical and supraclavicular fat pads. Her abdomen was asymmetric, with diffuse wide, purplish striae and a palpable mass at the left side (Figures 1A and 1B). Ecchymoses were noted on the extremities (Figure 1C).

Hormonal evaluation revealed a non-suppressed cortisol after a 1 mg dexamethasone test [22.6 μg/dL, normal value (NV) <1.8μg/dL], an elevated 24-hour urine free cortisol (314.19 μg/24 hours, NV 22 to 243 μg/24 hours) and a normal ACTH (8.46 pg/mL, NV 5 to 46 pg/mL), confirming an ACTH-independent Cushing's syndrome. Further tests revealed increased dehydroepiandrosterone-sulphate

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: September 30, 2021. Accepted: March 5, 2022.
Published online first: August 7, 2022.
https://doi.org/10.15605/jafes.037.02.10

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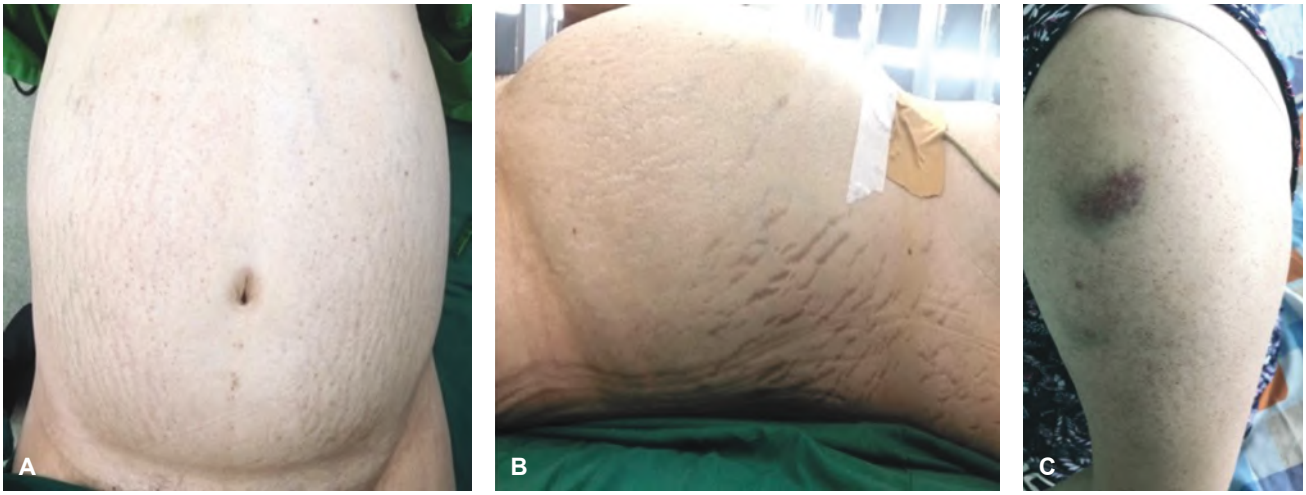

Figure 1. Physical findings included **(A)** globular asymmetric abdomen with **(B)** wide violaceous striae and **(C)** ecchymoses.

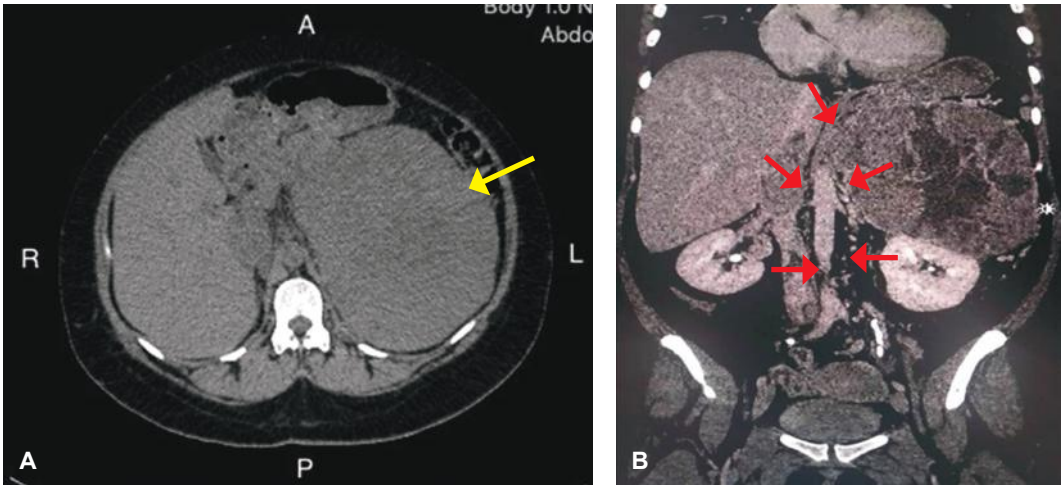

Figure 2. Computerized tomography prior to treatment. **(A)** Plain scan of the whole abdomen showed a heterogeneously large left adrenal mass measuring 19 cm x 14.4 cm x 14 cm in its greatest and perpendicular dimensions *(yellow arrow)*; **(B)** angiography of the aorta showed the extent of the tumor at different aortic segments: aortic root mid-ascending, proximal arch, mid-descending, distal descending, suprarenal abdominal and infrarenal abdominal. Enlargement of the inferior vena cava with intraluminal filling defects was seen along its entire course from T11 to the bifurcation of common iliac veins, as well as in the left renal, left common iliac, and left ovarian veins *(red arrows)*. The stomach and spleen were also displaced.

(DHEA-S) (1,402 µg/dL, NV 95.80 to 511 µg/dL) and an elevated 24-hour urine metanephrines (2.61 mg/24 hours, NV 0 to 1.0 mg/24 hours). Serum aldosterone, plasma renin activity and aldosterone/renin ratio (ARR) were within the normal reference range (Table 1). The patient had normocytic normochromic anemia with thrombocytosis, normokalemia, hyponatremia and hyperlipidemia. Abdominal computed tomography (CT) revealed a large, heterogeneously enhancing left adrenal mass measuring 19 cm x 14.4 cm x 14 cm, displacing the stomach and spleen (Figure 2A). Deep vein thrombosis was seen involving the IVC, left renal vein, and its suprarenal and ovarian tributaries due to tumor invasion by the adrenal mass. A CT angiography study showed that the mass had a venous connection from the IVC at the level of L2. The IVC was enlarged with an intraluminal filling defect along the entire course of the IVC from the level of T11 down to the bifurcation of common iliac veins, including the left renal vein, left common iliac, and left ovarian vein (Figure 2B).

The patient was medicated with verapamil 180 mg once daily (OD) and terazosin 5 mg OD for hypertension, enoxaparin 30 mg subcutaneous injection OD, and atorvastatin 40 mg OD for hyperlipidemia. The planned treatment was radical resection of the left adrenal neoplasm and adjacent organs with possible cardiopulmonary bypass, segmentectomy of the IVC and reconstruction with vascular prosthesis. The involvement of the IVC and extensive vascular tumor invasion made the operative plan technically difficult and risky, carrying a poor surgical prognosis. After a family conference to discuss alternative options for treatment, the patient, family and medical team decided on adjuvant chemotherapy with pretreatment open biopsy and palliative care.

Table 1. Diagnostic work-up based on recommendations of the ACC Working Group of the ENSAT[3]

Hormone study	Result	Reference value
Glucocorticoid		
8AM Cortisol after 1 mg overnight dexamethasone suppression test, µg/dL	22.6	<1.8
ACTH, pg/mL	8.46	5-46
24-hour urine free cortisol, µg/24 hours	314.19	22-243
Sex steroid		
DHEAS, µg/dL	1,402	95.80-511
Mineralocorticoid		
Aldosterone, ng/dL	13.27	3.78-23.30
PRA, ng/mL/hr	1.79	0.3-1.90
Aldosterone/renin ratio, ng/dL/ng/mL/hr	7.413	
Metanephrines and catecholamines		
24-hr urine metanephrines, mg/24 hours	2.61	0- 1.0

ENSAT - European Network for the Study of Adrenal Tumors

She was prepared preoperatively for the biopsy with terazosin to achieve adequate alpha blockade, increased oral fluids and liberal salt intake. A large and firm left adrenal mass with hypervascularity was noted on open biopsy (Figure 3**)**. Microscopically, the specimen showed diffuse sheets of cells having eosinophilic cytoplasm with clear cells comprising <25% of the field. (Figure 4). Focal areas showed highly pleomorphic tumor cells and mitosis in less than 5 per 50 high power fields (hpf) with no atypical mitotic figures. There were areas with hemorrhage and necrosis, with no lymphovascular invasion (Figure 4). The immunohistochemistry panel of the biopsy sample revealed positive results for melan A, inhibin, vimentin and synaptophysin, which favored a diagnosis of adrenal malignancy. Chromogranin, a marker for neuroendocrine differentiation and a test to rule out pheochromocytoma, was negative. Ki-67, an indicator of poor prognosis, was estimated at 30% (Figure 5). The final pathologic diagnosis was ACC Stage 4.

The patient was started on ketoconazole 200 mg every 8 hours to suppress adrenal cortisol production. Medical oncology service recommended palliative chemotherapy using etoposide, doxorubicin, and cisplatin combined with mitotane. Due to the unavailability of mitotane at the onset, the combination of cisplatin plus etoposide was given. The patient tolerated the initial cycle of chemotherapy and continued the rest of the chemotherapy sessions on an outpatient basis.

On the third month of follow-up, a repeat abdominal CT scan with contrast showed stable disease (Figure 6A). Follow-up tests including CBC, electrolytes, liver enzymes, bilirubin and alkaline phosphatase were all within normal range. On the fourth month of follow-up, she was given mitotane 2 g daily in four divided doses. An incremental increase of the daily dose by 1 gram every 1 to 2 weeks was given if without untoward side effects. Cisplatin and etoposide were also given in combination with mitotane for the next three months. She had bouts of nausea and vomiting which were relieved by ice chips and proton pump inhibitors. Subsequent blood tests (CBC, AST, ALT, FT4 and TSH, cortisol and lipid profile) were all normal.

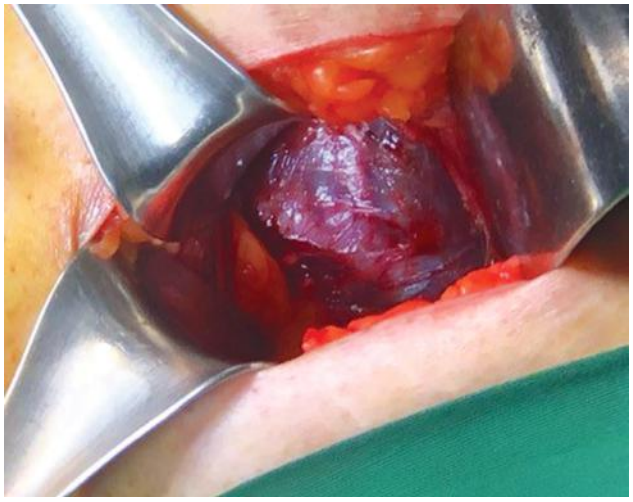

Figure 3. Open biopsy showing a large and firm left adrenal mass with hypervascularity.

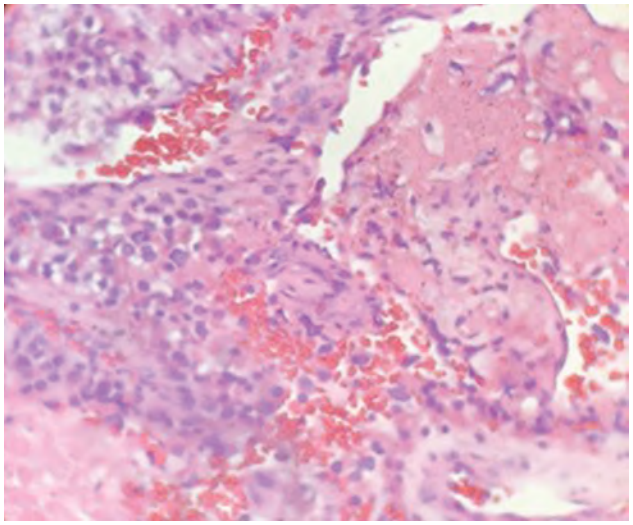

Figure 4. Histopathologic examination showed diffuse sheets of cells containing eosinophilic cytoplasm, <25% clear cells, focal areas with highly pleomorphic tumor cells, mitosis in less than 5 per 50 hpf and no atypical mitotic figures. Hemorrhage and necrosis without lympho-vascular invasion were also observed. (H&E, 200x).

Eight months post-chemotherapy, a surveillance abdominal CT scan showed progressive disease (Figure 6B). The patient continued with chemotherapy for another two months using the combination of doxorubicin and mitotane. Unfortunately, the patient's condition gradually deteriorated with persistent complaints of severe flank pain while on home palliative care.

DISCUSSION

ACC is a rare endocrine malignancy. An associated venous tumor thrombosis to the IVC is much rarer. There are only two cases of ACC with overt Cushing's syndrome and tumor thrombus invasion to the IVC documented in the literature.[6,10] In a literature review of 44 cases of ACC with tumor thrombus extending to the IVC, only 26

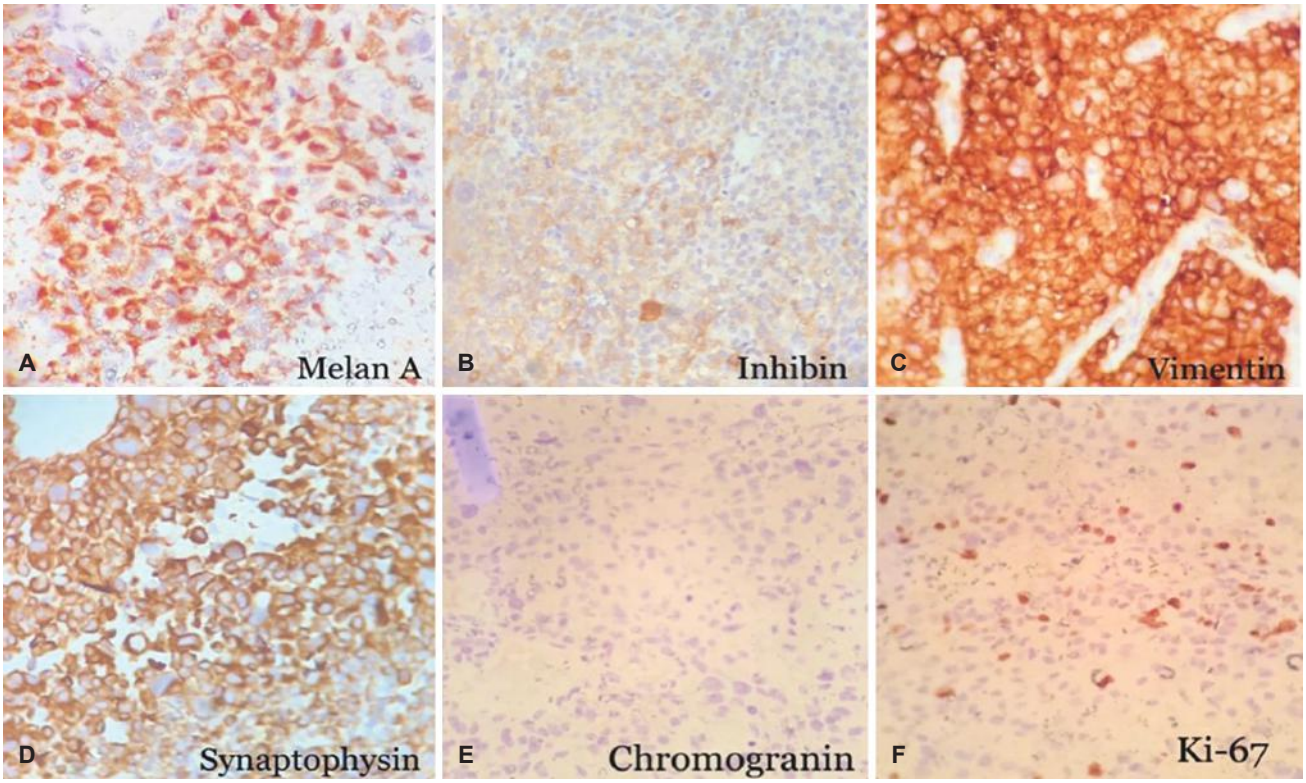

Figure 5. Immunohistochemical staining for was positive for **(A)** Melan A, **(B)** Inhibin, **(C)** Vimentin and **(D)** Synaptophysin and negative for **(E)** Chromogranin, **(F)** Ki-67 positivity was seen in 30% of neoplastic cells.

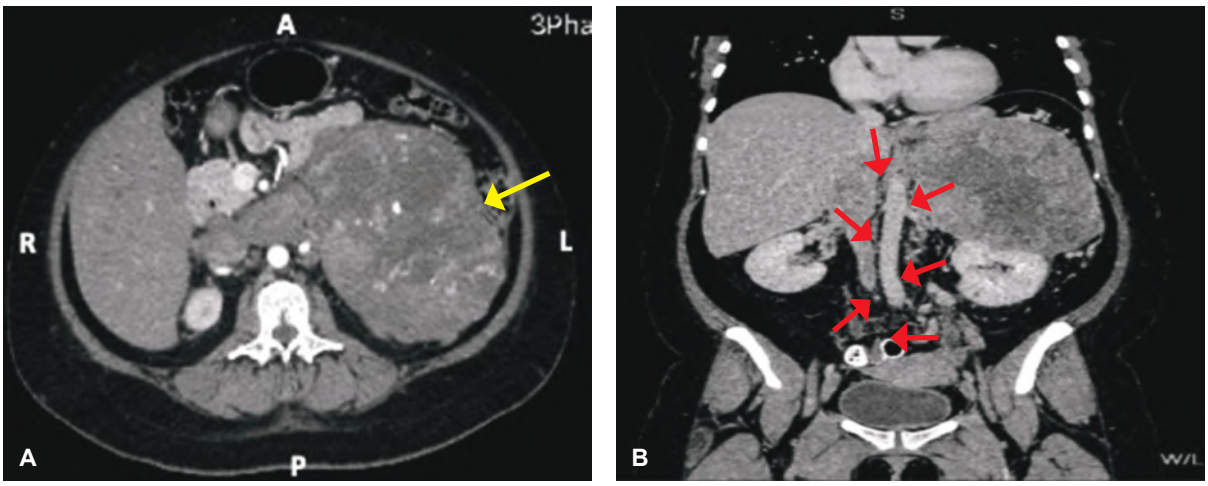

Figure 6. Computerized tomography of the abdomen with intravenous contrast after treatment. **(A)** Sagittal view taken three months after treatment. There was no interval change in the left adrenal mass size *(yellow arrow)*, with tumor thrombus involving the inferior vena cava (IVC) and left renal, left adrenal and bilateral common iliac veins. **(B)** Coronal view taken six months after treatment. The left adrenal mass was found be slightly increased in size, abutting the spleen and pancreas, with probable invasion of the adjacent left kidney. Similar findings of tumor thrombus involving the IVC and left renal, left adrenal and both common iliac veins were also seen *(red arrows)*.

were functioning tumors with a few manifesting virilization, heterosexual pseudo-precocious puberty or occult hypercortisolism demonstrable only with hormonal testing.[6-10] ACC is predominantly right-sided (32 right- versus 12 left-sided), usually large (range 1.8 to 25.5 cm, median 11.0 cm), with no apparent gender predominance half of cases occurring in men.[6-10] Tumor thrombosis, which may grow into the IVC, was more commonly found in right- compared to left-sided tumors. Chiche and colleagues documented a left-sided ACC which extended into the IVC through the renal vein, similar to our case.[7] Half of the cases also had an extension to the right atrium.[6,9]

ACC is often diagnosed late and already in advanced stages, as exemplified by our case. A large tumor burden and potential hormonal functionality highly impact the disease process. CS in the setting of ACC has a negative prognostic factor because the excessive cortisol has immune

suppressive effects which favor the further growth of the tumor and its metastases.[11] Adrenal cortical neoplasms may also be associated with findings that simulate pheochromocytoma (pseudo-pheochromocytoma).[12] These tumors may have neuroendocrine features which may explain the significant increase in the 24-hour urine metanephrines. The elevated DHEAS causes features of virilization and contributes to its aggressive course.

The European Network for the Study of Adrenal Tumors (ENSAT) published the standard diagnostic procedures for ACC.[2,13] After localization of the lesion with ACTH, appropriate imaging should be requested. In patients with low or normal ACTH, CT scan of the adrenals can evaluate the tumor size, malignant potential, intravascular extension and presence of metastases. Adrenal adenomas are usually <4 cm with Hounsfield (HU) density of <10 and >50% washouts after intravenous (IV) contrast, while ACC is heterogeneous with high pre-contrast density >10 HU and washout of <50% after IV contrast.[2-4] The risk for ACC increases with tumor size >6 cm.[2] An adrenal biopsy should only be considered in selected cases in which the tumor is considered inoperable.[12]

The Modified Weiss Scoring system is used for pathologic diagnosis.[14] It is composed of nine items, with three items each referring to to tumor architecture, cell nuclei and the presence of any type of invasion). A Weiss score ≥3 defines an ACC.[14] An important prognostic parameter is Ki-67. As a marker of cell proliferation, it can define the diagnosis and prognosis of ACC in both localized and metastatic disease. A Ki-67 of ≥5% is usually seen in ACC. The patient's Ki-67 of 30% confirmed the tumor's aggressiveness. Meanwhile, tumor staging, such as the TNM classification, is used to assess prognosis in ACC.[2,12] Stage I and II are strictly localized tumors with a size of ≤5 or >5 cm, respectively. Stage III is characterized by infiltration to the surrounding tissue, positive regional lymph nodes or a tumor thrombus in the vena cava and/or renal vein. Stage IV is defined by the presence of distant metastasis.[2,15]

Complete surgical resection of the tumor mass is the cornerstone of treatment in all patients with localized and locally advanced disease, even in cases with tumor thrombus invasion. Surgery becomes more complex and carries a higher morbidity and mortality rate the higher the tumor thrombus extends. A margin-free complete resection provides the only means to achieve long-term survival.[2,6-15] The presence of a tumor thrombus in the IVC and the renal vein is compatible with complete tumor resection and may need a cardiac bypass technique.[6] Unfortunately, there is no data for radical surgery with tumor thrombus invasion in the Philippines. Although invasive surgery is the only therapeutic option, Kim et al., reported a case of a large ACC with thrombus extension to the right atrium where despite the patient's refusal to undergo surgery, the tumor regressed spontaneously during follow-up.[15] The median survival post-surgery for metastatic and nonmetastatic cases with tumor invasion of the IVC was eight months.[13] A three-month survival only after surgery was noted in one case because of metastatic disease which showed that systemic chemotherapy is a better alternative than radical surgery.[10] There are no randomized controlled trials on the treatment of ACC with invasion to the IVC.

Our current knowledge is based on case reports and expert opinion due to the low incidence of ACC and the rare site for tumor invasion and extension. The infiltrative, expansile tumor thrombus extended from the left renal and adrenal veins to the entire course of the IVC. With only a 3.6 cm thrombus-free zone of the IVC before the right atrium and an area that is totally occluded, all these findings made surgery technically difficult and risky. Even with the utmost precaution, there was a high risk for pulmonary embolism, stroke and myocardial infarction.

The European Society of Clinical Endocrinology Clinical Practice Guidelines suggest against adrenal surgery in case of widespread metastatic disease, and recommend either mitotane monotherapy or combined mitotane, etoposide, doxorubicin and cisplatin depending on prognostic parameters.[12] Mitotane is the most effective and frequently used chemotherapeutic agent in metastatic adrenal carcinoma. A study revealed that mitotane in ACC provided a response rate of 48.6%, and longer median progression-free survival.[16] When mitotane is used together with drugs such as cisplatin, doxorubicin, and etoposide, the combination may produce a clinical response rate of about 50% even in advanced cases.[2,16] Treatment is 1 to 2 grams daily to be adjusted based on tolerance and attainment of therapeutic plasma levels. However, a study on mitotane alone in metastatic, unresectable, or incomplete resection cases have demonstrated a lower response rate and a lower survival rate.[16]

CONCLUSION

Our case illustrates that early diagnosis is crucial for preventing complications (such as extensive tumor invasion) and timely surgical treatment. Palliative care and chemotherapy remain as important treatment options for patients with ACC. Given the advanced stage upon diagnosis, aggressive nature and poor prognosis of the disease, there a need to determine other viable therapeutic options for metastatic ACC associated with venous invasion.

Ethical Consideration

Patient consent was obtained before the submission of the manuscript. The patient's family requested that facial features not be published.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Contribution Statement

KA, MHG, JMC and RA conceived the idea; validated the data; conducted the research; provided the study materials; prepared the original draft; reviewed and edited the manuscript.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Fatal Case of Possible Thyroid Crisis Induced by SARS-CoV-2 Infection: A Case Report

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Abstract

Thyroid crisis is an emergency due to impaired thyroid function caused by various conditions, particularly infections such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that result in the dysfunction of various vital organs. We report a case of a 31-year-old Indonesian female with a 2-year history of hyperthyroidism with elevated thyroid-stimulating hormone (TSH) receptor antibodies. (TRAb) who developed thyroid crisis possibly in association with SARS-CoV-2 pneumonia, sepsis, and disseminated intravascular coagulation (DIC). Prior to admission, she was treated for her hyperthyroidism with propylthiouracil and had been in stable remission for a year. She was admitted to the Emergency Room with complaints of watery stools, icteric sclerae, jaundice, coughing, and shortness of breath. The physical examination showed a World Health Organization (WHO) performance score of 4, delirium, blood pressure within normal limits, tachycardia, tachypnea, axillary temperature of 36.7°C, icteric sclerae, jaundice, and exophthalmos. There was a 3 cm palpable nodule on the right side of the neck. Auscultation of the lungs revealed bilateral pulmonary rales. Abdominal examination noted a palpable liver and enlarged spleen. Laboratory tests showed thrombocytopenia, electrolyte imbalance, hypoalbuminemia and elevated transaminases. The thyroid function tests showed a suppressed TSH level with an elevated free thyroxine (FT4) level. The SARS-CoV-2 polymerase chain reaction (PCR) swab test was positive. Initial patient management was with supportive therapy that included favipiravir and anti-hyperthyroidism medication; however, despite these interventions, her condition continued to deteriorate and she died after a few hours. This case demonstrates no difference in therapy between patients with thyroid crises and COVID-19 or other infections. Proper and timely treatment is important for reducing mortality rates.

Key words: COVID-19, SARS CoV-2, thyrotoxic crisis, thyroid storm, thyrotoxicosis

INTRODUCTION

SARS-CoV-2 infection causes coronavirus disease 2019 (COVID-19) and pulmonary and systemic inflammation, leading to multi-organ dysfunction.[1] Mortality increases due to respiratory failure and other complications such as cardiovascular failure and DIC, and also due to the presence of comorbidities such as autoimmune diseases that alter thyroid function (e.g., Graves' disease [GD]) and COVID-19-associated thyroid disease, particularly with delayed diagnosis and management.[2] Thyroid crises can be triggered by events such as surgery, infection, inadequate antithyroid drug (ATD) therapy, thyroid surgery trauma, or uncontrolled diabetes mellitus (DM), with upper respiratory tract infection (e.g., SARS-CoV-2 infection) being the second-most common cause.[3-6] COVID-19 affects organs and organ systems, including the endocrine system, where the pituitary-thyroid axis is the direct or indirect target of SARS-CoV-2, which can cause central hypothyroidism. Thyroid dysfunction can be found in SARS-CoV-2 infected patients where COVID-19 causes thyroid hormone imbalance in proportion to the degree of infection.[1,7]

CASE

In July 2021, a 31-year-old Indonesian female with complaints of diarrhea of more than three times a day without mucus or blood was admitted to the emergency room. She reported fever and scleral icterus for the last three days. She had a history of hyperthyroidism since 2019 with elevated TRAb of 4.02 IU/L (reference value ≤1.75 IU/L), currently in stable remission after one year of propylthiouracil. There was no history of surgery. She reported occasional nonproductive cough and shortness of breath but denied chest pain. She had no history of COVID-19 vaccination or contact with COVID-19 patients. Physical examination showed a WHO performance score

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: July 7, 2022. Accepted: September 7, 2022.
Published online first: November 9, 2022.
https://doi.org/10.15605/jafes.037.02.19

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of 4, Glasgow coma score (GCS) of 11 (E3M5V3), blood pressure of 120/70 mmHg, heart rate of 132 beats/minute with a weak pulse, respiratory rate of 26 beats/minute, and axillary temperature of 36.7°C with delirium, icteric sclera, jaundice, and exophthalmos. Neck examination revealed a palpable right-sided nodule measuring 3 cm in diameter, fixed, mobile on swallowing, and nontender. There was no cervical lymphadenopathy. Lung auscultation revealed bronchovesicular breath sounds and bilateral pulmonary rales but no wheezing. Abdominal examination showed palpable liver and spleen enlargement. Examination found both extremities within normal limits.

The initial complete blood count and the basic metabolic panel are shown in Table 1. Thrombocyte, sodium, potassium, and albumin values were decreased. Transaminases were significantly elevated. TSH was 0.1 mIU/L (0.25–0.5 mIU/L), and FT4 was 7.26 ng/dL (0.93–1.71 ng/dL). The patient tested positive for the SARS-CoV-2 antigen, and six hours later, the SARS-CoV-2 PCR swab result was positive with a threshold cycle (C_T) of 18.23 (reference C_T >38). Electrocardiogram showed sinus tachycardia at 125 beats/minute. Chest X-ray (CXR) reported a thyroid nodule on the right cervical area and bilateral pneumonia. A multi-slice computed tomography (MSCT) scan of the chest showed ground glass opacity on the posterior dorsal lung (Figure 1).

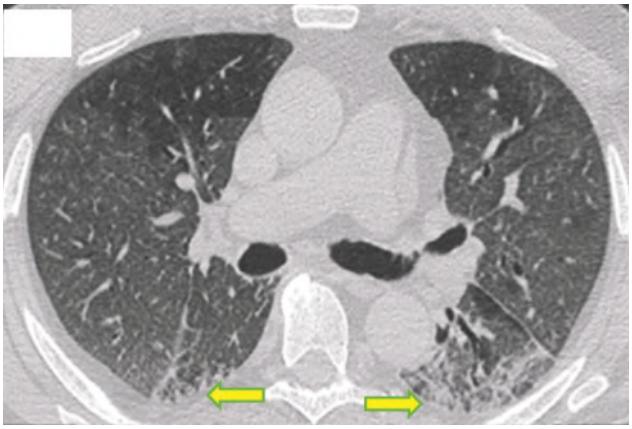

Figure 1. An axial non-contrast MSCT of the thorax showing minimal ground-glass opacities on the posterodorsal lung (arrow).

The patient had a Burch-Wartofsky Point Scale (BWPS) score of 75 (Table 2) which fulfills the criteria of thyroid storm. By the Japan Thyroid Association (JTA) thyroid storm criteria (Table 3), patient has definite thyroid storm (TS1). Admitting impression was sepsis-induced thyroid crisis due to COVID-19 infection and DIC. Initial patient management included monitoring vital signs (Figure 2), electrolyte correction, oxygen at 10 L/min via non-rebreathing mask, fluid resuscitation with acetate Ringer's solution at 30 cc/kg of body weight every 3 h, 40 mg of omeprazole administered intravenously every 12 h, 40 mg of propranolol administered nasogastrically every 6 h, 8 mg of dexamethasone administered intravenously every 24 h, 5 Lugol drops administered nasogastrically every 6 h, 60 mg of methimazole administered nasogastrically every 24 h, 2 mg of diazepam administered intravenously every 24 h, and the planned subcutaneous administration of 0.4 cc of enoxaparin every 24 h. Pulmonology service prescribed favipiravir.

Six hours after admission, the patient complained of worsening shortness of breath and became unconscious with a GCS of 9 (E2M5V2) and average blood pressure of 125/65 mmHg, heart rate of 123 beats/minute, temperature of 37°C, respiratory rate of 26 times/minute, 96% oxygen saturation, and ineffective breathing pattern. She was ideally for transfer to the Intensive Care Unit (ICU); however, the

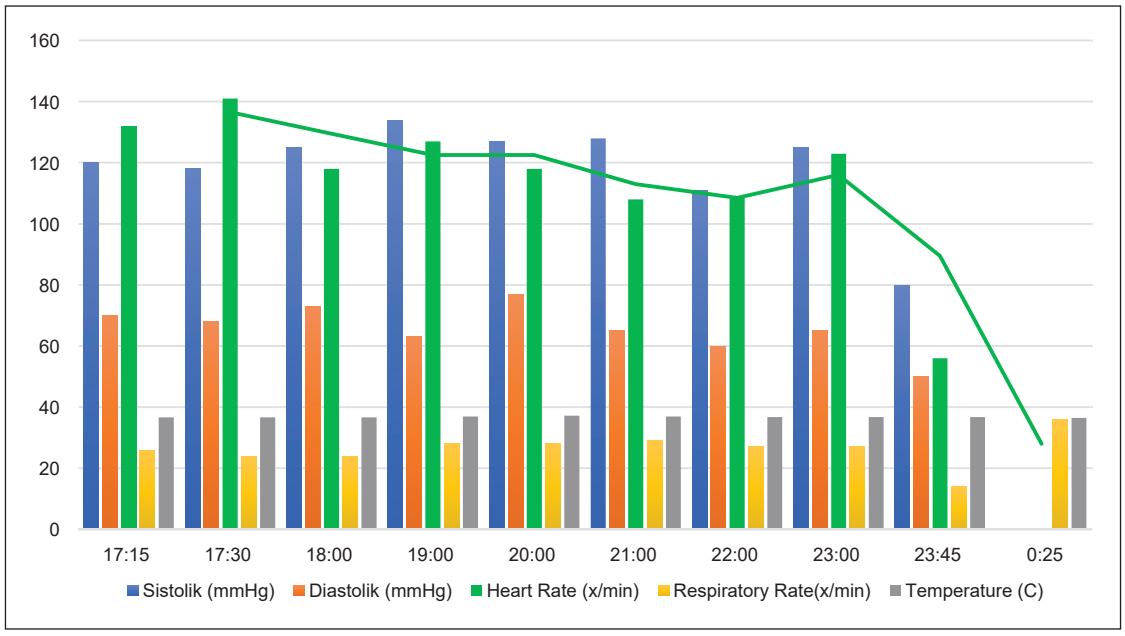

Figure 2. Vital signs of patient throughout admission.

hospital did not have an ICU for patients with COVID-19, and its laboratory could not perform diagnostic PCR tests for SARS-CoV-2 infection, delaying patient management. The patient died a few hours after the start of treatment.

Table 1. Clinical laboratory results

Measure	Reference Interval	Result
Leukocytes (per µL)	4,000–9,000	7,600
Absolute neutrophil count (%)	25.0–78.0	70.6
Absolute lymphocyte count (%)	17.0–57.0	16.3
Absolute monosyte count (%)	0.0–10.0	6.8
Absolute eosinophil count	0.0–10.0	3.3
Absolute basophil count	0.0–2.0	3.0
Erythrocytes (per µL)	3,760,000–5,700,000	3,700,000
Platelet count (per µL)	150,000–350,000	60,000
Hemoglobin (g/dL)	12.0–18.0	11.9
Hematocrit (%)	33.5–52.0	35.8
Sodium (mmol/L)	136–145	132.2
Potassium (mmol/L)	3.5–5.1	3.1
Chloride (mmol/L)	94–110	101
Urea (mg/dL)	6–4	15
Creatinine (mg/dL)	0.5–1.3	0.9
Albumin (g/dL)	3.7–5.3	3.1
Random blood glucose (mg/dL)	70–140	110
Alanine aminotransferase (U/L)	<41	200
Aspartate aminotransferase (U/L)	<37	392

Table 2. The patient's Burch and Wartofsky Point Scale (BWPS)

Criteria	Points
Thermoregulatory dysfunction	
Temperature (°F)	
99–99.9	**5**
100–100.9	10
101–101.9	15
102–102.9	20
103–103.9	25
>104	30
Central nervous system effects	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, or extreme lethargy)	**20**
Severe (seizure or coma)	30
Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate (diarrhea, nausea/vomiting, or abdominal pain)	10
Severe (unexplained jaundice)	**20**
Cardiovascular dysfunction	
Tachycardia (beats/min)	
90–109	5
110–119	10
120–129	15
130–139	**20**
>140	25
Atrial fibrillation	10
Congestive heart failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	**10**
Severe (pulmonary edema)	15
Precipitating history	
Positive	**0**
Negative	10
Total Score	**75 (Thyroid Storm)**

Criteria: ≥45, thyroid storm; 25–44, impending storm; <25, storm unlikely.

DISCUSSION

In this case report, the patient was diagnosed with thyroid storm consistent with the BWPS for thyrotoxicosis and the 2016 JTA and Japanese Endocrine Society criteria for thyroid storm.[4] Thyroid crisis is a life-threatening condition often triggered by acute conditions or mental stress, developing into thyrotoxicosis and manifesting as multi-organ failure (MOF),[8,9] with a reported 10.7% mortality rate in Japan.[9] The thyroid crisis was triggered in this patient by SARS-CoV-2 infection in July 2021, at the peak of the second wave of COVID-19 infections in Indonesia.

Chen et al., studied 50 patients with confirmed COVID-19 infections, finding that 56% had abnormal TSH values, with low TSH associated with poor prognosis.[10] In Indonesia in July 2021, 88,659 of 3,287,727 patients with confirmed COVID-19 died.[11] The THYRCOV study by Lania et al., reported thyroid function changes in response to COVID-19 infection. Of their 287 patients, 31 had thyrotoxicosis (20.2%) and 15 had hypothyroidism (5.2%). Moreover, they found a significant relationship between increased interleukin 6 levels and decreased TSH, causing thyrotoxicosis, more severe systemic inflammation, and lower free-triiodothyronine (FT3) levels.[12]

The pathological mechanism of changes in thyroid hormones in patients with SARS-CoV-2 infection occurs via direct viral mechanisms and angiotensin-converting enzyme 2 (ACE2) in the pituitary gland, which indirectly impacts systemic effects by activating proinflammatory

Table 3. The Japan Thyroid Association thyroid storm (TS) diagnostic criteria[4]

Prerequisite for diagnosis is presence of thyrotoxicosis with elevated levels of free triiodothyronine (FT3) or free thyroxine (FT4)

Symptoms

1. Central nervous system (CNS) manifestations: Restlessness, delirium, mental aberration/psychosis, somnolence/lethargy, coma (≥1 on the Japan Coma Scale or ≤14 on the Glasgow Coma Scale)
2. Fever: ≥38˚C
3. Tachycardia: ≥130 beats/minute or heart rate ≥130 in atrial fibrillation
4. Congestive heart failure (CHF): Pulmonary edema, moist rales over more than half the lung field, cardiogenic shock, or Class IV by the New York Heart Association or ≥ Class III in the Killip classification
5. Gastrointestinal (GI)/hepatic manifestations: nausea, vomiting, diarrhea, or a total bilirubin level ≥3.0 mg/dL

Thyroid Storm Diagnosis Grade adapted from Akamizu, et al.[9]

TS1 (First combination): Thyrotoxicosis and at least one CNS manifestation and fever, tachycardia, CHF, or GI/hepatic manifestation
TS1 (Alternate combination): Thyrotoxicosis and at least three combinations of fever, tachycardia, CHF, or GI/hepatic manifestation
TS2 (First combination): Thyrotoxicosis and a combination of two of the following: fever, tachycardia, CHF, or GI/hepatic manifestation
TS2 (Alternate combination): Patients who met the diagnosis of TS1, except that serum FT3 or FT4 levels are unavailable

Exclusion and provisions

Cases are excluded if other underlying diseases clearly cause any of the following symptoms: fever (e.g., pneumonia and malignant hyperthermia), impaired consciousness (e.g., psychiatric disorders and cerebrovascular disease), CHF (e.g., acute myocardial infarction), and liver disorders (e.g., viral hepatitis and acute liver failure). Therefore, when it is difficult to determine whether the symptom is caused by TS or is simply a manifestation of an underlying disease, it should be regarded as being due to a TS caused by these precipitating factors. Clinical judgment in this matter is required.

TS1, "Definite" TS; TS2, "Suspected" TS.

cytokines causing hyperinflammation and human leukocyte antigens in the autoimmunity response.[2,10] Hyperinflammatory syndrome is caused by SARS-CoV-2 infection, which increases proinflammatory cytokines that can cause patients to enter into a septic condition.

COVID-19 patients have hepatocellular damage caused by SARS-CoV-2 infection via ACE2 receptor expression. ACE2 expression in cholangiocyte cells causes cholestasis and cytokine storm conditions, increasing liver damage and hepatobiliary complications.[13] While acute liver failure in thyroid storm is associated with increased FT3 due to mitochondrial apoptosis in hepatocytes, the pathologic mechanism for thyrotoxicosis is secondary ischemic hepatitis due to peripheral vasodilation and excessive thyroid hormone release due to acute heart failure.[14,15] In this patient, diarrhea and jaundice were manifestations of a thyroid crisis.

Thyroid crisis triggered by SARS-CoV-2 infection causes coagulopathy due to increased pulmonary platelet consumption, intravascular coagulation, and microangiopathic thrombosis. Coagulopathy is caused by systemic inflammation and SARS-CoV-2-specific mechanisms that cause endothelial dysfunction.[7] When clinicians are aware of coagulation disorders in patients with SARS-CoV-2 infection, they should perform D-dimer, prothrombin time, and fibrinogen tests to assess their DIC scores.[16-18] DIC events can be triggered by thrombocytopenia in patients with thyroid crisis and SARS-CoV-2 infection and, in turn, increase the risk of venous thromboembolism (e.g., pulmonary embolism and cerebral venous thrombosis) and stroke due to arterial thrombosis and embolism that causes atrial fibrillation.[15] Low molecular weight heparin (LWMH) can be given as thromboprophylaxis, particularly in severe and critically ill patients. It has anticoagulant properties but can also limit viral entry into cells by interacting with the SARS-CoV-2 spike protein, decreasing heparinase activity, preventing plasma leakage, and neutralizing cytokines via other biological activities.[7] It is preferable to look for contraindications and measure bleeding and venous thromboembolism risk using the IMPROVE and PADUA scores when providing anticoagulants as thromboprophylaxis.[19,20] In this patient, the IMPROVE score was 2.5 (<7 indicates a low bleeding risk), and the PADUA score was 0 (<4 indicates a low venous thromboembolism risk). Therefore, we planned to administer 0.4cc/subcutaneous enoxaparin.

The Brazilian Society of Endocrinology and Metabolism and the THYRCOV study reported that thyroid dysfunction management during the COVID-19 pandemic was the same in patients with thyroid storm and co-infection with SARS-CoV-2 or other pathogens. They found that 16% of patients with SARS-CoV-2 infection treated for thyrotoxicosis experienced a two-fold greater thromboembolic event, an increased incidence of atrial fibrillation with suppressed TSH, and a higher mortality rate.[12]

The treatment of hyperthyroidism caused by GD in the current phase of the COVID-19 pandemic can be divided into two scenarios:[21] (1) treatment of patients with a prior diagnosis of GD and on regular treatment with anti-thyroid drugs (ATDs); (2) treatment of patients with recently diagnosed GD who have not yet started therapy.

Our patient belongs to the first scenario. At the current stage of the COVID-19 pandemic, when face-to-face consultations can be difficult, it is especially important not to interrupt ATD treatment since any relapse would require an urgent medical appointment and increase the risk of complications (e.g., thyroid storm), which can be triggered by infections such as COVID-19. In general, ATD treatment is maintained for 12–24 months, after which the medication can be suspended. Alternatively, prolonged use of low-dose ATDs may be considered since it is safe and may increase the chance of Graves' Disease remission. During the COVID-19 pandemic, telemedicine may be an alternative to manage patients with hyperthyroidism, and those with thyroid storm should be treated in infection centers with ICUs.

In the second scenario (patients with a recent GD diagnosis), ATDs should be the first therapeutic option due to possible current restrictions on nuclear medicine or surgical treatment. Surgical treatment should be performed in the rare circumstance of a patient not responding satisfactorily to ATDs, developing severe side effects to ATDs, or being unable to undergo radioiodine therapy.[21]

In our patient, we provided supportive therapy by providing oxygen, installing a heart monitor, nasogastric tube, and urinary catheter, and giving crystalloid fluid up to 28 drops/minute. We planned to transfer the patient to the ICU when she was started to develop hemodynamic instability, had DIC and Multiorgan failure (MOF) and an APACHE score >9 (based on 2016 JTA criteria) but the hospital where she was admitted in had no ICU for patients with COVID-19.

Our case report highlights the importance of educating patients with thyroid disorders during the COVID-19 pandemic. Patients with GD should not discontinue their therapy because doing so can increase the risk of infection, including SARS-CoV-2 infection. Hospitals should also provide infection center rooms for patients suspected of being infected with COVID-19 without waiting for PCR test results.[22]

CONCLUSION

We have reported a fatal case of possible thyroid crisis induced by SARS-CoV-2 infection, which directly or indirectly destroys the thyroid follicles, triggering a thyroid crisis. Prompt and appropriate management and treatment can reduce the incidence of multi-organ failure and mortality due to thyroid crisis induced by SARS-CoV-2 infection. There is no difference in treating thyroid crises before and during a COVID-19 pandemic. Maintaining a

euthyroid state is very important to prevent the relapse of thyroid disease.

Acknowledgments
The authors would like to thank Dr. Muhammad Faruk for his assistance in language polishing and formatting of this case report.

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

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

Author Contribution Statement
FH conceived the idea, validated research outputs, conducted investigation, provided study materials, curated the data, wrote the original draft preparation, reviewed and edited the manuscript, prepared data presentation, coordinated research activity planning, acquired financial support.

AMA conceived the idea, validated research outputs, conducted investigation, provided study materials, wrote the original draft preparation, reviewed and edited the manuscript, supervised the research activity planning.

HI conceived the idea, validated research outputs, conducted investigation, provided study materials, curated the data, wrote the original draft preparation, reviewed and edited the manuscript.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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Journal of the ASEAN Federation of Endocrine Societies

CASE SERIES

Use of Combination of Oral Levothyroxine and Liothyronine in Severe Hypothyroidism With Massive Pericardial Effusion

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Abstract

Thyroid hormone plays an important role in cardiovascular function. Pericardial effusions are commonly seen in cases of severe hypothyroidism. However, large to massive pericardial effusions with cardiac tamponade are exceptionally rare.

Herein, we present two cases of severe hypothyroidism with massive pericardial effusion. Our first case demonstrates that a patient with large pericardial effusion can be managed conservatively with aggressive thyroid hormone replacement therapy. In our second case, pericardiocentesis was performed in addition to thyroid hormone replacement therapy as the underlying aetiology of effusion could not be reasonably limited to hypothyroidism.

These two cases served to highlight and demonstrate rapid normalisation of thyroid function test by using aggressive oral thyroid hormone replacement therapy using liothyronine, in combination with levothyroxine, which led to resolution of pericardial effusion and prevent its re-accumulation.

Key words: hypothyroid, pericardial effusion, levothyroxine, liothyronine

INTRODUCTION

Primary hypothyroidism is characterized by decreased levels of thyroxine (T4) and triiodothyronine (T3) with compensatory high levels of thyroid stimulating hormone (TSH).

Overt hypothyroidism is associated with cardiovascular manifestations, which include increased systemic vascular resistance, decreased cardiac contractility, decreased cardiac output, atherosclerosis, coronary artery disease, bradycardia and conduction abnormalities. Another cardiac finding is pericardial effusion.[1,2] However, massive pericardial effusion is infrequent in cases of severe hypothyroidism. The incidence of pericardial effusion in hypothyroidism is 3% in the early mild stage and up to 80% in patients with myxedema.[3,4]

Herein, we present two patients with large pericardial effusion associated with severe hypothyroidism.

CASES

Case 1

A 62-year-old Indian female with past medical history of hypertension, obstructive sleep apnea, heart failure and hypothyroidism, presented with dyspnoea. Over the last three years, she presented with multiple decompensations of cardiac failure. An echocardiogram performed during the first hospitalization in 2018 revealed ejection fraction of 50% with minimal pericardial effusion. Her thyroid function test revealed free thyroxine (FT4) level of <3.1 pmol/L and TSH 174 mIU/L. She was started on low dose levothyroxine 25 mcg OD with planned slow upward titration of levothyroxine. Unfortunately, the patient did not follow up regularly and was not compliant with her levothyroxine dose of 150 mcg OD. In October 2020, she presented with overt clinical and biochemical hypothyroidism. She had marked coarse features with dry skin, loss of outer 3rd of eyebrow, delayed reflexes, signs of overt heart failure with muffled heart sounds. Her blood pressure was 166/90 mmHg and she was bradycardic with heart rate ranging from 50-60 beats per minute (bpm).

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: May 8, 2022. Accepted: July 26, 2022.
Published online first: September 5, 2022.
https://doi.org/10.15605/jafes.037.02.17

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There was no pulsus paradoxus. Her repeat FT4 was <3.2 pmol/L and TSH 138.4 mIU/L. Echocardiogram revealed global pericardial effusion ranging from 9-18 mm, with right atrium and right ventricular collapse.

Thyroxine absorption test was performed, with baseline FT4 <3.2 pmol/L (7.9-14.4 pmol/L), TSH 138.4 mIU/L (0.34-5.6 mIU/L) and FT4 19.2 pmol/L, TSH 166.2 mIU/L four hours after the test, thus demonstrating non-adherence to thyroxine as the cause of patient's persistent hypothyroidism. She was not compliant with her thyroxine regimen due to intermittent forgetfulness, which may have been due to hypothyroidism. She was commenced on levothyroxine 200 mcg once daily (2.2 mcg/kg/dose), in combination with liothyronine 10 mcg thrice daily. Her thyroid function test showed marked improvement on day 2 onwards (Figure 1). On day 5 of combination of levothyroxine and liothyronine therapy, her FT4 was 15 pmol/L (7.9-14.4 pmol/L) and TSH 5.2 mIU/L (0.34-5.6 mIU/L). On day 3, her FT3 level was 6.7 pmol/L (3.8-6.7 pmol/L). Repeat echocardiogram on Day 5 of combination therapy revealed only minimal pericardial effusion ranging from 4-9 mm with no right atrial or ventricular collapse. Repeated chest radiograph and electrocardiogram showed marked improvement post thyroxine hormone replacement therapy (Figures 2 and 3). She was discharged on levothyroxine 300 mcg once daily. Higher dose of levothyroxine was given as the patient was clinically and biochemically in severe hypothyroidism upon presentation. Dose reduction during early clinic review was planned. We carefully counselled the family members on the importance and necessity for directly observed therapy. During follow-up treatment, her thyroxine was down titrated to levothyroxine 150 mcg (1.6 mcg/kg/dose) once daily. She showed marked improvement clinically and biochemically.

Case 2

A 65-year-old Malay female with underlying hypertension, type 2 diabetes mellitus, chronic kidney disease stage 3A, history of ischaemic stroke 4 years ago and was semi-

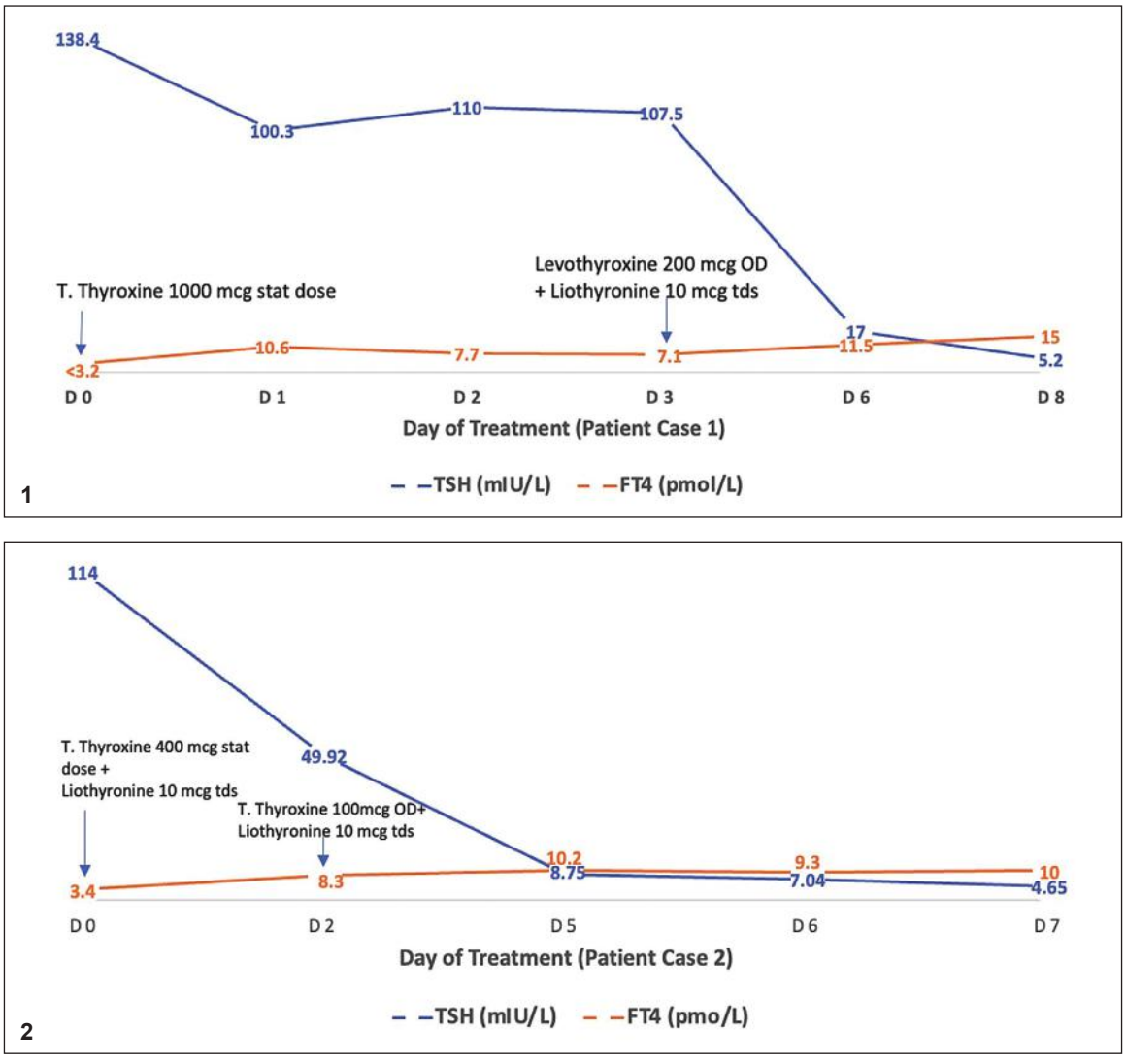

Figure 1. Graph **(1)** showed serial thyroid function tests for Case 1 at baseline and during course of treatment and graph **(2)** showed serial thyroid function tests for Case 2 at baseline and during course of treatment.

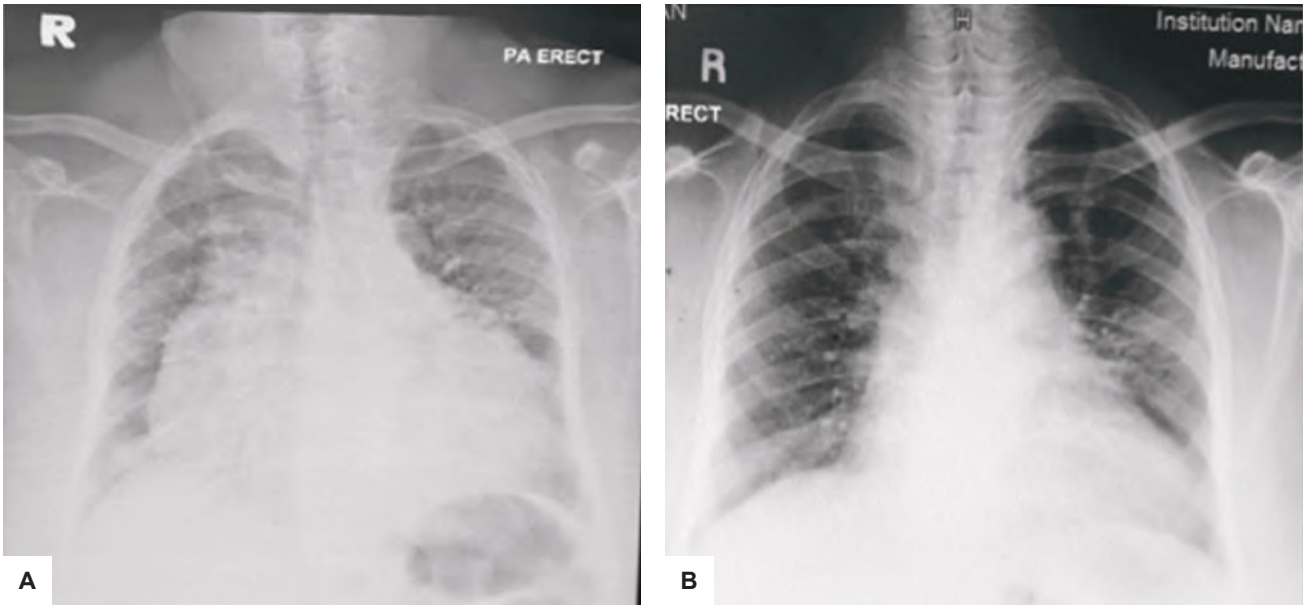

Figure 2. (A) PA erect chest radiography of Case 1 demonstrating cardiac shadow with globular appearance. **(B)** Chest radiography revealing reduction in cardio-thoracic ratio post commencement of thyroxine replacement therapy.

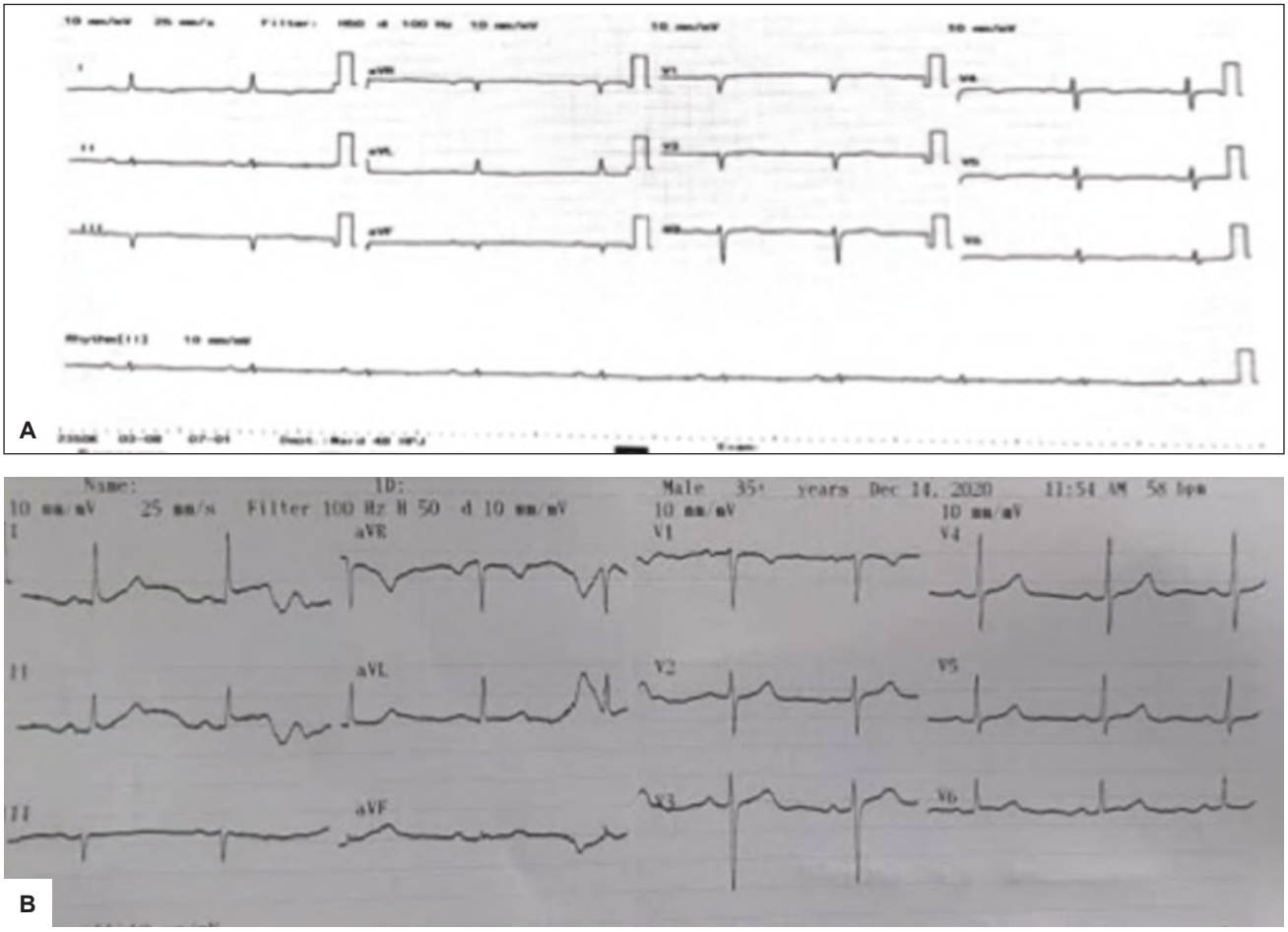

Figure 3. (A) Electrocardiogram of Case 1 upon presentation revealing low voltage QRS complexes. **(B)** Electrocardiogram of Case 1 post thyroid hormone replacement therapy.

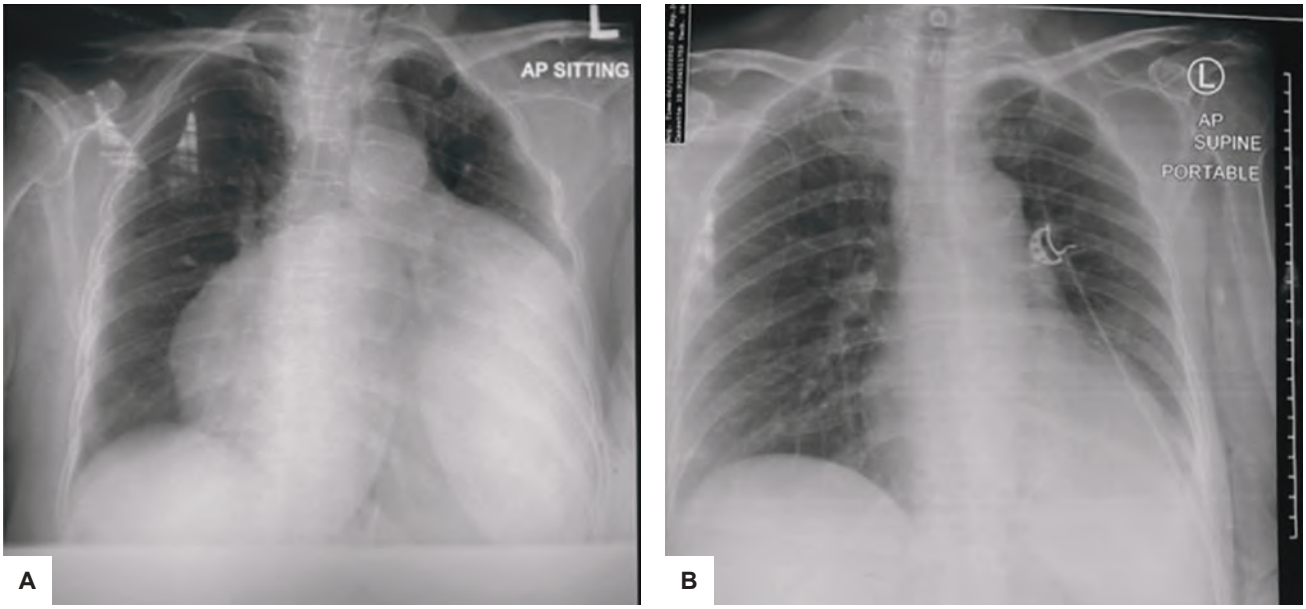

Figure 4. (A) Chest radiograph of Case 2 showing cardiomegaly with globular enlargement. **(B)** Chest radiograph post pericardiocentesis showing resolution of pericardial effusion.

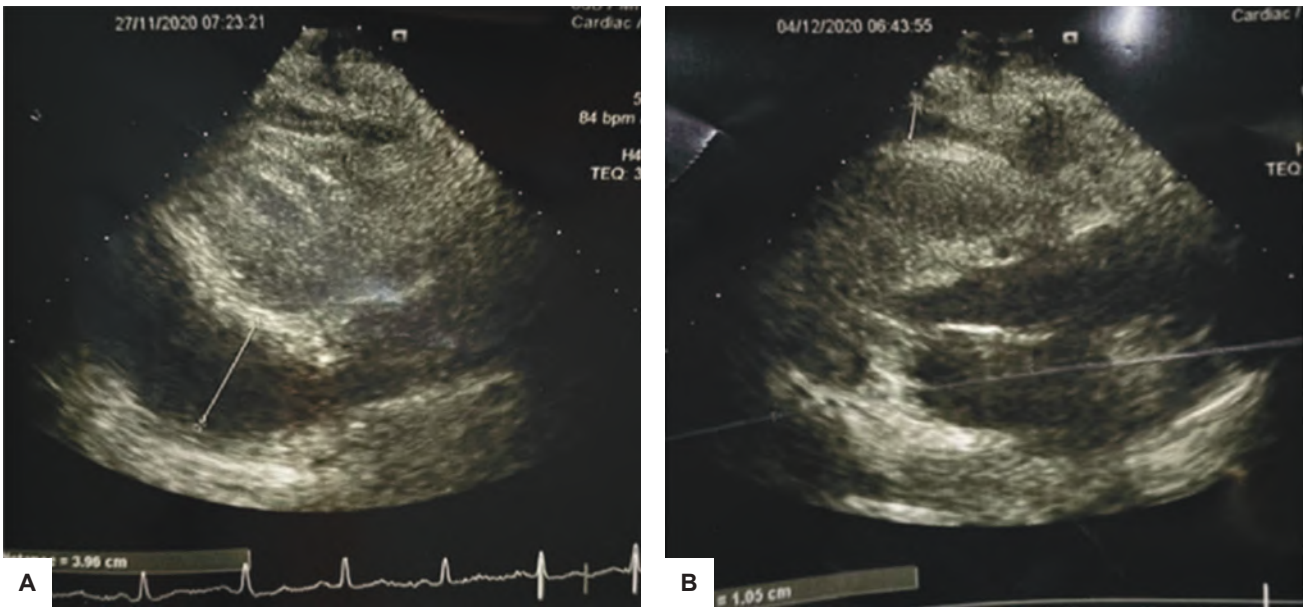

Figure 5. (A) Transthoracic echocardiogram parasternal long axis view of Case 2 demonstrating pericardiac effusion of 3.96 cm. **(B)** Transthoracic echocardiogram parasternal long axis view showing reduction in pericardial effusion size.

dependent for activities of daily living. She presented with complaints of dyspnoea of 1 year duration. Otherwise, she had no chest pain, no palpitation, no constipation, no weight gain. There was no history of pulmonary tuberculosis contact and no family history of malignancy. On physical examination, she had coarse, dry skin with slow mentation and obvious delayed relaxation of deep tendon reflexes. She was hemodynamically stable with blood pressure of 139/86 mmHg, absence of pulsus paradoxus or bradycardia (pulse rate 84 bpm). On auscultation, heart sounds were muffled. Respiratory examination was unremarkable. There was a 3 cm firm and mobile submandibular swelling with no goitre or surgical scar in the neck. Fine needle aspiration cytology of the submandibular swelling was performed and reported to have features of sialadenosis. Gynaecological assessment did not reveal any gynaecology pathology.

Blood investigation showed severe hypothyroidism with FT4 3.4 pmol/L (11.5-22.7 pmol/L) and TSH 114.47 mIU/L (0.55-4.78 mIU/L). Her initial electrocardiogram showed low voltage complexes with electrical alternans. Chest radiograph showed massive cardiomegaly (Figure 4). Echocardiogram revealed large global pericardial effusion ranging from 1.2-3.9 cm but no collapse of right ventricular free wall in diastole with left ejection fraction of 65 % (Figure 5). A provisional diagnosis of primary hypothyroidism with massive pericardial effusion was made.

She was commenced immediately on a single high dose 400 mcg levothyroxine followed by lower daily dose of 100 mcg (1.6 mcg/kg/dose) together with liothyronine of 10 mcg thrice daily. Her TSH decreased by half to 49.92 mIU/L (0.55-4.78 mIU/L), with FT4 of 8.3 pmol/L (11.5-22.7 pmol/L) after two days of combination therapy of levothyroxine and liothyronine, which subsequently normalized after one week of treatment, with TSH 4.65 mIU/L, FT4 of 10 pmol/L (Figure 1). Oral liothyronine was given for 10 days.

Repeat echocardiogram did not show improvement in pericardial effusion and it was decided to proceed with pericardial tapping for diagnostic purpose. One litre of pericardial fluid was drained. Echocardiogram reassessment post tapping showed more than 50% reduction of pericardial effusion, ranging from 5-9 mm, no right ventricular chamber collapse during diastole, with ejection fraction of 69% (Figure 5). Pericardial fluid analysis was reported to be acellular with absence of organisms on gram stain and Ziehl-Neelsen stain for acid fast bacilli (AFB). Fluid biochemistry analysis showed normal total protein of 58 g/L (57-82 g/L) and lactate dehydrogenase of 128 U/L (120-246 U/L). There was no growth on bacterial and tuberculosis culture media of the pericardial fluid. Her electrocardiogram showed normal voltage complexes.

Subsequently, the patient was discharged well with levothyroxine 100 mcg OD (1.6 mcg/kg/dose). During clinic review, she appeared well with no complaints of dyspnoea. Her thyroid function improved further and normalized at the second clinic visit with minimal pericardial effusion on echocardiogram reassessment.

DISCUSSION

We present 2 cases of severe hypothyroidism with massive pericardial effusion and highlight the haemodynamic stability despite the significant echocardiographic findings. The first case demonstrates that a patient with large pericardial effusion can be managed conservatively with aggressive thyroid hormone replacement therapy. In the second case, in addition to thyroid hormone replacement therapy, pericardiocentesis was performed as we considered the possibility of other etiologies besides hypothyroidism contributing to the persistent pericardial effusion.

Overt hypothyroidism is associated with some cardiovascular manifestations including heart failure, cardiomyopathy, arrhythmias, systemic diastolic hypertension, dyslipidemia, and atherosclerotic disease.[5,6] Hypothyroidism has also been implicated as a primary etiology of pericarditis, pericardial effusion, and, even more rarely, cardiac tamponade.[7,8] The "myxedema heart" was first described by Zondek in 1918 as a syndrome of cardiac alterations, including large cardiac silhouette, electrocardiogram (ECG) changes indicative of a large pericardial effusion including bradycardia, low voltage, nonspecific T-wave abnormalities, and electrical alternans, which reversed with thyroid hormone extract.[9] These findings were present in both patients which were confirmed with echocardiogram as gold standard for diagnosis for pericardial effusion.

The pathophysiology of pericardial effusions in hypothyroidism is not completely understood. In hypothyroidism, there is increased permeability of pericardial capillaries to albumin and decreased albumin drainage into the lymphatic vessels. This increases intrapericardial colloid pressure, thus resulting in fluid accumulation in the pericardial space by Starling equation.[10] Increased albumin permeability is proposed to be due to release of histamines by mastocytes induced by the low thyroid state or by the direct effect of hypothyroidism on the endothelial layers of pericardial capillaries.[11] Both cases presented with long standing symptoms prior to admission that led to discovery of massive pericardial effusion. The degree and duration of hypothyroidism seem to be the main determinants of the amount of fluid that accumulates in the pericardial sac.[3] Myxedema-associated effusion can be large, defined as >500 mL or echo-free space greater than 20 mm at its greatest width, but the distensibility of the pericardium and slow rate of fluid accumulation protects against hemodynamic compromise due to cardiac tamponade.[12,13] Our cases did not show hemodynamic instability as well. Contrary to the typical tachycardia, a normal heart rate may be present in hypothyroid mediated tamponade providing a clue to the etiology of the pericardial effusion.[7]

In case of myxedema-associated pericardial effusion, no particular clinical guidelines are available to direct its evaluation and treatment. Baldwin et al., suggested that once the diagnosis of hypothyroidism is determined to be the most likely etiology of pericardial effusion, hemodynamic stability should be carefully confirmed by physical examination, including use of manoeuvres to elicit presence of pulses paradoxus.[14]

Echocardiography in both cases demonstrate echocardiographic features with large pericardial effusions that were not associated with hemodynamic instability. In the first case, patient was given combination therapy of levothyroxine and liothyronine, resulting in marked improvement of thyroid function test within short period of time, and the pericardial effusion became minimal after thyroid hormone replacement alone.

Thyroid hormone replacement, in the form of levothyroxine, reverses the progression of fluid accumulation and prevents cardiac collapse. Pericardial effusions due to severe hypothyroidism will begin to resolve even prior to biochemical and clinical euthyroidism. According to previous studies, complete resolution of the effusion can occur within 4 to 26 weeks without invasive management.[7,15]

Aggressive thyroid hormone replacement therapy using oral liothyronine, in combination with oral levothyroxine were used in both cases, which resulted in rapid normalisation of thyroid function. In a case report of hypothyroidism presenting with recurrent pericardial tamponade

rapid reaccumulation of the effusion occurred despite prompt initiation of moderately high-dose levothyroxine treatment. Hence, liothyronine was added in addition to levothyroxine, which appeared to prevent further reaccumulation,[16] as seen in our cases.

In patients with risk factors for coronary artery disease, replacement of thyroid hormone should be done with caution to avoid precipitating acute coronary event especially with combination therapy. Our patients were monitored closely in Coronary Care Unit and medical ward with acute care setting, for new symptoms, arrhythmia and heart failure.

Liothyronine is more rapidly metabolised and has a more rapid effect than levothyroxine. Liothyronine may be used in severe hypothyroid states when there is a possibility that thyroxine conversion to triiodothyronine may be decreased.[17] Levothyroxine alone is the usual treatment for hypothyroidism and is used to replenish the thyroxine pool. It has a half- life of 7 days compared with the 1-day half-life of liothyronine. Meta-analysis by Chiu et al., concluded that weekly levothyroxine administration may be a feasible alternative for hypothyroid patients, particularly when adherence is a concern.[18]

The European Society of Cardiology guidelines for diagnosis and management of pericardial disease suggest that if a specific aetiology of pericarditis and effusion is suspected or high-risk features (such as fever, subacute onset, large pericardial effusion, cardiac tamponade, or lack of response to one week of anti-inflammatory therapy) are present, diagnostic pericardiocentesis is indicated. Pericardiocentesis or surgical intervention is also required when the clinical diagnosis of tamponade is made.[19] In our second case, pericardiocentesis was performed as the underlying etiology of effusion could not be reasonably limited to hypothyroidism.

It is important to note that major actions of thyroid hormone are mediated by binding to a receptor (TR) in the nucleus of target cells. The TR isoforms (TRα1, TRα2, TRβ1 and TRβ2) differ in their distributions in tissues. In comparison with narrow variations of thyroid hormone in a normal individual, the population normal ranges are broader.[20] Therefore, a numerically normal thyroid function test does not necessarily equate to euthyroidism in all tissues. It is important to also assess symptoms clinically despite normal laboratory results.

CONCLUSION

Pericardial effusion secondary to hypothyroidism will resolve with thyroid hormone replacement therapy. Pericardiocentesis should be reserved for cases requiring diagnostic sampling or for rare cases with evidence of cardiovascular compromise. Combination of levothyroxine and liothyronine therapy can be considered if rapid treatment of hypothyroidism is required and for resolution of severe pericardial effusion in patients without cardiovascular compromise.

Ethical Consideration
Patients' consents were obtained before submission of the manuscript.

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

Author Contribution Statement
PSW, SWL, CVT, MM, ZH conceived the study; developed the methodology; verified research outputs; conducted the research; provided the study materials; reviewed and edited the manuscript; presented the data; supervised and coordinated the research activity planning. PSW developed the software. PSW and SWL synthesized and curated the data and prepared the original draft.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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IMAGES IN ENDOCRINOLOGY

Atypical Eruptive Xanthoma: A Condition Confused With Monkeypox Rash

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Key words: chylomicronemia, eruptive xanthoma, lipemia retinalis

Since May 2022, monkeypox outbreaks have been reported in several countries outside Africa. The typical skin lesions of monkeypox begin as papules that appear in possible areas of inoculation, such as the skin or mucous membranes, followed by generalized pustules. Systemic symptoms appear simultaneously or a few days earlier than the lesions.

High levels of chylomicrons in the blood cause the milky appearance of the serum, retinal vessels and eruptive xanthomas.[1] Eruptive xanthomas are characterized by sudden eruptions of multiple erythematous to yellowish, dome-shaped papules on the extensor surfaces of the extremities, buttocks and hands.[2] However, they may present atypically as discrete vesicles or pseudo-pustules[3]

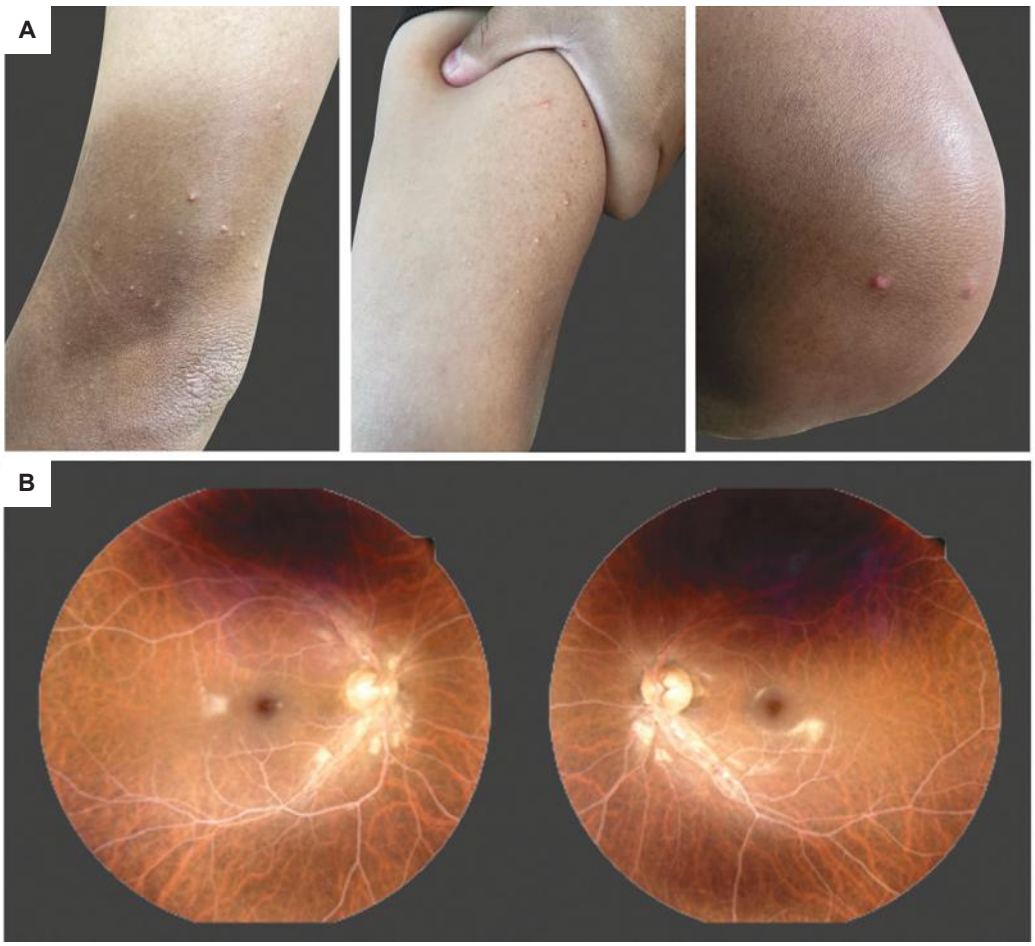

Figure 1. (A) A skin eruption that had appeared as erythematous-yellow, dome-shaped papules (2-7 mm in size) over the forearms, elbows, knees, and inner thighs. **(B)** Digital fundus microscopy revealed a stage III lipemia retinalis (salmon-colored retina with all vessels having milky appearance). The arteries and veins become indistinguishable.

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: June 30, 2022. Accepted: August 20, 2022.
Published online first: October 29, 2022.
https://doi.org/10.15605/jafes.037.02.18

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that may easily be confused with other dermatologic manifestations of systemic diseases such as monkeypox. Many of the patients with monkeypox presented with atypical symptoms not seen in previous outbreaks.[4] Additionally, these patients had fewer lesions than usual and did not present with a prodromal period.[5] Our present case highlights the importance of careful history-taking and physical examination in patients with skin lesions. Although the monkeypox rash may be similar to xanthomas in size and shape, they are usually vesicular with lesions in the same stage of development.

A 35-year-old Thai male with a history of obesity, multifactorial chylomicronemia and ketosis-prone type 2 diabetes mellitus presented with sudden-onset multiple skin papules on both arms and legs without fever two days after returning from Kuala Lumpur, Malaysia. He denied any associated symptoms like shortness of breath, abdominal pain or blurred vision. He denied unprotected sexual contact and close contact with an infected person or animal. Skin lesions appeared as multiple erythematous-yellow, dome-shaped papules on the extensor surfaces of the extremities and inner thighs without facial involvement. Based on his medical conditions and the characteristics of the lesions, eruptive xanthomas were suspected rather than pox-like vesicles. Fundus microscopy revealed a stage III lipemia retinalis or a salmon-colored retina with all vessels having a milky appearance. Subsequent investigations showed fasting hypertriglyceridemia at 12,590 mg/dL and hyperglycemia (270 mg/dL) with mild ketonemia (plasma ketone 1.6 mmol/L). Additional history-taking revealed that the patient consumed excessive amounts of fast food and soft drinks during his trip abroad. The patient was advised to consult with a dietitian and to limit fat and simple carbohydrate intake. He was prescribed fenofibrate and omega-3 fatty acids for hypertriglyceridemia and insulin for glycemic control. One week later, skin lesions resolved and lipemia retinalis disappeared once plasma triglyceride was lowered to 546 mg/dL.

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

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

Author Contribution Statement
YT conceived the idea, verified the results of the study, collected and analyzed the data, prepared the initial draft, reviewed and edited the manuscript, prepared the data presentation. NS provided study materials, curated the data. SN programmed the software, curated the data, managed the research activity planning and execution. TH supervised the research activity planning and execution and acquired financial support for the study.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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ETHICS REVIEW APPROVAL

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

a scanned copy of the Institutional Animal Care and Use Committee approval.

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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.
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3. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate.
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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.

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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.
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5. If appropriate, information should be provided on institutional review board/ethics committee approval.
6. Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

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5. A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
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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 Novem-ber 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.

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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.

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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.
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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.

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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.
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Illustrations and Photographs

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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.
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ARTICLE TYPES

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

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

Case Reports / 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.

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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.

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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.

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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.

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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*).

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For case reports/series, patient consent forms have been secured for the publication of information.

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