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# Journal of the ASEAN Federation of Endocrine Societies

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## ORIGINAL ARTICLES



## CASE REPORTS





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# Back to Basics

As of November 2018, JAFES is 9th in the Scimago Journal and Country rankings, among journals on endocrinology, diabetes, and metabolism in the Asiatic region; and is 188th in the world (out of 232).

Over the last 3 years that we have been indexed in Scopus, we have been able to muster a Scimago Journal Rank (SJR) of 0.108 (in 2015) to 0.136 (in 2017). The SJR is a "prestige indicator" which measures the scientific influence a published article may have to global scientific discussions. Our citation and document index ranges between 0.167 and 0.179. This indicator counts the number of citations received by our articles over the total number of articles we published. This is roughly equivalent to the Journal Impact Factor™ metric of Thomson and Reuters.

While the proportion has increased between our citable documents (original research, reviews, feature articles, case reports) and non-citable documents (editorials), the number of our cited articles still remains low. It is not that we cannot be found in the web. Our CrossRef membership and indexing in Scopus, Directory of Open Access Journals, APAMED Central, and Western Pacific Region Index Medicus, ensure that our contents are visible in online searches. Perhaps, further search engine optimization can improve our visibility.

Thinking beyond search engine optimization, and while remaining true to the JAFES goal of providing a platform for researchers in Southeast Asia, it would be crucial for us to re-examine the type of articles that the journal is publishing. Our articles have been mostly about clinical and observational studies. In comparison, most of the top endocrinology journals are publishing basic science research, down to the genome and protein level, elucidating the pathophysiology and mechanisms of disease. Those are basic, technically advanced, and potentially ground-breaking articles. It is apparent that JAFES needs to publish a good proportion of both clinical and basic science studies.

It is most important for us at the ASEAN Federation of Endocrine Societies, to realize this critical direction, at this day and age where the value of research is highlighted, funding has increased, and cutting-edge technologies have become available to researchers. Our member societies and respective country training institutions should invest in research, specifically targeting more basic science research questions, among its academic and clinical staff, and trainees. Endocrinology fellowships should also establish research tracks and partnerships with research institutions. More interdisciplinary study groups should be established. Certainly, these efforts have been initiated by many and require years for meaningful results.

Returning to the matter of metrics, our "H-index," which is a metric calculated by Scopus to measure the citation impact of publications of authors who publish in the journal, is currently at 1, a number that seems miniscule compared to other prestigious, well-established journals in the list. Renowned authors from the other side of the globe are not *yet* publishing in JAFES.

The *potential* is huge of conducting and publishing more basic research, possibly and partly in collaboration with more active researchers and authors from outside our region. The progressive accomplishments of JAFES may still be modest at this point, but give us hope and strength, and challenge us to go on.

We thank all of our authors, editors, societies, peer reviewers, and partners, for another productive year, as we look forward to a better 2019. Expect more innovations with JAFES next year.

**Elizabeth Paz-Pacheco**
Editor-in-Chief

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* To view JAFES' Scimago Journal and Country Rank, go to this link: https://www.scimagojr.com/journalsearch.php?q=21100395920&tip=sid&exact=no

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The symposium is jointly organised by members of the School of Clinical Medicine, University of Cambridge, the Nuffield Department of Medicine, Oxford University, Sunway Medical Centre, Sunway University and the Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia. It features distinguished experts in the areas of diabetes research, technology and application, from renowned global research institutions such as the University of Cambridge, the University of Oxford, Monash University, Australia and Monash Malaysia.

Speakers will relate their topics to current and emerging healthcare issues in Malaysia and Southeast Asia, such as the rapid rise in diabetes. Presentations will also cover the recent developments in, and the future potential of, diabetes research, techniques and therapies.

## Objective and Scope

The main aim of this international symposium is to discuss recent advances in diabetes research and how these are being extended to transform patient care.

## Target Audience

- Scientists
- Epidemiologist
- Medical consultants and practitioners
- Academics and researchers
- Healthcare industry representatives
- Allied health practitioners
- Government officials
- Publishers
- The general public with the objective of raising awareness of diabetes as a major emerging health issue

## Plenary Speakers

**Professor Sir Stephen O'Rahilly**
Professor of Clinical Biochemistry and Medicine
University of Cambridge

**Professor Nick Wareham**
Professor, Honorary Consultant
Addenbrooke's Hospital, Cambridge

**Professor Fiona Gribble**
Professor of Endocrine Physiology
University of Cambridge

**Professor John A Todd FRS**
Professor of Precision Medicine
University of Oxford

**Professor Rury Holman**
Professor of Diabetic Medicine
University of Oxford

**Professor Kieran Clarke**
Professor of Physiological Biochemistry
University of Oxford

**Professor Mark Cooper**
Head of Diabetes Department
Monash University Australia

**Professor Paul Zimmet AO**
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Monash University Malaysia

**Professor Dato' Anuar Zaini Md Zain**
Professor of Medicine
Jeffrey Cheah School of Medicine and Health Sciences
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** Full programme will be announced soon*

# CALLING FOR PAPERS - ORAL AND POSTER PRESENTATION

Besides the plenary sessions, the Organising Committee is inviting submissions of abstracts. Authors are welcomed to submit abstracts under one of the following categories: Oral or poster.

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**ABSTRACT SUBMISSION GUIDELINES**
Below are some of the suggested topics for reference. Other topics are also welcomed.

**Abstract Topics/Theme**

- Trends and prevalence of diabetes
- Prevention, clinical management and complications
- The healthcare system in managing diabetes
- Therapeutic drugs developments
- Information technology in management of diabetes

## Important Dates

| | |
|---|---|
| First announcement and Call for Papers | 1 September 2018 |
| Deadline for Submission of Abstract | 1 December 2018 |
| Notification of Abstract Acceptance | 15 January 2019 |
| Deadline for Early-bird Registration and Payment | 1 February 2019 |
| Deadline for Submission of Full Paper with camera ready format | 1 March 2019 |
| Deadline for Registration and Payment for Presenters | 20 March 2019 |
| Conference Dates | 26-27 March 2019 |

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

# The Multicenter, Open-Label, Observational LEAD-Ph Study: Real-World Safety and Effectiveness of Liraglutide in Filipino Participants with Type 2 Diabetes

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**Abstract**

Objective. Assess safety and effectiveness of liraglutide among Filipino participants with type 2 diabetes (T2D) in routine clinical practice.

Methodology. A 26-week, prospective, multicenter, open-label, observational study was conducted in adults with T2D prescribed liraglutide (1.2 mg or 1.8 mg) in routine clinical practice in the Philippines. Primary endpoint: incidence rate and type of serious adverse drug reactions (SADRs). Secondary endpoints included other aspects of safety, and effectiveness.

Results. Participants (n=1056) had a mean (standard deviation) age of 53.2 (12.0) years, and glycated hemoglobin ($HbA_{1c}$) level of 8.8% (2.0). Of 19 ADRs reported in 17 participants, none were SADRs (primary endpoint). No serious adverse events were reported. From baseline to week 26: the proportion of participants with major hypoglycemic episodes (requiring assistance) decreased from 2.0% to 0.2%; and with minor episodes (plasma glucose <3.1 mmol/L [<56 mg/dL]) decreased from 6.1% to 1.5%; serum creatinine remained unchanged. Among secondary effectiveness endpoints, improvements were seen from baseline to week 26 in $HbA_{1c}$ level, fasting and postprandial blood glucose levels, body weight, blood pressure, and fasting lipid profile.

Conclusion. During routine clinical use of liraglutide for T2D in the Philippines, no new safety concerns were identified and blood glucose was lowered effectively.

*Key words: glucagon-like peptides, liraglutide, type 2 diabetes mellitus, safety, observational study, Philippines*

## INTRODUCTION

Core pathophysiologic defects in the progression of type 2 diabetes (T2D) include progressive pancreatic β-cell failure resulting in insulin deficiency and increased tissue insulin resistance compounding the problem.[1] It has been recognized that impairments in the incretin effect (in which insulin secretion is amplified by incretin hormones in response to the ingestion of glucose), particularly the action of glucagon-like peptide 1 (GLP-1), also play a key role in the progression of T2D[2,3] and may be an important contributor to the observed hyperglycemia.[4] Targeting this impairment can form part of a dynamic management approach to counteract the progressive nature of T2D.[5,6] GLP-1-mediated effects include glucose-dependent stimulation of endogenous insulin secretion, modulation of glucagon secretion, reduced appetite and food intake, delayed gastric motility and emptying, inhibition of β-cell apoptosis and improvement of β-cell function.[4,7] Multiple physiologic effects of GLP-1, beyond glucose metabolism, mean that drugs that mimic the action of GLP-1 can target several core pathophysiological defects underlying the development of T2D.[7,8] GLP-1 receptor agonists (GLP-1 RAs) are therefore among the second-line treatment options for T2D according to the treatment algorithm from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), and can be added after 3 months of initial monotherapy if the target glycated hemoglobin ($HbA_{1c}$) level is not achieved.[9] Furthermore, the American Association of Clinical Endocrinologists (AACE) includes GLP-1 RAs as an acceptable first-line monotherapy – an alternative to metformin for patients with mild hyperglycemia ($HbA_{1c}$ <7.5%).[10]

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The GLP-1 RA liraglutide has 97% homology to native GLP-1, with the addition of a fatty acid side chain that confers a substantially prolonged half-life, enabling once-daily dosing.[11] The efficacy and safety of liraglutide as monotherapy or in combination with oral antidiabetic drugs (OADs) were demonstrated in the randomized, controlled trials of the Liraglutide Effect and Action in Diabetes (LEAD) study series.[12-17] Compared with active comparators in these trials, liraglutide generally improved $HbA_{1c}$, fasting plasma glucose, postprandial blood glucose (PPBG) levels, and β-cell function. It also demonstrated favorable effects on body weight.[12-17] Improvements in glycemic control and weight loss were sustained for up to 1–2 years of follow-up.[18-20] Based on findings from clinical trials, liraglutide was generally well tolerated with an acceptable incidence of hypoglycemic episodes; the most common adverse events (AEs) reported were gastrointestinal, including nausea, vomiting and diarrhea.[12-17,21] However, the gastrointestinal AEs tended to be transient and their incidence subsided over time.[22] Liraglutide was approved for the treatment of T2D in Europe in 2009 and subsequently in the USA in 2010.[23,24]

Studies of liraglutide in Asian populations with T2D to date include a double-blind active-control trial in participants from China, South Korea, and India,[25] an open-label active comparator trial in Chinese participants,[26] and an observational study in India.[27] Liraglutide was approved in the Philippines in February 2011 for the treatment of adults with T2D, as monotherapy or in combination with OADs and/or basal insulin when these agents, together with diet and exercise, do not provide adequate glycemic control.[28] Despite the studies, this approval, and the inclusion of GLP-1 RAs in the ADA/EASD and AACE guidelines (commonly referred to by healthcare practitioners in the Philippines),[9,10] local guidelines do not include GLP-1 RAs,[29] and experience of liraglutide use in the Philippines remains limited.

This prospective study was undertaken as a post-marketing surveillance commitment to the Philippine Food and Drug Administration (FDA). The data provide an assessment of the safety and effectiveness of liraglutide 1.2 mg and 1.8 mg among the Filipino population in a clinical practice setting.

## METHODOLOGY

### Study design

This was a 26-week, prospective, open-label, observational study in participants with T2D who were prescribed liraglutide in routine clinical practice. The study was conducted from September 1, 2011 to July 26, 2013 in 85 study centers in the Philippines by specialists and primary care physicians with experience in the management of T2D. The study is registered with ClinicalTrials.gov (NCT01345734).

Participants provided written informed consent prior to any study-related activity. This study was approved by the Ethics Review Board of the University of the Philippines-Philippine General Hospital and was conducted in accordance with the Declaration of Helsinki, and the Guidelines for Good Pharmacoepidemiology Practices.

### Patient inclusion and exclusion criteria

Participants were included if they were adults (aged ≥18 years) with T2D, either newly diagnosed and not on anti-diabetic medication or already receiving other antidiabetic medications, who required treatment intensification with liraglutide according to the clinical judgment of their treating physician and were capable of giving informed consent. Participants were excluded if they had type 1 diabetes, were or had previously been treated with liraglutide, were participating in another clinical study, had hypersensitivity to liraglutide or to any of the excipients (disodium phosphate dihydrate, propylene glycol, phenol, water for injections), were pregnant, breast-feeding or had the intention of becoming pregnant within the following 6 months, or had a high probability of being lost to follow-up during the study period, as assessed by the treating physician.

### Treatment

Liraglutide was administered (when deemed clinically warranted by the treating physician) in accordance with approved local labeling, as monotherapy or in combination with one or more OADs (dipeptidyl peptidase-4 inhibitors and/or exenatide therapy were discontinued at baseline, prior to liraglutide initiation) and/or basal insulin. Liraglutide was started at a dose of 0.6 mg once daily and increased by 0.6 mg, at intervals of at least 1 week, to a maintenance dose of 1.2 or 1.8 mg once daily by the investigator according to approved prescribing information. The study drug was self-administered at any (consistent) time, independent of meals, using an injection pen device.

### Assessments

Visits occurred at baseline (Visit 1), at approximately 13 weeks (Visit 2) and finally at approximately 26 weeks (Visit 3). The suggested frequency and timing of visits were based on accepted clinical practice for the management of T2D. Further, any procedure carried out during this study was conducted according to routine practice.

Participants were instructed to maintain a diary to record AEs and hypoglycemic episodes. Investigators asked about adverse drug reactions (ADRs), serious adverse events (SAEs), and medical events of special interest (MESIs; which included major and minor hypoglycemic episodes) at study visits and additionally gathered information on laboratory assessments (fasting lipid profile values and serum creatinine levels). ADRs were considered to be AEs (any undesirable medical event) for which a causal relationship with the product was suspected (i.e., judged possible or probable by the reporting healthcare professional) and any abnormalities from laboratory assessments that were regarded as clinically significant (i.e., of a severity requiring active management). Serious ADRs (SADRs) and SAEs were considered to be AEs or ADRs that resulted in death, a life-threatening experience, hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect, or which required intervention to avoid one of these outcomes. As standard, MESIs were considered to be events such as medication errors or transmission of an infectious agent via the study drug; in this study, MESIs additionally included pancreatitis, thyroid gland disorders, neoplasms,

and major hypoglycemia. Major hypoglycemia was defined as episode of hypoglycemia that the patient was unable to self-treat (including those events requiring administration of glucagon or intravenous glucose by another person); plasma glucose levels prior to the incident were recorded if available. (Minor hypoglycemia applied to events in which the patient was able to self-treat and for which plasma glucose <3.1 mmol/L [<56 mg/dL] was recorded. Episodes of minor hypoglycemia were reported in the case report form [CRF].)

Participants were also asked to record concomitant medications, and self-monitored blood glucose (SMBG) levels in their diaries. Most recent values of $HbA_{1c}$, fasting blood glucose (FBG), and PPBG and the dates of measurement since the last visit prior to starting liraglutide treatment (if available) were obtained from patient medical records at baseline. Most recent values of $HbA_{1c}$, FBG, and PPBG and date of measurement since last visit were obtained at study Visits 2 and 3. Serum creatinine levels, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at each visit only when available from the patient's medical record or patient recall.

### Endpoints

The primary endpoint was the incidence of SADRs during the study period (26 weeks of liraglutide therapy). Secondary safety endpoints comprised: numbers of SAEs and ADRs during the study period; numbers of major hypoglycemic events registered during the 13 weeks preceding each study visit and minor hypoglycemic events registered during the 4 weeks preceding each study visit, in both cases during liraglutide therapy; changes in serum creatinine levels, SBP and DBP.

Secondary effectiveness endpoints comprised: changes in $HbA_{1c}$ (by visit, and change from baseline to week 13 and week 26); percentages of participants reaching $HbA_{1c}$ targets of ≤6.5% and <7.0% at the end of the study; changes in FBG and PPBG levels (after breakfast, lunch, or dinner); and changes in body weight and related parameters (body mass index [BMI], waist circumference, and hip circumference) (by visit, and changes from baseline to week 13 and week 26). Other parameters monitored were changes, if any, in fasting lipid profile (by visit), frequency of SMBG (at baseline and week 26), and the prescription of antidiabetic (at baseline before and after initiation of liraglutide), antihypertensive, and lipid-lowering medications (by visit).

### Statistical analysis

A sample of 812 participants was required to obtain a 95% confidence interval (CI) (±1.5%) for an estimated SADR incidence of 5%. To allow for an expected 20% discontinuation rate, recruitment of 1000 participants was planned. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Differences across visits for continuous variables (such as weight, $HbA_{1c}$, FBG, or PPBG) were analyzed using a one-way analysis of variance (ANOVA) with study visit as a classification variable (two-sided *p* value). For continuous variables that reached statistical significance across visits using ANOVA, differences between study visits were then analyzed using a one-sided Dunnett's test and the *p* value presented (lower tail [except high-density lipoprotein cholesterol, upper tail]). Changes from baseline were expressed as least squares means with standard error (SE) and 95% CI from one-way ANOVA and, where appropriate, a one-sided *p*-value from the Dunnett's test. The number of hypoglycemic events was analyzed using the Wilcoxon signed-rank test. Discrete variables were summarized using frequency tables (N, %). Proportions of participants with missing data were indicated as % where appropriate.

## RESULTS

### Participants

Of 1056 participants enrolled and exposed to liraglutide (full analysis set [FAS]), 75.2% completed the study and were included in the effectiveness analysis set (EAS) (Figure 1). Commonly cited reasons for non-completion were discontinuation of liraglutide (n=137), lost to follow-up (n=115), and ADRs (n=5).

Baseline demographic and disease characteristics are shown in Table 1. There was a higher proportion of females than males (52.9% versus 47.1%). The population had a mean (SD) age of 53.2 (12.0) years, $HbA_{1c}$ of 8.8% (2.0), and diabetes duration of 9.2 (8.0) years. The most frequent diabetes complications at baseline were peripheral neuropathy (19.7%) and coronary heart disease (16.6%). The most frequently cited reason given by participants as to why they accepted the physician's suggestion for starting liraglutide was to improve weight control (cited by 90.2% of participants) (Table 2).

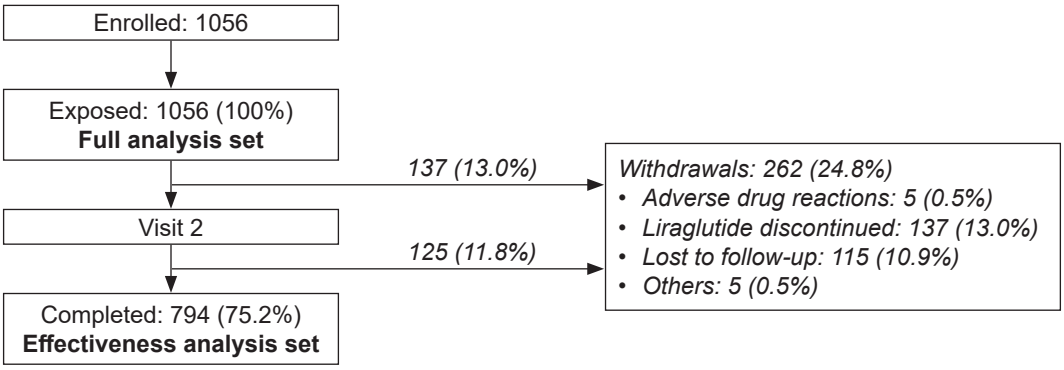


**Figure 1.** Participant disposition.

**Table 1.** Baseline demographic and disease characteristics

| | n* | Mean ± SD or n (%) |
|---|---|---|
| Sex, male / female | 1056 | 497 (47.1) / 559 (52.9) |
| Age, years | 1056 | 53.2 ± 12.0 |
| BMI, kg/m$^2$ | 1056 | 33.1 ± 5.9† |
| $HbA_{1c}$, % | 881 | 8.8 ± 2.0 |
| FBG, mg/dL | 719 | 185.7 ± 74.4 |
| PPBG, mg/dL | 190 | 235.7 ± 99.6 |
| Diabetes duration, years | 523 | 9.2 ± 8.0 |
| SBP, mmHg | 998 | 127.9 ± 13.3 |
| DBP, mmHg | 998 | 80.2 ± 8.9 |
| Diabetes complications | 1056 | |
| Peripheral neuropathy | | 208 (19.7) |
| Coronary heart disease | | 175 (16.6) |
| Nephropathy | | 109 (10.3) |
| Macroangiopathy‡ | | 106 (10.0) |
| Retinopathy | | 90 (8.5) |
| Autonomic neuropathy | | 41 (3.9) |
| Stroke | | 7 (0.7) |

*Data collection based on FAS; where n<1056, data were missing or unknown for the remaining participants. †Although the mean BMI is classified as obese, the range was from 18.7 (underweight) to 50.0 kg/m$^2$ (morbidly obese), and a number of participants with low BMIs were included in the study. ‡Including peripheral vascular disease. BMI, body mass index; DBP, diastolic blood pressure; FAS, full analysis set; FPG, fasting blood glucose; $HbA_{1c}$, glycated hemoglobin; PPBG, postprandial blood glucose; SBP, systolic blood pressure.

**Table 2.** Participants' reasons* for starting liraglutide treatment

| Reason cited | n (%) |
|---|---|
| Improve weight control | 953 (90.2) |
| Improve $HbA_{1c}$ | 874 (82.8) |
| Improve β-cell function | 720 (68.2) |
| Improve FBG | 543 (51.4) |
| Participant dissatisfied with previous therapy | 239 (22.6) |
| Improve PPBG | 227 (21.5) |
| Reduce risk of hypoglycemia | 113 (10.7) |
| Side effects from previous therapy | 31 (2.9) |
| Others | 7 (0.7) |

*More than one reason could be stated.
β, beta; FPG, fasting plasma glucose; $HbA_{1c}$, glycated hemoglobin; PPBG, postprandial blood glucose.

## Safety

### *SADRs, SAEs and ADRs*

No SADRs were reported during the study (primary endpoint), and there were also no reports of SAEs. There were 19 reported ADRs from 17 participants (Table 3). Although hypoglycemia events were to be reported on the CRF, separately from ADRs, four events of hypoglycemia were in fact recorded as ADRs; as ADRs, severities were thus not classified as major or minor hypoglycemia but instead as mild, moderate, or severe (three events were considered mild, one was moderate). Contrary to the protocol, an AE that was neither considered related to study drug (i.e., an ADR) nor serious (i.e., an SAE) was also recorded. This AE, frozen shoulder (periarthritis), occurred in a 33-year-old patient, was considered to be moderate in severity, and the patient did not recover fully by the end of the study.

The majority (16/19) of ADRs were mild, and all but one of the participants recovered fully. The exception was a 51-year-old participant with a mild case of diarrhea, deemed possibly related to study drug and for whom liraglutide was permanently withdrawn. A further four participants also withdrew from the study due to ADRs, specifically cushingoid features (moon face), hypoglycemia, nausea and vomiting, and dizziness. The participant with dizziness was not originally reported as a treatment withdrawal by the investigator but, because liraglutide was permanently discontinued, the participant has been included in these analyses.

**Table 3.** Summary of adverse drug reactions

| Type of Event/Outcome | Participants, n (%) | Number of Events |
|---|---|---|
| Any ADR | 17 (1.6) | 19 |
| Probably/possibly related | 10 (0.9)/7 (0.7) | 10/9 |
| Severe/moderate/mild | 0/3 (0.3)/14 (1.3) | 0/ 3/16 |
| SADR | 0 | 0 |
| Outcome | | |
| Fatal | 0 | 0 |
| Not recovered | 1 (0.1) | 1 |
| Recovered without sequelae | 16 (1.5) | 18 |
| ADRs leading to withdrawal* | 5 (0.5) | 6 |

Data for full analysis set (n=1056). One further participant was reported as experiencing frozen shoulder (periarthritis); as this was not considered to be an ADR, the event is not included in the data above. *Includes one participant for whom treatment was withdrawn but who was not originally reported by the investigator as having withdrawn.
ADR, adverse drug reaction; SADR, serious adverse drug reaction.

**Table 4.** Summary of ADRs by system organ class and preferred term

| Type of Event | Participants, n (%) | Events (n) |
|---|---|---|
| **All ADRs*** | 17 (1.6) | 19 |
| **Metabolism and nutrition disorders** | **4 (0.4)** | **4** |
| Hypoglycemia† | 4 (0.4) | 4 |
| **Gastrointestinal disorders** | **3 (0.3)** | **5** |
| Abdominal pain upper | 1 (0.1) | 1 |
| Diarrhea | 1 (0.1) | 1 |
| Nausea | 1 (0.1) | 1 |
| Vomiting | 2 (0.2) | 2 |
| **General disorders and administration site conditions** | **3 (0.3)** | **3** |
| Fatigue | 1 (0.1) | 1 |
| Injection site rash | 1 (0.1) | 1 |
| Malaise | 1 (0.1) | 1 |
| **Cardiac disorders** | **2 (0.2)** | **2** |
| Palpitations | 2 (0.2) | 2 |
| **Skin and subcutaneous tissue disorders** | **2 (0.2)** | **2** |
| Alopecia | 1 (0.1) | 1 |
| Rash | 1 (0.1) | 1 |
| **Endocrine disorders** | **1 (0.1)** | **1** |
| Cushingoid‡ | 1 (0.1) | 1 |
| **Nervous system disorders** | **1 (0.1)** | **1** |
| Dizziness | 1 (0.1) | 1 |
| **Psychiatric disorders** | **1 (0.1)** | **1** |
| Insomnia | 1 (0.1) | 1 |

Data for full analysis set (n=1056). *Two further events (increased alanine aminotransferase and aspartate aminotransferase, severity and outcome not reported) in one participant were reported but were invalid due to lack of participant identifiers. †Four events of hypoglycemia were mistakenly recorded as ADRs instead of MESIs. ‡Moon face.
ADR, adverse drug reaction; MESI, medical events of special interest.

Other than the four events of hypoglycemia inadvertently included as ADRs, the most commonly reported ADRs by system organ class (Table 4) were gastrointestinal disorders (five events in three participants [0.3%]: two ADRs of vomiting and one each of diarrhea, nausea, and upper abdominal pain) and general disorders and administration-site conditions (three events in three participants [0.3%]: fatigue, injection-site rash, and malaise).

### *Hypoglycemia*

The proportion of participants reporting hypoglycemic episodes decreased during the study period. At baseline

(i.e., for the 13 weeks preceding initiation of treatment with liraglutide), the proportion of participants with major hypoglycemic episodes was 2.0% (21/1056); this decreased to 0.6% (6/1056) of participants at week 13, and decreased further to 0.2% (2/1056) at week 26. The proportion of participants with minor hypoglycemic episodes at baseline was 6.1% (64/1056); this decreased to 2.5% (26/1056) of participants at week 13, and to 1.5% (16/1056) at week 26. It is important to note, however, that at each of these timepoints data were missing or unknown for a varied proportion of participants (ranging from 5.4 to 24.8%). Furthermore, these events did not include the four episodes reported as ADRs.

### *Serum creatinine*

Differences in serum creatinine during the course of the study did not reach statistical significance (mean [SE] change from baseline to week 26 was 0.02 ± 0.02 mg/dL [95% CI: –0.03; 0.06]; $p$=0.2327 [ANOVA], FAS, n=183).

## Effectiveness

### *Glycemic control*

There was a significant reduction in $HbA_{1c}$ levels from baseline to week 26 with liraglutide treatment (Figure 2); the mean (SE) change from baseline in $HbA_{1c}$ was -1.81% ± 0.05 [95% CI: -1.92; -1.71], $p$<0.0001 (n=577; baseline to week 26). The target $HbA_{1c}$ level <7.0% (the goal identified by the ADA/EASD) was reached by 197/794 (24.8%) participants in the EAS at week 13 (data missing for 171/794 [21.5%] participants) and by 322/794 (40.6%) participants at week 26 (missing data: 151/794 [19.0%] participants). The proportions of participants achieving $HbA_{1c}$ levels ≤6.5% (the AACE goal) at weeks 13 and 26 were 126/794 (15.9%) and 234/794 (29.5%), respectively (missing data as for target <7.0%).

FBG levels were also significantly reduced from baseline to week 26 with liraglutide treatment (Figure 3), with a mean

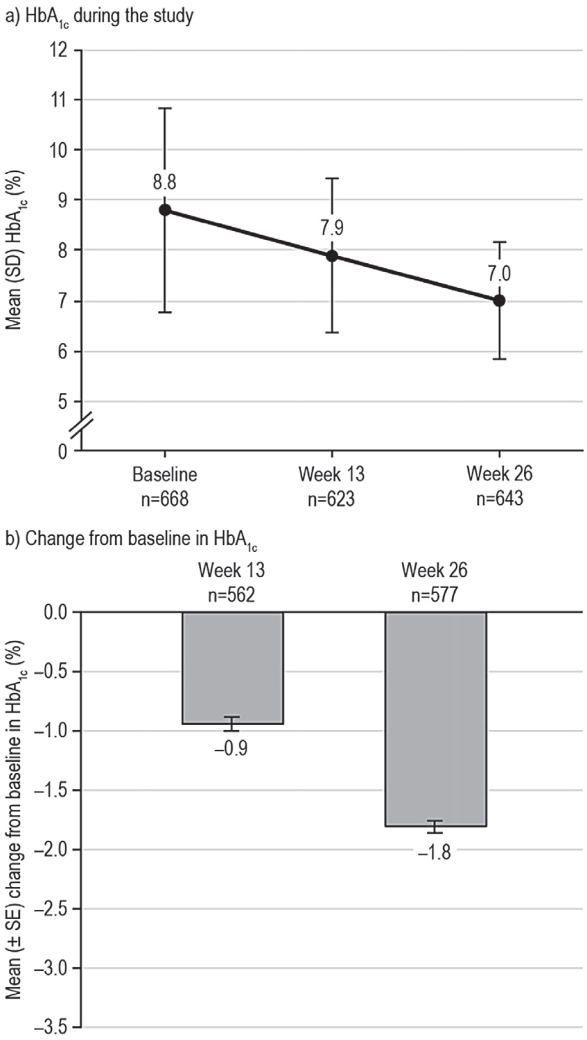


**Figure 2.** Glycemic control during the LEAD-Ph study: $HbA_{1c}$. From participants in the EAS with available data. The mean (± SE) change from baseline in $HbA_{1c}$ level at week 13 was –0.94 ± 0.06%, $p$<0.0001* (n=562), and –1.81 ± 0.05%, $p$<0.0001* (n=577) at week 26. *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; $HbA_{1c}$, glycated hemoglobin; SD, standard deviation; SE, standard error.

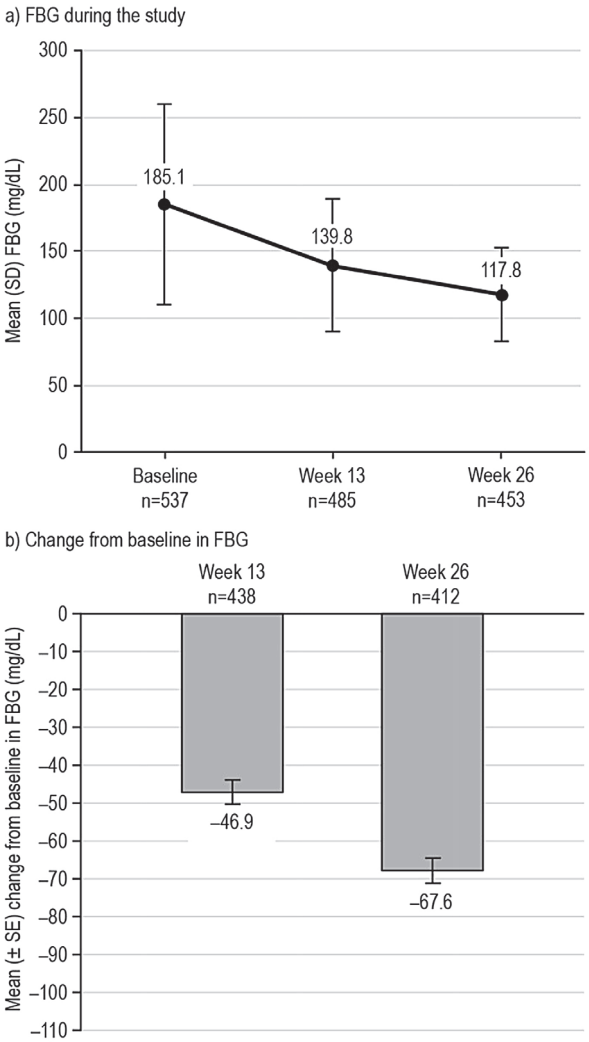


**Figure 3.** Glycemic control during the LEAD-Ph study: FBG. From participants in the EAS with available data. The mean (± SE) change from baseline in FBG level at week 13 was −46.94 ± 3.16 mg/dL, $p$<0.0001* (n= 438), and −67.61 ± 3.26 mg/dL, $p$<0.0001* at week 26 (n=412). *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; FBG, fasting blood glucose; SD, standard deviation; SE, standard error.

(SE) change of -67.61 ± 3.26 mg/dL [95% CI: -74.00; -61.22], $p$<0.0001 (n=412). Similarly, for the few participants with PPBG assessments after the same meal (breakfast) at each study visit available for analysis, there was a significant reduction in PPBG levels across visits with liraglutide treatment (Figure 4). The mean (SE) change in post-breakfast PPBG (baseline to week 26) was -109.27 ± 14.01 mg/dL [95% CI: -137.02; -81.52], $p$<0.0001 (n=51). Nevertheless, these PPBG data should be interpreted with caution, due to the low numbers of participants with data available (n=51–67).

### *Body weight, BMI and body measurements*

Body weight decreased during the study (Figure 5, Table 5). Accordingly, there was a concomitant significant change in BMI from baseline to week 26, and mean (SE) change of -1.37 ± 0.04 kg/m$^2$ [95% CI: -1.44; -1.29], $p$<0.0001 (both EAS, n=794). Participants with a higher BMI at baseline lost more weight during the study than participants with a lower baseline BMI. Participants with BMI ≥35 kg/m$^2$ had a significant reduction in body weight (baseline to week 26) with a mean (SE) weight change of -4.35 ± 0.19 kg [95% CI: -4.73; -3.98], $p$<0.0001 (n=291), compared with participants with BMI <25 kg/m$^2$ having a mean (SE) weight change of -2.05 ± 0.31 kg [95% CI: -2.65; -1.44] (n=53), which did not reach statistical significance. Waist and hip circumference measurements tended to decrease in participants with available data, although the participant numbers were low for these endpoints and differences did not reach statistical significance (Table 3).

### *Blood pressure*

Mean (SE) changes for SBP were -3.11 ± 0.41 mmHg [95% CI: -3.91; -2.30], $p$<0.0001 (n=750; baseline to week 13), and -5.31 ± 0.41 mmHg [95% CI: -6.12; -4.50], $p$<0.0001 (n=746; baseline to week 26). Mean (SE) changes for DBP were -2.93 ± 0.32 mmHg [95% CI: -3.57; -2.30]; $p$<0.0001 (n=750; baseline to week 13), and -5.35 ± 0.32 mmHg [95% CI: -5.99; -4.71]; $p$<0.0001 (n=746; baseline to week 26).

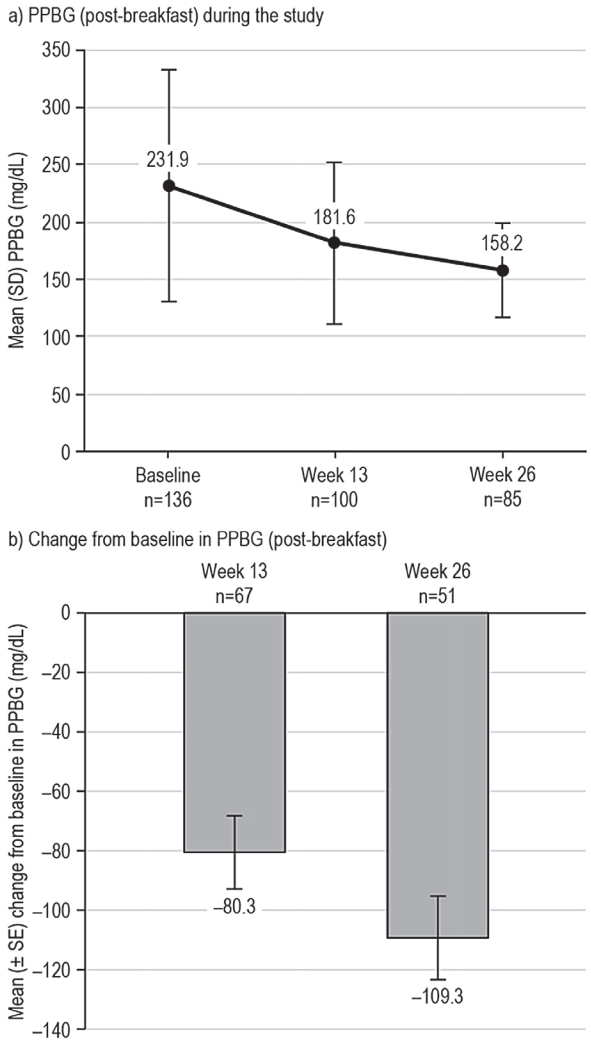


**Figure 4.** Glycemic control during the LEAD-Ph study: PPBG. From participants in the EAS with available data. The mean (± SE) change in post-breakfast PPBG level at week 13 was −80.32 ± 12.23 mg/dL, $p$<0.0001* (n=67), and −109.27 ± 14.01 mg/dL, $p$<0.0001* at week 26 (n=51). *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; PPBG, postprandial blood glucose; SD, standard deviation; SE, standard error.

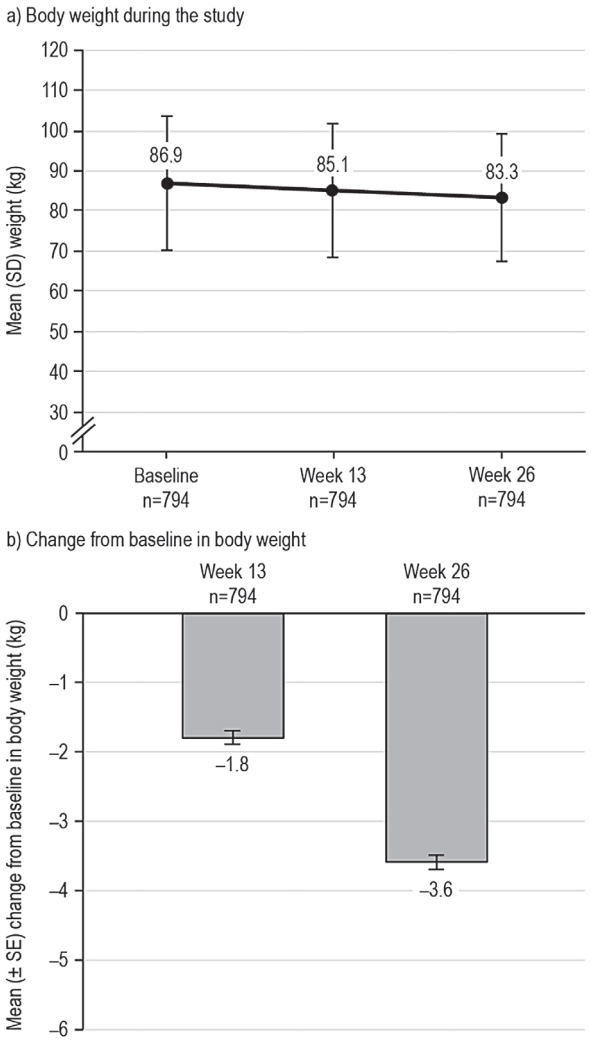


**Figure 5.** Changes in body weight during the LEAD-Ph study. From participants in the EAS with available data. The mean (± SE) change from baseline in body weight at week 13 was −1.79 ± 0.10 kg, $p$=0.0267* (n=794), and −3.58 ± 0.10 kg, $p$<0.0001* at week 26 (n=794). *Statistical difference at the 5% level, one-tailed. EAS, effectiveness analysis set; SD, standard deviation; SE, standard error.

**Table 5.** Changes to body weight, BMI, waist and hip circumference

| Parameter | Baseline | Week 13 | Week 26 |
|---|---|---|---|
| **Weight, kg** | | | |
| N | 794 | 794 | 794 |
| Mean ± SD | 86.9 ± 16.7 | 85.1 ± 16.2 | 83.3 ± 15.9 |
| Median [min, max] | 85.5 [42.0, 146.5] | 84.0 [42.0, 144.4] | 82.3 [41.0, 142.7] |
| Change from baseline, mean ± SE | - | –1.79 ± 0.10; $p$=0.0267*; n=794 | –3.58 ± 0.10; $p$<0.0001*; n=794 |
| **BMI, kg/m$^2$** | | | |
| N | 794 | 794 | 794 |
| Mean ± SD | 33.4 ± 5.9 | 32.7 ± 5.7 | 32.0 ± 5.6 |
| Median [min, max] | 33.0 [18.7, 50.0] | 32.2 [18.6, 49.3] | 31.6 [17.8, 48.8] |
| Change from baseline, mean ± SE | - | –0.68 ± 0.04; $p$=0.0174*; n=794 | –1.37 ± 0.04; $p$<0.0001*; n=794 |
| **Waist circumference, cm** | | | |
| N | 87 | 85 | 84 |
| Mean ± SD | 105.1 ± 13.9 | 104.2 ± 12.2 | 101.7 ± 12.8 |
| Median [min, max] | 105.0 [76.0, 142.0] | 103.0 [79.0, 140.0] | 101.5 [78.0, 137.0] |
| Change from baseline, mean ± SE | - | –1.74 ± 0.69; n.s.; n=65 | –4.35 ± 0.71; n.s.; n=62 |
| **Hip circumference, cm** | | | |
| N | 42 | 25 | 20 |
| Mean ± SD | 110.1 ± 12.5 | 108.0 ± 10.8 | 104.0 ± 7.8 |
| Median [min, max] | 109.0 [88.0, 148.0] | 106.0 [93.0, 148.0] | 105.0 [92.0, 122.0] |
| Change from baseline, mean ± SE | - | –0.29 ± 1.59; n.s.; n=21 | –2.75 ± 1.82; n.s.; n=16 |

Data for participants in the effectiveness analysis set with available data. *Statistical difference at the 5% level, one-tailed (Dunnett's test). BMI, body mass index; n.s., not significant across visits (ANOVA); SD, standard deviation; SE, standard error.

**Table 6.** Changes to fasting lipid profile

| Lipid, mg/dL | Baseline | Week 13 | Week 26 |
|---|---|---|---|
| **Total cholesterol** | | | |
| N | 439 | 250 | 209 |
| Mean ± SD | 182.4 ± 53.7 | 149.6 ± 41.1 | 139.3 ± 44.7 |
| Median [min, max] | 172.4 [53.7, 394.0] | 145.5 [51.8, 302.2] | 134.2 [39.4, 327.0] |
| Change from baseline, mean ± SE | - | –32.60 ± 3.30; $p$<0.0001*; n=206 | –45.56 ± 3.55; $p$<0.0001*; n=179 |
| **HDL cholesterol** | | | |
| N | 391 | 226 | 189 |
| Mean ± SD | 48.9 ± 17.4 | 54.1 ± 16.8 | 55.0 ± 13.4 |
| Median [min, max] | 47.3 [11.6, 166.2] | 54.0 [16.0, 138.5] | 54.1 [20.8, 108.6] |
| Change from baseline, mean ± SE | - | 5.15 ± 1.14; $p$=0.0001*; n=179 | 4.50 ± 1.21; $p$<0.0001*; n=156 |
| **LDL cholesterol** | | | |
| N | 394 | 226 | 190 |
| Mean ± SD | 101.6 ± 44.5 | 74.3 ± 34.6 | 69.2 ± 34.2 |
| Median [min, max] | 93.0 [17.0, 339.4] | 71.1 [17.2, 292.3] | 64.6 [17.0, 237.4] |
| Change from baseline, mean ± SE | - | –27.41 ± 3.38; $p$<0.0001*; n=175 | –32.63 ± 3.56; $p$<0.0001*; n=158 |
| **Triglycerides** | | | |
| N | 424 | 239 | 192 |
| Mean ± SD | 156.7 ± 69.5 | 135.2 ± 52.4 | 128.8 ± 43.9 |
| Median [min, max] | 141.5 [44.3, 406.0] | 126.0 [37.0, 364.0] | 120.5 [53.1, 317.1] |
| Change from baseline, mean ± SE | - | –30.00 ± 4.91; $p$<0.0001*; n=196 | –36.59 ± 5.40; $p$<0.0001*; n=162 |

Data for participants in the effectiveness analysis set with available data. *Statistical difference at the 5% level, one-tailed (Dunnett's test). HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; SE, standard error.

### *Fasting lipid profile*

Improvements in fasting lipid profiles were shown across the variables studied (Table 6). In the EAS, the mean (±SE) change in total cholesterol was -45.56 ± 3.55 mg/dL [95% CI: -52.53; -38.59]; $p$<0.0001 (n=179; baseline to week 26). High-density lipoprotein cholesterol increased by a mean (SE) of 4.50 ± 1.21 mg/dL [95% CI: 2.12; 6.88]; $p$<0.0001 (n=156; baseline to week 26), while the mean ± SE change in low-density lipoprotein cholesterol was -32.63 ± 3.56 [95% CI: -39.63; -25.63] mg/dL; $p$<0.0001 (n=158; baseline to week 26). Triglycerides similarly showed a reduction (mean [SE] change: -36.59 ± 5.40 mg/dL [95% CI: -47.21; -25.98]; $p$<0.0001 [n=162; baseline to week 26]).

### *Diabetes management*

Participants were asked to self-monitor their blood glucose levels; however, most did not. At baseline, a total of 301/794 (37.9%) participants reported checking their blood glucose levels. This number comprised 153 (19.3%) who checked daily, 118 (14.9%) who checked weekly, and 30 (3.8%) who

**Table 7.** Antidiabetic therapy before and after liraglutide initiation (at baseline)

| Concomitant Medications | n (%) |
|---|---|
| Before liraglutide prescription | |
| OAD – combinations (including metformin) | 438 (41.5) |
| OAD and insulin | 277 (26.2) |
| OAD – metformin only | 170 (16.1) |
| OAD and GLP-1 RA | 65 (6.2) |
| Insulin | 48 (4.5) |
| No therapy (but diagnosed T2D) | 35 (3.3) |
| OAD, insulin and GLP-1 RA | 18 (1.7) |
| GLP-1 RA only | 4 (0.4) |
| Insulin and GLP-1 RA | 1 (0.1) |
| After liraglutide prescription | |
| OAD and insulin | 293 (27.7) |
| OAD – metformin only | 290 (27.5) |
| OAD combinations (including metformin) | 249 (23.6) |
| None (liraglutide only) | 166 (15.7) |
| Insulin | 58 (5.5) |

GLP-1 RA, glucagon-like peptide-1 receptor agonist; OAD, oral antidiabetic drug; T2D, type 2 diabetes.

checked monthly. The remaining 493/794 (62.1%) did not regularly monitor their blood glucose levels. At week 26, the proportions of participants who reported undertaking regular SMBG decreased slightly to a total of 265/794 (33.4%), with 136 (17.1%) reporting daily monitoring, 110 (13.9%) weekly and 19 (2.4%) monthly (with 66.6% not reporting regular monitoring).

Before beginning treatment with liraglutide, most participants were treated with a combination of OADs (including metformin) (438 [41.5%]) or OADs and insulin (277 [26.2%]) (Table 7). After initiation of liraglutide (at baseline), similar proportions of participants were treated with a combination of liraglutide, OADs and insulin (293 [27.7%]), liraglutide and metformin alone (290 [27.5%]), and liraglutide combined with more than one OAD including metformin (249 [23.6%]), while 58 (5.5%) participants were treated with liraglutide and insulin. A total of 166 (15.7%) participants were treated with liraglutide monotherapy.

### *Changes in lipid-lowering and antihypertensive medications*

Use of lipid-lowering medication remained fairly stable during the study. At baseline, 20.0% (148/739) of participants in the EAS were treated with fibrates, and 90.0% (665/739) were treated with statins. After 26 weeks of treatment with liraglutide, these proportions were 20.9% (89/426) and 89.4% (381/426), respectively.

At baseline, most participants (570/664, 85.8%) were being treated with angiotensin II receptor blockers. Over the course of the study, this proportion increased slightly to 93.9%, although from considerably fewer participants with available data (355/378). There were decreases in all other types of antihypertensive treatment (angiotensin-converting enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics; data not shown).

## DISCUSSION

The LEAD-Ph study was a post-marketing surveillance commitment to the Philippine FDA, and was conducted to assess the safety and effectiveness of liraglutide over 26 weeks in participants with T2D during routine clinical practice in the Philippines. Overall, this study found no new safety concerns and demonstrated the clinical effectiveness of liraglutide in participants with T2D within this setting. There were no reports of SADRs (the primary endpoint), and participants treated with liraglutide for 26 weeks, as prescribed in the course of routine care, experienced statistically significant and clinically relevant improvements in $HbA_{1c}$, FBG, and PPBG levels. No SAEs, and few ADRs, were reported (19 events in 17 participants), and the reported incidence of hypoglycemia was also low.

A higher frequency of ADRs and SADRs might have been expected in LEAD-Ph, based on other observational studies of liraglutide use in European participants with T2D.[30,31] In a 12-month Belgian study, 58/245 (24%) of the participants reported ADRs and 6/245 (2.4%) reported an SADR, while in a French study, 458/3152 (14.5%) of the participants experienced an AE possibly related to liraglutide during 2 years of follow up.[30,31] There are limited data on the frequency of treatment-related AEs in observational studies involving Asian populations. In a 26-week, open-label, active-comparator trial of liraglutide, of 183 Chinese participants treated with liraglutide, the proportion of patients with AEs possibly/probably related to treatment was 43.2%.[26] However, in the observational 26-week LEAD-In study of liraglutide in routine clinical use in India, only 19/1416 (1.3%) of the participants reported 20 AEs, of which 19 were considered to be treatment-related, and no participant reported an SADR, which resonates with the findings of LEAD-Ph.[27] Other than the four events of hypoglycemia, the most frequently reported ADRs by system class during LEAD-Ph were gastrointestinal disorders. This accords with the findings from the LEAD clinical trials for liraglutide and the safety profile of the GLP-1 RA class, in which gastrointestinal AEs are the commonly observed AEs.[12-17,19,21,32-34] However, withdrawals due to gastrointestinal events are uncommon, as these events are generally transient and can be mitigated by weekly dose escalation.[12-17,19,21,32,33] During this study, 24.8% of participants in the FAS had withdrawn by week 26, approximately half of these withdrawals occurred by week 13, yet only 0.5% of participants in the FAS withdrew due to ADRs. Most withdrawals in LEAD-Ph were attributed to liraglutide discontinuations (13.0%), a reason for which may be financial constraints (participants were required to pay for liraglutide prescriptions and were not reimbursed in this observational study).

Notwithstanding similarities between LEAD-Ph and the Indian LEAD-In study, the absence of SADRs and the low frequency of ADRs for a study of the size of LEAD-Ph (n=1056 [FAS]) should be interpreted with caution. While training on safety reporting was provided to investigators at the start of the study and at site initiation visits, and repeated reminders were provided throughout the study, insufficient event reporting may have occurred. Additionally, the varied and significant proportion of participants with missing data may also have been a contributing factor.

The inadvertent reporting of an AE (frozen shoulder [periarthritis]) among the ADRs, and of four episodes of hypoglycemia as ADRs, suggests that there may have been confusion for some investigators regarding the reporting procedure. In addition, the study physicians may also have implemented slower titration protocols than was recommended in the package insert, with dose increases routinely separated by more than 1 week (data on liraglutide dose escalation were not collected during the study). Therefore, collection of data on liraglutide starting dose and dose changes, as well as compliance to therapy, might have provided additional insight for clinicians, and the absence of these data limits the conclusions that can be drawn from this study.

It is possible that a lower frequency of ADR reporting may occur generally in the Philippines and other Asian populations than in European countries where liraglutide has been studied, with perhaps less experience of the concept of pharmacovigilance monitoring. This supposition cannot be explored at this time, as there are no public databases from which to gather local data on ADR reporting, and studies examining the issue of underreporting are lacking. Thus, there are no solid data for comparison with other populations, but this gap in itself suggests that the

importance of safety reporting might be less prominent in the Philippines than elsewhere.

The significant improvements in $HbA_{1c}$, FBG, and PPBG levels while on treatment with liraglutide in this study provide confirmation of the real-world effectiveness of this treatment in Filipino participants with T2D. The change from baseline to week 26 in $HbA_{1c}$ levels (mean change -1.81%, $p<0.0001$, from 8.8% at baseline) was similar to that seen in LEAD-In (-1.6%, $p<0.0001$, from 8.8% at baseline),[27] and these effectiveness results are consistent with the LEAD clinical trials.[12-17,19,21,32,33] Given that liraglutide is also associated with a low risk of hypoglycemia,[35] it is perhaps not surprising that the incidence of hypoglycemia in the present study was low despite improvements in glycemic control. Importantly, the incidence was low even though 351/1056 (33.2%) participants were receiving concomitant insulin (with or without OAD); it is unclear to what extent Filipino participants receiving insulin may have additionally mitigated the risk of hypoglycemia by a habit of snacking. The trend towards weight reduction observed while on liraglutide among Filipino participants was also encouraging and is similar to that seen in the phase 3 LEAD clinical trials, with concomitant improvements in BMI and body measurements. Collectively, these findings are important for meeting physicians' and patients' expectations; improved weight control was the most frequently cited reason for starting liraglutide (90% of participants). Besides improvements in body weight and BMI, other clinical parameters included in this surveillance also point towards a lowering in the overall cardiovascular risk profile. Specifically, there were numerical improvements in fasting lipid profile, and there was a trend towards reductions in SBP and DBP.

In terms of the management of diabetes and use of concomitant medications, there were no notable changes during the study. A similar proportion of participants took OADs in combination with insulin before and after liraglutide initiation at baseline. The frequency of SMBG was low and reduced slightly from baseline to study end. Use of lipid-lowering and antihypertensive medication also remained fairly stable during the course of the study.

In addition to those limitations already mentioned, the varied and significant proportion of participants with missing data and high discontinuation rate (262/1056 [24.8%]) should be acknowledged. Further limitations include the absence of data for heart rate, which may be useful to include as an endpoint in subsequent studies, and self-monitoring of blood glucose was not performed by the majority of participants. Finally, this study was limited by the absence of a control group and lack of adjustment for missing data. It is also subject to the inherent limitations of its observational nature. Nevertheless, this study reports the first data on the use of liraglutide in the Philippines, and provides a useful insight into the safety and effectiveness of liraglutide in routine clinical practice among Filipino participants.

## CONCLUSIONS

During this observational study of the routine clinical use of liraglutide for T2D in the Philippines, no SADRs were reported, less than 2% of participants reported an ADR, and the incidence of hypoglycemia was reduced at the end of the study compared with baseline. Improvements in glycemic control, body weight, BMI, blood pressure, and fasting lipid profile were also observed. There were no notable changes in the management of diabetes during the study, or notable changes in concomitant medication use after liraglutide initiation at baseline. In summary, no new safety concerns were identified with the routine clinical use of liraglutide as a treatment for T2D in the Philippines and effectiveness results were generally consistent with previous studies.

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**Statement of Authorship**
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ORIGINAL ARTICLE

# Seventy-Two Hour Mortality Prediction Model in Patients with Diabetic Ketoacidosis: A Retrospective Cohort Study

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**Abstract**

Objective. This study aims to identify predictors of 72-hour mortality in patients with diabetic ketoacidosis (DKA).

Methodology. In this retrospective cohort study, data were obtained from medical records of adult patients with DKA in Cipto Mangunkusumo General Hospital from January 2011 to June 2017. Associations of predictors (age, type of diabetes, history of DKA, comorbidities, level of consciousness, renal function, bicarbonate, potassium, lactate, betahydroxybutyrate levels, and anion gap status) and 72-hour mortality were analyzed. The mortality prediction model was formulated by dividing the coefficient B by the standard error for all variables with $p<0.05$ in the multivariate analysis.

Results. Eighty-six of 301 patients did not survive 72 hours after hospital admission. Comorbidities (HR 2.407; 95% CI 1.181–4.907), level of consciousness (HR 10.345; 95% CI 4.860–22.019), history of DKA (HR 2.126; 95% CI 1.308–3.457), and lactate level (HR 5.585; 95% CI 2.966–10.519) were significant predictors from multivariate analysis and were submitted to the prediction model. The prediction model had good performance. Patients with total score less than 3 points were at 15.41 % risk of mortality, 3 – 4 points were 78.01% and 5 – 6 points were 98.22% risk of mortality.

Conclusion. The 72-hour mortality rate in Cipto Mangunkusumo General Hospital was 28.57%. The mortality prediction model had a good performance and consisted of comorbidities, history of DKA, level of consciousness and lactate level.

*Key words: prediction model, mortality, diabetic ketoacidosis*

## INTRODUCTION

The incidence of diabetic ketoacidosis (DKA) as an acute complication of diabetes mellitus (DM) has been increasing with the increasing prevalence of DM.[1] DKA is characterized by the presence of hyperglycemia, acidosis, and a positive ketone test.[2] DKA is a hyperglycemic crisis that can be fatal.[2] The mortality rate of DKA has been declining in developed countries (<10%) but increasing in developing countries.[3,4] Previous study from Suwarto et al.,[5] in 2007 – 2008 showed that the five-day mortality rate of DKA patients in Cipto Mangunkusumo General Hospital was 40%.

Several previous studies showed different mortality predictors of DKA patients. Age and comorbidities were consistently found as significant mortality predictors in several studies.[6-8] Level of consciousness, type of DM, total dose of insulin used in DKA management and frequency of DKA episodes were also statistically significant mortality predictors in previous studies.[5,9-11] Significant metabolic factors as DKA mortality predictors found in other studies were serum urea level, serum osmolarity, phosphate level, lactate level, renal function, and blood acidity.[6,12-16] Other laboratory parameters that are also impaired in DKA such as ketone, potassium and anion gap level have not been studied in relation to mortality in DKA patients.

Mortality of DKA patients generally occurs in the first 3 days of hospitalization, and it is recommended that DKA patients are admitted to an intensive care unit for the first 24–48 hours.[9] However, there are constraints due to limited intensive care unit capacity in Indonesia. Moreover, intensive care units are not evenly distributed throughout health facilities in Indonesia.

Given the seriousness of DKA, a prediction model is needed to assess the mortality risk of these patients within 72 hours of admission to hospital. Such a prediction model may provide a method for early stratification and prioritization of DKA patients with high mortality risk to receive treatment in an intensive care unit.

The aim of this study was to obtain a prediction model for 72-hour mortality risk in DKA patients. In addition, this study is also expected to provide information about 72-hour mortality rate of DKA patients in Cipto Mangunkusumo General Hospital and associated factors.

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## METHODOLOGY

This was a retrospective cohort study of DKA patients with all types of DM, aged ≥18 years, treated in the emergency unit of Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, from January 2011 to June 2017. Data were obtained from medical and electronic health records in the hospital. Patients with incomplete or no medical records and those who were discharged against medical advice before 72 hours were excluded. DKA was diagnosed according to the following criteria: blood glucose >250 mg/dL, acidemia (pH <7.3 or bicarbonate level <18 mEq/L), and positive ketone test. Patients with high blood osmolarity level diagnosed as having hyperosmolar hyperglycemic state (HHS) were excluded. This study was approved by the Medical Ethics Committee of the Faculty of Medicine, University of Indonesia.

The outcome was defined as the 72-hour mortality of DKA patients. Eleven predictors were analyzed: age, comorbidities, history of DKA, level of consciousness, type of DM, and initial laboratory parameters including renal function (eGFR), potassium, bicarbonate, beta-hydroxybutyrate, lactate levels and anion gap status. All data are presented categorically. Laboratory tests included in analysis were results on admission. Beta-hydroxybutyrate was chosen because it is produced as much as two to three times versus acetoacetate and acetone in ketonemia. Using acetoacetate or acetone measurement only may lead to false negative results in the actual assessment of ketonemia. Comorbidities were defined according to the Charlson Comorbidity Index (CCI) and patients were divided into two groups: those with a CCI score of <5 (mild–moderate comorbidity) and those with a score of ≥5 (severe comorbidity).[17]

Minimum sample calculation to find the relationship between dependent and independent variables used calculations for logistic regression analysis with the formula "ten outcomes per variable" where the minimum number of samples is multiplication between the number of independent variables studied multiplied by 10 then divided by prevalence. From calculation and based on the mortality rate from previous study by Suwarto et al.,[5] minimum sample for this study was 275 subjects.

Data were analyzed using SPSS Statistics 20.0. Univariate analysis was used to identify associations between the outcome and predictors, and was performed by survival analysis with the log-rank test. The significance level used was $\alpha$=0.05, and a significant association was defined as a *p*-value <0.05. Kaplan–Meier curve was used for survival analysis and followed by Cox proportional-hazard regression. All variables with $p$<0.25 in univariate analysis were included in the multivariate analysis. The cut off point *p*-value <0.25 in univariate analysis was chosen because more traditional levels such as 0.05 can fail in identifying variables known to be clinically important. In the iterative process of variable selection, covariates are removed from the model if they are non-significant (*p*-value ≥0.05) and not a confounder. The mortality prediction model was formulated by dividing the coefficient B by the standard error for all variables with $p$<0.05 in the multivariate analysis. Performance of the mortality prediction model was assessed using the receiver operating curve (ROC) and bootstrapping analysis using the Hosmer–Lemeshow calibration.

## RESULTS

A total of 345 DKA patients aged ≥18 years were included. Fifteen patients were excluded because they had been discharged against medical advice, 4 patients because of incomplete medical records, and 25 patients because of no medical records found. Thus, a total of 301 patients were included in the analysis.

Patient characteristics are presented in Table 1. The most common precipitating factor was infection (57.1%), of which lung infection (45.3%) and DM ulcers (22.7%) were most common. Comorbidities recorded in this study were coronary heart disease 15.28%, cerebrovascular disease 11.96%, heart failure 10.29%, gastrointestinal bleeding 8.31%, malignancy 4.98%, chronic renal failure on dialysis 3.65%, and others 3.99%.

**Table 1.** Characteristics of subjects

| Characteristics | Category | n (%); N = 301 |
|---|---|---|
| Sex | Male | 127 (42.2) |
| | Female | 174 (57.8) |
| Age | <60 years old | 204 (67.8) |
| | >60 years old | 97 (32.2) |
| | Median: 55.0 (4 5.0 – 61.0) | |
| Type of diabetes | Type 1 DM | 15 (5.0) |
| | Type 2 DM | 269 (89.4) |
| | Other types of DM | 17 (5.6) |
| History of DKA | Yes | 80 (26.6) |
| | No | 221 (73.4) |
| Comorbidities | CCI total score <5 | 280 (93.0) |
| | CCI total score >5 | 21 (7.0) |
| Level of consciousness (GCS)** | 15 | 161 (53.5) |
| | 9-14 | 103 (34.2) |
| | 3-8 | 37 (12.3) |
| Potassium level (mEq/L) | No hyperkalemia | 228 (75.7) |
| | Hyperkalemia (>5,5) | 73 (24.3) |
| | Median: 4.5 (3.9 – 5.5) | |
| Bicarbonate level (mEq/L) | 10 – 18 | 190 (63.1) |
| | <10 | 111 (36.9) |
| | Median: 11.8 (7.6 – 15.3) | |
| Anion gap | <12 | 15 (5.0) |
| | >12 | 286 (95.0) |
| | Median: 26.5 (20.2 – 30.9) | |
| Beta hydroxybutirate (mmol/L) | <6 | 285 (94.7) |
| | >6 | 16 (5.3) |
| | Median: 2.6 (1.3 – 4.3) | |
| Lactate level (mmol/L) | <2 | 138 (53.1) |
| (n=260) | 2-4 | 69 (26.5) |
| | >4 | 53 (20.4) |
| | Median: 1.9 (1.2 – 3.3) | |
| Renal function/eGFR (mL/min) | >60 | 94 (31.2) |
| | 15 – 60 | 152 (50.5) |
| | <15 | 55 (18.3) |
| | Median: 40.9 (19.7 – 69.2) | |

* Median (interquartile range) was used for continuous data

** Glasgow Coma Scale

The mortality rate within 72 hours was 28.57%. Six predictors were significantly associated with the 72-hour mortality rate in the univariate analysis: age ($p$=0.011), history of DKA ($p$<0.001), comorbidities ($p$<0.001), level of consciousness ($p$<0.001), renal function ($p$=0.018), and lactate level ($p$<0.001). These six predictors and three

others with a *p*-value <0.25 in the univariate analysis were included in the multivariate analysis: type of DM (*p*=0.104), bicarbonate level (*p*=0.076), and anion gap status (*p*=0.144). The final step of the multivariate analysis is presented in Table 2.

**Table 2.** Multivariate analysis of predictors of 72 hours mortality

| Variables | Hazard Ratio/HR (CI 95%) | P value |
|---|---|---|
| Comorbidities | 2.407 (1.181 – 4.907) | 0.016 |
| Level of consciousness (GCS)* | | |
| 15 | Reff | |
| 9-14 | 4.116 (2.048 – 8.270) | <0.001 |
| 3-8 | 10.345 (4.860 – 22.019) | <0.001 |
| History of DKA | 2.126 (1.308 – 3.457) | 0.02 |
| Lactate level (mmol/L) | | |
| <2 | Reff | |
| 2-4 | 3.117 (1.609 – 6.037) | 0.001 |
| >4 | 5.585 (2.966 – 10.519) | <0.001 |

* Glasgow Coma Scale

A mortality prediction model was formulated by dividing the coefficient B by the standard error for all variables with a *p*-value <0.05 in multivariate analysis. The final prediction model of 72-hour mortality in DKA patients is presented in Table 3. The prediction model was analyzed according to the ROC curve (Figure 1) and presented area under the curve (AUC) value of 0.893 (95% CI 0.856–0.929).

**Table 3.** Prediction model of 72-hour mortality in DKA patients

| Variables | Category | Score |
|---|---|---|
| History of DKA | No | 0 |
| | Yes | 1 |
| Level of consciousness (GCS)* | 15 | 0 |
| | 9-14 | 1 |
| | 3-8 | 2 |
| Lactate level (mmol/L) | <2 | 0 |
| | 2-4 | 1 |
| | >4 | 2 |
| Comorbidities | CCI total score <5 | 0 |
| | CCI total score >5 | 1 |
| Minimum total score | | 0 |
| Maximum total score | | 6 |

* Glasgow Coma Scale

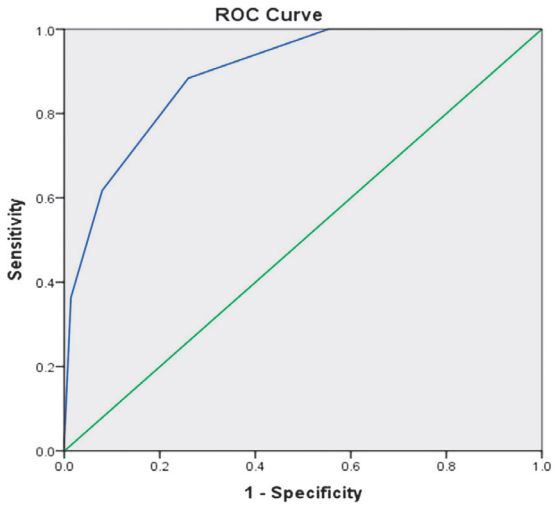


**Figure 1.** Area Under Curve (AUC) of 72 h mortality prediction model after Receiving Operator Curve (ROC).

Based on the cutoff points for sensitivity and specificity, in the mortality prediction model based on the total score, the best cut off point for estimating the 72-hour mortality of DKA patients was 2. Tables 4 and 5 present the probability of death in the first 72 hours for DKA patients based on 0–6 points for the total score in the prediction model. From Table 5, a score of >2 predicts a significantly higher mortality than a score of 2 or less.

**Table 4.** The prognostic rule based on patients having zero to six points of total score from mortality prediction model

| Points | Number of subjects (n) | | Risk of mortality (%) |
|---|---|---|---|
| | Alive | Dead | |
| 0 | 96 | 0 | 2.80 |
| 1 | 63 | 10 | 10.61 |
| 2 | 39 | 23 | 32.82 |
| 3 | 14 | 22 | 66.79 |
| 4 | 2 | 22 | 89.23 |
| 5 | 1 | 7 | 97.15 |
| 6 | 0 | 2 | 99.29 |

**Table 5.** Performance of integer-based mortality prediction model

| Points | Number of subjects (n) | | Risk of mortality (%) |
|---|---|---|---|
| | Alive | Dead | |
| 2 | 198 | 33 | 15.41 |
| 3-4 | 16 | 44 | 78.01 |
| 5-6 | 1 | 9 | 98.22 |

A calibration test was performed for the mortality prediction model with a *p*-value of 0.208 before and after 1000 bootstrap samples. The prediction model showed good quality and strong discrimination.

## DISCUSSION

Diabetic Ketoacidosis (DKA) is an acute complication of DM that is characterized by hyperglycemia, ketosis, and acidosis. It often accompanies type 1 DM, although patients with type 2 DM may also experience DKA as a result of catabolic stress associated with acute illness.[18] A study in the United States showed DKA can accompany metabolic disorders caused by absolute or relative insulin deficiency and increased counterregulatory hormones produced in response to precipitating factors such as infection, myocardial infarction, stroke, pancreatitis, or trauma.[19] Several medications such as corticosteroids can affect carbohydrate metabolism, which can trigger DKA.[3] Insulin withdrawal is the predominant precipitating factor for DKA in the United States.[2] This is different from the situation in Indonesia, where the main precipitating factor for DKA is infection (78.5–93%).[20] It is important to identify the precipitating factors as part of DKA management and prevention of recurrence of DKA.

DKA represents a hyperglycemic crisis that can be fatal.[2] Several studies have found that the mortality rate of DKA has declined during the past 20 years.[3] A study in United States found that the overall mortality from DKA in adult patients was <1%. The mortality rate for DKA was reported as >5% in elderly patients and in those with other life-threatening illnesses.[4] Moreover, the mortality rate of DKA remains

high in developing countries.[3] Suwarto et al.,[5] reported in 2007–2008 that the mortality rate for DKA patients within 5 days of admission to Cipto Mangunkusumo General Hospital was as high as 40%.

Efstathiou et al.,[9] reported that death caused by DKA occurs mainly during the first 3 days of hospital admission and suggested that patients should be treated in the intensive care unit during the first 24–48 hours. Administration of low-dose insulin infusion as a part of DKA management requires intensive monitoring of blood glucose level, which is not applicable in a general ward. However, intensive care units are not available in every hospital in Indonesia. As the top national referral hospital in Indonesia, Cipto Mangunkusumo General Hospital has limited bed capacity in its intensive care unit. This may hinder the implementation of standard treatment for DKA patients, in particular admission to the intensive care unit. This is the reason why developing a model to predict mortality risk in DKA patients is very important.

Some studies have focused on factors associated with DKA mortality. However, not all of these factors were significant after further statistical analysis, and the significance of these factors was not always consistent when included in other studies. The screening systems available for rating the severity of DKA differ between countries and generally include only laboratory parameters. This may cause bias because laboratory parameters do not always correlate significantly with mortality.[5,21-22] The preexisting prognostic score used by Efsthatiou et al.,[9] included variables such as pH <7.0, regular insulin dose >50 IU within the first 12 hours, serum glucose level >16.7 mmol/L after 12 hours, decreased level of consciousness, and fever within 24 hours. However, it can be difficult to implement this scoring system for estimating the mortality risk immediately after a patient's arrival in the emergency room because some variables in this scoring system cannot be determined before the patient is treated.

The aim of our research was to develop a mortality prediction model for DKA patients in the first 72 hours after admission. The last step in the multivariate analysis identified four predictors of mortality in DKA patients: a history of DKA, comorbidities, level of consciousness, and lactate level. A history of DKA was significantly associated with 72-hour mortality in the multivariate analysis ($p$=0.020); HR 2.126 (95% CI 1.308–3.457). Some studies have found similar results. A study in Chicago classified patients according to the number of DKA episodes: first episode, 2–3 previous episodes, and ≥4 episodes. Mortality was higher in the group with the most previous episodes of DKA.[23] Mills et al.[1] found that patients previously admitted to hospital with DKA had a 2.76-times higher risk of mortality within 21 months compared to those without a history of DKA. However, there is no well-defined pathophysiology that can explain the relationship between DKA recurrence and mortality. Recurrent episodes of DKA can be related to various causes, such as eating disorders, social problems, psychiatric disorders, and poor compliance with medication, as shown by a high $HbA_{1c}$ level.[13,24]

Our study also found that patients with severe comorbidities (CCI score ≥5) had a mortality risk 2.4 times higher than those with mild to moderate comorbidities. This result is consistent with the results of a retrospective study by Ko et al.,[8] which found higher mortality in elderly subjects with other comorbidities, such as infection, liver failure, upper gastrointestinal bleeding, and cancer. Another retrospective cohort study by Barski et al.,[10] reported that death was not caused by the metabolic complication of DKA but instead resulted from the patients' comorbid diseases, such as sepsis and multiple organ failure. Comorbidities are also included in the mortality prediction model by Efsthatiou et al.,[9] which found that patients with comorbidities had 16-times higher risk of death. Comorbidities might cause disruption to organ function, facilitate complications, and interfere with the implementation of the standard treatment protocol for DKA, which may later contribute to a higher mortality rate.

The level of consciousness is a clinical symptom that must be assessed in DKA patients. The Glasgow Coma Scale (GCS) is one of the best methods to assess the level of consciousness. Altered consciousness can be caused by several events including acidosis, increased osmolality, direct effects of ketone bodies, reduced blood supply to the brain, less uptake and use of glucose by brain cells, and other precipitating factors such as severe infection and stroke.[5,25] Altered consciousness may also result from brain edema as a complication of fluid therapy in DKA.[26] Altered consciousness is one of the parameters used in determining the severity of DKA and is often associated with mortality. In our study, the level of consciousness was significantly associated with 72-hour mortality: HR 4.116 (CI 95% 2.048–8.270) ($p$<0.001) for a GCS score of 9–14 and HR 10.345 (CI 95% 4.860–22.019) ($p$<0.001) for a GCS score of 3–8. This suggests that a lower GCS score indicates a greater risk of death in DKA patients. Suwarto et al.,[5] also reported a similar finding. Venkatesh et al.,[12] found that the average GCS score was significantly higher in DKA survivors (GCS 14–16) compared with non-survivors (GCS 10) ($p$<0.0001).

Increased lactate level is used to assess the severity and predict mortality in various conditions. Lactate level is considered to be increased at >2 mmol/L and to be greatly increased at >4 mmol/L. Increasing lactate level may occur because of tissue hypoperfusion as a result of macro- and/or microcirculation dysfunction, mitochondrial dysfunction, hypermetabolic state, and disturbance of liver function.[27] In our study, 69.8% of patients with a lactate level of >4 mmol/L did not survive. A higher lactate level was significantly associated with mortality in the multivariate analysis: the HRs (95% CIs) were 3.117 (1.609–6.037) for a lactate level of 2–4 mmol/L ($p$=0.001) and 5.585 (2.966–10.519) for a lactate level of >4 mmol/L ($p$<0.001). Suwarto et al.,[5] also reported that lactate levels were higher in non-survivors (4.2 mmol/L) than in survivors (1.7 mmol/L). The role of lactate level in predicting mortality was also shown by Hendarto who reported that 80% of the patients who died within 24 hours of treatment had an initial blood lactate level of ≥2 mmol/L.[16]

The last step in the multivariate analysis in our study, which included a history of DKA, comorbidities, level of consciousness, and lactate level, was later applied to a scoring system in which the quality of each predictor corresponded to its association with mortality. The calculation was further divided by the smallest divisor value (value point) and ended with rounding the score into

a natural number to ease the application of this model in everyday practice. This prediction model showed strong calibration and discrimination. Analysis of the contribution of the total score to the 72 hour mortality risk showed that for a total score of 0–2, the probability was 15.41%, for 3–4, the probability was 78.01%, and for 5–6, the probability was very high at 98.22%. These data show that a high total score indicates a high probability of death within 72 hours of admission to the emergency room.

Our mortality prediction model can be applied when identifying priority candidates for admission to the intensive care unit. This prediction model may provide a basis for clinicians deciding to admit DKA patients with a low mortality risk to the general ward. Clinicians from a primary healthcare or lower level hospital in Indonesia may handle DKA patients with low mortality risk without needing to refer them to a higher-level hospital. DKA patients with a higher risk of mortality could then be prioritized to receive more aggressive treatment.

Strengths of our study include a research sample over 6.5 years that comprised DKA patients with various types of DM. The predictor variables included both laboratory and clinical parameters, such as the level of consciousness, comorbidities, and age. This study also included multivariate analysis and a prediction model, and appears to be the first of its kind in Indonesia. The prediction model derived from this study had good internal validation for estimating 72-hour mortality risk in DKA patients.

Our study had some limitations. This was a retrospective cohort study with data obtained from medical and electronic health records in Cipto Mangunkusumo General Hospital. Some predictors such as the type of DM could not be confirmed by beta-cell function testing or the presence of antibody to insulin, which may have introduced bias into the study. A retrospective study also makes it difficult to evaluate nonclinical parameters, such as the referral system, which may have affected the medical service for each patient. The retrospective design of this study also led to difficulty in testing the predictive ability of the model. In addition, our study was completed in the top referral hospital in Jakarta, and the collected data may not therefore be representative of all DKA patients in all hospitals across the country. This mortality prediction model may only be applied in type 2 DM, since most of our subjects (90%) were type 2 DM patients. Finally, with regards to limitations of this study, further studies with prospective design are still needed to directly validate the performance of mortality prediction models in DKA patients.

## CONCLUSION

The 72-hour mortality rate in DKA patients in Cipto Mangunkusumo General Hospital was 28.57%. Factors associated with mortality of DKA patients in the first 72 hours are a previous history of DKA, comorbidities, level of consciousness, and lactate level. Inclusion of these four predictors produced a prediction model for 72-hour mortality in DKA patients with strong performance.

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

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ORIGINAL ARTICLE

# Pulse Oximetry as a Screening Test for Hemodynamically Significant Lower Extremity Peripheral Artery Disease in Adults with Type 2 Diabetes Mellitus*†

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**Abstract**

Objective. The main objective is to determine if digital pulse oximetry is an acceptable screening tool to detect hemodynamically significant lower extremity peripheral artery disease (PAD) in patients 50 years old and above with type 2 diabetes mellitus (T2DM) seen at the University of Santo Tomas Hospital (USTH).

Methodology. A total of 78 subjects (155 limbs) were included. Using duplex ultrasonography as the reference standard for the presence of hemodynamically significant lower extremity PAD, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were obtained for abnormal percent oxygen saturation ($SpO_2$) gradients and for ankle-brachial index (ABI).

Results. Of the 155 limbs, 38.7% had hemodynamically significant stenosis. Pulse oximetry had 76.7% sensitivity (95% CI, 65.2% to 88.1%), 85.3% specificity (95% CI, 78.0% to 92.6%), 76.7% PPV (95% CI, 66.5% to 84.4%) and 85.3% NPV (95% CI, 78.4% to 90.2%). ABI had 40.7% sensitivity (95% CI, 30.1% to 51.3%), 88.2% specificity (95% CI, 80.0% to 96.3%), 68.6% PPV (95% CI, 53.6% to 80.4%) and 70.1% NPV (95% CI, 65.1% to 74.5%). Combining both produces 88.1% sensitivity (95% CI, 78.5% to 97.8%), 74.2% specificity (95% CI, 65- 83.4%), 68.4 PPV (95% CI, 60.3% to 75.6%) and 90.8% NPV (95% CI, 83.0% to 95.2%).

Conclusion. The results of this study suggest that pulse oximetry has a higher sensitivity than ABI as a screening tool for hemodynamically significant lower extremity PAD in T2DM patients 50 years old and above. Combining these two tests may be done to achieve a higher sensitivity.

*Key words: type 2 diabetes mellitus, peripheral artery disease, oximetry*

## INTRODUCTION

Peripheral arterial disease of the lower extremities is a condition wherein the lumen of the arteries in the extremities becomes progressively obstructed by plaque, resulting in reduced blood flow to the lower limbs. This is frequently atherosclerotic in origin, and is considered a coronary artery disease equivalent.[1-3] In the Philippine setting, the prevalence of PAD among the general adult population increased from 0.4% in 2003 to 1.2% in 2008.[4] In patients with diabetes, the prevalence of PAD increases with age, from 20% in those over 40 years of age to 29% in those over 50 years.[5]

While early detection and treatment of PAD may prevent disability and death, the diagnosis is potentially missed because majority of patients are asymptomatic, or present with leg symptoms not typical of intermittent claudication.[6-9] In the Limburg PAD Study, younger age groups and diabetes were more significantly associated with asymptomatic PAD.[10]

When screening for PAD, relying on history alone may underdiagnose those who are asymptomatic. The gold standard for peripheral arterial disease diagnosis is conventional angiography, but non-invasive vascular imaging modalities such as duplex ultrasonography are more frequently performed. In the clinics, the most widely used screening test for PAD is the ankle-brachial index. Throughout the literature, there is a wide variation in specificity and sensitivity reported by different authors. In a critical review of ABI studies, Khan reported more

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than 90% sensitivity and more than 95% specificity in diagnosing 50% stenosis of the lower extremity arteries.[11] Similarly, Guo reported 91% sensitivity and 86% specificity for hemodynamically significant stenosis.[3] While ABI has been demonstrated to be highly sensitive and specific in diagnosing PAD in patients with significant stenosis, results have been inconsistent in those with less severe stenosis or with calcified vessels.[12]

The American Diabetes Association (ADA) recommends routinely screening all patients with diabetes above age 50 and in all diabetics with risk factors (e.g. smoking, hyperlipidemia, hypertension or duration of diabetes >10 years) for PAD under age 50.[5] The premise and the interpretation of the ABI is relatively simple: the lower the index, the more severe the disease. While generally accepted as a screening test, the ABI also has some limitations. Factors that may impede proper measurement of blood pressure will affect the ABI reading. Calcification of the peripheral arteries —a phenomenon commonly referred to as medial arterial calcification—can make the arteries incompressible, notably in patients who are elderly, or those with diabetes, chronic kidney disease or rheumatic disease. The ABI tends to be elevated due to artefactual elevations in occlusion pressures. This is an important concern because peripheral arterial disease is more prevalent in these patients compared to the general population.[13-17]

For patients with diabetes, using the ABI as a screening test for PAD in the clinics may yield false negative results. The Strong Heart Study demonstrated a similar association with mortality in those with high and low ABI, with a suggested upper limit of normal not to exceed 1.40.[18] An option for a screening test that will be unaffected by arterial calcifications would be ideal.

Pulse oximetry measures peripheral blood hemoglobin oxygen saturation. Low blood flow in an extremity produces lower oxygen saturation in the blood.[19,20] The pulse oximeter works by combining spectrophotometry and optical plethysmography, providing continuous, safe, non-invasive and instantaneous measurement of blood oxygenation without need for any special training.[21] There is no user calibration or site preparation required. The sensors are small, lightweight, easy to apply, noninvasive and readily available.[22] Different brands of pulse oximeters may display different values, depending on the internal calibration of the oximeter.[20] The sensor can also be attached to several locations in the body (e.g. ear lobes, fingertips, toes) that are suitable for monitoring peripheral oxygen saturation. Besides $SpO_2$, most pulse oximeters also offer other display features, including pulse rates. This important feature allows real-time assessment of the quality and reliability of the measurement. If the patient's heart rate taken by the pulse oximeter differs considerably from the actual heart rate, the $SpO_2$ reading may not be appropriate.

Numerous studies have evaluated and compared the accuracy of different pulse oximeters over a wide range of clinical conditions.[23,24] In general, the accuracy of most non-invasive pulse oximeters is acceptable for a wide range of clinical applications. Most manufacturers report that their instruments are accurate to ±2% in the $SpO_2$ range of 70 to 100%, and ±3% for saturations between 50% and 69%.[25,26] Clinical and technical conditions that may affect accuracy include low vascular peripheral perfusion during hypotension, hypothermia, or vasoconstriction; venous congestion leading to artifacts due to venous pulsation; motion artifacts; effect of fetal hemoglobin; and interference by electrical energy and stray light.[24,27]

The use of pulse oximetry as a non-invasive method in the evaluation of peripheral arterial occlusive disease has been sporadic in the last 20 years. Ignjatović reported reduced $SpO_2$ in tissues vascularized by stenotic atherosclerotic arteries.[28] Results of subsequent studies that investigated the potential of pulse oximetry as a screening test for PAD are conflicting. Kwon and Lee tested $SpO_2$ in 49 patients with known lower extremity arterial disease pre- and post-treatment, defining a decrease of more than 5% in saturation at the toe compared to the finger as an abnormal pulse oximetry result. They reported a sensitivity of 87.06% and a specificity of 87.8%. While the sensitivity, specificity, positive and negative predictive values of $SpO_2$ were not statistically significant, there was a significant improvement in $SpO_2$ post treatment.[29] Parameswaran and colleagues targeted patients with asymptomatic diabetes mellitus, using the toe $SpO_2$ cut-off value of a decrease of 2% lower than the finger or on 12-inch elevation of the foot. They found that pulse oximetry of the toes was comparable to ABI in screening for lower extremity arterial disease, with pulse oximetry having a sensitivity of 77% and a specificity of 97%.[19] Using the same criteria in the study by Parameswaran wherein a patient was considered positive for peripheral vascular disease if at least one of the limbs tested positive, Kumar reported a 74.1% sensitivity and 95% specificity for pulse oximetry in patients with asymptomatic diabetes mellitus.[21] In contrast, another study by Ena and colleagues reported that pocket pulse oximeters showed insufficient sensitivity (42.6%) but acceptable specificity (77.2%) as a screening method for detecting peripheral arterial disease in patients with diabetes mellitus.[30]

In the Philippines, there is limited access to duplex ultrasonography, as it is not available in all areas. If a simple tool like digital pulse oximetry will be found to be useful in screening for peripheral artery disease, the complications of peripheral artery obstruction may be addressed at an earlier time. This study aims to determine if digital pulse oximetry is an acceptable screening tool to detect hemodynamically significant lower extremity PAD among adult patients 50 years old and above with T2DM. Specifically, it seeks to evaluate the sensitivity, specificity, PPV and NPV of digital pulse oximetry using a ≥2% toe-finger oxygen saturation gradient on 12-inch leg elevation in comparison to ABI in the assessment of hemodynamically significant lower extremity artery occlusion compared to arterial duplex ultrasonography as the reference standard. These parameters will also be evaluated in hemodynamically significant lower extremity artery stenosis with areas of total occlusion versus those without areas of total occlusion compared to arterial duplex ultrasonography as the reference standard.

## METHODOLOGY

### Study design and sample size

We performed a cross-sectional criterion-referenced study with arterial duplex ultrasonography as the reference

standard on patients 50 years old and above with T2DM seen at the USTH from August to December 2017. Non probability sampling was used (Figure 1).

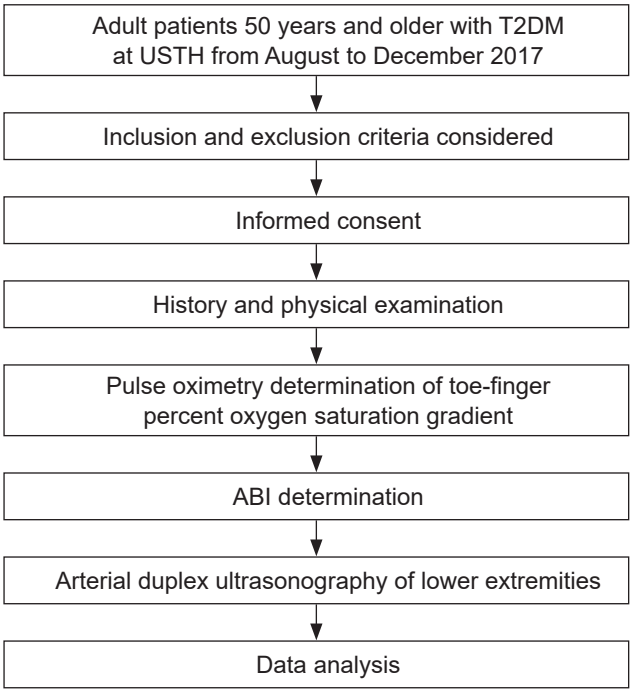


**Figure 1.** Summary of the study procedures and methods.

With the reported prevalence of PAD in patients with T2DM 50 years old and older to be at 29%, and expected sensitivity of 77% and specificity of 97% for pulse oximetry, given a 95% confidence level and the desired precision of 0.2 for sensitivity, a sample size of 63 patients was needed.[5,19]

### Inclusion and exclusion criteria

Patients 50 years old and above with T2DM seen at the USTH from August to December 2017 were included. Those with comorbidities affecting peripheral limbs (i.e. Raynaud's, vasculitides) and those on oxygen supplementation were not included in the study. Subjects with nail polish who refused to have it removed were likewise excluded from the study. In patients with amputated limbs, compartment syndrome, or gross skin ulcerations, the involved limb was not included in the study.

### Definition of measurement of outcomes

The reference standard for the determination of the presence of lower extremity PAD for this study was its diagnosis via arterial duplex ultrasonography. Participants were placed on a supine position on the examining bed with their lower extremities exposed. The duplex ultrasound scans of the lower limb arteries were performed using the LOGIQ™ E9 Pro-series by General Electric Japan. The Kappa level (95% confidence interval) of agreement between the duplex ultrasound and angiographic assessments for distinguishing hemodynamically significant (>50%) stenosis was 0.55.[31]

The bilateral lower extremity arterial segments were insonated at an angle of less than 60 degrees, starting at the level of the distal external iliac artery down to the dorsalis pedis artery using a 5-7 MHz linear transducer. For the purpose of this study, only the data from the distal external iliac artery and femoro-popliteal segments were obtained for analysis. In arteries with different categories of lesions, the most severe lesion was taken for comparison. The severity of stenosis was determined by the luminal diameter ratio at the site of the stenosis and the normal adjacent segment, reported as percent diameter reduction. Hemodynamically significant stenosis is defined by a 50 to 99% diameter reduction, including occlusions.[31-33]

For percent oxygen saturation, a handheld pulse oximeter (HD-76, Wilcare, New Jersey, USA) was applied to the index finger and both great toes with the patient in supine position at room air. If the $SpO_2$ signal was not obtainable due to necrosis or loss, the signal from the next toe was used. The result was positive for PAD if the $SpO_2$ of the big toe taken with the foot in resting position or on 12-inch leg elevation had a difference of at least 2% compared to the index finger $SpO_2$.[19]

ABI measurements were performed using a sphygmomanometer cuff and a handheld Doppler probe (Hadeco® Smart Doppler, Kyoto, Japan). Using the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and ADA 2003 Consensus Statement definition, an abnormal ankle-brachial index is a value of less than or equal to 0.9.[5,34]

All pulse oximetry and blood pressure determinations were taken with the patient in supine position at room air. After obtaining consent from the patient, pulse oximetry readings were taken by the primary investigator and recorded in a separate sheet. ABI measurements were performed after pulse oximetry measurements by a separate vascular technician who was blinded to the pulse oximetry readings and clinical profile of the study patients. Arterial duplex ultrasonography was performed by a single trained and experienced vascular technologist blinded to the ABI and pulse volume waveform results. Duplex ultrasonography results were interpreted by a vascular cardiologist blinded to both the pulse oximetry and ABI readings.

### Data analysis

Descriptive analysis of baseline characteristics were performed using means and percentages. Using duplex ultrasonography as the reference standard for determination of presence of hemodynamically significant lower extremity PAD, sensitivity, specificity, PPV and NPV were obtained for abnormal $SpO_2$ gradients and for ABI. Since values were obtained at the limb level and not at the patient level, we shall consider the patient as a cluster, and computations were made in consideration for clustered data.[35] Values were obtained using the ratio estimator method for computation for clustered data.[36] Confidence intervals (CI) at 95% were obtained for each value.

### Ethical considerations

Pulse oximetry and ABI determination are both non-invasive procedures with no potential harm to the patients. This study was approved by the USTH Institutional Review Board and Ethics Committee. Signed informed consent was obtained from each subject. Privacy and confidentiality of data and results are protected.

## RESULTS

Seventy-eight subjects were included in the study, and a total of 155 limbs were evaluated. Half of the subjects were male, with a mean age of 65.6 years and a mean duration of diabetes at 9.6 years. Diabetes medication requirements were varied: 30.8% were on insulin, 50% were on oral medications alone and 19.2% were not on any medications for diabetes at the time of study. Hypertension (74.4%) and dyslipidemia (60.3%) were the most common co-morbidities. Claudication was the most commonly reported symptom (47.4%) (Table 1).

Out of 155 limbs, only 9.7% had no evidence of stenosis, with the remaining having mild to severe stenosis with areas of total occlusion (Table 2). Arteries with at least 50% stenosis are deemed hemodynamically significant as these would require treatment.[31] The results showed 38.7% had hemodynamically significant stenosis; of these 60 limbs, 25 had areas of total or 100% occlusion.

Of the 155 total limbs included in the study, 60 (38.7%) were positive for peripheral arterial disease using pulse oximetry test criteria (Table 4). Using arterial duplex ultrasonography as the standard, the sensitivity, specificity, PPV and NPV for pulse oximetry were 76.7%, 85.3%, 76.7% and 85.3% respectively. ABI had a lower sensitivity of 40.7% and specificity of 88.2%, yielding a PPV of 68.6% and NPV of 70.1%. Combining pulse oximetry and ABI, with a positive result defined as either a positive pulse oximetry result or an ABI of ≤0.9, sensitivity was determined to be 88.1% and specificity 74.2%, yielding a PPV of 68.4% and NPV of 90.8%.

Duplex ultrasonography can identify arteries with 100% or total occlusion. Findings for limbs with areas of total occlusion are listed in Table 5. Pulse oximetry in these limbs yielded a sensitivity of 92% and a specificity of 71.5%. The PPV and NPV for pulse oximetry were 38.3% and 97.9% respectively. ABI had a 41.7% sensitivity and 80.5% specificity, which gave a 28.6% PPV and 88% NPV. Combining pulse oximetry and ABI yielded a sensitivity of 95.86% and a specificity of 58.6%, which then gave a PPV of 30.3% and a NPV of 98.7%.

**Table 1.** Clinical characteristics

| Characteristic | Total (n=78) |
|---|---|
| Male gender (%) | 39 (50) |
| Mean age, year | 65.6 |
| Outpatient (%) | 47 (60.3) |
| Duration of diabetes, year | 9.6 |
| Diabetes treatment (%) | |
| Insulin | 24 (30.8) |
| Oral medication | 39 (50) |
| None | 15 (19.2) |
| Co-morbidities (%) | |
| Smoking | 18 (23.1) |
| Hypertension | 58 (74.4) |
| Heart disease | 20 (25.6) |
| Dyslipidemia | 47 (60.3) |
| Previous amputation | 1 (1.3%) |
| Clinical presentation (%) | |
| Claudication | 37 (47.4) |
| Paresthesia | 24 (30.8) |
| Hyperpigmentation | 24 (30.8) |

**Table 2.** Distribution of lower limb findings by arterial duplex ultrasonography

| Severity of stenosis (% stenosis) | Number of limbs (%) (n=155) |
|---|---|
| None | 15 (9.7) |
| Mild (1 to 19%) | 43 (27.7) |
| Moderate (20 to 49%) | 37 (23.9) |
| Severe/hemodynamically significant (50 to 99%) | 60 (38.7) |
| Without areas of total occlusion | 35 (22.6) |
| With areas of total occlusion | 25 (16.1) |

**Table 3.** Substratification of ABI results according to ACC[b]/AHA[c] criteria

| ABI[a] | Interpretation | Number of limbs (%) (n=152) |
|---|---|---|
| >1.40 | non-compressible/falsely elevated | 22 (14.2) |
| 1-1.4 | normal | 82 (52.9) |
| 0.91-0.99 | equivocal | 13 (8.4) |
| 0.4-0.90 | mild-moderate arterial disease | 34 (21.9) |
| <0.4 | severe arterial disease | 1 (0.6%) |

[a] ABI, ankle-brachial index
[b] ACC, American College of Cardiology
[c] AHA, American Heart Association

## DISCUSSION

In this study population of diabetics of at least 50 years of age, ABI determination was found to have 40.7% sensitivity in detecting hemodynamically significant stenosis. 77% of the subjects had an ABI above the cut-off value of 0.9. However, when further sub-stratified, 14.2% have ABI results of >1.4, attributed to a greater percentage of poorly compressible or falsely elevated ankle pressures. This can be due to medial arterial calcification, which is usually seen in patients with diabetes and in the elderly, underestimating the presence of arterial occlusion. While the ADA recommends performing the ABI as a screening test for patients with diabetes 50 years and above, ABI determination alone is not a sensitive screening test in this particular subset of patients.

Compared to ABI determination, measurement of digital oxygen saturation is not affected by the presence of medial arterial calcification. Abnormal pulse oximetry is defined as a greater than 2% difference between finger and toe oxygen saturation, and can possibly be used to detect lower extremity peripheral arterial disease.[19,39] However, studies on pulse oximetry and PAD had variable sensitivity results. Studies of the groups of Kwon and Parameswan included an additional pulse oximetry determination following elevation of the leg from a baseline supine position. This maneuver may account for increased sensitivity in their studies.[19,29] In our study, we considered the result positive for PAD if the $SpO_2$ of the big toe taken with the foot in resting position or on 12-inch leg elevation had a difference of at least 2% compared to the index finger $SpO_2$. The results showed that pulse oximetry has a sensitivity of 76.7% for the detection of hemodynamically significant stenosis, higher than the sensitivity for ABI.

An ideal screening test is highly sensitive, inexpensive, easy to perform, non-invasive or causes minimal discomfort, and consistent. Both pulse oximetry and ABI determination are inexpensive and non-invasive. In terms of ease and comfort, the investigators have found pulse oximetry to be faster, less complicated to perform and less prone to intra- and inter-observer variability than ABI.

**Table 4.** Comparison of pulse oximetry and ABI[a] in detecting hemodynamically significant stenosis on arterial duplex ultrasound

| Test result | Hemodynamically significant stenosis (%) | | Total | Sensitivity (95% CI[b]) | Specificity (95% CI) | PPV[c] (95% CI) | NPV[d] (95% CI) |
|---|---|---|---|---|---|---|---|
| | Present | Absent | | | | | |
| **Pulse oximetry** | | | | 76.7 (65.2-88.1) | 85.3 (78.0-92.6) | 76.7 (66.5- 84.4) | 85.3 (78.4-90.2) |
| Positive | 46 (30) | 14 (9) | 60 | | | | |
| Negative | 14 (9) | 81 (52) | 95 | | | | |
| Total | 60 (39) | 95 (61) | 155 | | | | |
| **ABI** | | | | 40.7 (30.1-51.3) | 88.2 (80.0-96.3) | 68.6 (53.6-80.4) | 70.1 (65.1-74.5) |
| ≤0.9 | 24 (16) | 11 (7) | 35 | | | | |
| >0.9 | 35 (23) | 82 (54) | 117 | | | | |
| Total | 59 (39) | 93 (61) | 152 | | | | |
| **Combined** | | | | 88.1 (78.5-97.8) | 74.2 (65-83.4) | 68.4 (60.3-75.6) | 90.8 (83.0-95.2) |
| Positive[e] | 52 (34) | 24 (16) | 76 | | | | |
| Negative[f] | 7 (8) | 69 (74) | 76 | | | | |
| Total | 59 (39) | 93 (61) | 152 | | | | |

[a] ABI, ankle-brachial index
[b] CI, confidence interval
[c] PPV, positive predictive value
[d] NPV, negative predictive value
[e] Combined positive, defined as either positive pulse oximetry test result or ABI ≤0.9
[f] Combined negative, defined as negative pulse oximetry test result and ABI >0.9

**Table 5.** Comparison of pulse oximetry and ABI[a] in detecting hemodynamically significant stenosis with areas of total occlusion on arterial duplex ultrasound

| Test result | Total occlusion (%) | | Total | Sensitivity (95% CI[b]) | Specificity (95% CI) | PPV[c] (95% CI) | NPV[d] (95% CI) |
|---|---|---|---|---|---|---|---|
| | Present | Absent | | | | | |
| **Pulse oximetry** | | | | 92.0 (81.5-100) | 71.5 (63.5-79.5) | 38.3 (31.6-45.5) | 97.9 (92.5-99.4) |
| Positive | 23 (15 | 37 (24) | 60 | | | | |
| Negative | 2 (1) | 93 (60) | 95 | | | | |
| Total | 25 (16) | 130 (84) | 155 | | | | |
| **ABI** | | | | 41.7 (26.1-57.2) | 80.5 (72.3-88.6) | 28.6 (18.2-41.9) | 88.0 (83.9-91.3) |
| ≤0.9 | 10 (7) | 25 (16) | 35 | | | | |
| >0.9 | 14 (9) | 103 (68) | 117 | | | | |
| Total | 24 (16) | 128 (84) | 152 | | | | |
| **Combined** | | | | 95.8 (87.9-100) | 58.6 (50.4-66.8) | 30.3 (25.8-35.2) | 98.7 (91.6-99.8) |
| Positive[e] | 23 (15) | 53 (35) | 76 | | | | |
| Negative[f] | 1 (1) | 75 (49) | 76 | | | | |
| Total | 24 (16) | 128 (84) | 152 | | | | |

[a] ABI, ankle-brachial index
[b] CI, confidence interval
[c] PPV, positive predictive value
[d] NPV, negative predictive value
[e] Combined positive, defined as either positive pulse oximetry test result or ABI ≤0.9
[f] Combined negative, defined as negative pulse oximetry test result and ABI >0.9

Both tests have their respective limitations. In patients with gangrenous digits or extensive wounds, pulse oximetry cannot be performed. In patients with cellulitis, fractures or open wounds in the foreleg, ankle BP determination, likewise, cannot be done. Our results showed that if both pulse oximetry and ABI determination were performed in combination, where either one of the tests being positive would be considered positive for hemodynamically significant stenosis, this produced a higher sensitivity of 88.1% compared to performing either test alone.

PAD prevalence and incidence are known to be both sharply age-related.[40] In our study, 91.3% are at least 50 years old, which may explain the high percentage of lower extremity stenosis on arterial duplex ultrasound, ranging from mild to severe. Out of the 38.7% of limbs with hemodynamically significant stenosis, 41.7% of these limbs had areas of total arterial occlusion. Because of the importance of diagnosing totally occluded arteries, we also tested the sensitivity of pulse oximetry and ABI in detecting limbs with areas of total occlusion (Table 5). Both pulse oximetry and ABI had greater sensitivity in identifying limbs with areas of total occlusion than those with hemodynamically significant stenosis alone. Combining ABI and pulse oximetry yielded a sensitivity of 95.86%. Our findings indicate that pulse oximetry is a sensitive screening tool in detecting limbs with areas of total occlusion.

### Strengths and limitations of the study

Our study was able to include a larger number of patients compared to other previous investigations. Having each procedure done by separate individuals minimized measurement bias. A limitation of this study is that it was performed in a single institution.

### Recommendations

In order to make this more reflective of the general Philippine population, a multi-center study can be performed with more participants. We recommend more research be done with pulse oximetry and its potential applications. Other areas for research include pulse oximetry pre- and post-exercise, to determine effects on sensitivity in screening for PAD. Correlation of the location of stenosis in the lower extremity with ABI and pulse oximetry test results is another subject of investigation.

## CONCLUSION

In screening for hemodynamically significant lower extremity arterial stenosis in patients with diabetes age 50 years old and above, pulse oximetry had a sensitivity of 76.7%, while ABI determination had a sensitivity of 40.7%. The combination of the two tests increased sensitivity to 88.1%. Screening for lower limb arteries with areas of total occlusion produces higher sensitivity values: 92% for the pulse oximetry, 41.7% for ABI and 95.86% when both tests are combined.

The results of this study suggest that pulse oximetry has a higher sensitivity than ABI as a screening tool for hemodynamically significant lower extremity arterial disease in diabetic patients 50 years old and above. Combining these two tests may be done to achieve a higher sensitivity.

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

**Author Disclosure**
Dr. Siao and Dr. So declared no conflict of interest. Dr. Maria Honolina S. Gomez has participated in local advisory boards for Boehringer Ingelheim, Novo Nordisk and Pfizer. She also received honoraria as a clinical trial investigator for Takeda, Sanofi Aventis and GlaxoSmithKline. She has received speaker honoraria from Boehringer Ingelheim, Pfizer, Novartis, Novo Nordisk and Torrent Pharmaceuticals. She reports no conflict of interest with regard to this paper.

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ORIGINAL ARTICLE

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# Association of Dialysis Malnutrition Score with Hypoglycemia and Quality of Life among Patients with Diabetes on Maintenance Hemodialysis

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**Abstract**

Objective. To determine the association between Dialysis Malnutrition Score (DMS), hypoglycemia and quality of life among patients with Diabetes on Maintenance Hemodialysis (MHD).

Methodology. Ninety-two diabetic patients on maintenance hemodialysis were assessed using a standardized data collection tool, Dialysis Malnutrition Score, WHOQoL-BREF questionnaire, anthropometric measurements and hourly blood sugar monitoring during the dialysis session. Association among DMS, hypoglycemia and quality of life were assessed along with other associated variables.

Results. Based on the DMS, 62% of patients were malnourished. Those with malnutrition were significantly older ($p$=0.0006) and female ($p$=0.013). Only 6.5% of the participants developed hypoglycemia during dialysis. Those with poor nourishment in the DMS showed a significant trend of decrease in the quality of life (physical ($p$<0.001), psychological ($p$<0.001) and social ($p$=0.004) and is associated with the occurrence of hypoglycemia ($p$<0.001).

Conclusion. Malnutrition is prevalent in diabetic patients on MHD using DMS. A higher DMS score is highly correlated with increased risk of hypoglycemia and decreased quality of life hence detection of malnutrition is important to prevent further nutritional depletion, hypoglycemia and poor patient outcomes by implementing preventive measures such as nutritional counselling and psychosocial interventions.

*Key words: malnutrition, Dialysis Malnutrition Score, hypoglycemia, quality of life, dialysis*

## INTRODUCTION

According to the International Diabetes Federation, in 2017, 425 million adults are currently estimated to have diabetes and the Philippines is one of the world's emerging diabetes hotspots with 3.7 million Filipinos diagnosed with the disease.[1] The increasing prevalence of diabetes has also led to an increase in the number of complications such as diabetic kidney disease (DKD). DKD, which occurs in 20-40% of all diabetics,[2] is the single strongest predictor of mortality in patients with diabetes and remains to be the most common reason for progressing to end stage renal disease (ESRD) requiring maintenance hemodialysis (MHD).[3,4] DKD predisposes patients to protein energy wasting (PEW), with a 40-70% prevalence among patients on MHD.[5-7] PEW is associated with deterioration of disease condition, impaired wound healing, predisposition to hypoglycemia, depression, increased morbidity, mortality, hospitalization rate and susceptibility to infection which results in poor quality of life.[8-11] Routine screening of PEW in dialysis patients is seldom done because of difficulty of an accurate determination of the nutritional status which requires procedures such as anthropometric, body composition and biochemical measurements; and functional, dietary and subjective assessments which are time consuming, not cost effective and inconvenient to most dialysis centers.[12-13]

There are different tools used to detect PEW in patients with MHD and these were proven to be correlated with dietary intake, anthropometric measurements and laboratory assessments related to nutrition.[7,10,13-15] Previously, the Subjective Global Assessment (SGA) was the most commonly used method but is only semi-quantitative which has restricted reliability and precision.[16] Subsequently, a fully quantitative nutritional scoring system, the Modified Subjective Global Assessment or Dialysis Malnutrition Score (DMS) and Malnutrition Inflammation Score (MIS), were developed which incorporated the advantages of SGA and extended its reliability and precision.

DMS consists of 7 variables such as weight change, dietary intake, gastrointestinal symptoms, functional capacity, co-morbidity, decreased fat stores and signs of muscle wasting. MIS, on the other hand, includes the 7 components of the DMS plus 3 new components: BMI, serum albumin and TIBC. Both the DMS and MIS correlated significantly

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in MHD patients and are valid tools to be used for nutrition screening, it also has advantage that it can detect small changes in nutrition status overtime which can guide the physician for the assessment of nutrition intervention.[16] DMS and MIS has a sensitivity of 94% and 87% and specificity of 88% and 96%, respectively in comparison with SGA.[17] With these tools, detection of malnutrition can be easily done within minutes. DMS is a more sensitive, practical and simpler tool to detect malnutrition in routine hospital assessments.[14]

There are very limited local studies regarding the nutritional status of dialysis patients and the use of such tools to detect malnutrition reliably and conveniently. DMS can be used in all dialysis centers; it can anticipate early nutritional depletion, help the physician prevent any health deterioration, morbidity and mortality by implementing preventive measures such as nutritional counselling and psychosocial interventions which can reduce the risk of complications and can be valuable towards improving quality of life and patients' outcomes.

## OBJECTIVES

This study aims to determine the association between Dialysis Malnutrition Score (DMS), hypoglycemia and quality of life among patients with Diabetes on Maintenance Hemodialysis (MHD) in Chinese General Hospital and Medical Center. It also aimed to determine the following: the prevalence of malnutrition among patients with Diabetes on MHD using DMS, the prevalence of hypoglycemia among patients with DKD on MHD, the quality of life of patients with DKD on MHD using WHOQoL-BREF questionnaire, the correlation between DMS and WHOQoL-BREF in diabetic patients on MHD and the association between the occurrence of hypoglycemia and DMS in diabetic patients on MHD.

## METHODOLOGY

This is a cross-sectional study conducted between August to November 2017 at the Hemodialysis Unit of Chinese General Hospital and Medical Center, Manila, Philippines. All adult patients, at least 18 years of age with Diabetes Mellitus on maintenance hemodialysis for at least 3 months were included. The exclusion criteria were as follows: kidney transplant patients, acute infection or sepsis, multi-organ failure, coma, hospitalization in the last 3 months, ongoing oral or parenteral nutritional supplementation, use of steroidal, anti-inflammatory or immunosuppressive agents, receiving protein supplementation including amino acids or any nutritional supplements except for folic acid within 3 months prior to enrollment, history of psychological disorder such as schizophrenia and patients participating in other studies involving nutrition.

### Data collection tools and methods

#### *Patient's data*

Written informed consent was obtained from a total of 92 participants. A standardized data collection tool was prepared for each subject and data was collected prospectively through interview, review of medical records and laboratory data from the dialysis charts. The questionnaire included the patient's age, gender, occupation, civil status, educational background, financial status, hemodialysis schedule, hemodialysis duration, diabetes duration, creatinine, serum albumin, comorbid conditions and medications (Appendix 1).

#### *Dialysis Malnutrition Score (DMS)*

A validated Modified Subjective Global Assessment or Dialysis Malnutrition Score (DMS) (Boado J et al., Nutritional Assessment of patients on maintenance hemodialysis using Dialysis Malnutrition Score) consists of 7 features: weight change, dietary intake, GI symptoms, functional capacity, co-morbidity, subcutaneous fat and signs of muscle wasting (Appendix 2). Patients were interviewed and charts reviewed to gather the pertinent medical history. For weight change, the overall change in the post dialysis dry weight was obtained. The lowest score of one was given if there was no weight change or if patient had gained weight. Score of two was given for minor weight loss (<5%), score of three for weight loss of >10%, score of four for weight loss of 10-15% and score of five for any weight loss over 15% in the last 6 months. Dietary intake was scored one if it was considered as a regular solid intake with no recent change in the amount or quality of the meals, two for sub-optimal solid diet, three for full liquid diet or any moderate overall decrease, four for hypocaloric liquid and five for starvation. Gastrointestinal (GI) symptoms were scored one if there was no symptom, two for nausea, three for vomiting or any moderate GI symptoms, four for diarrhea and five for severe anorexia. Functional capacity was scored one for normal functional capacity and/or any considerable improvement in the level of previous functional impairment, two for any mild to moderate difficulty with ambulation, three for difficulty with normal activity, four for difficulty with light activity and five for bed/chair-ridden state. The co-morbidity was scored one if there was no medical problems and if the patient has been on MHD for less than one year; two if there was mild co-morbidity or if the patient has been on MHD for one to two years; three if there was moderate co-morbidity or if the patient had been dialyzed for two to four years, or if the patient was >75 years of age; four if there was severe co-morbidity or if the patient had been dialyzed for over four years; and five if there were very severe, multiple co-morbidities. Subcutaneous fat was scored by assessing subcutaneous fat deposition in four body areas: below the eyes, triceps, biceps and chest. Signs of muscle wasting were obtained by examining the temple, clavicle, scapula, ribs and quadriceps. Each component was assigned a score from 1 (normal), 2 to 4 (moderate malnutrition) and 5 (severe malnutrition). A lower score (7-10) denotes tendency towards a normal nutritional status while a higher score (>10) is considered to be an indicator of the severity of malnutrition.

#### *Anthropometric measurement*

Body dry weight, height and skin-fold measurements were performed immediately after termination of dialysis session. Triceps skin–fold (TSF) in millimeters was measured using skin–fold caliper and Mid-arm circumference (MAC) in centimeters was measured using a tape measure. Body mass index was calculated using the formula $kg/m^2$. All the above measurements were performed two times on the non-access arm of each dialysis patient and the average result of the two measurements were registered as the final result.

### *Blood glucose measurement*

During one session of the participant's dialysis, the serum glucose levels were measured immediately before starting hemodialysis and hourly until the end of the session using One Touch Select glucose meter and glucose meter strips manufactured by Johnson and Johnson. Values less than 70 mg/dL were considered as hypoglycemia with or without symptoms.

### *Quality of life*

All subjects were provided with a validated WHOQOL-BREF questionnaire in Filipino (Dela Vega, S. Improving the quality of life of Filipinos) for the assessment of quality of life for patients on Hemodialysis. WHOQOL-BREF Questionnaire was developed by the WHOQOL Group with fifteen internal field centers, simultaneously in an attempt to develop a quality of life assessment. It has 4 major domains: physical health, psychological, social relationships and environment with two individually scored items about individual's overall perception of quality of life and health. The four domain scores are scaled in a positive direction with higher scores indicating a higher quality of life. The 4 domains are then scored, labeled and transformed to a 0-100 scale using the transformation scale score.

### Statistical analysis

We computed a sample size requirement of 91 subjects, based on 90% power and 5% level of significance to detect a correlation coefficient of 0.334 from the reference article by Sohrabi Z.[11] Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Spearman's rank correlation was used to determine the correlation between DMS and QoL scores. Logistic regression was initially planned to determine predictors of malnutrition in diabetic ESRD patients on maintenance hemodialysis, but it was impractical due to a very low number of patients with hypoglycemia in our study. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at 0.05 $\alpha$-level of significance. STATA 15.0 was used for data analysis.

### Ethical considerations

This study was conducted in accordance to the ethical principles based on the Declaration of Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee (NEC) of the Philippines. This study was approved by the Research and Ethics Review Board (RERB). All patients provided written informed consent.

## RESULTS

Among the 180 patients on maintenance hemodialysis, there were 101 patients with diabetes. Five were excluded due to hospitalization because of acute infection, 4 were on enteral feeding, hence, a total of 92 patients were included in the analysis. Of the 92 patients, there were 35 (38%) patients who were classified as well-nourished by DMS scoring, 53 (57.6%) who were moderately malnourished, and four (4.35%) severely malnourished. Overall, they had a median age of 69 years, median duration of diabetes of 10 years, and 48.91% were female, less than 10% were working, and the majority were able to finish college (49%).

Their baseline socio-demographics and anthropometrics are presented in Table 1.

**Table 1.** Distribution of participants according to socio-demographic profile and clinical characteristics (N=92)

| | Frequency (%); Mean±SD; Median (Range) |
|---|---|
| Age (years) | 69 (30 – 98) |
| Male | 47 (51.09) |
| Female | 45 (48.91) |
| Employed | 9 (9.78) |
| With at least tertiary education | 51 (55.43) |
| Civil status | |
| Single | 14 (15.38) |
| Married | 49 (53.26) |
| Widowed | 29 (31.87) |
| Comorbidities | |
| Hypertension | 66 (71.74) |
| Coronary artery disease | 29 (31.52) |
| CVA (infarct/hemorrhage) | 25 (27.17) |
| Goiter | 5 (5.43) |
| COPD/TB | 3 (3.26) |
| Bronchial asthma | 1 (1.09) |
| Seizure disorder | 1 (1.09) |
| Liver disease | 1 (1.09) |
| Medications | |
| Anti-diabetic | |
| Oral hypoglycemic | 39 (42.39) |
| Insulin or both | 24 (26.09) |
| None | 17 (18.48) |
| Both | 12 (13.04) |
| Erythropoietin | 91 (98.91) |
| Iron supplement | 77 (83.70) |
| Antihypertensive | 67 (72.83) |
| Antiplatelet | 31 (33.70) |
| Duration of diabetes (year) | 10 (1 – 40) |
| Hemodialysis Schedule | |
| Twice a week | 24 (26.09) |
| Thrice a week | 68 (73.91) |
| Duration of dialysis (year) | 2 (0.25-10) |
| Triceps skin fold (mm) | 19 (8 – 210) |
| Mid-arm circumference (cm) | 29.5 (17 – 58) |
| Dry weight (kg) | 60.24±14.31 |
| BMI (kg/m$^2$) | 22.75±4.46 |
| Underweight | 14 (15.22) |
| Normal | 32 (34.78) |
| Overweight | 33 (35.87) |
| Obese | 13 (14.13) |
| Serum albumin (g/L) | |
| <30 | 16 (17.39) |
| 30 – 34 | 19 (20.65) |
| 35 – 39 | 22 (23.91) |
| ≥40 | 35 (38.04) |

A greater proportion among those with malnutrition were older (71 years versus 63 years, $p$<0.001), were female (57.89% versus 34.29%, $p$=0.028), and were widowed (42.11% versus 14.29%, $p$=0.014). We had insufficient evidence to demonstrate a difference between groups in terms of employment, education, and duration of dialysis (Table 2).

Of 92 patients, there were six patients (6.52%) who had hypoglycemia, four of whom were moderately malnourished and two who were severely malnourished. WHOQoL-BREF scores are presented on Table 3.

**Table 2.** Clinical characteristics of patients, by DMS category (N= 92)

| | Total (n=92) | Well-nourished (n= 35) | Moderate and severe malnutrition (n=57) | p-value |
|---|---|---|---|---|
| Age (years) | 69 (30–98) | 63 (31–82) | 71 (30–98) | **<0.001*** |
| Female sex | 45 (48.91) | 12 (34.29) | 33 (57.89) | **0.028†** |
| Employed | 9 (9.78) | 4 (11.43) | 5 (8.77) | 0.727‡ |
| With at least tertiary education | 51 (55.43) | 20 (57.14) | 31 (54.39) | 0.796† |
| Civil status | | | | **0.014†** |
| Single | 14 (15.38) | 8 (22.86) | 6 (10.53) | |
| Married | 49 (53.26) | 22 (62.86) | 27 (47.37) | |
| Widowed | 29 (31.87) | 5 (14.29) | 24 (42.11) | |
| Duration of dialysis (years) | 2 (0.25 – 10) | 1 (0.25 – 8) | 3 (0.25 – 10) | 0.110 |

Numerical data are summarized as either median (range) or mean±standard deviation; categorical data as frequency (%).
Statistical tests used: * - Mann Whitney U test; † - Chi-square Test of Independence; ‡ - Fisher's Exact Test;

**Table 3.** Dialysis malnutrition scores, hypoglycemia, and quality of life of 92 adult patients with diabetic kidney disease on maintenance hemodialysis

| | Total (n=92) | Well (n= 35) | Moderate and severe (n=57) | p-value |
|---|---|---|---|---|
| Hypoglycemia | 6 (6.52) | 0 | 6 (10.53) | 0.079‡ |
| WHOQOL-BREF | | | | |
| Q1 – overall life | 49.73±23 | 55.71±22.76 | 46.05±22.55 | 0.050§ |
| Q2 – overall health | 40.22±20.95 | 44.29±21.93 | 37.72±20.11 | 0.145§ |
| Physical | 45.34±18.28 | 54.18±16.78 | 39.91±17.12 | **<0.001§** |
| Psychological | 55.43±13.52 | 62.5±9.26 | 51.10±13.94 | **<0.001§** |
| Social relationships | 56.97±17.04 | 64.29±17.34 | 52.49±15.35 | **0.001§** |
| Environment | 54.59±13.18 | 57.68±10.43 | 52.69±14.37 | 0.078§ |

Numerical data are summarized as mean±standard deviation; categorical data as frequency (%).
Statistical tests used: ‡ - Fisher's Exact Test; § - Independent t-test

**Table 4.** Correlation between Dialysis Malnutrition Scores and WHOQoL-BREF Scores (N = 92)

| | Correlation Coefficient (Rho) | Interpretation | p-value |
|---|---|---|---|
| Q1 – overall life | -0.2709 | Negative, weak relationship | 0.009 |
| Q2 – overall health | -0.1868 | Negative, very weak relationship | 0.075 |
| Physical | -0.5383 | Negative, moderate relationship | <0.001 |
| Psychological | -0.4688 | Negative moderate relationship | <0.001 |
| Social relationships | -0.3594 | Negative, weak relationship | 0.004 |
| Environment | -0.1451 | Negative, very weak relationship | 0.168 |

Statistical test used: Spearman's rank correlation.

WHOQoL-BREF scores range from zero to 100, with higher scores indicating better quality of life. The quality of life scores were relatively low, scoring below 60 points overall and across domains. The well-nourished group had significantly higher scores in physical, psychological, and social relationships domains.

We observed statistically significant and negative weak to moderate correlations between DMS and overall life, and on the domains of physical, psychological, and social relationships (Table 4).

## DISCUSSION

DMS stratifies patients into well nourished, moderately malnourished and severely malnourished which has an impact on patients' outcome when not detected and properly addressed. In this study, based on the DMS, 58% had moderate malnutrition and 4% were severely malnourished. Using the DMS, in the study of Afshar et al., which included 54 patients on MHD in Iran, 35% had moderate malnutrition and 6% had severe malnutrition[10] while that of Soodeh et al., had 67% malnutrition rate among the 112 chronic hemodialysis Iranian patients.[18]

It appears that the nutritional status of our patients are almost similar with other countries. There was only one study done in the Philippines using DMS for hemodialysis patients done by Boado et al. It included 33 patients on MHD, of which 81% had malnutrition.[12] It had higher rate of malnutrition compared to our study probably because a large proportion of the population (88%) were on twice a week dialysis in contrast to our population wherein majority (74%) were on thrice a week hemodialysis schedule.[12] In the study of Divina et al., the lesser frequency of dialysis showed significant association with the development and severity of malnutrition due to inadequacy of dialysis.[7]

An older age and female sex predispose patients to malnutrition such as in the study of Miguel et al.[21] In the study by Kalantar-Zadeh et al., women also had a stronger tendency to malnutrition but was not significant.[6] Some studies have found that age has an adverse effect on the incidence of malnutrition which can be due to underlying psychological disorders such as depression and economic or physical disability in the preparation and consumption of food.[9] Many changes associated with the process of aging can promote malnutrition and is frequently associated with decreases in taste acuity and smell, deterioration in dental health and decrease in physical activity which may affect nutrient intake.[20] In the study of Boado et al., and Sohrabi et al., dialysis duration was not associated with malnutrition which is the same in this study.[11]

In our study, overall life and health status appeared to be lower with poorer state of nutrition. The trends of the physical domain scores (pain and discomfort, energy, sleep), psychological health (positive feelings, memory and concentration, self esteem, bodily image and appearance, negative feelings) and social relationships (personal and social support, sexual activity) of the malnourished group were notably lower as compared to the well-nourished group. In the study of Rambod et al., negative correlations were found between nutritional status and quality of life aspects,[21] Bilgic et al., also found a significant association between MIS and poor quality of life[22] and Spiegel et al., showed that nutritional biomarkers were correlated with quality of life[23] which are all consistent with this study. Quality of life is a predictor of survival in HD patients[24] hence correlation between nutritional status using the DMS and quality of life focuses on the effects of malnutrition status on patients' survival. The decrease in quality of life is an important determinant of hospitalization and death in patients on MHD. Our study is also similar to the study of Sathvik et al., which used the WHOQOL-BREF in 75 hemodialysis patients from India, the evidence did not support a significant difference in mean environment (safety and security, home and physical environment) score across groups because most of the patients revealed that they have enough time for recreational activities with their families and they have a decent home or physical environment. They were also satisfied with their access to health services in the hospital.[25]

Screening for malnutrition using DMS is of utmost importance not only because it is the first step to correct malnutrition but also because it can prompt a reduction of unnecessary anti-hyperglycemic therapy preventing hypoglycemic episodes because hypoglycemia is associated with significant morbidities leading to both physical and cognitive dysfunction and further deterioration of patients' general health.[26-28] In our study, only 6 participants or 6.5% had episode of hypoglycemia without symptoms during dialysis. Four of those who developed hypoglycemia were on sulfonylurea while 2 of the participants were on insulin. Two out of the 6 participants who developed hypoglycemia also had episodes of hypoglycemia at home probably due to a delay in the metabolism and excretion of insulin and oral hypoglycemic agents. This is less than the 15.2% in the study of Cho et al., which included 1685 Asian patients with or without diabetes on hemodialysis and peritoneal dialysis for at least 1 month.[27] This is probably due to the difference in population studied. In Cho et al.'s study, 74% of the patients who had hypoglycemia were diabetics and they also reported that 15.6% of patients with hypoglycemia had clinical malnutrition.[27] Patients with DMS detected malnutrition often have poor appetite, decreased hepatic glycogen stores, reduced availability of gluconeogenic, insulin resistance and glucose intolerance which can lead to decreased weight and hypoglycemia hence evaluation of nutritional status using DMS with optimal dose of dialysis is important to prevent PEW and subsequent hypoglycemia.[28-31]

## CONCLUSION

Malnutrition is prevalent in diabetic patients on MHD using DMS which calls for more attention to early identification and management. A higher DMS score is highly correlated with increased risk of hypoglycemia and decreased quality of life hence detection of malnutrition is important to prevent further nutritional depletion, hypoglycemia and poor patient outcomes by implementing preventive measures such as nutritional counselling and psychosocial interventions.

### Limitations

There was limited sample size and the adequacy of dialysis (Kt/V) was not determined because of lack of available data and funding. The participants also have different timing of dialysis or shifts which may affect the detection of hypoglycemia. The causality of the association between DMS, hypoglycemia and quality of life cannot be proven, which is an inherent nature of cross-sectional studies.

### Recommendations

Further studies with larger sample size, same dialysis shifts and equal number of participants in each classification of DMS are suggested to decrease bias. More longitudinal studies are needed to assess the association of DMS with hypoglycemia, quality of life and related risk factors.

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## APPENDIX 1

**Data Collection Form**

Patient Number: _____ Age: _____ Occupation: _____ Set of HD: _____

Gender:
○ Male ○ Female

Civil Status:
○ Single ○ Married ○ Widowed

Educational Background:
○ Primary ○ Secondary ○ Tertiary ○ Postgraduate

Financial Status:
○ <7,890 pesos/month
○ 7,890 to 15,780 pesos/month
○ 15,780 to 31,560 pesos/month
○ 31,560 to 78,900 pesos/month
○ 78,900 to 118,350 pesos/month
○ 118,350 to 157,800 pesos/month
○ >157,800 pesos/month

HD schedule:
○ 2x/week ○ 3x/week ○ 4x/week

Duration of Dialysis: _____

Pre-HD weight: _____ Post-HD weight: _____ Height: _____ BMI: _____

Albumin: _____ TIBC: _____ URR: _____

Co-morbid condition:
○ Hypertension
○ Coronary Artery Disease
○ Liver Disease
○ Seizure Disorder
○ CVA infarct or hemorrhage
○ Last Hospitalization: _____
○ Thyroid/Goiter
○ Bronchial Asthma
○ COPD/TB
○ Cancer: _____
○ Psychiatric Illness
○ Previous Surgery: _____
○ DM Duration: _____

Medications:
○ Anti DM
  ○ Insulin _____ took prior to HD _____ Y _____ N _____
  ○ OHA _____ took prior to HD _____ Y _____ N _____
○ Erythropoietin _____
○ Multivitamins ○ Iron Supplements ○ Amino acids
○ Steroids _____
○ Others: _____

Food Recall:
1:
2:
Energy kcal/day: _____ CHO _____ CHON _____ Fats _____

CBG: Fasting _____ 1st hour _____ 2nd hour _____ 3rd hour _____ 4th hour _____
Hypoglycemic symptoms: _____

## APPENDIX 2

**Dialysis Malnutrition Score**

A. Patients-related medical history:

| 1. Weight change (overall change in past 6 months) | | | | |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| no weight change or gain | minor weight loss (<5%) | weight loss 5 to 10% | weight loss 10 to 15% | weight loss >15% |
| 2. Dietary intake | | | | |
| 1 | 2 | 3 | 4 | 5 |
| no change | sub-optimal solid diet | full liquid diet or moderate overall decrease | hypo-caloric liquid | starvation |
| 3. Gastrointestinal symptoms | | | | |
| 1 | 2 | 3 | 4 | 5 |
| no symptoms | nausea | vomiting or moderate GI symptoms | diarrhea | severe anorexia |
| 4. Functional capacity (nutritionally-related functional impairment) | | | | |
| 1 | 2 | 3 | 4 | 5 |
| none (improved) | difficulty with ambulation | difficulty with normal activity | light activity | bed/chair-ridden with no or little activity |
| 5. Co-morbidity | | | | |
| 1 | 2 | 3 | 4 | 5 |
| dialysis <12 months and healthy otherwise | dialysis 1-2 years or mild co-morbidity | dialysis 2-4 years or age >75 or moderate co-morbidity | dialysis >4 years or severe co-morbidity | very severe multiple co-morbidity |

B. Physical Exam:

| 1. Decreased fat stores or loss of subcutaneous fat (below eyes, triceps, biceps, chest) | | | | |
|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 |
| no change | | moderate | | severe |
| 2. Signs of muscle wasting (temple, clavicle, scapula, ribs, quadriceps, knee, interosseous) | | | | |
| 1 | 2 | 3 | 4 | 5 |
| no change | | moderate | | severe |

C. Malnutrition Score: (sum of all numbers)

## APPENDIX 3

**Dialysis Malnutrition Score Results**

| | Total (N = 92) | DMS | | |
|---|---|---|---|---|
| | | Well Nourished (N = 35) | Moderate (N = 53) | Severe (N = 4) |
| % Weight change in past 6 months | | | | |
| None | 44 (47.83) | 31 (88.57) | 13 (24.53) | 0 |
| <5 | 16 (17.39) | 0 | 16 (30.19) | 0 |
| 5–10 | 15 (16.30) | 4 (11.43) | 10 (18.87) | 1 (25) |
| 10–15 | 4 (4.35) | 0 | 3 (5.66) | 1 (25) |
| >15 | 13 (14.13) | 0 | 11 (20.75) | 2 (50) |
| Dietary intake | | | | |
| No change | 53 (57.61) | 35 (100) | 18 (33.96) | 0 |
| Sub-optimal solid diet | 31 (33.70) | 0 | 30 (56.60) | 1 (25) |
| Full liquid diet or moderate overall decrease | 8.70 | 0 | 5 (9.43) | 3 (75) |
| Hypo-caloric liquid | 0 | 0 | 0 | 0 |
| Starvation | 0 | 0 | 0 | 0 |
| Gastrointestinal symptoms | | | | |
| No symptoms | 80 (86.96) | 34 (97.14) | 43 (81.13) | 3 (75) |
| Nausea | 10 (10.87) | 1 (2.86) | 8 (15.09) | 1 (25) |
| Vomiting or moderate GI symptoms | 2 (2.17) | 0 | 2 (3.77) | 0 |
| Diarrhea | 0 | 0 | 0 | 0 |
| Severe anorexia | 0 | 0 | 0 | 0 |
| Functional capacity | | | | |
| None (improved) | 41 (44.57) | 31 (88.57) | 10 (18.87) | 0 |
| Difficulty with ambulation | 11 (11.96) | 2 (5.71) | 9 (16.98) | 0 |
| Difficulty with normal activity | 12 (13.04) | 1 (2.86) | 10 (18.87) | 1 (25) |
| Light activity | 10 (10.87) | 0 | 9 (16.98) | 1 (25) |
| Bed/chair ridden with little or no activity | 18 (19.57) | 1 (2.86) | 15 (28.30) | 2 (50) |
| Comorbidity | | | | |
| Dialysis <12 mos and healthy otherwise | 28 (30.43) | 14 (40) | 14 (26.42) | 0 |
| Dialysis 1–2 years or mild comorbidity | 14 (15.22) | 9 (25.71) | 5 (9.43) | 0 |
| Dialysis 2–4 years or age > 75 or moderate co-morbidity | 27 (29.35) | 7 (20) | 18 (33.96) | 2 (50) |
| Dialysis > 4 years or severe co-morbidity | 23 (25) | 5 (14.29) | 16 (30.19) | 2 (50) |
| Very severe multiple comorbidity | 0 | 0 | 0 | 0 |
| Decreased fat stores | | | | |
| No change | 54 (58.70) | 35 (100) | 19 (35.18) | 0 |
| (2) | 21 (22.83) | 0 | 21 (39.62) | 0 |
| Moderate | 14 (15.22) | 0 | 12 (22.64) | 2 (50) |
| (4) | 2 (2.17) | 0 | 1 (1.89) | 1 (25) |
| Severe | 1 (1.09) | 0 | 0 | 1 (25) |
| Signs of muscle wasting | | | | |
| (1) No change | 56 (60.87) | 35 (100) | 21 (39.62) | 0 |
| (2) | 17 (18.48) | 0 | 17 (32.08) | 0 |
| (3) Moderate | 14 (15.22) | 0 | 13 (24.53) | 1 (25) |
| (4) | 4 (4.35) | 0 | 2 (3.77) | 2 (50) |
| (5) Severe | 1 (1.09) | 0 | 0 | 1 (25) |

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ORIGINAL ARTICLE

# Validity of Ankle Brachial Index using Palpation Method in Screening for Peripheral Arterial Disease in Type 2 Diabetes Mellitus Patients at a Tertiary Hospital in the Philippines

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**Abstract**

Introduction. Peripheral Artery Disease (PAD) is a significant marker of cardiovascular disease and is prevalent but underdiagnosed. Ankle-Brachial Index (ABI) is the recommended screening test for PAD. However, not all clinics have a Doppler ultrasound. ABI by palpation offers a more feasible alternative.

Objective. This study aims to determine the validity of ABI measurement by palpation method in the screening of PAD.

Methodology. This prospective validation study utilized a cross-sectional analytic design. Three physicians performed the ABI by palpation method and their result was compared to the Doppler ABI. The accuracy indices for validation was computed per physician conducting the ABI by palpation and also as an average of all 3 palpation method readings. During the course of sampling, there were no patients with severe PAD found during the prospective period.

Results. The accuracy of Ankle Brachial Index using Palpation method yielded the following ranges, sensitivity between 63.16 % - 73.68%, specificity of 94.06% - 98.02%, PPV within 85.37% - 95.45%, and NPV within 80.73% - 86.84% in predicting PAD. The accuracy indices were clinically acceptable. Meanwhile, the raters' usage of Ankle Brachial Index using Palpation method demonstrated a substantial agreement with ABI by Doppler Method performed by the angiologist (Cohen Kappa >0.60).

Conclusion. The ABI by palpation is a good screening tool for PAD, but the person performing it must be adequately trained to do the procedure. The procedure is affordable and convenient, and should be done routinely during clinic visits in the physical examination of patients with known risk factors for PAD.

*Key words: diabetes mellitus, ankle-brachial index, palpation*

## INTRODUCTION

### Burden of Peripheral Arterial Disease

Peripheral Arterial Disease (PAD) in the lower extremities is the narrowing or blockage of the vessels that carry blood from the heart to the legs.[1] It is primarily caused by atherosclerosis, the buildup of fatty plaque in the arteries.[2] The third most prevalent form of atherosclerotic cardiovascular disease, PAD is a disease of high human and social impact.[3]

In a prevalence study conducted by Sang Youl Rhee et al., in several Asian countries, including the Philippines, the prevalence of PAD in high risk Asian type 2 diabetes patients is 17.7%.[4] The role of risk factors such as diabetes mellitus, tobacco use, older age, hypertension, and hypercholesterolemia, and others, with the development of PAD have been well-defined.[5-7]

In a 10-year prospective study by Criqui et al., PAD patients with and without a history of cardiovascular disease had a significantly increased risk of dying from any cause or as a result of cardiovascular disease or coronary artery disease than age-matched controls. All-cause mortality was 3.1 times greater and cardiovascular disease mortality was 5.9 times greater in patients with PAD than in those without PAD.[8]

### Significance of the study

With the increased morbidity and mortality resulting from PAD, screening for high risk population like in patients with diabetes is recommended. Early identification of PAD will reduce the severity of the disease and the possibility of amputations.[3] Preventative measures, such as promoting risk factor reduction, are more cost-effective than the surgeries and rehabilitation required to treat advanced PAD.[3]

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However, most physicians do not have a doppler ultrasound in the clinic. This makes it hard for patients to be tested, especially those in the underserved rural areas who have difficult access to diagnostic centers capable of doing the ABI. In our local setting, the latest 2010 Philippine Statistics Authority survey showed that of the 92.3 million population in the Philippines, more than half or 54.7% of the total population lived in the rural areas.[9]

ABI by palpation offers several advantages over the standard doppler ABI such that it is more affordable, can be done at any time in the clinic, and eliminates the need for specialized equipment. Most of these advantages over the standard doppler ABI eliminate the limitations of diabetic patients not being able to have the ABI screening done, especially those who live in the rural areas.

### ABI by doppler as a reference standard

Measurement of the ABI by using a doppler ultrasound is the first and primary method for establishing the diagnosis of PAD.[10] An ABI ≤0.90 using the doppler ultrasound has been demonstrated to have high sensitivity and specificity for the identification of PAD even compared with the gold standard of invasive arteriography.[10] In fact, the American Heart Association and American College of Cardiology (AHA/ACC) 2016 guidelines state that studies for anatomic imaging assessment such as computed tomography angiography, magnetic resonance angiography, or invasive arteriography are generally reserved for those in whom revascularization is being considered.[11] These procedures especially the invasive arteriography, are more expensive, require trained specialists who may not be readily available, and the dye used in the procedure confers additional risk for kidney damage in the already at-risk individuals for kidney disease. The resting doppler ABI is the initial diagnostic test for PAD and may be the only test required to establish the diagnosis and institute guideline-directed management and therapy.[11]

### Review of related literature

At the time of this study, we found only 2 related articles in PubMed. In the study done by Borreros II et al., the ABI by palpation had a sensitivity of 90.4%, specificity of 86.1%, positive predictive value of 76.5%, and a negative predictive value of 94.7%.[12] The researcher did the screening of patients for risk factors and the palpation ABI. Majority of subjects, 85%, were hypertensive, while 23% were diabetic.

Another study in Italy done by Migliacci et al., utilized a more complex methodology by letting 24 physicians screen different sets of 10 patients by palpation against the standard doppler ABI.[13] Sensitivity of the palpation method was 88%, specificity 82%, positive predictive value 18%, negative predictive value 99%. There were no data regarding inter-reader agreement of findings.

#### *General objective*

To determine the validity of ABI measurement by palpation method in the screening of PAD.

#### *Specific objectives*

1. To determine the validity of the ABI measurement by palpation using Doppler method as reference standard in the detection of the various degrees of PAD using the following measures:
   a. Sensitivity
   b. Specificity
   c. Positive predictive value
   d. Negative predictive value
   e. Accuracy
2. To determine the degree of agreement of the 3 ABI results by palpation method.

## METHODOLOGY

### Study design

This is a prospective validation study utilizing a Cross-Sectional Analytic study design. This was conducted at the outpatient department of Makati Medical Center from October 2017 to December 2017.

### Sampling method

This study utilized a Convenience Sampling method to achieve the minimum sample size.

### Sample size

The sample size was computed using the equation:

$$n = \frac{z^2 * P(1-P)}{\Delta^2} \quad (1)$$

*n* will be will be (*a*+*c*) if we use *Sensitivity* as *P*, and *n* will be (*b*+*d*) if we use *Specificity* as *P* in formula (1)

$$N = \frac{(a+c)}{Prevalence} \quad (2)$$

$$N = \frac{(b+d)}{1-Prevalence} \quad (3)$$

Specification on the sample size used for sensitivity and specificity study.[14]

The sample size in this study was computed as Total sample size = N.

At first, the researcher managed to access the sensitivity and specificity indices from related literature as values in the equation for "P", either sensitivity or specificity were expressed in symbol "P" as factor in the equation.

By using the usual single proportion sample size formula (Formula Step 1), the sample size is computed wherein the "P" was used, estimated at a certain precision CI at 95%, symbol Δ.

After the initial sample size "n" was computed, the prevalence rate of disease was determined from the related literature. Then, using formula 2 or 3, the final Total sample size was computed "N".

The total N was determined using either the sensitivity or specificity index.

The computed sample size, based on 95% confidence level, relative error of 10%, prevalence of PAD among at risk DM

type 2 patients of 17.7% and assumed sensitivity of ABI was noted to be at 90.4% while the specificity of 86.1%. The assumed sensitivity of 90.4% and specificity of 86.1% were based on the result of the study done by Borreros & delos Santos in 2012.[12] On the other hand, the prevalence was based on the study done by Sang Youl Rhee, et al.[4]

Using the following values such as, sensitivity of 90.4%, CI at 95% precision of +/-17%, and PAD prevalence rate of 17.7%, then, the computed sample size was 68 cases. However, during the prospective sampling period, the researcher was able to collect 79 subjects, with a total of 158 ABI readings. However, the researcher made an analysis of 158 ABI readings for analysis to increase the power of the statistical inference which was above the computed minimum sample size.

### Subjects

#### *Inclusion criteria*

1. 18-49 years old with Diabetes Mellitus Type 2 *plus* at least 1 other risk factor for atherosclerosis
2. 50 years old and above with Diabetes Mellitus Type 2 *alone* or with other risk factors for atherosclerosis

Exclusion criteria

1. Single or double leg amputee
2. Patients on with AV fistula or on lifetime hemodialysis

*Disclosure on support from Otsuka pharmaceuticals*

The Angiologist and his doppler ultrasound equipment were provided for free by Otsuka pharmaceuticals. Although the standard ABI is available in Makati Medical Center, our experience with the patients at the outpatient department is that they are mostly unable to have the test done on follow up due to financial constraints. Hence, the procedure was provided free of charge for the patients who participated in the study. No monetary compensation was given to Otsuka pharmaceuticals for the services rendered. No medications were prescribed to any patient in the course of the study since the scope of the study was purely diagnostic. If a patient was found to have PAD, the procedure result was forwarded to his attending physician so he can be started on appropriate management. All patients received a copy of their ABI results.

*The physicians performing the palpation ABI*

In this study, the requirement qualification for the physicians recruited to do the ABI by palpation is at a minimum general physician level, since the study application is geared towards rural area practice. The investigators, however, take into account the possibility of getting low inter-rater agreement score if levels of training significantly differ. As of this writing, the investigators did not find a similar study to use as reference for physician training levels to do the ABI by palpation since literature on the topic is very limited. We recruited 3 endocrinology fellows-in-training in Makati Medical Center to do the ABI by palpation since they underwent the same level of training on how to do the ABI. They all had ABI lectures with return demonstrations in their 3-day intensive training course for diabetes educators. Immediately prior to testing, they also had an hour review on how to do the procedure with the angiologist in this study.

### Data collection

The study was started only after the approval of the Institutional Review Board. All diabetic patients at increased risk of PAD according to the 2016 AHA/ACC guidelines were invited to participate in the study. The researcher explained the study rationale, procedures and subjects' extent of participation to the patients. They voluntarily signed consent forms prior to participating in the study.

The primary investigator screened patients for risk factors and past medical histories but was not involved in testing patients. Evident signs of vascular disease such as presence of AV fistula or a previous leg amputee were excluded to prevent testing bias. All raters of the ABI, 3 by palpation and 1 by doppler ultrasound were blinded of all patient data such as risk factors or previous vascular events like stroke or myocardial infarction. They were also blinded of the other party's findings.

Upon arrival at the testing site, the patients were instructed to rest for 10 minutes. The cuff is inflated progressively to 20 mmHg above the level of flow signal disappearance and then slowly deflated to detect signal reappearance. The first detected pulse by palpation or doppler is recorded as the systolic pressure. Systolic pressures were recorded on both brachial arteries first then the dorsalis pedis and posterior popliteal arteries of both lower extremities. The ABI's were calculated from the average of two determinations as the ratio between the highest systolic blood pressure of the ankle and the highest systolic blood pressure of the upper limbs. If there was a discrepancy in the pressure between the bilateral arms, the higher of the two systolic pressures was used.

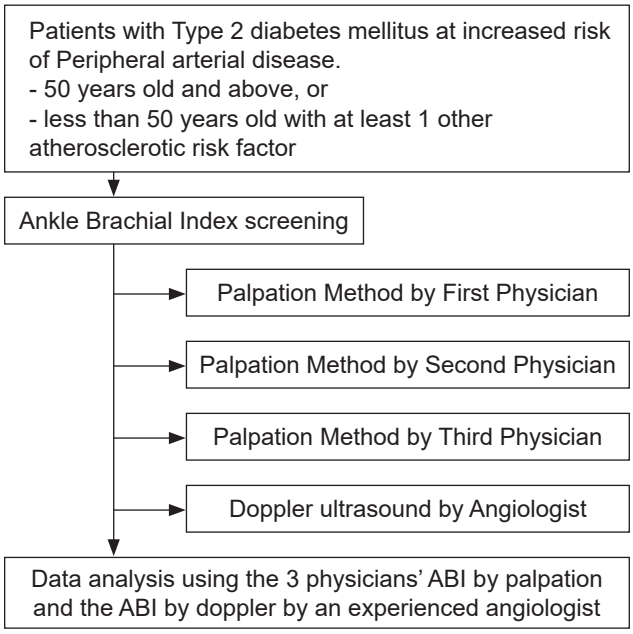


**Figure 1.** Study design flow.

Screening by palpation was done by 3 physicians successively, with 3-minute rest in between, then followed by the ABI by doppler ultrasound by the angiologist. Each step in all 4 assessments, was done in a separate patient cubicle to maintain privacy. The physicians and the

angiologist were blinded about patient data and risk factors such as previous stroke or myocardial infarction. Only the primary investigator had access to the data. All testing physicians and the angiologist were blinded of the findings of the other party.

### Data management and statistical tools

Categorical data such as gender and risk factors were expressed in frequency and percentage while the continuous variables, namely, age, BMI, and length of DM, with normal distribution were described in mean and standard deviation. Also, PAD rates were computed. In testing associations between physician assessment vs gold standard, Chi square test of independence was used with $p$-value >0.05$\alpha$ were considered significant. Cohen Kappa (unweighted) with matrices of 2x2 and 5x5 were used in testing agreement between physician's palpation method and Doppler. SPSS ver 21 was used as statistical software package.

## RESULTS

We tested 79 subjects, with a total of 158 ABI readings. Majority, 67%, of subjects were females (Table 1). The average age of the study population was 63.51±10.53 years old. The average body mass index (BMI) was 24.42±2.29 kg/m$^2$. The estimated years from first diagnosis of DM from recall is 7.60±5.89 years. Only 16.5% of the study population had a smoking history. The most common comorbidity was chronic kidney disease (67.09%), and the least common comorbidity in this study population were both Coronary Artery Disease and Cerebrovascular Disease.

In this study, the prevalence of PAD in reference to the (gold) standard Doppler ABI was 24.05% Meanwhile, using the Palpation technique, the ABI PAD rates such as 20%, 20.89%, and 24.05% were based on the assessment by physicians' 1, 2 and 3 respectively (Table 2). The test of differences in the detection rates of PAD based on the assessment by Physicians 1, 2 and 3 did not show significant independence ($p$=0.200), thus, implying that the three (3) physicians' assessment of PAD using the palpation ABI were significantly consistent.

**Table 1.** Baseline characteristics

| General Characteristics | Descriptive (n=79) |
|---|---|
| Age in years, mean±sd | **63.51±10.53** |
| Sex | |
| Females | 53(67.1%) |
| Males | 26(32.9%) |
| Average BMI, mean±sd | **24.42±2.29** |
| Presence of risk factors | |
| Estimated years from first diagnosis of DM, mean±sd | **7.60±5.89** |
| Smoker | 13(16.5%) |
| Hypertensive | 41(51.9%) |
| Dyslipidemic | 25(31.6%) |
| Coronary Artery Disease | 1(1.3%) |
| Cerebrovascular Disease | 1(1.3%) |
| Chronic Kidney Disease | 53 (67.09%) |
| -stage 1 | 16 |
| -stage 2 | 27 |
| -stage 3 | 8 |
| -stage 4 | 2 |
| -stage 5 | 0 |

Using the palpation method (Table 3), of the 44 PAD cases detected by physician 1, 42/44 (95%) were PAD on the gold standard, 35/41 (85%) PAD detected by physician 2 which was consistent with gold standard, and 36/39 (92%) PD as detected by physician 3 were consistent with gold standard. The ranges of precision by the 3 physicians in detecting PAD when matched with the gold standard were within 85%-95%. Further analysis of PAD assessment between the physicians vs gold standard revealed that physician 1 vs gold standard yielded a Cohen kappa index of 0.755, Cohen kappa of 0.647 between physician 2 vs gold standard, and Cohen kappa of 0.636 achieved between physician 3 vs gold standard. The Cohen kappa indices between the 3 physicians and gold standard indicated that there is a good consistency or agreement between the physicians' assessment and PAD outcome based on ABI by Doppler method angiologist.

In this study, all 3 physicians using the ABI by palpation method to screen for PAD had sensitivity, 73.68%, 67.3% and 63.16% respectively (see Table 4). Specificity was at 98.02%, 94.06% and 96.7% respectively. Positive predictive value was at 95.45%, 85.37% and 92.31% respectively. And

**Table 2.** Classification of severity of PAD by ABI

| Rater | Assessment | | | | | | PAD Rate |
|---|---|---|---|---|---|---|---|
| | Non-compressible | Normal | Borderline | Mild PAD | Moderate PAD | Severe PAD | |
| Palpation Physician 1 | 6 | 85 | 29 | 37 | 1 | 0 | 20.0% |
| Palpation Physician 2 | 8 | 83 | 34 | 32 | 1 | 0 | 20.89% |
| Palpation Physician 3 | 7 | 102 | 17 | 29 | 3 | 0 | 24.05% |
| Angiologist (Gold Standard) | 19 | 90 | 11 | 29 | 9 | 0 | **Prevalence: 24.05%** |

**Table 3.** Assessment of ABI results by Palpation Method and Doppler Method

| ABI by Palpation Method | | ABI by Doppler Method – Angiologist | | Total | Kappa Agreement | McNemar test p-value |
|---|---|---|---|---|---|---|
| | | (+) PAD | (-) PAD | | | |
| Physician 1 | (+) PAD | 42 | 2 | 44 | 0.755 CI 0.646-0.863 | 0.00235 |
| | (-) PAD | 15 | 99 | 114 | | |
| Physician 2 | (+) PAD | 35 | 6 | 41 | 0.647 CI 0.517-0.777 | 0.03469 |
| | (-) PAD | 17 | 95 | 112 | | |
| physician 3 | (+) PAD | 36 | 3 | 39 | 0.636 CI 0.853-0.997 | 0.000277 |
| | (-) PAD | 21 | 88 | 109 | | |

Note: values <0 indicate no agreement, 0-0.2 slight agreement, 0.21-0.4 fair agreement, 0.41-.06 moderate agreement, 0.61-0.8 substantial agreement, 0.81-1.0 almost perfect agreement.

negative predictive value was higher at 86.84%, 84.82% and 80.73% respectively. Overall accuracy was at 89.24%, 84.97% and 83.78% respectively, with an average of 86.0%.

Secondary analysis in Table 5 showed that physician 1's assessment had weak correlation with angiologist findings when it comes to normal, non-compressible, and borderline (rho=0.206 (weak), $p$=0.068). Physician 2's assessment has also weak association with angiologist's assessment (rho=0.105 (weak), $p$=0.357). Meanwhile, physician 3's judgement, yielded significant correlation with (rho=0.302** (weak), $p$=0.007) angiologist when it comes to the variations with normal, non-compressible, and borderline. Despite the effect of weak ordinal correlation on the assessment such as normal, non-compressible, and borderline, it was still noted that when it comes to presence of PAD, as shown in Table 3, there were substantial agreement between the physicians' assessment of PAD and angiologist s gold standard. These results implied that palpation method has limitation in detecting normal, non-compressible, and borderline status of patients yet palpation method is accurate when a clear presence of PAD is detected.

## DISCUSSION

The accuracy of Ankle Brachial Index using Palpation method yielded the following ranges, sensitivity between 63.16 % - 73.68%, specificity of 94.06% - 98.02%, PPV within 85.37% - 95.45%, and NPV within 80.73% - 86.84% in predicting PAD. There is a significant difference in sensitivity of ABI by palpation amongst the 3 physicians. A possible factor is that the first physician with the highest sensitivity in testing is a second-year senior endocrine fellow while the other 2 physicians with sensitivity less than 70% are both first-year fellows. More experience and mastery of the procedure might have played a significant difference in complicated cases like in the presence of bipedal edema. Also, although the Cohen kappa indices between the 3 physicians and angiologist indicated that there is a good consistency or agreement of assessment and PAD outcome between physician and angiologist in general, note that there is a significant increase in degree of agreement between physician rater and angiologist with the first physician or the senior endocrine fellow as compared to the other two first-year endocrine fellows. Otherwise the testing conditions were the same for all 3 physicians which makes the difference largely subjective to the operator. In a previous study done by Borreros et al., where the researcher was the unblinded physician rater compared to the doppler ABI,[11] the sensitivity of palpation ABI was 90% and the specificity was 86.1%. Another similar study by Migliacci in Italy also had a sensitivity 88% and a specificity of 82%. On the other hand, the doppler ABI has a sensitivity of 79-90% and a specificity of 81-98% in various studies.[15-17]

The prevalence of PAD in this study was 24.05%. This was higher in comparison to the PAD-SEARCH Study by Rhee et al, a multi-Asian country study which included the Philippines, where the prevalence of PAD in that study was 17.7%.[4] This might be due to the population difference which is purely Filipino in this study versus a mix of

**Table 4.** Validation of ABI assessment by Palpation Method

| Accuracy indices | Predicting PAD using ABI | | | Absolute range (min – max) |
|---|---|---|---|---|
| | Physician 1 | Physician 2 | Physician 3 | |
| Sensitivity | 73.68% CI 62.3%-85.1% | 67.30% CI 54.6%-80.1% | 63.16% CI 50.6%-75.7% | 63.16 -73.68 |
| Specificity | 98.02% CI 95.3%-100% | 94.06% CI 89.4%-98.7% | 96.70% CI 93.0%-100.4% | 94.06 - 98.02 |
| Likelihood Ratio + | 37.21 CI 9.35-148.04 | 11.33 CI 5.10-25.19 | 19.15 CI 6.19-59.33 | 11.33 - 37.12 |
| Likelihood Ratio - | 0.27 CI 0.173-0.415 | 0.35 CI 0.23-0.51 | 0.38 CI 0.27-0.54 | 0.27 - 0.38 |
| Pred value positive | 95.45% CI 89.3%-100% | 85.37% CI 74.5%-96.2% | 92.31% CI 83.9%-100.7% | 85.37 - 95.45 |
| Pred value negative | 86.84% CI 80.6%-93.1% | 84.82% CI 78.2%-91.5% | 80.73% CI 73.3%-88.1% | 80.73 - 86.84 |
| Overall accuracy | 89.24% CI 84.4%-94.1% | 84.97% CI 79.3%-90.6% | 83.78% CI 77.8%-89.7% | 83.78 - 89.24 |

**Table 5.** Association and agreement of assessment between 3 ABI by Palpation readings categorized according to severity of PAD vs the Gold Standard (Doppler Method (Angiologist)

| Assessors | ABI by Doppler Method (Angiologist) | | | | | | Test of association | Ordinal Level of Correlation, strength of correlation |
|---|---|---|---|---|---|---|---|---|
| | Normal | Non-compressible | Borderline | Mild PAD | Moderate PAD | Total | $x^2$ Tests | Spearman rho |
| Physician 1 | | | | | | | | |
| Normal | 27 | 9 | 2 | 4 | 1 | 43 | | |
| Non-compressible | 0 | 1 | 0 | 2 | 0 | 3 | | |
| Borderline | 9 | 0 | 2 | 3 | 1 | 15 | 0.082 | rho=0.206 (weak), p=0.068 |
| Mild PAD | 9 | 0 | 2 | 4 | 2 | 17 | | |
| Moderate PAD | 0 | 0 | 0 | 1 | 0 | 1 | | |
| Physician 2 | | | | | | | | |
| Normal | 24 | 8 | 2 | 6 | 1 | 41 | | |
| Non-compressible | 2 | 2 | 0 | 1 | 1 | 6 | | |
| Borderline | 10 | 0 | 2 | 3 | 0 | 15 | 0.008 | rho=0.105 (weak), p=0.357 |
| Mild PAD | 9 | 0 | 2 | 4 | 1 | 16 | | |
| Moderate PAD | 0 | 0 | 0 | 0 | 1 | 1 | | |
| Physician 3 | | | | | | | | |
| Normal | 32 | 8 | 4 | 3 | 1 | 48 | | |
| Non-compressible | 1 | 2 | 0 | 4 | 0 | 7 | | |
| Borderline | 4 | 0 | 1 | 2 | 1 | 8 | <0.001 | rho=0.302** (weak), p=0.007 |
| Mild PAD | 8 | 0 | 1 | 5 | 1 | 15 | | |
| Moderate PAD | 0 | 0 | 0 | 0 | 1 | 1 | | |

different Asian populations. The higher prevalence in purely Filipino population is also reflected in the study by Borreros et al.,[11] where the prevalence of PAD was at 33.2%.

### Limitations and recommendations

There are no subjects that were found to have severe PAD and not many subjects found to have mild and moderate PAD in this study. Computing individual validation per category would result in underpowered analysis. A bigger sample population would have overcome these limitations. A bigger sample population would also possibly include patients with more severe risk factors such as a history of CAD or stroke.

There are several other limitations in this study that should be taken into consideration. One, palpation is largely subjective and is dependent on the technique and senses of the one performing the ABI. Two, the physicians performing the ABI by palpation noted that patients with pedal edema were hard to assess which might have affected their results while, on the other hand, this would less likely affect the soundwave measurement of the doppler ultrasound. Third, all patients in this study have diabetes mellitus type 2. This patient population is more likely to have arterial calcifications depending on the duration and control of the condition and this might have also affected the ABI by palpation results.

## CONCLUSION

The ABI by palpation is a good screening tool for PAD but the one performing the procedure must be adequately trained to do the procedure. The procedure is inexpensive and convenient and should be incorporated into the physical examination of every clinic visit of patients at risk of PAD. This will significantly improve the specificity and negative predictive value of physical exam assessment.

This is an important clinical assessment tool especially in the developing countries like the Philippines. With the rising incidence of diabetes mellitus worldwide, the need to screen for PAD increases as well.

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

**Author Disclosure**
The authors declared no conflict of interest.

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ORIGINAL ARTICLE

# Comparison of the Harris-Benedict Equation, Bioelectrical Impedance Analysis, and Indirect Calorimetry for Measurement of Basal Metabolic Rate among Adult Obese Filipino Patients with Prediabetes or Type 2 Diabetes Mellitus

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**Abstract**

Objectives. To compare mean basal metabolic rate (BMR) estimated using Harris-Benedict equation (HB) and Bioelectrical Impedance Analysis (BIA) and the BMR measured using Indirect Calorimetry (IC) among adult obese Filipino patients with prediabetes or type 2 diabetes mellitus (T2DM).

Methodology. This was a multi-center, cross-sectional study based on review of outpatient medical records of adult, obese Filipino patients with pre-diabetes or type 2 diabetes mellitus who were seen prior to weight loss intervention at the Outpatient Clinic of St. Luke's Medical Center-Quezon City and the Metabolic and Diabetes Center of Providence Hospital from August 2017 to January 2018. BMR was derived using three methods: Harris-Benedict equation, Bioelectrical Impedance Analysis and Indirect Calorimetry.

Results. A total of 153 subjects were included in the study. Eighty subjects (52%) have pre-diabetes while 73 subjects (48%) were diagnosed with T2DM. The mean BMR measured using IC is 1299±252 kcal/day while estimated mean BMR predicted using HB equation and BIA were 1628±251 kcal/day and 1635±260 kcal/day, respectively. Compared to measurement by IC, HBE and BIA significantly overestimated the mean BMR by 329 and 336 kcal/day, respectively (*p*-value=<0.0001). IC measured BMR showed strong positive correlation with weight and moderate positive correlation with height. Multiple stepwise regression analysis yielded the BMR prediction equation: BMR (kcal/day) = -780.806 + (11.108 x weight in kg) + (7.164 x height in cm).

Conclusion. Among obese Filipinos with T2DM or prediabetes, HB equation and BIA tend to overestimate the BMR measured using IC.

*Key words: basal metabolic rate, Harris-Benedict equation, bioelectrical impedance analysis, indirect calorimetry*

## INTRODUCTION

The measurement of basal metabolic rate (BMR), defined as the energy required for performing vital body functions at rest, is the largest component of energy expenditure. Several studies reported that fat-free mass or the lean body mass plays a major role in the variations in BMR. Other factors that affect the BMR includes age, sex, diet, thyroid status, exercise, and stress.[1] Since the BMR represents the major component of daily energy expenditure in humans, it is an important calculation for developing, understanding and executing weight-related interventions.[2]

There are several methods to measure energy expenditure, but there is no consensus about which is the most accurate for specific populations.[3] The measurement of BMR via prediction equations, bioelectrical impedance analysis (BIA) and indirect calorimetry (IC) is a common practice in weight clinics and for research.[4] The gold standard for BMR measurement is IC, whereby oxygen consumption and carbon dioxide production in expired air are directly measured for calculation of energy expenditure. Although IC is extremely valid, it is not widely available, has a high cost, is time consuming and requires specialized personnel for its execution. Thus, the majority of BMR estimates for weight loss interventions rely on BMR prediction equations.[5]

The most widely used prediction equation is the Harris-Benedict Equation (HBE), which was developed in 1918 as a simple, easy-to-use and universally available method for calculation of BMR.[6] However, in spite of their widespread use, previous studies have found that prediction equations were inaccurate in various clinical settings. These equations generally take into consideration anthropometric variables such as age, body weight and height of the subjects. As a consequence, they do not permit a valid estimation of BMR in subjects with

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obesity.[3] Additionally, previous studies show that the predicted BMR equations derived from Caucasian subjects overestimated the BMR of the Asian subjects.[7-9] These prediction equations estimate BMR by incorporating the patient's height, weight, gender and age, but not race.

Moreover, literature also supports the inclusion of fat-free mass as a variable in measuring BMR due to its strong correlation with BMR. While fat-free mass is more difficult to measure than body weight, modern technology has resulted in techniques that are efficient, inexpensive and reliable for use in clinical setting. Bioelectrical impedance analysis (BIA) determines the electrical impedance or resistance to flow of an electric current through body tissues, to estimate total body water, which can then be used to determine fat-free mass.[10] However, results of BIA may be influenced by the hydration status, prandial/fasting state, exercise, diuretic use, menstrual period, ethnicity, age or body shape.[3]

Subsequently, improved equations have been developed in an attempt to improve estimates of BMR and reflect racial variations. Among these are equations of Liu et al.,[8] and Yang et al.,[11] which have been developed predominantly for healthy Asian subjects. Similarly, Mifflin et al.,[12] and Owen et al.,[13] have developed predictive equations for overweight and obese Caucasians. However, there is lack of data on the measurement of BMR in adult obese Filipinos with T2DM or prediabetes. Hence, comparing the existing methods of measuring BMR and developing a predictive equation for this group is our interest.

## OBJECTIVES

### General objective

To compare the BMR estimated using Harris-Benedict equation and BIA and the BMR measured using IC among adult obese Filipino patients with pre-diabetes or T2DM.

### Specific objectives

1. To compare mean BMR estimated using Harris-Benedict equation and BIA and the BMR measured using IC among adult obese Filipino patients with pre-diabetes or T2DM.

2. To determine the correlation between measured BMR (using IC) and the following factors:
   a. Age
   b. Sex
   c. Height
   d. Weight
   e. Body mass index (BMI)
   f. Neck circumference
   g. Wrist circumference
   h. Waist circumference
   i. Hip circumference
   j. Waist-to-hip ratio
   k. Fat-free mass

3. To develop a predictive equation to estimate the basal metabolic rate among adult obese Filipino patients with pre-diabetes or type 2 diabetes mellitus.

## METHODOLOGY

This was a multi-center, cross-sectional study based on review of outpatient medical records of patients who were seen prior to weight loss intervention at the Outpatient Clinic of St. Luke's Medical Center-Quezon City and the Metabolic and Diabetes Center of Providence Hospital-Quezon City from August 2017 to January 2018. Included were adult Filipino patients aged 18 years to 65 years old diagnosed with pre-diabetes or T2DM based on the American Diabetes Association criteria with computed body mass index (BMI) of ≥25 kg/m$^2$, complete anthropometric measurements (weight, BMI, neck circumference, wrist circumference, waist circumference, hip circumference, waist-to-hip ratio), and basal metabolic rate data derived using HB, BIA, and IC. Exclusion criteria included type 1 diabetes or types of diabetes other than type 2 diabetes mellitus, current steroid use, chronic use of steroid defined as any dose ≥1 week duration within the past 3 months of IC measurement, history of any thyroid conditions, including but not limited to history of thyroid cancer, hypothyroidism, thyrotoxicosis or any history of abnormal thyroid function tests or history or current intake of any of the following medications: carbimazole, strumazole, methimazole, propylthiouracil, liothyronine or levothyroxine, history of use of illicit drug or other psychoactive drugs, recent myocardial infarction, stroke or major surgery within the past 3 months of IC measurement, pregnant or breastfeeding patients, significant weight loss ≥5% within 3 months prior to measurement of BMR, and patients who have underwent weight loss intervention prior to measurement of BMR.

From the patients' medical records, the following data were collected: age, sex, anti-diabetic medications, anthropometric measurements (height, weight, BMI, neck circumference, wrist circumference, waist circumference, hip circumference, waist-to-hip ratio), body composition (total body fat, total muscle, visceral fat) and basal metabolic rate (Harris-Benedict equation, BIA, indirect calorimetry).

The BMR was determined using three methods. In men, the Harris-Benedict equation formula used was: BMR=66.4730 + 13.7516 x weight in kg + 5.0033 x height in cm – 6.7550 x age in years. In women, BMR=655.0955 + 9.5634 x weight in kg + 1.8496 x height in cm – 4.6756 x age in years.

The second method of estimating BMR was through use of the KaradaScan HBF-362 Bioelectrical Impedance Machine developed by Omron (Kyoto, Japan). The subjects' age, sex, and height were entered into the machine. A standard 2 kilogram deduction was entered as an adjustment for clothing weight in all subjects. Subjects were then asked to stand barefoot on the metal foot-plates of the machine while holding the handles for 30 seconds.

BMR was measured by indirect calorimetry using Fitmate™GS portable desktop indirect calorimeter developed by Cosmed (Rome, Italy). Previously, Nieman et al., (2006) showed that the FitMate™ system was both reliable and valid during rest and exercise.[10] Prior to BMR measurement using IC, patients fulfilled the following guidelines: no food intake for at least 5 hours, has not exercised for at least 4 hours, has not consumed caffeine for a least 4 hours, has not consumed stimulatory nutrition

supplements (such as ephedra or synephrine containing) for at least 4 hours, has not smoked for at least 1 hour, and is not pregnant or lactating. The procedure was conducted in a darkened, quiet room. Soft music was provided upon patient's request. The canopy hood with veil was placed over a patient's head. The patient was placed in a semi-reclined position and instructed to comfortably breathe inside the canopy hood, where the expired gas dilutes with room air. The procedure lasted for approximately 20 minutes.

All anthropometric measurements, BIA and IC were done at the Diabetes and Metabolic Center of Providence Hospital conducted by either of the two trained personnel. Fat-free mass (in kg) was determined using the following equation: Free fat mass = weight in kilograms – (weight in kilograms x total body fat percentage measured by BIA).

The sample size was calculated using the computation for difference between 2 means, with level of significance at 0.05 and power set at 95%. Values for the difference in mean and standard deviation were based on a similar study by Ikeda et al.,[14] wherein the mean BMR estimated using Harris-Benedict equation was 1388±309 kcal/day and the mean BMR measured using IC was 1260±219 kcal/day. The minimum sample size required in the study is at least 135.

### Statistical analysis

The estimated mean BMR derived from BIA and Harris-Benedict equation was compared to the mean BMR measured by IC using paired t-test. The results were reported as the mean±standard deviation (SD). The degree of agreement between the estimated and measured BMR was evaluated by Bland-Altman limits of agreement analysis. The limits of agreement was defined as the mean difference ±2 standard deviations. The estimated accuracy was defined as the percentage of the subjects whose predicted BMR was within ±10 % of measured BMR. Overestimation and underestimation was defined as >10 % and <10 % of measured BMR, respectively. For the correlation of measured BMR with age, anthropometric measurements and sex, the Pearson's correlation coefficient and Spearman's rank correlation were used. Multiple stepwise regression analysis was used to derive a predictive equation to estimate BMR among adult obese Filipino patients with pre-diabetes or type 2 diabetes mellitus.

### Ethical consideration

The study has been approved by Institutional Ethics Review Committee (IERC) of St. Luke's Medical Center-Quezon City (RPC-007-01-18). Patient confidentiality was respected by ensuring anonymity of patient records by securing the records in a private room. All study data were recorded and investigators were responsible for the integrity of the data i.e., accuracy, completeness, legibility, etc. The manner of disseminating and communicating the study results guaranteed the protection of confidentiality of patient data.

Data collection was done by the main investigator. Patient code instead of name was used as identifier. Only the ages and sex of the patients were revealed. To ensure confidentiality, research records were kept in a locked file, and all electronic information were coded and secured using a password-protected file. The study files will be kept by the investigator in a locked cabinet for 3 years, after which paper records will be shredded and recycled. Records stored on a computer hard drive will be erased to remove all data from the storage device. For data stored on USB drive, the storage device will be physically destroyed. Any trial-related monitoring, audits, IERC review, and regulatory inspections shall be allowed by providing direct access to source data/documents.

## RESULTS

A total of 153 subjects were included in the study. The clinical and demographic characteristics of the subjects are shown in Table 1. Mean age of patients was 41.8±2.3 years old (range: 20 to 64 years old). There is a larger percentage of female (70%) subjects (n=107). Eighty subjects (52%) have pre-diabetes while 73 subjects (48%) were diagnosed with T2DM. Most patients with pre-diabetes were managed with lifestyle modification (95%). Eighty-one percent of diabetic patients were on oral diabetes agents only.

There were significant differences between the mean height ($p$-value=<0.0001), weight ($p$-value<0.0001), neck circumference ($p$-value<0.0001), waist circumference ($p$-value<0.0001), and waist-to-hip ratio ($p$-value<0.0001) among male and female subjects, with male subjects having higher anthropometric measurements compared to females. With the exception of weight ($p$-value=0.267) and wrist circumference ($p$-value=0.097), all anthropometric measurements of T2DM subjects were significantly higher when compared to pre-diabetic subjects (Table 1).

As shown in Table 1, with regards to body composition, females have significantly higher total body fat ($p$-value=<0.0001) than male subjects while total muscle and visceral fat ($p$-value=<0.0001 and 0.008, respectively) were higher in male subjects. The mean BMI were similar for both males and females at 32.6±4.69 kg/m$^2$ and 31.8±4.95 kg/m$^2$, respectively ($p$-value=0.180). Despite having similar BMI, male subjects were significantly leaner than female subjects, with fat-free mass of 70.86±8.8 kg and 49.29±5.2 kg, respectively ($p$-value=<0.0001). There were no differences in the body composition between pre-diabetic and T2DM subjects ($p$-value=0.444, 0.416 and 0.171 respectively) except for fat-free mass. Despite having comparable mean BMI ($p$-value=0.242), type 2 diabetic subjects are significantly leaner than prediabetic subjects ($p$-value=0.004).

These measurements were above the cutoffs for overweight/obesity and central obesity associated with cardiometabolic diseases among Filipino adults identified in the study of Pagsisihan et al.[15] In the said study, optimal cut-offs for overweight/obesity and central obesity in males and females are BMI of 24 and 23 kg/m$^2$, waist circumference of 84 and 77 cm, and waist-to-hip ratio of 0.91 and 0.85 respectively.

Table 2 shows the comparison between measured BMR using IC and estimated BMR using HB equation and BIA. The mean BMR measured using IC is 1299±252 kcal/day. Estimated mean BMR predicted using HB equation and BIA were 1628±251 kcal/day and 1635±260 kcal/day, respectively. The mean BMR estimated using the

**Table 1.** Demographic characteristics, anthropometric measurements, and body composition of the subjects (N=153)

| Characteristics | Mean±SD or Percent (%) (n/N) | | | | | |
|---|---|---|---|---|---|---|
| Mean age (years±SD) | 41.8±12.3 | | | | | |
| Sex | | | | | | |
| Male | 46 (30%) | | | | | |
| Female | 107 (70%) | | | | | |
| Classification | | | | | | |
| Prediabetes | 80 (52%) | | | | | |
| Lifestyle modification only | 76 (95%) | | | | | |
| On metformin | 4 (5%) | | | | | |
| T2DM | 73 (48%) | | | | | |
| On oral anti-diabetic agents only | 59 (81%) | | | | | |
| On combination insulin and oral anti-diabetic agents | 7 (11%) | | | | | |
| On insulin only | 0 (0%) | | | | | |
| With GLP-1 agonist | 9 (12%) | | | | | |
| | Male (n=46) | Female (n=107) | p-value | Prediabetes (n=80) | T2DM (n=73) | p-value |
| Anthropometric measurements | | | | | | |
| Height (cm±SD) | 169±6.3 | 157±6.4 | 0.000* | 159±7.9 | 162±8.9 | 0.012* |
| Weight (kg±SD) | 93±13.4 | 78±12.3 | 0.000* | 81±14.1 | 86±14.5 | 0.267 |
| Neck circumference (cm±SD) | 40±5.1 | 36±3.67 | 0.000* | 36±4.8 | 38±4.02 | 0.012* |
| Waist circumference (cm±SD) | 107±15.4 | 96±15.2 | 0.000* | 96±18.7 | 102±11.2 | 0.002* |
| Hip circumference (cm±SD) | 110±11.9 | 107±11.6 | 0.073 | 106±11.8 | 110±11.6 | 0.044* |
| Wrist circumference (cm±SD) | 19.3±12.9 | 17±10.15 | 0.182 | 19±15.2 | 16±1.09 | 0.097 |
| Waist-to-hip ratio | 0.97±0.1 | 0.90±0.12 | 0.000* | 0.90±0.15 | 0.94±0.05 | 0.000* |
| Body composition | | | | | | |
| Total body fat (%) | 28.09±26.3 | 36.9±4.4 | 0.000* | 34.53±6.1 | 34±22.33 | 0.416 |
| Total muscle (%) | 27.24±2.9 | 22.4±3.5 | 0.000* | 23.5±3.9 | 24.2±4.1 | 0.171 |
| Visceral fat (%) | 21.06±7.2 | 16.9±10.7 | 0.008* | 18.75±11.6 | 18.02±7.9 | 0.444 |
| Fat-free mass (kg) | 70.86±8.8 | 49.29±5.2 | 0.000* | 53.14±10.6 | 58.6±12.4 | 0.004* |
| Mean BMI (kg/m$^2$±SD) | 32.6±4.69 | 31.8±4.95 | 0.180 | 31.8±4.53 | 32.5±5.23 | 0.242 |
| Overall mean BMI (kg/m$^2$±SD) | 32.06±4.8 | | | | | |

* significant (p-value<0.05)

**Table 2.** Comparison between measured BMR using IC and estimated BMR (BIA, HB equation)

| | Mean BMR + SD (kcal/day) | ΔBMR | p-value |
|---|---|---|---|
| Indirect Calorimetry | 1299±252 | | |
| Harris-Benedict equation | 1628±251 | 329 | <0.001* |
| Bioelectrical impedance analysis | 1635±260 | 336 | <0.001* |

* significant (p-value<0.05)

**Table 3.** Proportion of accurate, underestimated and overestimated BMR predictions for all subjects

| | Underestimation (n,%) | Accurate within + 10% (n,%) | Overestimation (n,%) |
|---|---|---|---|
| Harris-Benedict equation | 0 | 19 (12%) | 134 (88%) |
| Bioelectrical impedance analysis | 0 | 15 (11%) | 138 (90%) |

* significant (p-value<0.05)

HB equation and BIA significantly overestimated the mean BMR measured using IC by 329 and 336 kcal/day, respectively (*p*-value=-<0.0001).

Table 3 summarizes the percentages of accurate, underestimated and overestimated BMR predictions by HB equation and BIA for all subjects. A value is considered accurate when the difference between the estimated BMR and measured BMR (calculated as estimated BMR-measured BMR/measured BMR) is not greater than±10%. The percentages of estimated BMR (HB equation and BIA) within ±10% of the measured BMR (IC) were only 12% and 11%, respectively. In 88% and 90% of the subjects, BMR were overestimated when HB equation and BIA, respectively, were used to derive the BMR.

The individual differences between measured and predicted BMR plotted against the average of the measured BMR and predicted BMR are shown in the Bland-Altman plots in Figure 1 and 2. Bland-Altman plots displayed the calculated mean of the estimated and measured BMRs against the calculated difference between the estimated and measured BMR for each subject. The mean difference (estimated BMR − measured BMR) was defined by the solid red horizontal line. On the y-axis, the distance of the mean difference line from the zero-difference point visually represented bias. Data points were plotted closest to the zero-difference point for participants whose BMR was most closely predicted to the measured BMR. Two solid horizontal lines, located 2 SD above and below the mean difference line, corresponded to the limits of agreement defined by Bland and Altman.[16] To define limits of agreement, they recommended that at least 95% of the data points should lie within ±2SD of the mean difference.

In Figure 1, showing the agreement between estimated BMR using Harris Benedict equation and measured BMR using IC, 144 out of 153 (94%) data points lie within ±2SD, 4 (2.6%) out of 153 data points fall beyond -2SD and 5 (3.3%) out of 153 data points lie above +2SD. Figure 2 presents the agreement between estimated BMR using BIA and measured BMR using IC. One hundred forty-three out of 153 (93%) data points lie within ±2SD, 7 out of 153 (4.6%) data points fall beyond -2SD and 3 out of 153 (2%) data points lie above +2SD. Using the cut-off of at least 95% as proposed by Bland and Altman,[16] there is a lack of agreement between IC and HB equation, and between IC and BIA.

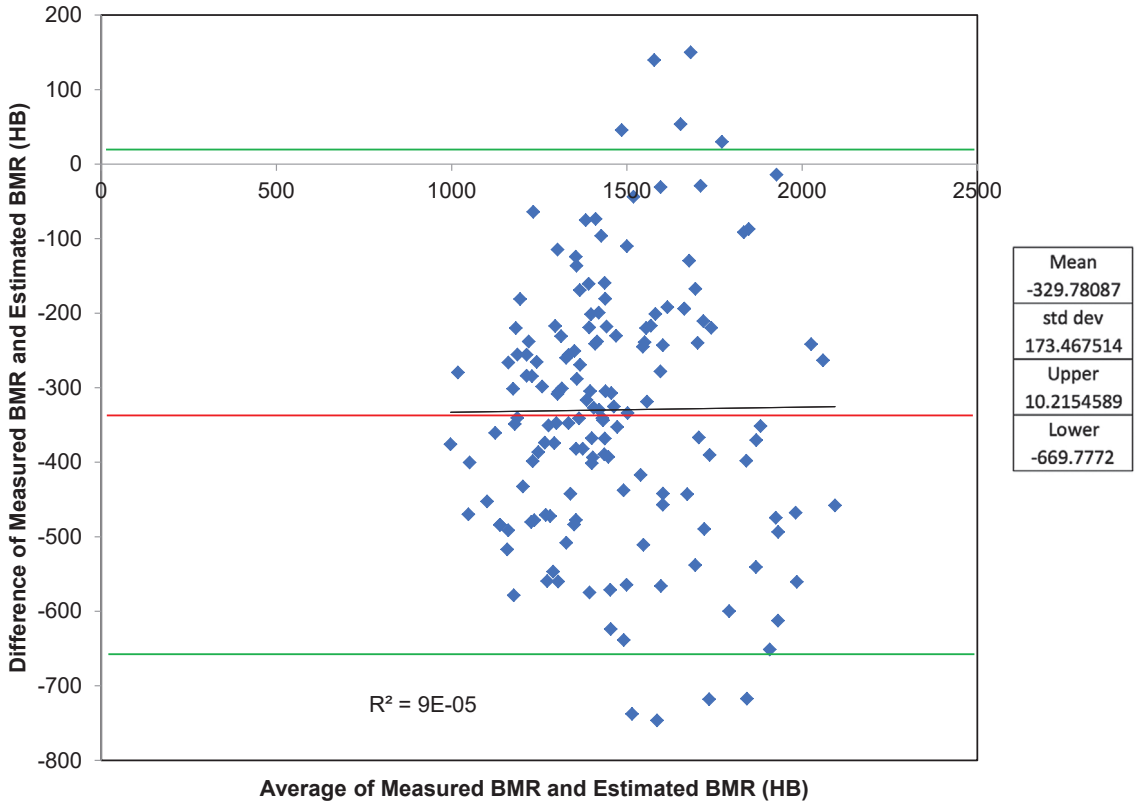


**Figure 1.** Bland-Altman plot displaying the agreement and bias between the BMR Predicted with the HB equation and the measured BMR using IC. Reference lines represent the mean (red line) of the prediction equation (bias) and the limits of agreement (±2 SD) (green lines). Regression line, coefficient of determination ($R^2$) and *p*-value for the slope are provided.

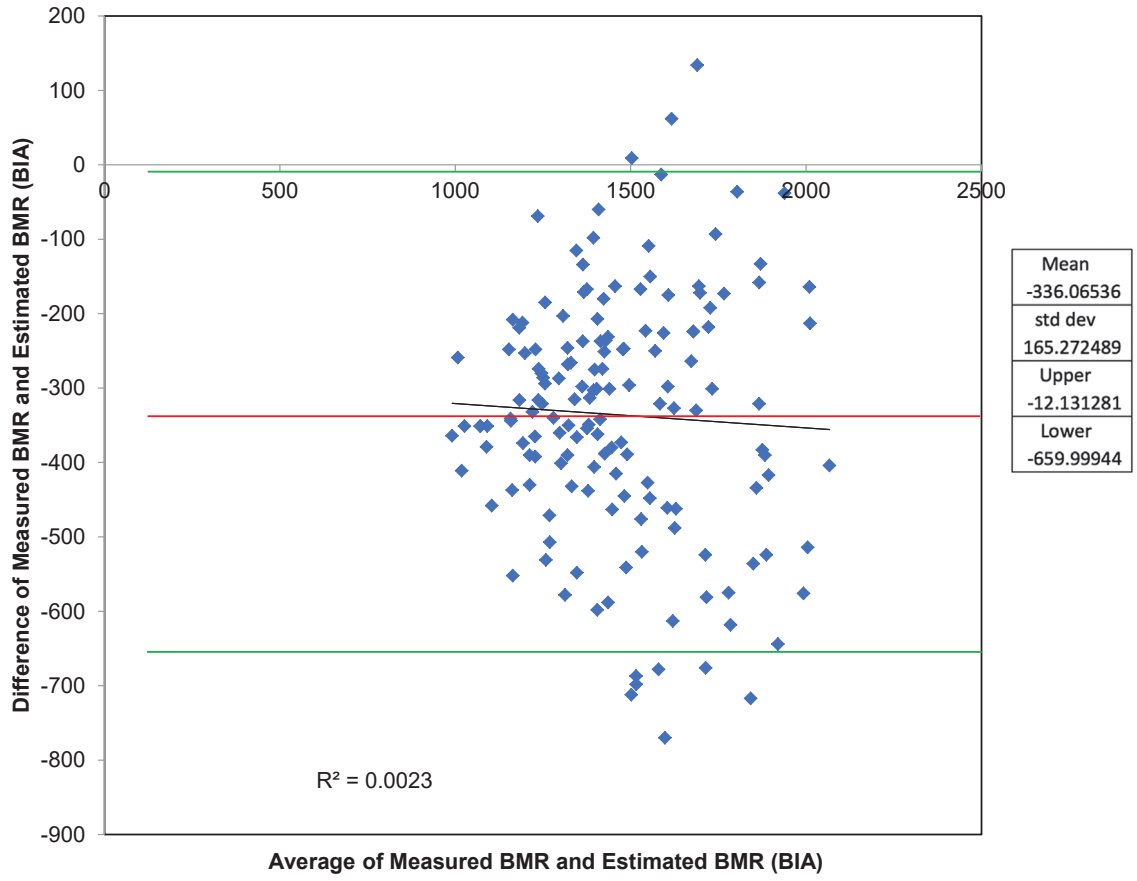


**Figure 2.** Bland-Altman plot displaying the agreement and bias between the BMR predicted with BIA and the measured BMR using IC. Reference lines represent the mean (red line) of the prediction equation (bias) and the limits of agreement (±2 SD) (green lines). Regression line, coefficient of determination ($R^2$) and *p*-value for the slope are provided.

Table 4 shows the association of several variables with measured BMR. Measured BMR showed positive correlation with male sex, height, weight, BMI, neck circumference, wrist circumference, waist circumference, hip circumference, waist-to-hip ratio, and fat-free mass (r=0.538, r=0.578, r=0.762, r=0.482, r=0.507, r=0.048, r=0.498, r= 0.474, and r=0.219, r=0.571 respectively), while age showed negative correlation (r=-0.156). Weight was strongly correlated with measured BMR while other variables are only weakly to moderately correlated with measured BMR.

**Table 4.** Correlation of variables with measured BMR (using IC)

| | Correlation Coefficient (r) |
|---|---|
| Age | -0.107 |
| Male sex | 0.538 |
| Height | 0.578 |
| Weight | 0.762 |
| BMI | 0.482 |
| Neck circumference | 0.507 |
| Wrist circumference | 0.048 |
| Waist circumference | 0.498 |
| Hip circumference | 0.474 |
| Waist-to-hip ratio | 0.219 |
| Fat-free mass | 0.571 |

Multiple standard stepwise regression analysis was performed to derive the prediction equation to estimate BMR among adult obese Filipino patients with pre-diabetes or type 2 diabetes mellitus based on IC as the dependent variable, and age, sex, height, weight, BMI, neck circumference, waist circumference, hip circumference and waist-to-hip ratio and fat-free mass as independent variables. The summary of the derivation of the new equation is shown in Table 5. The table shows that only height and weight were significant predictors of BMR. Regression equation with weight as the only independent variable contributed to 58% (adjusted $R^2$=0.577) of BMR variability. The inclusion of height to the model increased the predictive power to 62% ($R^2$=0.617). Hence, the regression equation for predicting the BMR was:

BMR (kcal/day) = -780.806 + (11.108 x weight in kg) + (7.164 x height in cm).

## DISCUSSION

Measurement of energy expenditure is an essential element in the estimation of energy requirements in humans. In this study, the measured BMR of 153 adult Filipino obese patients with prediabetes or T2DM using indirect calorimetry was compared with the results from BMR estimated by HB equation and bioelectrical impedance analysis. Previous studies reported that existing predictive equations derived from Caucasian subjects are not suitable for the Asian population because they tend to overestimate the BMR.[9,14,17] Similarly, our result showed that HB equation and BIA overestimate the BMR compared to IC by 329 kcal/day and 336 kcal/day, respectively. The mean BMI of all subjects in the study was 32.06±4.8 kg/m$^2$ with mean total fat percentage of 34.3%. A review by Deurenberg[18] showed that compared to whites, Asian population had a higher fat percentage at similar BMI. This was also the finding in the study of Wouters-Adriaens et al.,[19] in which Asian subjects had an average BMI of 23.4 kg/m$^2$ and a fat percentage of 26.9% while white subjects had similar average BMI of 22.4 and lower fat percentage of 20.1%. They elucidated that the difference in body composition between Asians and whites explained the overestimation of predictive equations in Asian subjects. In a study by Frankenfeld[5] involving adult volunteers across different BMI categories (BMI 22.2 to 61.8 kg/m$^2$), it was reported that the magnitude of error in the HB equation increases with increasing BMI. This result is in agreement with the present study in which BMR values of pre-diabetic or T2DM obese subjects derived from HB equation are overestimated.

In addition, body composition influences energy expenditure, and subsequently may have an effect on the predictive ability of the HB equation. In obese individuals, resting energy expenditure is lower than would be predicted by BMR equations, due to a greater proportion of fat mass versus metabolically active fat free mass. This was reported in the study of Douglas et al.,[20] which assessed the effects of weight history status on the ability of HB formula to predict measured resting energy expenditure. In their study, HB formula significantly overestimated resting energy expenditure among overweight subjects, and was more accurate among normal weight and weight-reduced women, with nearly 300 kcal/day difference in the predicted resting and measured energy expenditure in the overweight group. This was similar to our result which showed that BMR derived using HB equation and BIA overestimate the BMR measured using IC by 329 kcal/day and 336 kcal/day, respectively. They attributed this discrepancy between predicted resting and measured energy expenditure values to body composition. The lower proportion of weight as fat-free mass, which is the largest determinant of resting energy expenditure, in overweight subjects may explain the overestimation of resting energy expenditure by HB formula.

In our study, the HB overestimated the BMR in 86.9% of the subjects. This finding was congruent to that of Miller et al.,[21] which reported that HB equation overestimated the BMR in 86.8% of the young overweight or obese Hispanic women subjects. The disparity was explained by the different population used in the development of the HB equation, which included female participants who were predominantly of normal weight. In addition, the HB sample also differ from the individuals of the abovementioned study because of the dramatic decline in the activity with modern transportation and conveniences. In contrast, among overweight Singaporean Chinese subjects, the HB formula overestimated BMR by an average of 545 KJ (equivalent to 130 kcal) in only 42% of subjects.[17] They rationalized that the HB equation is based on gender, height, weight and age and developed in Caucasian subjects, hence overestimation is expected. It should be noted that in this study, the subjects had lower mean BMI of 26.4±5.4 kg/m$^2$ compared to the subjects in our study. Overestimation of the BMR can hinder successful weight loss intervention programs due to inaccurate computation of an individual's energy requirements.

The Bland-Altman limits of agreement analysis (LOA) showed BMR generated from HB equation and BIA lack agreement with BMR measures using IC. Due to the wide

limits of agreement for both HB equation (LOA=10.21 to -669.77 kcal/day) and BIA (LOA=-12.13 to -659.99) when compared to IC (Figure 1 and 2), clinicians need to be aware of the limitations of this prediction equation and BIA for estimating individual energy requirements.

In the adult obese Filipino subjects with pre-diabetes or T2DM evaluated in this study, the best correlation found with measured BMR was weight (r=0.762). This result is in agreement with the study on adult obese and overweight Chinese with T2DM wherein weight had significant positive correlation with BMR. In the said study, obese patients with T2DM had significantly higher BMRs than overweight patients and controls with normal.[22] In contrast to our finding, the aforementioned study showed that male sex negatively correlated with measured BMR. Previous studies have suggested that males have higher BMR than females independent of sex differences in body composition.[23,24] However, it was reported that once adjusted for both fat-free mass and fat mass, the impact of sex is not significant. Men generally display a higher absolute resting metabolic rate than women because of their larger quantity of fat-free mass.[24] As in earlier studies,[26,27] the present study showed that age was negatively correlated with measured BMR. Reduction in fat-free mass quality[28] and decline in both mass and cellular fraction of organs and tissues[29] may account for this age-related decline in BMR.

The derived equation confirmed that BMR is highly correlated with height and weight while the addition of other variables (age and sex) did not contribute significantly to the prediction model. As shown in Table 5, by adding height as the second predictor, the adjusted R square column increased from 0.577 to 0.617. However, R square hardly increased any further by adding a third variable. The Sig. F Change confirms this: the increase in R square from adding a second predictor is statistically significant, (F(1,150)=16.708, *p*-value=0.000). Subsequent addition of a third predictor did not significantly improve r-square any further. Hence, there is no point in including more than 2 variables in the derived model. The newly developed equation based on IC can explain approximately 62.2% of the variance in estimated BMR of the subjects, which will be confirmed in a separate group of subjects in another study.

## CONCLUSION

Among obese Filipinos with T2DM or prediabetes, HB equation or BIA, albeit easy and convenient to use, tends to overestimate the BMR measured using IC.

**Limitation of the study and recommendation**

The limitation of our study is that the subject recruitment was restricted to those who have access to healthcare facilities and may not be representative of the whole population. Since this study strictly examined data from adult obese Filipinos with pre-diabetes or T2DM, results are not generalizable to other racial/ethnic groups or subjects with different conditions. Further studies involving larger, more heterogeneous cohorts, such as patients with normal BMI, are needed. Likewise, we recommend a cross-validation study on a separate group of adult obese Filipino patients with pre-diabetes or T2DM using the computed prediction equation.

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**Statement of Authorship**

All authors certified fulfillment of ICMJE authorship criteria.

**Author Disclosure**

The authors declared no conflict of interest.

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None.

**Table 5.** Model summary for derivation of new BMR equation

| Model | R | R Square | Adjusted R Square | Std. Error of the Estimate | Change Statistics | | | | | Durbin-Watson |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | R Square Change | F Change | df1 | df2 | Sig. F Change | |
| 1 | .762a | .580 | .577 | 164.370 | .580 | 208.437 | 1 | 151 | .000 | |
| 2 | .789b | .622 | .617 | 156.435 | .042 | 16.708 | 1 | 150 | .000 | |
| 3 | .793c | .629 | .621 | 155.575 | .007 | 2.663 | 1 | 149 | .105 | |
| 4 | .796d | .634 | .624 | 154.910 | .006 | 2.282 | 1 | 148 | .133 | |
| 5 | .799e | .639 | .627 | 154.390 | .005 | 1.999 | 1 | 147 | .160 | |
| 6 | .802f | .644 | .629 | 153.933 | .005 | 1.875 | 1 | 146 | .173 | |
| 7 | .804g | .647 | .630 | 153.831 | .003 | 1.193 | 1 | 145 | .276 | |
| 8 | .805h | .648 | .629 | 153.967 | .002 | .744 | 1 | 144 | .390 | |
| 9 | .806i | .650 | .628 | 154.241 | .001 | .489 | 1 | 143 | .485 | |
| 10 | .806j | .650 | .625 | 154.770 | .000 | .024 | 1 | 142 | .877 | |
| 11 | .806k | .650 | .622 | 155.314 | .000 | .007 | 1 | 141 | .932 | .400 |

a. Predictors: (Constant), Weight
b. Predictors: (Constant), Weight, Height
c. Predictors: (Constant), Weight, Height, WaistToHipRatio
d. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference
e. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference, Age
f. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference, Age, FatFreeMass
g. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference, Age, FatFreeMass, BMI
h. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference, Age, FatFreeMass, BMI, NeckCircumference
i. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference, Age, FatFreeMass, BMI, NeckCircumference, Sex
j. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference, Age, FatFreeMass, BMI, NeckCircumference, Sex, WaistCircumference
k. Predictors: (Constant), Weight, Height, WaistToHipRatio, WristCircumference, Age, FatFreeMass, BMI, NeckCircumference, Sex, WaistCircumference, HipCircumference
l. Dependent Variable: IC

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ORIGINAL ARTICLE

# Single Nucleotide Polymorphism at +276 G>T of the Adiponectin Gene and Plasma Adiponectin Level in Myanmar Type 2 Diabetic Patients

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**Abstract**

Objective. The aim of the study was to investigate the association between single nucleotide polymorphisms (SNP) at rs 1501299 (SNP+276 G>T) of the adiponectin gene and plasma adiponectin levels in type 2 diabetes mellitus (T2DM) patients in Myanmar.

Methodology. One hundred T2DM patients and 104 non-diabetic subjects were included in this cross-sectional analytical study. Genotype frequencies were determined by polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) method. Plasma adiponectin level was measured by enzyme-linked immunosorbent assay (ELISA).

Result. Genotype frequencies (GG, GT, TT) of SNP+276 in diabetic patients were 39%, 48% and 13%, respectively. The GT and TT genotypes were more frequent in T2DM patients (OR 1.98, 95% CI, 1.10-3.55; $p$=0.02 and OR 4.07, 95% CI, 1.34-12.3; $p$=0.01), respectively. The T allele of SNP+276 was significantly associated with T2DM (OR 1.96, 95% CI, 1.27-3.01; $p$=0.002). Mean plasma adiponectin level was significantly lower than in T2DM patients (27.41±16.7 µg/mL) compared to non-diabetic subjects (37.19±26.77 µg/mL) ($p$=0.002).

Conclusion. SNP+276 at rs 1501299 of the adiponectin gene was associated with type 2 diabetes and low plasma adiponectin levels in this Myanmar population.

*Key words: adiponectin gene, SNP, type 2 diabetes*

## INTRODUCTION

Adiponectin is one of the most abundant proteins derived from adipose tissue. It is encoded by the adiponectin gene, located on chromosome 3q27. It has important roles in energy homeostasis, glucose and lipid metabolism, and anti-inflammatory responses in the vascular system. It is likely to modulate insulin sensitivity and to play a role in both human and animal models of insulin resistance. Insulin resistance is a fundamental element in the etiology of type 2 diabetes mellitus and is quite often associated with obesity.

The two main actions of adiponectin pertain to its insulin-sensitizing effect and anti-atherosclerotic activity. Adiponectin acts through 2 types of receptors, AdipoR-1 and AdipoR-2. AdipoR-1 is most abundantly expressed in skeletal muscle, while AdipoR-2 is found more frequently in the liver. Adiponectin decreases tissue triglyceride (TG) content and up-regulates insulin signalling via activation of peroxisome proliferator-activated receptor-$\alpha$ (PPAR-$\alpha$) action.

Reduction of TG content in muscle is mediated by adiponectin by activation of adenosine monophosphate-activated protein kinase (AMPK). In skeletal muscle, adiponectin binds AdipoR-1 and stimulates phosphorylation of acetyl-Coenzyme A carboxylase (ACC). This leads to inhibition of ACC activity and a consequent reduction in malonyl-Coenzyme A levels, effectively depressing carnithine palmitoyl transferase-1 (CPT-1) activity and increasing fatty acid oxidation. These changes lead to decreased tissue TG content which contributes to improve insulin signal transduction.

In the liver, adiponectin binds AdipoR-2 and inhibits gluconeogenesis by AMPK-dependent phosphorylation. It decreases the expression of key enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, effectively decreasing hepatic glucose production.

Diabetes mellitus is a multi-factorial, polygenic metabolic disorder which can affect nearly every organ system in the body. The prevalence of T2DM is increasing in South East

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Asia, from 39.3 million in 2003 to a projected 81.6 million in 2025. The risk of developing T2DM is determined by both genetic and environmental factors. Insulin resistance is considered to be the core factor in its pathogenesis. Genetic and epidemiological studies strongly suggest that insulin resistance is, at least in part, genetically determined.

Fifty-two candidate genes in various biochemical, regulatory and signal transduction pathways are thought to be involved in the pathogenesis of T2DM. Adiponectin is one such gene.[1] Genome-wide scans in humans have mapped a susceptibility locus for T2DM and the metabolic syndrome to chromosome 3q27, where the gene encoding adiponectin is also located. It spans 17 kilo bases and consists of 3 exons and 2 introns.[2]

Genetic variations in the adiponectin gene can affect plasma adiponectin concentration. It is estimated that a 30 to 70% variation in normal circulating adiponectin level can be attributed to genetic factors. Serum concentrations of adiponectin are heritable, making it a strong candidate gene for T2DM, obesity and coronary artery disease (CAD).[3] A total of 42 single nucleotide polymorphisms in the adiponectin gene and its regulatory region with a minor allele frequency of more than 1.5% have been identified.

Many studies investigating the association of genetic variations in the adiponectin gene with plasma adiponectin level and T2DM have recently been published.[4] The association between adiponectin gene polymorphisms and plasma adiponectin level in T2DM has been demonstrated in various studies on Asian populations and Western populations. The G>T polymorphism of SNP+276 in intron 2 of the adiponectin gene has been found to be related to type 2 diabetes in Japanese subjects, Iranian obese individuals and in non-diabetic Greek women.[3,5,6] Adiponectin gene polymorphisms affect the development of diabetes, obesity and insulin resistance, and are influenced by differences in genetic background and environmental factors in various ethnic populations.[7]

There are 3 forms of genotype distribution (GG, GT, TT) at rs 1501299 (+276 G>T) of the adiponectin gene, when the base guanine (G) changes to thymine (T). This SNP occurs when the normal wild type G allele is changed into a T allele (GT or TT). This was found to be associated with an increased risk for T2DM. Moreover, because hypoadiponectinemia has been strongly linked to obesity, insulin resistance and T2DM, it may be used to predict the overall risk of developing insulin resistance and overt T2DM. Low serum adiponectin was associated with impaired glucose tolerance and T2DM in a Finnish population.[8] Plasma adiponectin was determined to be an independent predictor of T2DM in Asian Indian and Jordanian study populations.[9,10]

The association between plasma adiponectin level and SNP+276 G>T of the adiponectin gene in T2DM has subsequently been found in various ethnic groups such from Japan, China, Korea, India, Malaysia, Egypt, and also those of Caucasian, African American origin. Although not consistent, many studies have also found the association between this genetic variation and plasma adiponectin level in different study groups. This study will investigate the genetic variation of the adiponectin gene and determine the association between SNP+276 G>T and its gene product, adiponectin, in a population from Myanmar, in relation to T2DM.

## METHODOLOGY

### Study population

This cross-sectional, analytical study recruited patients with T2DM from the out-patient department and diabetes clinic of North Okkalapa General Hospital. Non-diabetic subjects were selected by simple random sampling from Quarter B, North Okkalapa Township, Yangon, Myanmar. The randomly selected subjects with fasting plasma glucose (FPG) less than 6.1 mmol/L (110 mg/dL) were considered as non-diabetic, based on the World Health Organization 2006 criteria.[11]

### Study procedure

A sample of 5 mL venous blood was taken from all subjects for the determination of plasma adiponectin levels and genotyping. Separation of plasma from the blood sample was done by centrifugation at 1500 rpm for 20 minutes. Deoxyribonucleic acid (DNA) extraction was done on the day of sample collection at the Common Research Laboratory, University of Medicine 2, Yangon. The extracted DNA were stored as dry form at -20°C. The remaining plasma samples were stored at -20°C in deep freeze for determination of adiponectin and genotyping. These were carried out within 6 months of sample collection.

Determination of plasma glucose level was done by enzymatic colorimetric test (Human GmBH-Germany). Determination of plasma adiponectin level was done by ELISA method (DRG International, Inc., USA).

DNA extraction was done by salting out method. Purity of DNA was checked by agarose gel electrophoresis. Specific DNA fragments consisting of SNP+276 was amplified from genomic DNA by specific primer set and the products were identified in 2% agarose gel and seen at 241 bp. These PCR products were digested with restriction enzyme (BsmI) (New England Biolabs®, USA) and the products were separated by 2% agarose gel to analyze for RFLP. Three different genotypes were noted. The following primers were used for SNP+276 genotyping by PCR-RFLP:

| Primer | Sequence 5'–3' |
|---|---|
| rs1501299 | Forward primers<br>CCT GGT GAG AAG GGT GAG AA |
| rs1501299 | Reverse primers<br>AGA TGC AGC AAA GCC AAA GT |

### Statistical analysis

Plasma adiponectin levels were expressed as means and standard deviations. Genotype and allele frequencies were expressed as percentages. Mean plasma adiponectin levels were compared across genotypes using ANOVA and Tukey HSD test, and between T2DM and non-diabetic subjects by Student's t-test. Hardy-Weinberg equilibrium and the association between disease status and the genetic variants were tested by Pearson's Chi-square test. Odds ratios, 95% confidence intervals and all statistical tests were carried out using SPSS® software v. 16.0.

### Ethical considerations

The research was done according to the international ethical guidelines of the Council for International Organization of Medical Science. Ethical approval was obtained from the Ethical Review Committee of University of Medicine 2, Yangon.

## RESULTS

A total of 204 participants consisting of 100 patients with T2DM and 104 non-diabetic subjects fulfilled the inclusion criteria and were accounted for analysis in this study. The age range in this population was 35 to 65 years old. Although majority of the participants were female, there was no significant difference in sex distribution between 2 groups of participants ($p$=0.41).

Mean body mass index was significantly higher in patients with T2DM (24.81±5.23) compared to non-diabetic subjects (23.53±3.88) ($p$<0.05).

Figure 1A shows the PCR products of adiponectin gene. Specific DNA fragments consisting SNP+276 were amplified from genomic DNA by a specific primer set. The products were then identified in 2% agarose gel and seen at 241 bp. These PCR products were digested with *BsmI*. The digested products were separated by 2% agarose gel to analyze for RFLP.

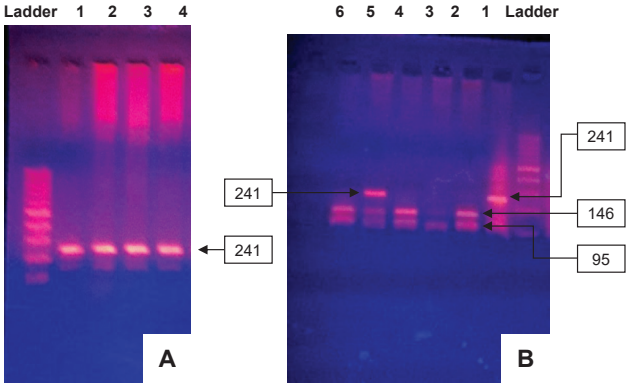


**Figure 1.** Restriction enzyme digests on 2% agarose gel. **A.** PCR products of SNP+276. **B.** genotyping of SNP+276.

Three different genotypes were noted (Figure 1B). Lane 2 showed homozygous wild (GG) genotype, seen as 2 bands at 95 bp and 146 bp. At Lane 5, heterozygous (GT) genotype was seen as 3 bands at 95 bp, 146 bp and 241 bp. Lane 1 showed homozygous mutant (TT) genotype which was seen as a single band at 241 bp.

A one-way ANOVA between subjects was conducted to compare the plasma adiponectin levels with different genotypes (GG, GT and TT) (Table 1). Post hoc comparisons using the Tukey HSD test indicated that there was a statistically significant difference between the mean adiponectin level of patients with GG genotype (31.64±18.95) compared to TT (19.77 ± 11.85) (Table 2).

**Table 1.** Comparison of plasma adiponectin levels with different genotypes of SNP+276 in T2DM patients*

| Genotype | GG | GT | TT |
|---|---|---|---|
| GG | - | 0.13 | 0.01 |
| GT | 0.13 | - | 0.13 |
| TT | 0.01 | - | - |

*$p$ values were calculated using the Tukey HSD test

**Table 2.** Mean plasma adiponectin levels of different genotypes of SNP+276 in T2DM patients

| Genotype | Mean plasma adiponectin, µg/mL | $p$ value |
|---|---|---|
| GG | 31.64±18.95 | - |
| GT | 25.92±15.02 | - |
| TT | 19.77±11.85 | 0.05 |

## DISCUSSION

Type 2 diabetes mellitus is one of the most common metabolic diseases and poses a substantial burden on health care systems globally. There is compelling data that genetic susceptibility to T2DM is polygenic. Genome-wide association studies have identified almost 50 loci associated with T2DM risk. Adiponectin gene polymorphism may play a causal role in the pathogenesis of insulin resistance and T2DM.[12]

Among the adiponectin gene SNPs, the intronic SNP+276 G>T at rs 1501299 is considered the important known genetic risk factor for the development of insulin resistance and T2DM. Since adiponectin regulates both glucose and lipid metabolism, derangement of these processes due to reduced adiponectin levels will lead to insulin resistance and subsequent T2DM. Many studies have demonstrated the association of reduced plasma adiponectin levels with T2DM. The aim of the present study was to provide supportive evidence for the involvement of the adiponectin gene and its effect on plasma adiponectin levels in T2DM patients from Myanmar.

In this study, SNP+276 G>T of heterozygous (GT) and homozygous (TT) genotypes were significantly more frequent in T2DM patients than in non-diabetic subjects. These are consistent with findings of greater frequency of GT and TT in obese T2DM patients from Saudi Arabia, South India and Finland.[13-15] The genotype frequencies in this study (GG 39.4%, GT 48.1% and TT 12.5%) are closest to the findings in Finland (GG 45%, GT 43% and TT 12%), and are comparable with distribution frequencies worldwide.[15] The genotype distribution of SNP +276 conformed to the Hardy-Weinberg equilibrium principle in both the T2DM ($\chi^2$=0.41, df =1, $p$=0.522) and non-diabetic groups ($\chi^2$=0.67, df=1, $p$=0.413). Since the comparison was made in patients with T2DM and non-diabetic subjects, the genotypes GT and TT do not give a greater risk for DM but is associated

**Table 3.** Analysis of association of SNP+276 GT genotype and T2DM

| Genotype | T2DM (n=100) | Non-diabetic (n=104) | OR | 95% CI | $p$ value |
|---|---|---|---|---|---|
| GG | 39 (39%) | 61(59%) | 1.0 | - | - |
| GT | 48 (48%) | 38 (37%) | 1.98 | 1.10-3.55 | 0.02 |
| TT | 13 (13%) | 5 (5%) | 4.07 | 1.34-12.30 | 0.01 |

$X^2$ = 9.48, $p$ = 0.008

**Table 4.** Association of allele frequencies of SNP+276 and T2DM

| Allele | T2DM (n=100) | Non-diabetic (n=104) | Odds ratio | 95% CI | *p* value |
|---|---|---|---|---|---|
| G | 126 (63%) | 160 (77%) | 1.0 | - | - |
| T | 74 (37%) | 48 (23%) | 1.96 | 1.27-3.01 | 0.002 |

$X^2 = 9.43$, $p = 0.002$

with the presence of T2DM (OR 1.98, 95% CI, 1.10-3.55, *p*=0.02 and OR 4.07, 95% CI, 1.34-12.3, *p*=0.01, respectively) (Table 3). These results were similar to the findings in a study of Taiwanese diabetic patients which demonstrated that T2DM was more common in subjects with GT and TT genotypes.[7]

Analysis of allele frequencies of SNP+276 showed that the risk allele T was found more frequently in T2DM patients compared to non-diabetic subjects (OR 1.96, 95% CI, 1.27-3.01, *p*=0.002) (Table 4). The higher risk of developing T2DM in T allele carriers was seen in studies on Taiwanese and Saudi Arabian populations.[13,16] These support the possible susceptibility role of the T allele of SNP+276 for T2DM. This polymorphism might be a predisposing factor to T2DM in the Myanmar population.

In the current study, the mean plasma adiponectin level of T2DM patients (27.41±16.7 μg/mL) was significantly lower compared to the non-diabetic subjects (37.19±26.77 μg/mL). Mean plasma adiponectin levels of GT and TT genotypes were also lower than that of GG. There was a statistically significant difference in the mean plasma adiponectin levels of GG and TT genotypes. These were consistent with studies on Japanese and Asian Indian populations, and in a meta-analysis including 13 prospective studies of Caucasian, Asian Indian, African and native American ethnic groups.[9,17,18] SNP+276 G>T appears to influence plasma adiponectin levels and subsequent development of T2DM. While the relatively small study population may not represent the whole Myanmar population, the results remain relevant in the analysis of various ethnic groups and adiponectin gene polymorphisms.

There is no general agreement regarding the mechanism of SNP+276 and observed decreased plasma adiponectin levels. Because SNP+276 is situated in intron 2 of the adiponectin gene away from the consensus splice site, it does not have a known function. It may be a marker of some other variants that affecting adiponectin gene expression. It has been demonstrated that the SNP+276 G>T is in almost complete linkage disequilibrium with several polymorphisms placed in the 3′ untranslated regions (3′UTR).[19] 3′UTR is a region with a pivotal role in the control of gene expression by binding proteins that regulate mRNA processing, translation or degradation.

Insulin sensitizers, exemplified by the group of PPAR-ϒ agonist thiazolidinediones, have been shown to increase plasma adiponectin levels in mice and humans. Novel therapeutic strategies for T2DM may then involve up-regulation of adiponectin receptors and stimulation of adiponectin receptors using small molecule agonists.

**Study Limitations**

This study was able to demonstrate the interesting association between the SNP+276 and T2DM and its effect on plasma adiponectin levels. One of the limitations was the use of FPG only to exclude diabetes mellitus, instead of the standard 75 g oral glucose tolerance test and glycosylated haemoglobin ($HbA_{1c}$). This poses the possibility of inclusion of diabetic patients who may only have elevated 2-hour post-load glucose or high $HbA_{1c}$ in the non-diabetic group. Moreover, the correlation between plasma adiponectin level and insulin resistance was not included in this study. Other various confounding factors and their covariate effects were not considered during the analysis of the association between SNP and presence of T2DM.

## CONCLUSIONS

The findings demonstrated that the odds of having type 2 diabetes was increased four-fold in the presence of the T allele of SNP +27. Genotypes GG and GT were associated with lower plasma adiponectin levels. The current study provided additional evidence for the potential involvement of the adiponectin gene as a risk factor for T2DM in the Myanmar population. It may be recommended that the non-diabetic subjects who had risk alleles of SNP+276 and their family members undergo periodic screening for diabetes.

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**Statement of Authorship**

All authors certified fulfillment of ICMJE authorship criteria.

**Author Disclosure**

The authors declared no conflict of interest.

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None.

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ORIGINAL ARTICLE

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# Prevalence of Sexual Dysfunction and its Associated Factors among Women with Diabetes Mellitus Type 2 at Makati Medical Center Outpatient Department

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**Abstract**

Objective. This study aims to determine the prevalence of sexual dysfunction among premenopausal Filipino women with type 2 diabetes mellitus at the outpatient department of a tertiary hospital through the use of the Female Sexual Function Index (FSFI) and identify factors that could be associated with sexual dysfunction.

Methodology. Seventy-five women with type 2 diabetes mellitus, aged 38 to 49 years old, received the FSFI questionnaire. Their age, history of hypertension, smoking habit, alcohol intake, body mass index, waist circumference, fasting blood sugar, $HbA_{1c}$, creatinine, lipid profile, albuminuria or proteinuria, presence of microvascular complications such as diabetic retinopathy, neuropathy and nephropathy and their association with sexual dysfunction was determined.

Results. Seventy-two percent of the participants have sexual dysfunction scoring lowest in the lubrication, orgasm and pain domains. Age ($p$=0.016), a high body mass index ($p$=0.001), a fasting blood sugar above 100 mg/dl ($p$=0.006) and the presence of microvascular complications of diabetes mellitus namely, retinopathy ($p$=0.046) nephropathy ($p$=0.004) and neuropathy ($p$=0.001) were associated with sexual dysfunction.

Conclusion. The prevalence of sexual dysfunction is high among premenopausal Filipino women with type 2 diabetes mellitus, and is associated with age, a high body mass index, an uncontrolled fasting blood sugar and the presence of microvascular complications of diabetes mellitus.

*Key words: sexual dysfunction, type 2 diabetes mellitus, premenopause, diabetic neuropathies, diabetic retinopathy, diabetic nephropathies*

## INTRODUCTION

The American Psychiatric Association defines sexual dysfunction as a heterogeneous group of disorders that are typically characterized by a clinically significant disturbance in a person's ability to respond sexually or to experience sexual pleasure.[1] Sexual problems are common complications of individuals with diabetes in both men and women. Unfortunately, sexual health is an often neglected aspect in the management of diabetes mellitus.[2-4]

Most studies on sexual dysfunction involves men and erectile dysfunction which affects 60 to 86.1% of men with diabetes mellitus.[5] In contrast, sexual dysfunction among women mostly includes problems in sexual desire, sexual satisfaction, orgasmic, lubrication and arousal disorder.[2-4] Documented rates of sexual dysfunction among women with type 2 diabetes ranges from 25% to 88%.[2,4,6-9]

Though studies on sexual dysfunction are gradually increasing, there are currently no data that shows the prevalence of sexual dysfunction and the risk factors associated with it among Filipino women with diabetes mellitus.

## OBJECTIVES

The objectives of this study are to determine the prevalence and characterize the sexual dysfunction among premenopausal Filipino women with type 2 diabetes mellitus seen at the outpatient department of Makati Medical Center. This study also aims to determine whether age, history of hypertension, smoking habit, history of alcohol intake, body mass index, waist circumference, certain metabolic factors such as FBS, $HbA_{1c}$, creatinine, lipid profile, albuminuria or proteinuria and whether the presence of microvascular complications of diabetes mellitus such as diabetic neuropathy, retinopathy and nephropathy are associated with sexual dysfunction among premenopausal Filipino women with type 2 diabetes mellitus.

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## METHODOLOGY

### Study design

This cross-sectional analytic study was conducted at the outpatient department of Makati Medical Center from October 2017 to January 2018.

Subjects included female Filipinos with type 2 diabetes mellitus, 30 to 50 years old, premenopausal, with a current heterosexual partner and has had at least 1 sexual contact in the past 4 weeks. They must have been able to read, comprehend and understand either Filipino or English and must have consented to join the study.

The diagnosis of diabetes mellitus is based on the Unite for Diabetes Philippines Clinical Practice Guidelines: Fasting blood sugar of ≥126 mg/dl; plasma glucose of ≥200 mg/dl 2 hours after an oral glucose tolerance test; random blood sugar >200 mg/dl with classic symptoms of hyperglycemia or hyperglycemic crisis.[10]

Premenopause, according to the World Health Organization (WHO) and International Menopause Society, is defined as the period that encompasses the entire female reproductive period up to the final menstrual period or prior to menopause.[11]

Subjects with the following were excluded: Type 1 diabetes mellitus, prediabetes (impaired fasting glucose, impaired glucose tolerance), gestational diabetes, menopause, presence of sexual disorder before getting diabetes mellitus, existence of sexual disorder in patient's spouse, known history of psychiatric illness, a history of mastectomy, total hysterectomy or current pregnancy.

### Sampling method

This study utilized a purposive sampling method to achieve the minimum sample size. Purposive sampling is a non probability method wherein patients who consult at the outpatient department and fit the inclusion criteria were selected and enrolled once they have signed an informed consent.

### Sample size and power calculation

With 53.6% prevalence of female sexual dysfunction,[2] 5% margin of error, 90% confidence interval, and 10% prediction of non-response or drop out, the computed sample size was 75 subjects.

### Data gathering

Data gathering commenced once the participant is able to meet the inclusion criteria and has signed an informed consent. The participant's age, smoking habit, history of alcohol consumption were determined. The participant's height, weight, waist circumference, blood pressure were measured using a standard measuring device. The Body Mass Index (BMI) was determined by dividing weight (kg) by the height in meter squared ($m^2$). Based on the WHO criteria for BMI cut-off, participants were classified as either underweight (BMI<18.5), normal (BMI 18.5-24.9) overweight (25-29.9), or obese (BMI>30).

The participants' most recent fasting blood sugar (FBS), $HbA_{1c}$, lipid profile, creatinine, and urinalysis were retrieved from their records. Their estimated glomerular filtration rate (eGFR) was determined using the CKD-EPI formula with the use of Calculate by QxMD software.

Previous studies have shown that the presence of metabolic syndrome is associated with sexual dysfunction as compared with matched control without metabolic syndrome.[9,12] Based on the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III 2005 revision) the presence of any three of the following criteria are considered for the diagnosis of metabolic syndrome for females; an FBS of greater than 100 mg/dl, triglyceride level of 150 mg/dl and above, high density lipoprotein (HDL) of less than 50 mg/dl, waist circumference greater than 35 inches, hypertension (systolic BP of above 130 mmHg or diastolic BP above 85 mmHg) or taking medications to control diabetes mellitus, dyslipidemia or hypertension.[13] Based on the 2018 American Diabetes Association Standards of Medical Care in diabetes, an $HbA_{1c}$ of above 7% is considered uncontrolled.[14]

Diabetic retinopathy was determined by reviewing patient's chart for previous results of dilated fundoscopy. A dilated fundoscopy is the visualization of the patient's retina done by an experienced ophthalmologist or optometrist which is standard of care and is recommended to be done at the time of diagnosis of type 2 diabetes mellitus.[14]

Diabetic neuropathy was assessed using the 10-g Semmes-Weinstein monofilament test which was performed by the primary investigator. Participants were examined lying down, with their eyes closed. Using a 10-g monofilament, four sites (1st, 3rd, and 5th metatarsal heads and plantar surface of distal hallux) were tested on each foot. Diabetic neuropathy is defined as the loss of the ability to detect the pressure at one or more site.[15]

Diabetic nephropathy was determined through the presence of albuminuria or proteinuria as determined by reviewing the participant's record of urinalysis for proteinuria, a positive micral test, albumin to creatinine ratio of 30 and above, or a computed eGFR of less than 30 ml/min/1.73$m^2$ based on the CKD-Epi formula.

### Determination of sexual dysfunction

Sexual dysfunction was measured using the Female Sexual Function Index (FSFI) self-administered questionnaire (Appendix A). The FSFI is a brief, multidimensional self-report questionnaire measure of sexual functioning in women. It was developed for the specific purpose of assessing six domains of sexual functioning among females namely desire, arousal, lubrication, orgasm, satisfaction and pain during sexual intercourse.[2] The minimum and maximum scores are 2 and 36 respectively (Appendix B). Women with a score under 26.55 are classified as presenting with sexual dysfunction.[2-4,16] A Filipino version of the Female Sexual Function Index was translated and validated by Rillon-Tabil et al.[17] Depending on the participant's preference, either the English version or the Filipino version of the FSFI was used for this study (Figure 1). Participants were

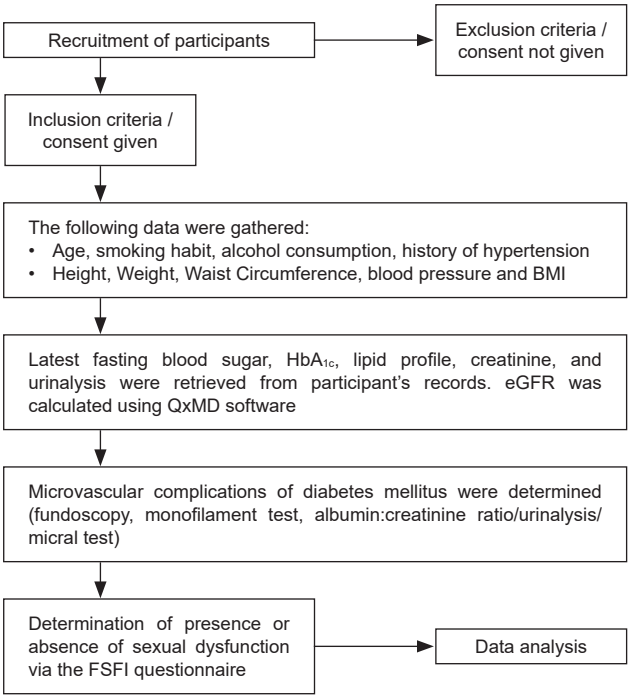


**Figure 1.** Flow chart.

oriented that the questionnaire may contain delicate questions regarding sex. A pre-labeled FSFI questionnaire which corresponds to the participant's identifier was handed to them and they were allowed to answer the questionnaire on their own and at their own pace.

### Data processing and analysis

Descriptive statistics were used to summarize the demographics and clinical characteristics of the patients. Frequency and proportion were used for categorical variables and mean and standard deviation for interval/ ratio variables. Unpaired sample T-test was used to determine the difference of means of those with sexual dysfunction against those without sexual dysfunction. Chi-square/ Fischer's Exact Test, whichever is applicable, was used for categorical variable. Simple logistic regression was performed with the sexual dysfunction as the dependent variable and other variables as the independent variables to compute for the unadjusted odds ratio. Multiple logistic regression was also performed using all the independent variables that were used in simple logistic regression to obtain the adjusted odds ratio. Stepwise variable selection method was also used to determine the significant factors associated with sexual dysfunction. *P*-values that were less than 0.05 level of significance were considered significant. All valid data were included in the analysis performed using STATA 15.0.

### Ethical considerations

The protocol was approved by the Institutional Review Board of the Makati Medical Center. Participants were enrolled in the study after obtaining a written informed consent. Data gathered from this study are entered in conformance with the principles of confidentiality. Participants are anonymized and assigned to consecutive case numbers. Age and control number were used as participant identifiers in case report forms to serve as reference to source documents. Participants were oriented that the questionnaire used in this study may contain delicate questions regarding sex. Participants were oriented that they can withdraw and their data can be excluded from the study anytime.

## RESULTS

All of the 75 participants recruited for this study were able to complete the questionnaire and included in the final analysis. Two participants (2.7%) opted to use the Filipino version of the FSFI. Participants were aged 38 to 49 years old with a mean age of 45. Sixty percent of the participants are in the 45 to 50-year-old age group with a mean age of 47, while those that were below 45 years old had a mean age of 42. Seventy-six percent had a high BMI and 45% had a waist circumference above 35 inches. Eighty-eight percent had an elevated FBS and 60% had an uncontrolled $HbA_{1c}$. Thirty-nine percent had an elevated triglyceride, 75% had a low HDL and 56% had an elevated low density lipoprotein (LDL). Forty-four percent were hypertensive, 20% were smokers and 24% were alcoholic beverage drinkers.

Seventy-two percent of the participants were found to have sexual dysfunction. Using Chi-square/ Fischer's Exact Test, the variables that were associated with sexual dysfunction were age ($p$=0.016), a high body mass index ($p$=0.001) and FBS of more than 100 mg/dl ($p$=0.006) (Table 1).

**Table 1.** Association of sexual dysfunction with clinical characteristics of the participants

| Variable | Sexual dysfunction present (Std Dev) n= 54 | Sexual dysfunction absent (Std Dev) n= 21 | p-value |
|---|---|---|---|
| Age less than 45-year-old | 17 (31.48) | 13 (61.9) | 0.016 |
| Age 45 to 50-year-old | 37 (68.52) | 8 (38.1) | |
| BMI (normal) | 7 (12.96) | 11 (52.38) | 0.001 |
| BMI (overweight) | 23 (42.59) | 6 (28.57) | |
| BMI (obese) | 24 (44.44) | 4 (19.05) | |
| Waist circumference above 35 inches | 28 (51.85) | 6 (28.57) | 0.069 |
| FBS above 100mg/dl | 51 (94.44) | 15 (71.43) | 0.006 |
| $HbA_{1c}$ above 7% | 34 (62.96) | 11 (52.38) | 0.119 |
| Triglyceride 150 mg/dl and above | 24 (44.44) | 5 (23.81) | 0.099 |
| HDL less than 50 mg/dl | 43 (79.63) | 13 (61.9) | 0.113 |
| LDL 100 mg/dl and above | 29 (53.7) | 12 (57.14) | 0.788 |
| With Hypertension | 27 (50.0) | 6 (28.57) | 0.093 |
| Smoker | 13 (24.07) | 2 (9.52) | 0.157 |
| Alcoholic beverage drinker | 15 (27.78) | 3 (14.29) | 0.219 |

BMI - Body Mass Index, FBS - Fasting Blood Sugar, HDL - High Density Lipoprotein, LDL - Low Density Lipoprotein

**Table 2.** Comparison of FSFI score of participants with and without sexual dysfunction

| Variable (Min to Max Score) | Sexual dysfunction present Mean score (Std Dev) | Sexual dysfunction absent Mean score (Std Dev) | p-value |
|---|---|---|---|
| Desire (1.2 – 6.0) | 2.89 (0.86) | 4.02 (0.78) | < 0.00 |
| Arousal (0 – 6.0) | 2.29 (1.62) | 4.36 (1.25) | < 0.00 |
| Lubrication (0 – 6.0) | 2.16 (1.80) | 4.61 (1.34) | < 0.00 |
| Orgasm (0 – 6.0) | 2.067 (2.07) | 4.99 (1.30) | < 0.00 |
| Satisfaction (0.8 – 6.0) | 3.01 (2.12) | 5.43 (1.17) | < 0.00 |
| Pain (0 – 6.0) | 2.037 (1.92) | 4.61 (1.32) | < 0.00 |
| Total | 14.46 (8.54) | 28.02 (5.7) | < 0.00 |

**Table 3.** Association of sexual dysfunction with participant demographics and metabolic factors using simple logistic regression and multiple logistic regression

| Variables | Unadjusted Odds Ratio (95% C.I.) | p-value | Adjusted Odds Ratio (95% C.I.) | p-value |
|---|---|---|---|---|
| Age less than 45-year-old | Reference | Reference | Reference | Reference |
| Age 45 to 50-year-old | 3.53 (1.23 – 10.12) | 0.019 | 3.33 (0.73 – 15.12) | 0.12 |
| Hypertension | 2.5 (0.84 – 7.41) | 0.10 | 1.66 (0.38 – 7.25) | 0.50 |
| Smoker | 3.01 (0.62 – 14.70) | 0.17 | 0.33 (0.005 – 18.24) | 0.59 |
| Alcoholic beverage drinker | 2.31 (0.59 – 8.99) | 0.23 | 0.37 (0.01 – 12.12) | 0.58 |
| BMI (normal) | Reference | Reference | Reference | Reference |
| BMI (overweight) | 6.02 (1.63 – 22.23) | 0.007 | 6.73 (1.07 – 42.27) | 0.04 |
| BMI (obese) | 9.43 (0.002 – 39.03) | 0.002 | 9.1 (0.54 – 152.69) | 0.12 |
| Waist Circumference (35 inches and above) | 2.62 (0.91 – 7.98) | 0.074 | 1.83 (0.17 – 20.16) | 0.62 |
| FBS (above 100 mg/dl) | 6.8 (1.51 – 30.49) | 0.012 | 2.04 (0.28 – 14.68) | 0.48 |
| $HbA_{1c}$ (above 7%) | 1.73 (0.82 – 3.63) | 0.146 | 39.69 (0.15 – 103.38) | 0.19 |
| Triglyceride (150 mg/dl and above) | 2.56 (0.82 – 7.99) | 0.106 | 8.63 (0.53 – 140.13) | 0.13 |
| HDL (less than 50 mg/dl) | 2.405 (0.80 – 7.24) | 0.118 | 12.59 (0.97 – 163.88) | 0.05 |
| LDL (100 mg/dl and above) | 0.87 (0.31 – 2.40) | 0.788 | 0.54 (0.093 – 3.17) | 0.49 |
| Albuminuria/Proteinuria | 12.73 (1.38 – 102.03) | 0.017 | 19.25 (0.84 – 441.31) | 0.06 |

BMI- Body Mass Index, FBS- Fasting Blood Sugar, HDL- High Density Lipoprotein, LDL- Low Density Lipoprotein

Among those who were identified to have sexual dysfunction, the three domains that scored the lowest were lubrication, orgasm and pain (Table 2).

Using simple logistic regression to determine the individual effect of each variable and obtain the unadjusted odds ratio (OR), it was age (OR 3.53, 95% CI 1.23 – 10.12, *p*=0.019), an overweight BMI (OR 6.02, 95% CI 1.63 – 22.23, *p*=0.007), an obese BMI (OR 9.43, 95% CI 0.002 – 39.03, *p*=0.002), an elevated FBS (OR 6.8, 95% CI 1.51 – 30.49, *p*=0.012) and proteinuria (OR 12.73, 95% CI 1.51 – 30.49, *p*=0.017) that showed a possible association with sexual dysfunction (Table 3).

Using multiple logistic regression, which accounts for the effect due to all the additional variables and determines the adjusted OR, it was having an overweight BMI (OR 6.73, 95% CI 1.07 – 42.27, *p*=0.04) that showed a possible association with sexual dysfunction (Table 3).

Finally, using stepwise variable selection method to determine the significant factors associated with sexual dysfunction, it was a high BMI (OR 3.07, 95% CI 1.40 – 6.71, *p*=0.005), and albuminuria or proteinuria (OR11.65, 95% CI 1.38 – 98.13, *p*=0.024) that showed a possible association with sexual dysfunction (Table 4).

**Table 4.** Association of sexual dysfunction with BMI and albuminuria/proteinuria using stepwise variable selection

| Variables | Adjusted Odds Ratio (95% C.I.) | p-value |
|---|---|---|
| Body mass index | 3.07 (1.40 – 6.71) | 0.005 |
| Albuminuria/Proteinuria | 11.65 (1.38 – 98.13) | 0.024 |

Using Chi-square / Fischer's Exact Test, the presence of microvascular complications of type 2 diabetes mellitus such as retinopathy (*p*=0.046) nephropathy (*p*=0.004) and neuropathy (*p*=0.001) was associated with sexual dysfunction (Table 5).

## DISCUSSION

Sexual dysfunction is a common problem worldwide.[18] In the Philippines where the prevailing attitude toward sex is mostly conservative, sexual dysfunction is not routinely discussed between patient and physician and is often neglected. A study done by Lewis in 2012 showed that more Filipino women have difficulties in lubrication (50%) and achieving orgasm (56%) as compared with women from other Asian countries.[19]

Studies have shown that sexual dysfunction is more frequent in women with diabetes mellitus compared with control.[9] However, data on sexual dysfunction

**Table 5.** Association of sexual dysfunction with microvascular complications of diabetes mellitus

| Variable | Sexual dysfunction present (Std Dev) (n=54) | Sexual dysfunction absent (Std Dev) (n=21) | p-value |
|---|---|---|---|
| Retinopathy | 9 (16.67) | 0 (0.00) | 0.046 |
| Neuropathy | 21 (28.0) | 0 (0.00) | 0.001 |
| Nephropathy | 21 (38.89) | 1 (4.76) | 0.004 |

among women with diabetes mellitus are conflicting. A major problem with published clinical studies assessing the effect of diabetes mellitus on sexuality in women is the inconsistency between study designs, making it difficult to directly compare across studies and draw firm conclusions.[9,20] Unlike research done on male sexual dysfunction, the lack of a measurable physical parameter to measure sexual dysfunction among females is a common, inevitable limitation of studies done on female sexual health, making interviews and questionnaires of different versions the only available approaches to this issue.[21] In recent studies, the FSFI questionnaire has been widely used to establish the presence of sexual dysfunction.[9]

The meta-analysis by Pontiroli et al., showed that the risk for sexual dysfunction is higher among women with type 2 diabetes mellitus as compared with women with type 1 diabetes mellitus.[9] Celik et al., stated that the high frequency of sexual dysfunction and the lower sexual quality of life in women with type 2 diabetes mellitus are considered to be resulting from the fact that most women with type 2 diabetes were in the older age group and most of them were in menopause. Moreover, the development and diagnosis of type 2 diabetes mellitus, in contrast to type 1 diabetes mellitus, occurs later in life when relationships and sexual expectations are already established. This new diagnosis may require adaptive changes in behavior and relationship patterns, potentially creating marital tension and intimacy conflict, which ultimately leads to or exacerbates sexual problems.[20]

Studies also showed that the risk of having sexual dysfunction among premenopausal women with either type 1 or type 2 diabetes mellitus were significant as compared with women with diabetes mellitus in their menopause.[20-21] The relatively less significant difference in the menopause groups might be the result of the overwhelming senescence and the natural worsening of sexual functions in both diabetic and control groups with aging.[21]

In this study, we decided to include only women with type 2 diabetes mellitus who are in their reproductive years. Seventy two percent of the participants were found to have sexual dysfunction as compared with documented rates of sexual dysfunction among women with diabetes mellitus that ranged from 25% to 88%.[2, 4, 6-9] By using Chi-square/ Fischer's Exact Test, it was shown that age was significantly associated with sexual dysfunction ($p$=0.016). Using simple logistic regression, the 45 to 50-year-old age group showed a possible association with sexual dysfunction ($p$=0.019), however this was no longer shown in the subsequent multiple logistic regression and stepwise variable selection analysis. The computed odds ratio in the simple logistic regression (OR 3.53, 95% CI 1.23 – 10.12) suggests that the odds of having sexual dysfunction among Filipino, female type 2 diabetics in the 45-50 age group is 3.5 times higher as compared with those aged less than 45 years old.

Among the participants who were identified to have sexual dysfunction, the three domains that scored the lowest were lubrication, orgasm and pain. In comparison with the study done in China in 2012, where premenopausal participants with type 2 diabetes mellitus scored lowest in the satisfaction, arousal and desire domain, these results are consistent with the study by Lewis, that showed more Filipino women have difficulties in lubrication and achieving orgasm as compared with women from other Asian countries.[19,21]

Previous studies showed sexual dysfunction is associated with a high BMI and the metabolic syndrome, while other independent variables consistent with the clinical and metabolic correlates reported in several studies showed no statistically significant correlation with sexual dysfunction.[9,12,18,22] In this study, by using Chi-square/ Fischer's Exact Test, it was shown that BMI was significantly associated with sexual dysfunction ($p$=0.001). By using simple logistic regression to determine the individual effect of each variables, having an overweight ($p$=0.007), and an obese BMI ($p$=0.002) showed a possible association with sexual dysfunction. When accounting for the effects due to all the additional variables through multiple logistic regression, it was only having an overweight BMI ($p$=0.04) that showed a possible association with sexual dysfunction. On further analysis using the stepwise variable selection, a high BMI ($p$=0.005) showed a possible association with sexual dysfunction. The calculated adjusted odds ratio in the stepwise variable selection (OR 3.07, 95% CI 1.40 – 6.71) suggests that among premenopausal Filipino females with type 2 diabetes mellitus and a high BMI, the odds of having sexual dysfunction is three times higher as compared to those with a normal BMI.

Of the five criteria that defines the metabolic syndrome, only an elevated FBS of more than 100mg/dl was noted to be significantly associated with sexual dysfunction based on Chi-square/ Fischer's Exact Test ($p$=0.006) and is also suggested in the simple logistic regression ($p$=0.012). The computed odds ratio in the simple logistics regression (OR 6.8, 95% CI 1.51 – 30.49) suggests that the odds of sexual dysfunction among Filipino, female type 2 diabetics with an elevated FBS of more than 100 mg/dl is 6.8 times higher as compared to those without an elevated FBS. One must be cautious in interpreting this data since FBS measurement can be varied depending on multiple factors and does not reflect a long term picture of a patient's diabetes status. Moreover, the wide confidence interval suggests that the sample size in this study is small and that conclusions should be replicated with a study that involves a larger sample size.

Diabetic end-organ complications may play a role in female sexual dysfunction, however the relationship of complications and sexual dysfunction was indicated only by few articles and was excluded by most studies.[9, 21] In our study, based on Chi-square/ Fischer's Exact Test, all of the three microvascular complications of diabetes mellitus namely diabetic retinopathy, nephropathy and neuropathy were associated with sexual dysfunction or a low FSFI score. The microvascular complications of diabetes mellitus were no longer included in the logistic regression analysis due to null participants with no sexual dysfunction in the diabetic retinopathy and diabetic neuropathy subgroup (Table 5).

Similar to the cross sectional study done by Vafaeimanesh et al.,[2] our study also showed that there is significant correlation between diabetic retinopathy and the presence of sexual dysfunction ($p$=0.046).

Previous studies reported diabetic neuropathy and sexual dysfunction in different ways.[9] Among women with diabetes mellitus, psychological morbidity may be a possible determinant.[8] A study by Elyasi stated that depression is common in women with Type 2 DM and sexual dysfunction is highly prevalent among those with depression.[23] Among men, peripheral neuropathy is a common cause of erectile dysfunction, however, there is little relevant literature among women to associate peripheral neuropathy with sexual dysfunction.[24] In this study the presence of diabetic neuropathy as documented by the inability to identify at least one out of 4 test points in the 10-g Semmes-Weinstein monofilament test was significantly associated with the presence of sexual dysfunction ($p$=0.001).

Few studies address sexual dysfunction among women with diabetic nephropathy. Elyasi found no significant association between sexual dysfunction and complications of diabetes mellitus.[23] In contrast, the study done by Vafaeimanesh showed that the presence of diabetic nephropathy as documented by the presence of albuminuria was significantly associated with the presence of sexual dysfunction.[2] In this study, the presence of albuminuria or proteinuria ($p$=0.024) and diabetic nephropathy ($p$=0.004) were significantly associated with the presence of sexual dysfunction based on Chi-square/ Fischer's Exact Test.

The presence of albuminuria or proteinuria showed possible association with sexual dysfunction in the simple logistic regression ($p$=0.017) and stepwise variable selection ($p$=0.024). Although the computed adjusted odds ratio in the stepwise variable selection (OR 11.65, 95% CI 1.38 – 98.13) suggests that the odds of having sexual dysfunction is twelve times higher in the presence of albuminuria or proteinuria, the wide confidence interval suggests that the sample size in this study is small and that conclusions should be replicated with a study that involves a larger sample size.

In our institution, it was identified that the prevalence of sexual dysfunction is high among premenopausal Filipino females with type 2 diabetes mellitus. It is therefore recommended to screen for sexual dysfunction among this group. Clinicians can opt to use the FSFI as an objective tool to assess for the presence of sexual dysfunction and identify specific domains that could be of particular concern for the patient. Since among women, sexual dysfunction mostly includes problems in sexual desire, satisfaction, orgasmic, lubrication and arousal[2-4] the management of sexual dysfunction may require a multidisciplinary approach for optimal management, and referral to an OB-Gynecologist or a psychiatrist should be considered whenever necessary. In this study, women scored lowest on lubrication, orgasm and pain domains and based on this findings, clinicians can advise patients on methods to achieve adequate lubrication such as proper hydration, proper stimulation, or the use of artificial lubricants in order to lessen pain and hopefully achieve improvement in orgasm. Other possible causes of pain such as infection, vaginismus, or genital skin conditions should also be identified and addressed properly. Patients should also be advised to maintain or achieve a normal BMI which has been an identified risk factor associated with sexual dysfunction.[9,12,18,22] This study was able to identify that the microvascular complications of diabetes mellitus may be associated with sexual dysfunction. Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control. Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications.[14]

### Limitations of the study and recommendations

As in many studies about sexual dysfunction, a small population size is a limitation in the interpretation of data. In this study, some variables have very wide confidence interval (e.g. confidence interval for FBS and albuminuria). This is due to a bias called sparse data bias low event per variable, categorical covariates with very low or high prevalence, and narrowly distributed continuous predictors. Moreover, due to the small sample size, the regression analyses done in our study is not valid and at best provides only an estimate and should be validated in future studies with a larger sample size.

It is therefore recommended that a prospective study that involves a larger number of participants that may involve multiple centers be done as follow-up. It is also suggested that studies be done on whether an improvement in body mass index or treatment of diabetic retinopathy, neuropathy or nephropathy would result in an improvement of FSFI score or overall sexual health.

## CONCLUSION

Seventy-two percent of premenopausal Filipino women with type 2 diabetes mellitus seen at the outpatient of Makati Medical Center were found to have sexual dysfunction. Among the participants who were identified to have sexual dysfunction, the three domains that scored the lowest were lubrication, orgasm and pain. Age, a high body mass index, an uncontrolled fasting blood sugar and presence of diabetic retinopathy, neuropathy or nephropathy is associated with sexual dysfunction.

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

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## APPENDIX A

### Female Sexual Function Index (FSFI)

Subject Identifier _____ Age _____ Date _____
INSTRUCTIONS: These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:
Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse.
Sexual intercourse is defined as penile penetration (entry) of the vagina.
Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

**CHECK ONLY ONE BOX PER QUESTION.**
Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how **often** did you feel sexual desire or interest?
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never

2. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?
□ Very high
□ High
□ Moderate
□ Low
□ Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?
□ No sexual activity
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never

4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?
□ No sexual activity
□ Very high
□ High
□ Moderate
□ Low
□ Very low or none at all

5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?
□ No sexual activity
□ Very high confidence
□ High confidence
□ Moderate confidence
□ Low confidence
□ Very low or no confidence

6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?
□ No sexual activity
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never

7. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?
□ No sexual activity
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never

8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?
□ No sexual activity
□ Extremely difficult or impossible
□ Very difficult
□ Difficult
□ Slightly difficult
□ Not difficult

9. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?
□ No sexual activity
□ Almost always or always
□ Most times (more than half the time)
□ Sometimes (about half the time)
□ A few times (less than half the time)
□ Almost never or never

10. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?
□ No sexual activity
□ Extremely difficult or impossible
□ Very difficult
□ Difficult
□ Slightly difficult
□ Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?
- □ No sexual activity
- □ Almost always or always
- □ Most times (more than half the time)
- □ Sometimes (about half the time)
- □ A few times (less than half the time)
- □ Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?
- □ No sexual activity
- □ Extremely difficult or impossible
- □ Very difficult
- □ Difficult
- □ Slightly difficult
- □ Not difficult

13. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?
- □ No sexual activity
- □ Very satisfied
- □ Moderately satisfied
- □ About equally satisfied and dissatisfied
- □ Moderately dissatisfied
- □ Very dissatisfied

14. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?
- □ No sexual activity
- □ Very satisfied
- □ Moderately satisfied
- □ About equally satisfied and dissatisfied
- □ Moderately dissatisfied
- □ Very dissatisfied

15. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?
- □ Very satisfied
- □ Moderately satisfied
- □ About equally satisfied and dissatisfied
- □ Moderately dissatisfied
- □ Very dissatisfied

16. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?
- □ Very satisfied
- □ Moderately satisfied
- □ About equally satisfied and dissatisfied
- □ Moderately dissatisfied
- □ Very dissatisfied

17. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?
- □ Did not attempt intercourse
- □ Almost always or always
- □ Most times (more than half the time)
- □ Sometimes (about half the time)
- □ A few times (less than half the time)
- □ Almost never or never

18. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?
- □ Did not attempt intercourse
- □ Almost always or always
- □ Most times (more than half the time)
- □ Sometimes (about half the time)
- □ A few times (less than half the time)
- □ Almost never or never

19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?
- □ Did not attempt intercourse
- □ Very high
- □ High
- □ Moderate
- □ Low
- □ Very low or none at all

**Thank you for completing this questionnaire.**

## APPENDIX B

### FSFI scoring

The individual domain scores and full scale (overall) score of the FSFI can be derived from the computational formula outlined in the table below. For individual domain scores, add the scores of the individual items that comprise the domain and multiply the sum by the domain factor (see below). Add the six domain scores to obtain the full scale score. It should be noted that within the individual domains, a domain score of zero indicates that the subject reported having no sexual activity during the past month. Subject scores can be entered in the right-hand column.

| Domain | Question | Score Range | Factor | Minimum Score | Maximum Score | Score |
|---|---|---|---|---|---|---|
| Desire | 1,2 | 1 - 5 | 0.6 | 1.3 | 6.0 | |
| Arousal | 3,4,5,6 | 0 - 5 | 0.3 | 0 | 6.0 | |
| Lubrication | 7,8,9,10 | 0 - 5 | 0.3 | 0 | 6.0 | |
| Orgasm | 11,12, 13 | 0 - 5 | 0.4 | 0 | 6.0 | |
| Satisfaction | 14,15,16 | 0 (or 1) - 5 | 0.4 | 0.6 | 6.0 | |
| Pain | 17,18,19 | 0 - 5 | 0.4 | 0 | 6.0 | |
| Full Scale Score Range | | | | 2.0 | 36.0 | |

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ORIGINAL ARTICLE

# Validity and Reliability of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 – Tagalog among Adult Filipinos with Differentiated Thyroid Cancer*

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**Abstract**

Objective. This study aims to determine the convergent and discriminant validity and internal consistent reliability of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Tagalog among adult Filipinos with differentiated thyroid cancer (DTC).

Methodology. 104 adult Filipinos with DTC at various disease stages self-administered the EORTC QLQ-C30 version 3 Tagalog and Short Form-36 (SF-36) version 2 Tagalog. Concurrent validity between conceptually-related scales from both tools was determined. Convergent and discriminant validity of multi-item scales of the EORTC QLQ-C30 Tagalog were assessed by Spearman's correlation. Cronbach's α was computed.

Results. The EORTC QLQ-C30 Tagalog showed moderate correlation with similar scales in the SF-36 Tagalog particulary for physical, role and social functioning, pain, and global health (r=0.42-0.48, $p$<0.001). It showed satisfactory item-domain convergent and discriminant validity for all scales except pain, fatigue, physical and cognitive functioning. Internal consistent reliability was good with cronbachs α ranging from 0.77 to 0.88 for global health, emotional and role functioning and symptom scale of nausea/vomiting.

Conclusion. The EORTC QLQ-C30 Tagalog had acceptable convergent and discriminant validity and internal consistent reliability for the scales of global health, role, social and emotional functioning and nausea/vomiting when applied among adult Filipinos with DTC.

*Key words: thyroid neoplasms, quality of life, validation studies, EORTC QLQ-C30*

## INTRODUCTION

An assessment of disease and treatment outcomes of any patient with cancer is usually incomplete without an evaluation of health-related quality of life (HRQoL). In recent years, there has been a growing body of literature focusing on this outcome measure not only among patients with more common cancers like breast and colon, but also others including thyroid.[1]

In the Philippines, thyroid cancer is ranked eighth of the top ten cancers, with an estimate of 3288 new cases among men and women in 2015.[2] In tertiary centers with facilities for total thyroidectomy and radioactive iodine (RAI), mortality rates are low at 0.3% for papillary thyroid cancer and 2.5% for follicular thyroid cancer.[3] While increased survival and good response to treatment are established among Filipino thyroid cancer patients, there are currently no published studies about the HRQoL in this specific population.

One reason for the paucity of HRQoL-related research on thyroid cancer in the Philippines is the limited number of validated tools in Tagalog to assess different quality of life dimensions. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is one of the most widely used tools for quality of life assessment initially developed in Europe and used in around 3000 studies worldwide since its development.[4] It is a general cancer questionnaire, with its latest version (version 3) having been translated in Tagalog and pre-tested among 15 Filipino patients with different cancers as per procedure from the EORTC Quality of Life Group.[6] The psychometric properties of the Tagalog version have been previously evaluated in a sample of adult Filipino females with breast cancer but not in thyroid cancer patients.[7]

Recently, a thyroid cancer-specific module in Tagalog was also developed and validated to be used alongside the pre-tested EORTC QLQ-C30 Tagalog.[8] Application of the

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** Data from this study has been presented at the Philippine Society of Endocrinology, Diabetes and Metabolism (PSEDM) convention as part of the Philippine Research Initiative on Diabetes and Endocrinology session at the EDSA Shangrila Manila, on March 22, 2018, and at the Seoul International Congress of Endocrinology and Metabolism (SICEM) poster session at the Grand Walkerhill Seoul, South Korea, on April 20, 2018.*

two questionnaires on patients with differentiated thyroid cancer (DTC) during the module development process revealed low correlation between scales from the two tools suggesting each tool reveals unique aspects in HRQoL and thus may be administered together.[8]

This study was done in order to evaluate the convergent and discriminant validity. concurrent validity, as well as internal consistent reliability of the EORTC QLQ-C30 Tagalog before clinical application in larger scale studies on HRQoL among Filipino patients with DTC can be initiated.

## METHODOLOGY

### Setting

The Philippine General Hospital outpatient clinics (medicine, surgery, thyroid) was the study site for patient recruitment. It is a tertiary hospital in Manila catering to around 10,000 patients with benign and malignant thyroid diseases per year being referred from across the Philippines.[9]

### Study design and sample size

This cross sectional-analytical study was part of a larger study seeking to determine factors affecting quality of life among adult Filipinos with differentiated thyroid cancer who have undergone thyroidectomy with or without RAI (Protocol No 2017-296-01).

A sample size of 96 subjects each responding to 30 items achieves 80% power to detect the difference between the coefficient alpha under the null hypothesis of 0.70000 and the coefficient alpha under the alternative hypothesis of 0.80000 using a two-sided F-test with a significance level of 0.05000. With a 10% allowance for non-response, a total of 106 subjects were recruited for the study.

We recruited 106 adult Filipinos age 19 or above, with histopathologic-confirmed diagnosis of DTC at least two months after any form of thyroidectomy and/or RAI, at any disease stage, and who can understand and read Tagalog consecutively attending the outpatient clinics. Respondents with acute illness or chronic illness in acute decompensation, with concomitant malignancy, cognitive impairment or severe eye disease precluding questionnaire completion were excluded. After giving written informed consent, all eligible patients answered two questionnaires, the EORTC QLQ-C30 Tagalog version 3 and the Short Form 36 Tagalog version 2 (SF-36), the reference used to evaluate concurrent validity. All questionnaires were self-administered after appropriate instructions from research assistants, who were available to answer any questions before and until the patient completed the forms. Respondents answered questionnaires in a quiet room before or after seeing their physician with no time limits imposed.

Medical charts were reviewed for clinical data and interviews were done to complete information on demographics not available in the chart. Thyroid cancer staging was based on the American Joint Committee on Cancer (AJCC) classification system, 7th edition, for differentiated thyroid carcinoma.[10] Response to Therapy was based on recommendations from the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer.[11]

### Study tools

#### *A. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Tagalog*

The EORTC QLQ-C30 version 3 Tagalog is a thirty-item general cancer questionnaire consisting of one global health scale, five functional domain scales (physical, social, role, cognitive, emotional), and several cancer-related symptoms (fatigue, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Responses to questions under the five functional domains and symptoms are rated on a four-point scale, from "not at all" to "very much", while responses to questions under global quality of life are rated on a seven-point scale from "very poor" to "excellent". All domain and item scores were linearly transformed into a scale of 0 to 100 as per EORTC Scoring Manual.[12] A high score for a functional domain and global health scale means a relatively high level of functioning while a high score for each symptom means a higher level of problems.

#### *B. Short Form-36 Tagalog*

The SF-36 is a thirty-six-item questionnaire that evaluates general health status across any population, with or without disease.. It assesses domains such as physical health, role limitation due to physical or emotional problems, bodily pain, vitality, social functioning, mental functioning and general health. Items are scored on a three or five-point scale depending on the domain. Raw scores are transformed into a 0-100 scale as per developers' scoring instructions. Higher scores mean better level of functioning and quality of life.

The second version of the SF-36 was used as the reference to evaluate concurrent validity with the EORTC QLQ-C30 Tagalog as the former had been previously translated in Tagalog and validated among a large sample of community and urban-dwelling Filipinos.[13] Furthermore, it is comprehensive and evaluates similar dimensions in quality of life with the EORTC QLQ- C30.

### Ethical consideration

Ethical clearance was obtained from the University of the Philippines Manila Research Ethics Board. Permission to use EORTC QLQ-C30 and SF-36 Tagalog versions were obtained from their respective developers.

### Statistical analysis

Descriptive statistics were used to summarize the clinical and demographic characteristics of the respondents. Frequency and proportion were used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. Spearman's correlation coefficient was computed to measure concurrent validity between homologous scales of the EORTC QLQ-C30 and SF-36, as well as to correlate the scores of individual items to its own domain and other domains for convergent and discriminant validity respectively. Convergent validity was satisfied if item-

domain correlation was ≥0.45 while discriminant validity was satisfied if the correlation coefficient between an item with its own domain was higher than other domains.[14] Scaling success rate for convergent validity was computed as the percentage of item to within-scale correlations ≥0.45 over total number of correlations. Scaling success rate for discriminant validity was computed as the percentage of items with correlations that are higher within-scale than with other scales over total number of correlations.

Cronbach's $\alpha$ was used to measure internal consistent reliability of the domains of the EORTC QLQ C-30 Tagalog. Internal consistent reliability was met if $\alpha$ is at least 0.70.[14] Data were encoded using Microsoft Excel and analyzed using STATA 15.

## RESULTS

A total of 104 respondents were included in the final analysis. Two patients were excluded: one due to an extensive number of missing answers to items (>50%); and the other due to having another malignancy aside from DTC on chart review (Figure 1).

The mean age of respondents was 43 years. Many were from Metro Manila (40%), and Region 4 (32%), Region 3 (17%), which are Tagalog-speaking provinces. Majority were female (84%) and finished high school (58%), were married (54%) and unemployed (66%). The most common type of cancer was papillary thyroid cancer and its variants, which is consistent with national figures.[2] Majority also underwent total thyroidectomy (77%) without neck dissection (75%) and received RAI (70%) at different doses (Table 1). Respondents took about an average of nine minutes (range 5-25) to accomplish the EORTC QLQ-C30 Tagalog and twenty minutes (range 5-56) to accomplish the SF-36 Tagalog.

Correlation between homologous scales of EORTC QLQ-C30 Tagalog and SF-36 Tagalog was moderate particularly in the scales of physical functioning, role functioning, pain, global health and social functioning. Weak correlation was found in the scales of fatigue and vitality as well as emotional functioning and mental health (Table 2).

Multi-trait scaling analysis of the Tagalog version of the EORTC QLQ-C30 showed satisfactory convergence particularly for the scales of global health, role functioning, emotional functioning, social functioning and the symptom scale of nausea/vomiting (Table 3 and Table 4), where correlation of items with their own domain was ≥0.45. Discriminant validity was also demonstrated for the same aforementioned domains save for item 26 under social functioning which correlated more with the role functioning scale. Convergent and discriminant validity criteria were not satisfied for physical functioning, cognitive functioning, fatigue and pain scales.

Internal consistent reliability was demonstrated for the Tagalog version of the EORTC QLQ-C30 for the scales global health, role functioning, emotional functioning and symptom scale of nausea and vomiting (Table 5). Overall cronbach's $\alpha$ for functional domains was 0.72 and 0.78 for symptom scales.

**Table 1.** Distribution of Respondents According to Clinical and Demographic Characteristics N = 104

| | Frequency (%); Mean + SD |
|---|---|
| Age (years) | 43.91±12.89 |
| Sex | |
| Male | 16 (15.38) |
| Female | 88 (84.62) |
| Marital Status | |
| Single | 28 (26.92) |
| Single with Partner | 12 (11.54) |
| Married | 57 (54.81) |
| Widowed/Widower | 7 (6.73) |
| Educational Attainment N=103 | |
| Elementary | 18 (17.48) |
| High School | 60 (58.25) |
| College | 24 (23.30) |
| Masters/Post graduate | 1 (0.97) |
| Employment Status | |
| Unemployed | 69 (66.35) |
| Employed | 35 (33.65) |
| Co-morbidity+ | |
| None | 67 (64.62) |
| Hypertension | 23 (22.12) |
| Dyslipidemia | 8 (7.69) |
| Diabetes | 7 (6.73) |
| Others | 13 (12.50) |
| Type of Thyroid Cancer | |
| Papillary | 58 (55.77) |
| Micropapillary | 13 (12.50) |
| Follicular variant | 22 (21.15) |
| Micropapillary and follicular variant | 1 (0.96) |
| Follicular | 10 (9.62) |
| Stage N=103 | |
| Age < 45 | |
| I | 44 (83.02) |
| II | 9 (16.98) |
| Age > 45 | |
| I | 24 (48.00) |
| II | 8 (16.00) |
| III | 5 (10.00) |
| IV | 13 (26.00) |
| Type of Thyroid Surgery | |
| Any thyroidectomy + Completion Thyroidectomy | 14 (13.46) |
| Any thyroidectomy + Extensive Non-thyroid Surgery (e.g. Tracheal resection) | 3 (2.88) |
| Endoscopic Thyroidectomy | 2 (1.92) |
| Lobectomy with Isthmusectomy | 3 (2.88) |
| Near Total Thyroidectomy | 1 (0.96) |
| Total Thyroidectomy | 81 (77.88) |
| Neck Dissection | |
| None | 78 (75.00) |
| With Neck Dissection | |
| Radical | 4 (3.85) |
| Selective | 9 (8.65) |
| Unknown | 13 (12.50) |
| Ancillary procedure | |
| None | 102 (98.08) |
| Chemotherapy | 1 (0.96) |
| Radiation therapy | 1 (0.96) |
| RAI Dose (Cumulative) [n = 103] | |
| None | 31 (30.10) |
| With RAI | 72 (69.90) |
| Response to Treatment | |
| Excellent | 20 (19.23) |
| Biochemical incomplete | 10 (9.90) |
| Indeterminate | 15 (14.42) |
| Structural Incomplete Response | 11 (10.58) |
| Cannot be assessed* | 48 (46.15) |

* Cannot be assessed - those who have no thyroglobulin and anti-thyroglobulin results on file or are not due for testing at the time of quality of life assessment.
\+ A patient may have more than one comorbidity.

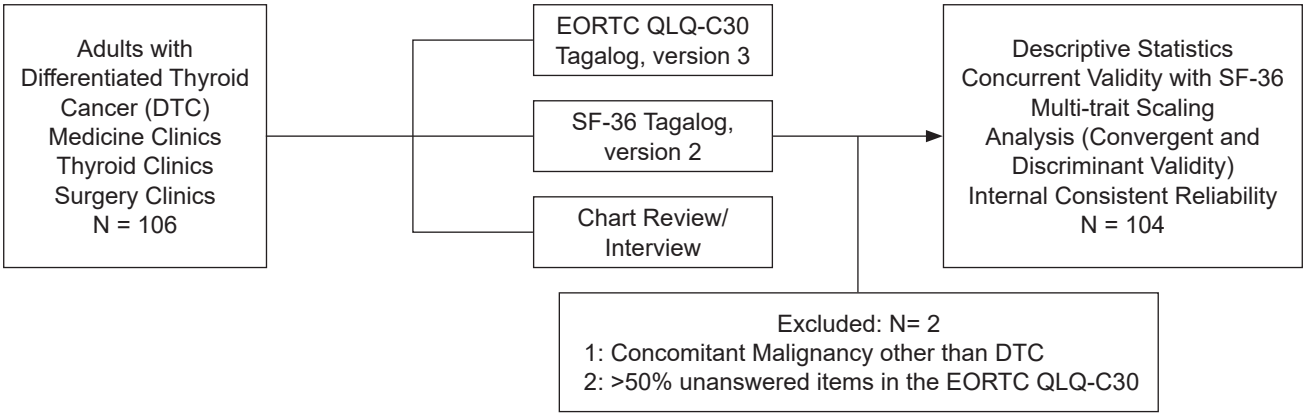


**Figure 1.** Participant flow.

**Table 2.** Concurrent Validity between Similar Scales in the EORTC QLQ-C30 and SF-36

| EORTC QLQ C-30 v3 Tagalog | SF 36 v2 Tagalog | Correlation coefficient (r) |
|---|---|---|
| Physical Functioning | Physical Functioning | 0.468*** |
| Role Functioning | Role Functioning – physical | 0.457*** |
| | Role Functioning – emotional | 0.434*** |
| Pain | Bodily Pain | -0.488*** |
| Global Health | General Health | 0.426*** |
| Fatigue | Vitality | -0.353*** |
| Social Functioning | Social Functioning | 0.444*** |
| Emotional Functioning | Mental Health | 0.332*** |

Spearman correlation coefficient; * $p<0.05$, ** $p<0.01$, *** $p<0.001$. Negative values are due to scoring procedures.
r = .00 to .20 very weak; r = .21 to .40 weak, r = .41 to .60 moderate; r = .61 to .80 strong; r = .81 to 1.00 very strong

**Table 3.** Concurrent Validity between Similar Scales in the EORTC QLQ-C30 and SF-36

| Item | Description | PF | RF | EF | CF | SF | FA | NV | PA | GH |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Strenuous Activity | 0.374* | 0.374 | 0.271 | 0.246 | 0.221 | 0.399 | 0.242 | 0.358 | -0.24 |
| 2 | Long Walk | 0.492 | 0.369 | 0.292 | 0.327 | 0.259 | 0.424 | 0.247 | 0.381 | -0.114 |
| 3 | Short Walk | 0.367* | 0.135 | 0.069 | 0.127 | 0.041 | 0.069 | 0.277 | 0.22 | 0.079 |
| 4 | Stay in bed/chair | 0.052* | 0.057 | 0.303 | 0.192 | 0.171 | 0.095 | -0.04 | 0.109 | -0.154 |
| 5 | Need help in eating/dressing or washing | 0.214* | 0.017 | 0.271 | 0.178 | 0.104 | 0.084 | 0.032 | 0.219 | -0.12 |
| 6 | Limited Work | 0.353 | 0.638 | 0.267 | 0.267 | 0.401 | 0.349 | 0.076 | 0.518 | -0.203 |
| 7 | Limited Hobbies | 0.334 | 0.638 | 0.272 | 0.314 | 0.409 | 0.4 | 0.218 | 0.41 | -0.218 |
| 21 | Feeling tense | 0.24 | 0.294 | 0.502 | 0.372 | 0.237 | 0.411 | 0.176 | 0.428 | -0.287 |
| 22 | Feeling worry | 0.299 | 0.28 | 0.659 | 0.439 | 0.496 | 0.474 | 0.175 | 0.325 | -0.313 |
| 23 | Irritable | 0.392 | 0.202 | 0.542 | 0.312 | 0.362 | 0.398 | 0.126 | 0.351 | -0.23 |
| 24 | Depressed | 0.235 | 0.147 | 0.569 | 0.466 | 0.383 | 0.417 | 0.181 | 0.33 | -0.291 |
| 20 | Concentration | 0.252 | 0.296 | 0.309 | 0.377* | 0.252 | 0.212 | 0.296 | 0.442 | -0.251 |
| 25 | Memory | 0.339 | 0.246 | 0.525 | 0.377* | 0.326 | 0.358 | 0.316 | 0.373 | -0.362 |
| 26 | Relation of Illness with Family Life | 0.146 | 0.484 | 0.43 | 0.324 | 0.47 | 0.346 | 0.198 | 0.308 | -0.268 |
| 27 | Relation of Illness with Social Life | 0.33 | 0.282 | 0.408 | 0.282 | 0.47 | 0.444 | 0.359 | 0.374 | -0.222 |
| 10 | Need rest | 0.256 | 0.187 | 0.295 | 0.092 | 0.222 | 0.305* | 0.03 | 0.318 | -0.12 |
| 12 | Feel weak | 0.262 | 0.274 | 0.466 | 0.279 | 0.311 | 0.423* | 0.153 | 0.369 | -0.263 |
| 18 | Tired | 0.366 | 0.429 | 0.439 | 0.391 | 0.462 | 0.353* | 0.326 | 0.382 | -0.231 |
| 14 | Nausea | 0.28 | 0.108 | 0.21 | 0.324 | 0.311 | 0.27 | 0.782 | 0.256 | -0.129 |
| 15 | Vomiting | 0.288 | 0.202 | 0.192 | 0.378 | 0.301 | 0.168 | 0.782 | 0.252 | -0.16 |
| 9 | Pain | 0.234 | 0.294 | 0.26 | 0.299 | 0.307 | 0.419 | 0.31 | 0.231* | -0.105 |
| 19 | Relation of Pain with Daily Activity | 0.448 | 0.494 | 0.447 | 0.444 | 0.318 | 0.363 | 0.135 | 0.231* | -0.302 |
| 29 | Overall Health | -0.215 | -0.237 | -0.328 | -0.298 | -0.214 | -0.303 | -0.158 | -0.215 | 0.729 |
| 30 | Overall Quality of Life | -0.119 | -0.198 | -0.35 | -0.4 | -0.311 | -0.231 | -0.124 | -0.288 | 0.729 |

* - items that did not meet convergent validity criteria
Italicized items – items that did not meet discriminant validity criteria
Bold Items - items under one scale
PF - Physical Functioning, RF - Role Functioning, EF - Emotional Functioning, CF - Cognitive Functioning, SF - Social Functioning, FA - Fatigue, NV - Nausea and Vomiting, PA - Pain, GH - Global Health

**Table 4.** Convergent and Discriminant Validity for Multi-item Scales of the EORTC QLQ-C30 Tagalog

| | Convergent Validity | Discriminant Validity | Item Convergent Validity Scaling Success Rate (%)* | Item Divergent Validity Scaling Success Rate (%)+ |
|---|---|---|---|---|
| Functional domain | | | | |
| Physical Functioning | 0.052 to 0.492 | -0.240 to 0.424 | 20 | 40 |
| Role Functioning | 0.638 | -0.218 to 0.518 | 100 | 100 |
| Emotional Functioning | 0.502 to 0.659 | -0.313 to 0.496 | 100 | 100 |
| Cognitive Functioning | 0.377 | -0.362 to 0.525 | 0 | 0 |
| Global Health | 0.729 | -0.400 to 0.155 | 100 | 100 |
| Social Functioning | 0.470 | -0.268 to 0.484 | 100 | 50 |
| Symptom domain | | | | |
| Fatigue | 0.305 to 0.423 | -0.263 to 0.466 | 0 | 0 |
| Pain | 0.231 | -0.302 to 0.494 | 0 | 0 |
| Nausea and Vomiting | 0.782 | 0.160 to 0.488 | 100 | 100 |

* Item convergent validity scaling success (%) i.e. number of item-scale correlations > 0.45/total number of correlations x100
\+ Item divergent validity scaling success (%) i.e. number of item-scale correlations with values higher within scale than with other scales / total number of correlations x 100

**Table 5.** Internal Consistent Reliability of Multi-item Scales of the EORTC QLQ-C30 Tagalog

| Scale | Cronbach's α |
|---|---|
| Global Health | 0.84 |
| Physical functioning | 0.51 |
| Role functioning | 0.78 |
| Emotional functioning | 0.77 |
| Cognitive functioning | 0.55 |
| Social functioning | 0.64 |
| Fatigue | 0.55 |
| Nausea and vomiting | 0.88 |
| Pain | 0.38 |

## DISCUSSION

The few existing studies on health-related quality of life among cancer patients in the Philippines mostly enroll patients with more prevalent cancers or those with terminal cancers using the EORTC QLQ-C30 Tagalog.[7,15-16] No studies have been done on emerging and relatively indolent cancers such as DTC. This study provides preliminary data on construct validity and internal consistent reliability of a tool that may facilitate comparisons in HRQoL domains with other types of cancers or with DTC from other countries.

Concurrent validity was demonstrated for scales of the EORTC QLQ-C30 Tagalog and SF-36 Tagalog measuring similar quality of life dimensions, i.e., physical functioning, social functioning, role functioning, global health, and pain where correlation was moderate. This finding corroborates with other studies which use different translations on populations with a multitude of cancer diagnoses. Correlation coefficients were in the range of 0.40 to 0.62 (physical functional, role functioning, social functioning) in Singapore, 0.34 to 0.53 (global health, social functioning) in Germany and 0.32 to 0.57 (global health, physical, role functioning, social functioning) in Turkey.[17-19] Weak correlation was found between fatigue and vitality scales in this study as well as emotional functioning and mental health. Reasons for this are unclear. Intuitively, items under fatigue and vitality measure similar concepts relating to loss of energy or tiredness while items for emotional functioning and mental health measure related concepts such as feeling anxious, depressed and happy. Moderate to strong correlations are found in many studies comparing scales of fatigue and vitality, while weak correlation was also found in a study in Turkey and Indonesia comparing emotional and mental functioning.[19-20] The weak correlation for the current population may be due to the way the respondents interpreted and answered the translated items, or because the response anchors in one or both questionnaires.

Convergent and discriminant validity was established for the domains of global health, emotional functioning, role functioning, social functioning and nausea and vomiting confirming that the local translation did not compromise the hypothesized structure of the third version of the EORTC QLQ-C30 for these scales. Scaling errors however were noted for the physical functioning domain which had items with low correlation coefficients within its own scale or which correlated more with fatigue (Item 1), or emotional functioning (Item 4, 5). One possible explanation for this finding would be that the sampled respondents answered questions on physical function based on how physically tired or worried they were about their illness. These observations were previously reported in studies among Ethiopian and Indonesian cancer patients.[20-21] Furthermore, low correlation coefficients for physical functioning items were also reported in Singapore, South Korea and Italy and attributed to skewed responses where the questionnaire was tested on a relatively functional cancer population with few physical impairments similar to the ones enrolled in this study.[17,22-23,] For validation studies, sampling a heterogenous population with different disease severity or functional impairment is important as it allows a wide range of responses and yield better correlation.[14]

Items under pain and cognitive functioning also did not meet convergent and discriminant validity criteria and may be due to the effects of translation of some terms. Pain is "*sakit*" in Tagalog, which is a homonym, and may refer to a sensation, which is the intended construct being measured by the scale in the English version or "*sakit*" as illness or disease. Some patients may have interpreted questions on pain as the latter thereby resulting in absence of convergence as well as a higher correlation with other functional scales. Item 25 where the term "*pag-aalala*" was used under cognitive functioning also had a higher correlation with emotional functioning. "*Pag-aalala*" is another homonym and may mean the act of remembering, the intended concept of item 25, or worry, the concept of item 22 under emotional functioning depending on one's pronunciation. Like pain, there may have been a variable interpretation by some patients of the meaning of "*pag-aalala*" thus leading to compromised convergent and discriminant validity.

The global health, role functioning, emotional functioning and nausea and vomiting scales showed good internal consistent reliability with $\alpha$ ranging from 0.77 to 0.88. Save for role functioning, these scales were also the same scales with good psychometric performance when tested on a South Korean population with various cancers.[22] The physical and social functioning, fatigue, pain and cognitive functioning scales had suboptimal reliability with cronbach's $\alpha$ ranging from 0.38 to 0.64. Low cronbach's $\alpha$ has been consistently reported for the cognitive functioning scale not only in the English version but also in numerous other translations.[17,19-22,24-26] On inspection, items comprising the cognitive functioning scale in the English version already measure distinct aspects of cognition, i.e., memory and concentration, and thus the respective translations in Tagalog also resulted in low inter-relatedness between items. During questionnaire development however, scales with low cronbach's alpha may be retained if it is outweighed by its clinical relevance in the population it is used on.[14] The suboptimal $\alpha$ for the other scales may be due to the different interpretations by the respondents of constructs especially for scales containing homonymous terms as earlier described. The limitation of this study is that although it enrolled patients at different disease stages and received different types of surgery with none to varying doses of RAI, it still sampled a relatively functional group of patients following up at the outpatient department thus the population may not have been representative enough of the entire DTC population. Although thyroid cancer and its treatment does not usually lead to physical disability compared to other cancers unless there is bone fracture or diffuse lung metastases for instance, it would be more informative to explore how scales perform if more of the respondents included are patients admitted or recently discharged after thyroidectomy, patients immediately post RAI, and patients on chemotherapy or radiotherapy as adding these groups of patients could result in more diverse responses and thus different impairments in the domains and symptom scales of the questionnaire. The study was also done in a single center, introducing selection bias and is another inherent limitation. Moreover, because of the cross-sectional design, the study questionnaire's test-retest reliability and responsiveness were not tested. Nonetheless, this study provides preliminary evidence supporting the validity and reliability of the EORTC QLQ-C30 Tagalog for certain scales when administered to adult Filipinos with differentiated thyroid cancer.

## CONCLUSION

The EORTC QLQ-C30 Tagalog shows acceptable construct validity and internal consistent reliability for the scales of global health, role functioning, social functioning, emotional functioning, nausea and vomiting when administered to adult Filipinos with differentiated thyroid cancer. Further studies of longitudinal design and more diverse patient populations are recommended to corroborate the study findings and test responsiveness. Improvements in the translation of some items under the pain scale and cognitive functioning may be needed.

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

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ORIGINAL ARTICLE

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# Association of Metabolic Syndrome with the Severity of Airflow Obstruction in Patients with Chronic Obstructive Pulmonary Disease*

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**Abstract**

Background. Metabolic Syndrome (MetS) is common in Chronic Obstructive Pulmonary Disease (COPD) patients but their association is still an unsettled issue. The aim of this study was to determine the association of MetS with the severity of airflow obstruction.

Methodology. This was a cross-sectional analytic study of 157 patients with COPD. They were classified using the Global Initiative for Chronic Obstructive Lung Diseases (GOLD). MetS was assessed using two well-recognized criteria. Demographics, clinical data, lifestyle-related characteristics, fasting blood sugar (FBS) and lipid profile were obtained. Multiple logistic regression was used to determine the association of MetS with the severity of airflow obstruction.

Results. 40.13% and 17.20% of patients had MetS using the NCEP/ATP III-AHA/NHBLI and IDF criteria, respectively. MetS was not associated with severity of airflow obstruction. Of the MetS components, only elevated blood pressure (BP) was significantly associated with severity of airflow obstruction (GOLD II: OR=3.28, $p$<0.001; GOLD III: OR=4.04, $p$=0.2; GOLD IV: OR=6.21, $p$=0.04). Elevated FBS was also associated with GOLD IV (OR=16.09, $p$=0.02). Significant factors associated with MetS in COPD patients were body mass index, inhaled steroid, number of pack-years, and GOLD II.

Conclusion. MetS is not associated with severity of airflow obstruction. Only certain components of MetS showed significant associations such as elevated BP with GOLD II-IV and elevated FBS with GOLD IV.

*Key words: metabolic syndrome, airflow obstruction, chronic obstructive pulmonary disease*

## INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in the world.[1] It coexists with other diseases that may have a significant impact on prognosis. Among these disease entities is the Metabolic Syndrome (MetS), a clustering of metabolic abnormalities that occur in the same individual which appear to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality. Studies have shown that the presence of MetS is more frequent in COPD than in those with normal lung function, two common entities that share common inflammatory pathway.[2,3]

MetS is found to be twice more common in COPD when compared to the general population with prevalence ranging from 25.6 to 60.9%.[4] MetS has been evaluated as a risk factor for chronic lung diseases. The exact nature of the relationship between MetS and lung function impairment remains unknown, and therefore, deserves further investigation.[5]

How people with COPD develop MetS remains unclear, but it has been postulated that its pathogenesis is multifactorial.[6,7] There are several risk factors such as smoking, genetics, obesity, physical inactivity, and airflow limitation that link the pathogenic mechanism between these two. Among these factors, smoking has the strongest association. The potential mechanism responsible for the development of MetS and COPD in a smoker is primarily due to systemic inflammatory response.[4] Hence, systemic inflammation is considered a hallmark of both MetS and COPD. The existing interaction among the pro-inflammatory proteins released from both pulmonary and adipose tissues and the systemic compartment play a vital role in the development of these two diseases.[6]

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Evidences also show the influence of each component risk factor of MetS in patients with COPD. Obesity, the most studied in terms of linking to certain respiratory disorders, decreases expiratory reserve volume and functional residual capacity.[1,6] Among COPD patients, the prevalence of dyslipidemia and diabetes mellitus was found to be 48.3% and 3-12%, respectively.[4,8] The latter is even higher in more severe stages of the disease which could be related to the inflammatory process or due to the therapeutic side effect with the use of corticosteroids.[9,10] In patients with COPD, 31% to 33% are also hypertensive.[11]

In the Philippines, data from the Department of Health show that COPD ranks seventh among the leading causes of mortality.[12] Overall, there are 17.3 million Filipinos who currently smoke tobacco.[13] The prevalence of COPD is higher in men than in women and increases steadily with age from 40 years to more than 70 years.[14]

MetS is also common among Filipinos and low high-density lipoprotein (HDL) is the most common component. The prevalence of MetS in the Philippines is found to be 18.6% by the National Cholesterol Education Program/ Adult Treatment Panel III criteria modified by the American Heart Association/National Heart, Lung and Blood Institute (NCEP/ATP III-AHA/NHLBI) criteria. MetS has been shown to be associated with atherosclerotic cardiovascular disease, stroke, and diabetes mellitus.[15]

There is no data that describes the association of MetS with the severity of airflow obstruction among Filipinos with COPD since it is likely that these two entities and their relationship vary from population to population.[16] Because these two diseases are affecting more Filipinos, we need more data for public health intervention.

Among patients with COPD, it is important to identify patients who have MetS early in their course so that early lifestyle intervention and treatment may be initiated. The morbidity[17] and mortality[18] associated with the development of MetS among patients with COPD further intensify the burden of the disease. This study aims to increase awareness among other physicians of the high burden of MetS among COPD patients in our country. This study also hopes to establish the basis for screening MetS among COPD patients. Screening will identify additional MetS cases, facilitating early detection that may help improve COPD treatment outcomes.

The aim of the present study was to determine the association of MetS with the severity of airflow obstruction among patients with COPD in a tertiary government institution, and to determine significant factors associated with MetS in these patients.

## METHODOLOGY

### Eligibility criteria

This was a cross-sectional analytic study which included patients aged 40 years old and above diagnosed with COPD using spirometry attending the Pulmonary Medicine outpatient clinic of the University of the Philippines – Philippine General Hospital (UP – PGH), a tertiary government hospital in Manila, Philippines. Patients who were clinically diagnosed with COPD seeking consult for the first time were confirmed by undergoing spirometry. Once eligible, patients were recruited by the investigator to participate in the study.

Those who had an acute exacerbation, i.e., increase in cough, sputum production, worsening dyspnea, or sputum purulence within three weeks,[2] and those with asthma or history of asthma were excluded. In addition, those having any active infectious diseases such as pulmonary tuberculosis either clinically diagnosed or bacteriologically confirmed, inflammatory diseases such as collagen vascular diseases, inflammatory bowel disease that could cause an increase in C-reactive protein (CRP) levels, and those with malignancy were also excluded from the study.

Using NCSS-PASS 12 (Power Analysis and Sample Size) software, the minimum sample size requirement was at least 157 participants based on the logistic regression power analysis of 95%, odds ratio of 1.993, and 5% alpha error.

The study was approved by the University of the Philippines Manila Research Ethics Board and all patients signed an informed consent.

### Diagnosis of COPD

The diagnosis of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015 criteria.[2] A clinical diagnosis of COPD was consistent in any patient who had dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for this disease.

Spirometry was required to make the diagnosis in this clinical context. The presence of a post-bronchodilator $FEV_1/FVC$ <0.70 (forced expiratory volume at 1 second/ forced vital capacity) confirmed the presence of persistent airflow limitation, thus of COPD.

Severity of airflow obstruction was defined analogously to the GOLD guidelines[2] which are as follows: GOLD I or mild airflow obstruction: $FEV_1$ ≥80 % predicted; GOLD II or moderate airflow obstruction: 50% ≤ $FEV_1$ <80% predicted; GOLD III or severe airflow obstruction: 30% ≤ $FEV_1$ <50% predicted; and GOLD IV or very severe airflow obstruction: $FEV_1$ ≤30 % predicted.

### Diagnosis of metabolic syndrome

MetS was diagnosed by two well-recognized criteria: the NCEP/ATP III-AHA/NHLBI and the International Diabetes Federation (IDF).

Using the NCEP/ATP-AHA/NHLBI criteria,[19] three out of the five individual risk components fulfilled MetS. They are as follows: elevated waist circumference defined as ≥90 cm in men or ≥80 cm in women; elevated triglycerides defined as ≥1.7 mmol/L or on drug treatment for elevated triglycerides; decreased HDL-C defined as <1.03 mmol/L in men or <1.29 mmol/L in women or on drug treatment for reduced HDL-C; elevated BP defined as >130/85 mmHg or on anti-hypertensive drug treatment in a patient with a history of hypertension; and, elevated FBS defined as ≥5.6 mmol/L or on drug treatment for elevated glucose.

Using the IDF criteria,[20] central obesity defined by waist circumference with ethnicity specific values: ≥90 cm for males and ≥80 cm for females is required for the diagnosis of MetS and two of the four factors previously mentioned. The four factors are the same as the above parameters for elevated triglycerides, decreased HDL-C, elevated FBS except for elevated BP which has higher cut-off value: systolic BP ≥140 mmHg or diastolic BP ≥ 85 mmHg or on treatment of previously diagnosed hypertension. If body mass index (BMI) is >30 kg/m$^2$, central obesity can be assumed and waist circumference does not need to be measured.

### Outcome measurements

After recruitment, participants' medical history, demographic data, and lifestyle-related characteristics were obtained through interviews. On the same visit, participants underwent anthropometric measurements and laboratory testing.

We defined individuals as *never smokers* (those who never smoked or who smoked fewer than 100 cigarettes in their lifetime), *former smokers* (those who smoked at least 100 cigarettes in their entire life but were not currently smoking at the time of interview), or *current smokers* (those who smoked at least 100 cigarettes in their entire life and are still smoking). Pack-years (packs of cigarettes per day multiplied by smoking years) was used as the smoking index.[21] Alcohol intake was likewise probed. Exercise was determined by patient's self-reporting. Other variables that were collected in the study were COPD-related symptoms, time since diagnosis (in years), and intake of steroids as part of their COPD pharmacotherapy.

Anthropometric measurements such as height in centimeters (cm) and weight in kilograms (kg) were measured after removal of shoes using a wall-mounted stadiometer and a weighing scale, respectively. Waist circumference was measured at the end of normal expiration, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid-axillary line. Hip circumference was measured at the largest circumference of the buttocks.[19,22] Waist-to-hip circumference ratio was also determined. BMI was calculated as weight in kilograms divided by the height in meters squared (kg/m$^2$). Analyses of BMI was conducted using WHO-defined BMI categories for public health action in Asians: *acceptable risk or normal weight* (18.5 to <23.0 kg/m$^2$), *increased risk or overweight* (23.0 to <27.5 kg/m$^2$), and *higher high risk or obese* (≥27.5 kg/m$^2$).[23] An average BP in mmHg was calculated from two measurements with the subjects in a sitting position after five minutes of rest.

After an overnight fast, five milliliters of venous blood were collected from each patient for measurement of serum levels of total cholesterol, triglycerides, HDL-C, low-density lipoprotein cholesterol (LDL-C) and fasting glucose (FBS). Collected specimens were brought immediately to the laboratory, where they were centrifuged and analyzed.

Patients who were diagnosed with MetS were referred back to their respective attending physicians for counseling, lifestyle intervention, health promotion, and were given necessary treatment based on the current guidelines.

### Data analysis

Continuous variables were presented using means and standard deviations (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data, while categorical variables were presented as frequencies and percentages. Normality of distribution for continuous variables was tested using the Shapiro-Wilks test. Student's T test and Wilcoxon tank sum test were used to compare continuous variables between two groups with normal and non-normal distribution, respectively. Chi-square test was used to compare categorical variables. Prior to variable selection, tests for collinearity, confounding, and interaction were performed. Multicollinearity was assumed if the variable inflation factor was >10. Confounding was considered if the change in odds ratio in the crude and adjusted logistic model was >10%. After checking for interaction, no variables were identified to significantly modify the relationship of COPD and MetS. During the univariate analysis, variables found to be significant at p-value <0.2 were entered into an exploratory multivariate logistic regression model.

After the univariate analysis, variables that were included in the variable selection included age, age at diagnosis of COPD, duration of COPD, use of inhaled steroids, smoking duration, classification of smoking, number of pack years, exercise, BMI, waist-hip ratio, and GOLD classification. Multivariate logistic regression was then performed to examine the factors associated with MetS in patients with COPD. Independent predictors of MetS were identified using the hierarchical method of variable selection. The significant variables ($p$<0.05) after hierarchical stepwise elimination formed the final predictive model. Statistical analyses were performed using STATA 13.

## RESULTS

We recruited 157 participants from August 2017 to April 2018. The demographic, anthropometric, clinical and biochemical, and lifestyle-related characteristics of the study population are summarized in Table 1. Majority of the participants were males (80.89%). Mean (SD) age was 64.3 (9.47) years. Based on the BMI categories for Asians, most of the patients had normal weight. A larger number of patients with COPD were on steroid treatment (68.15%), previous smokers (80.89%), and alcohol drinkers (82.17%). The median number of pack-years was 34 years while the median number of smoking duration was 30 years. Mean forced expiratory volume at 1 second (FEV1) of the study patients was 0.78. Most subjects recruited were classified as COPD GOLD I (45.22%). 36 (23%) had elevated waist circumference, 30 (19%) had elevated triglycerides, 57 (36%) had reduced HDL-C, 72 (46%) were hypertensive, and 62 (39%) had elevated FBS.

Table 2 shows the differences in the characteristics of patients with and without MetS. Significant characteristics of patients associated with MetS were seen in relation to smoking history, smoking duration, steroid use, exercise and number of pack-years. Most patients with MetS were previous smokers. Of those with MetS, only six patients were still smoking at the time of recruitment while two were never smokers. Majority of patients who were never

smokers were females. Most of them had occupational-related COPD such as concrete-manufacturing workers, street vendors and coal-miners while others were second-hand smokers. Among those who were on steroid treatment, all were on maintenance inhaled steroids.

**Table 1.** Demographic, anthropometric, clinical and biochemical profile, and lifestyle related characteristics of the study population, n=157

| Characteristics | Study Population n=157 |
|---|---|
| Age (years), mean (SD) | 64.3 (9.47) |
| Sex | |
| Male, n (%) | 127 (80.89%) |
| Female, n (%) | 30 (19.11%) |
| BMI (kg/m$^2$), mean (SD) | 21.12 (4.10) |
| Underweight, n (%) | 45 (28.66%) |
| Normal weight, n (%) | 65 (41.40%) |
| Overweight, n (%) | 35 (22.30%) |
| Obese, n (%) | 12 (7.64%) |
| Waist circumference (cm), mean (SD) | 79.8 (11.59) |
| Male, mean (SD) | 81.0 (11.90) |
| Female, mean (SD) | 73.9 (7.80) |
| SBP (mmHg), mean (SD) | 125.3 (14.84) |
| DBP (mmHg), mean (SD) | 80.3 (11.09) |
| Total cholesterol (mmol/L), mean (SD) | 4.65 (1.15) |
| Triglycerides (mmol/L), mean (SD) | 1.34 (0.51) |
| HDL-C (mmol/L), mean (SD) | 1.3 (0.46) |
| Male, mean (SD) | 1.3 (0.41) |
| Female, mean (SD) | 1.5 (0.61) |
| LDL-C (mmol/L), mean (SD) | 2.9 (0.88) |
| FBS (mmol/L), mean (SD) | 5.7 (1.63) |
| Inhaled steroid use, n (%) | 107 (68.15%) |
| Smoking history | |
| Never Smokers, n (%) | 17 (10.83%) |
| Previous Smokers, n (%) | 127 (80.89%) |
| Current Smokers, n (%) | 13 (8.28%) |
| Smoking duration (years), median (IQF) | 30 (20) |
| Pack-years, median (IQF) | 34 (37) |
| With alcohol intake, n (%) | 129 (82.17%) |
| With exercise, n (%) | 75 (47.77%) |
| $FEV_1$, median (IQF) | 0.78 (0.25) |
| GOLD | |
| I, n (%) | 71 (45.22%) |
| II, n (%) | 62 (39.49%) |
| III, n (%) | 17 (10.83%) |
| IV, n (%) | 7 (4.46%) |

Table 3 shows the prevalence of MetS according to various criteria with the severity of airflow limitation in patients with COPD. Both the NCEP-ATP III-AHA/NHLBI and the IDF criteria were good criteria in diagnosing MetS across GOLD classification in patients with COPD. However, a larger number of patients was diagnosed with MetS using the NCEP/ATP III-AHA/NHLBI criteria [n=63 (40.13%)] in comparison to the IDF criteria [n=27 (17.20%)]. In the GOLD classification, GOLD II has the largest percentage of patients with MetS using both criteria (52.38% in the NCEP/ATP III-AHA/NHLBI while 51.85% in the IDF criteria).

Among the individual risk components of MetS as shown in the multivariate analysis in Table 4, only elevated BP was significantly and consistently associated with the severity of airflow obstruction (OR=3.28, 95% CI 1.59-6.76, p<0.001 in GOLD II; OR=4.04, 95% CI 1.28-12.69, *p*=0.05 in GOLD III; OR=6.21, 95% CI 1.07-36.10, p=0.04 in GOLD IV). In addition, elevated FBS was significantly associated with GOLD IV (OR=16.09, 95% CI 1.44-179.50, *p*=0.02).

In the multivariate logistic analysis shown in Table 5, MetS was not associated with increasing severity of airflow obstruction in COPD patients. However, other factors significantly associated with MetS in patients with COPD were inhaled steroid use, BMI, number of pack-years, and GOLD II. For every 1 unit increase in BMI, there is a 31% increase in the odds of having MetS. Similarly, for every 1 additional pack year incurred, there is a 3% increase in the odds of having MetS. Those who used inhaled steroid as part of their COPD pharmacotherapy have threefold likelihood of having MetS. Also, among the GOLD classification, patients classified as GOLD II were three times more likely to have MetS.

## DISCUSSION

The results of our study showed that MetS was not associated with the severity of airflow obstruction. However, we found that certain components of MetS were associated with the severity of airflow obstruction and that the prevalence of MetS in COPD was higher than in the general population.[4]

**Table 2.** Comparison of demographic and clinical characteristics of patients with and without MetS

| Characteristics | Without MetS n=94 | With MetS n=63 | p-value |
|---|---|---|---|
| Age (years), n (SD) | 63.2 (9.73) | 66.1 (8.85) | 0.05 |
| Sex | | | |
| Male, n (%) | 73 (57.48%) | 54 (42.52%) | 0.21 |
| Female, n (%) | 21 (70%) | 9 (30%) | |
| Smoking history | | | |
| Never Smokers, n (%) | 15 (88.24%) | 2 (11.76%) | |
| Previous Smokers, n (%) | 72 (56.69%) | 55 (43.31%) | 0.04 |
| Current Smokers, n (%) | 7 (53.85%) | 6 (46.15%) | |
| Smoking duration (years), median (IQF) | 28.5 (27) | 34 (17) | 0.04 |
| Inhaled steroid use, n (%) | 62 (54.39%) | 52 (45.61%) | 0.02 |
| Pack-years, median (IQF) | 25.5 (22) | 48 (37) | <0.001 |
| With alcohol intake, n (%) | 76 (58.91%) | 53 (41.09%) | 0.59 |
| With exercise, n (%) | 51 (68%) | 24 (32%) | 0.04 |
| $FEV_1$, median (IQF) | 0.81 (0.24) | 0.72 (0.24) | 0.09 |

**Table 3.** Metabolic syndrome according to the NCEP/ATP III-AHA/NHLBI and IDF Criteria among COPD patients

| Criteria for MetS | GOLD I | GOLD II | GOLD III | GOLD IV |
|---|---|---|---|---|
| NCEP/ATP III-AHA/NHLBI (n=63) | 20 (31.75%) | 33 (52.38%) | 6 (9.75%) | 4 (6.35%) |
| IDF (n=27) | 10 (37.40%) | 14 (51.85%) | 3 (11.11%) | 0 |

**Table 4.** Multivariate analysis of the individual risk components of metabolic syndrome using the NCEP/ATP III-AHA/NHLBI with the severity of airflow limitation

| | Odds Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| Elevated waist circumference | | | |
| GOLD I | Reference | | |
| GOLD II | 1.21 | 0.35-4.10 | 0.77 |
| GOLD III | 3.89 | 0.64-23.69 | 0.14 |
| GOLD IV | 1 | | |
| Elevated triglycerides | | | |
| GOLD I | Reference | | |
| GOLD II | 1.88 | 0.77-4.59 | 0.17 |
| GOLD III | 1.63 | 0.43-6.13 | 0.47 |
| GOLD IV | 1 | | |
| Decreased HDL | | | |
| GOLD I | Reference | | |
| GOLD II | 1.36 | 0.65-2.84 | 0.41 |
| GOLD III | 0.39 | 0.10-1.51 | 0.17 |
| GOLD IV | 0.82 | 0.14-4.67 | 0.82 |
| Elevated blood pressure | | | |
| GOLD I | Reference | | |
| GOLD II | 3.28 | 1.59-6.76 | <0.001 |
| GOLD III | 4.04 | 1.28-12.69 | 0.02 |
| GOLD IV | 6.21 | 1.07-36.10 | 0.04 |
| Elevated fasting blood sugar | | | |
| GOLD I | Reference | | |
| GOLD II | 1.50 | 0.67-3.37 | 0.32 |
| GOLD III | 0.89 | 0.24-3.27 | 0.86 |
| GOLD IV | 16.09 | 1.44-179.50 | 0.02 |

**Table 5.** Multivariate logistic regression analysis of factors associated with metabolic syndrome among COPD patients

| Variables | Odds Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| GOLD Classification | | | |
| GOLD I | Reference | | |
| GOLD II | 3.31 | 1.41-7.75 | 0.01 |
| GOLD III | 2.04 | 0.56-7.42 | 0.28 |
| GOLD IV | 5.09 | 0.77-33.80 | 0.09 |
| Inhaled steroid use | 3.13 | 1.19-8.24 | 0.02 |
| Body mass index | 1.31 | 1.15-1.50 | <0.001 |
| Number of pack-years | 1.03 | 1.01-1.05 | 0.003 |
| Smoking duration | 0.98 | 0.95-1.02 | 0.36 |

Among the individual risk components of MetS, elevated BP was shown to be significantly associated with airflow obstruction across all GOLD classification. On the other hand, elevated FBS was significantly associated with very severe airflow obstruction or GOLD IV. Also, the rate of MetS among patients with COPD in the present study was 40.13% using the NCEP/ATP III-AHA/NHLBI.

Two previous reports showed that MetS was associated with impaired lung function but this relationship was only significant with restrictive lung impairment and not airflow obstruction.[24,25] However, in the present analysis, certain components of MetS were significantly associated with airflow obstruction. We found out that among these components, increased BP was the main effect linked with airflow obstruction. This resonates with reports of previous studies in various settings. Marquis et al.,[26] reported that among MetS components, high BP, in addition to abdominal obesity, were more frequent in COPD men. Recent analysis of data from 20,296 subjects which included 11,258 men and 9,038 women aged ≥45 years in two large combined cohort studies showed that subjects with GOLD stage III or IV had a higher prevalence of hypertension.[3] The INDACO project in Italy, a pilot study on the incidence of comorbidities in COPD patients referred to pneumology units, showed a 52.1% prevalence rate of hypertension among COPD patients.[11] Watz et al.,[27] in their study, also showed that hypertension was highly prevalent across all groups of COPD patients. A recent systematic review even showed that the most prevalent component of MetS in COPD was hypertension.[28] The pathological mechanisms responsible for hypertension in COPD are hypoxia-related vasoconstriction, free radical injury, endothelial dysfunction, and arterial stiffness.[4] Control of hypertension in COPD subjects can decrease cardiovascular-related mortality.[29] Note that these were observational studies comparing severity of airflow obstruction with normal lung function. We found no studies comparing severity of airflow obstruction using GOLD 1 as reference standard.

In contrast with our results, Lam et al.,[30] detected no association between airflow obstruction and increased BP. They found that among the five components of MetS, only central obesity was significantly associated with airflow obstruction.

We also found out that increased FBS was associated with very severe airflow obstruction. The prevalence of hyperglycemia in COPD is approximately about 3-12%. Systemic inflammation and steroid use could be important contributory factors responsible for both COPD and hyperglycemia.[4] Similarly, Mannino et al.,[3] also found out that COPD patients with severe and very severe airflow obstruction had a higher prevalence of diabetes (OR 1.5, 95% CI 1.1–1.9).

Across several studies on various countries, the frequency of MetS was highest in COPD GOLD II.[27,31,32] This could be due to a relatively higher influence of lifestyle on the body composition and metabolic health in the earlier stages of COPD in comparison to the COPD-induced triggers on wasting process in the more severe stages.[28] Moreover, in most of these studies, the most number of patients recruited were classified as GOLD II. This could also explain the higher prevalence of MetS in those with early stages of COPD. This was also true with our results that the frequency of MetS was significantly highest in COPD GOLD II. This was supported by the previous studies mentioned earlier.

Indeed, the prevalence of MetS in COPD is highly variable among studies. This is dependent on the criteria being used to diagnose MetS, the study inclusion criteria and the country or ethnicity being studied.[32] Several pathogenic mechanisms have been proposed which tried to establish the link between MetS and COPD, however, these are still poorly understood. These mechanisms include common pathophysiological mechanisms such as systemic inflammation, adipose tissue inflammation, physical inactivity, hypogonadism and the effect of steroids.[6,33,34]

It is notable that MetS was significantly higher using the NCEP/ATP-AHA/NHLBI criteria in comparison with IDF. This is consistent with the study of Morales et al.,[15] that among the different criteria of MetS, the NCEP/ATP-AHA/NHLBI criteria was able to detect most number of MetS compared with other diagnostic criteria. Moreover, the present NCEP/ATP-AHA/NHLBI statement, in contrast to IDF, maintains the previous ATP III criteria established

in 2001 except that the threshold for impaired fasting glucose was reduced from 110 mg/dl to 100 mg/dl, which corresponds to the criteria used by the American Diabetes Association which was eventually adapted in our local setting. In contrast, the IDF clinical definition for MetS makes the presence of abdominal obesity necessary for its diagnosis, which could be one reason that MetS is lower in Filipinos using the IDF criteria.[19]

Smoking is an established risk factor for COPD and has been associated with increased MetS prevalence and increased cardiovascular disease risk.[35] Given that this has been suggested as one of the major causes of systemic inflammation in association with COPD and MetS, the higher frequency of smokers in our sample may have contributed to the higher frequency of MetS. This is further supported by a population-based survey conducted in nine Asia-Pacific territories which revealed that among Filipinos with COPD, more than half were smokers.[36] Current statistics also indicate that nearly 30% of adult Filipinos smoke making COPD the seventh cause of mortality in our local setting.[37] The potential mechanism responsible for development of COPD and the MetS in a smoker is primarily due to systemic inflammatory response.[4]

Lastly, among the factors associated with MetS and COPD, we found out that BMI, number of pack-years, inhaled steroid use, and GOLD II were significant factors associated with MetS in COPD patients. Steuten et al.,[38] conducted a study to look at the association of severity of COPD and BMI and found out that COPD severity is affected by increasing BMI. A recently published study from Italy showed a statistical correlation among pack-years and the development of MetS.[39] There is a positive dose–response relationship between the daily number of cigarettes smoked and the duration of smoking and the risk of MetS. Even former smokers are at increased risk for the development of Mets because the risk has been shown to even persist for up to 20 years after smoking cessation.[40,41] Additionally, MetS is substantial in early stages of COPD such as GOLD I and GOLD II.[42]

The metabolic effects of systemic glucocorticoid therapy are well known affecting various parameters of the MetS.[4] In comparison with the oral or parenteral routes, inhaled corticosteroids (ICS) are known to produce relatively less systemic adverse effects.[43] All participants in our study who were on steroid therapy were using ICS. Our findings showed that those who were treated with ICS were three times more likely to have MetS. Though the systemic bioavailability of ICS is claimed to be minimal, a significant proportion of ICS can still reach the systemic circulation especially at high doses. In addition, the effects of ICS on the circulation is also dependent on the daily dosage as well as its pharmacodynamic and pharmacokinetic properties.[43] This could potentially explain the relationship of ICS and MetS in our study as we did not explore further the dosages of the ICS our study participants were taking.

The current analysis has few limitations. First, this study was a cross-sectional study which made it difficult to adequately describe the causal relationships of detected associations. Second, since systemic inflammatory response is a potential mechanism linking Mets and COPD, this study did not measure any marker of inflammation such as CRP, fibrinogen, interleukin-6, *etc*. Prospective longitudinal studies are needed for better understanding of the temporal relationship between MetS components and systemic inflammatory profile in patients with COPD among Filipinos. Third, we did not gather data on dietary intake as a possible confounder or effect modifier of the association of MetS and severity of airflow obstruction in patients with COPD. Lastly, we were not able to explore the dosages of ICS used by the participants as this may ascertain the potential association of ICS treatment and MetS in our study.

## CONCLUSION

In conclusion, our results showed that MetS was not associated with the severity of airflow obstruction. However, certain components of MetS such as elevated BP and elevated FBS were associated with the severity of airflow obstruction with the latter linked to very severe airflow obstruction or GOLD IV. Factors that were significantly associated with MetS among patients with COPD were BMI, use of inhaled steroids, and number of pack-years. COPD patients with moderate airflow obstruction were also three times more likely to have MetS. We recommend screening for MetS with early stages of COPD.

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

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CASE REPORT

# Conversion of Primary Hypothyroidism to Hyperthyroidism: A Case Report

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**Abstract**

A 51-year-old Caucasian male developed Graves' thyrotoxicosis following long-standing treatment for hypothyroidism. After a short period of treatment with carbimazole, he developed agranulocytosis and required total thyroidectomy. In this relevant case report, we review several pathogenetic mechanisms that explain the transformation of autoimmune hypothyroidism into Graves' disease and the possible approaches to the management of agranulocytosis secondary to antithyroid medications. Further studies are required to determine the best way to manage severe thyrotoxicosis when agranulocytosis develops due to antithyroid medications.

*Key words: hypothyroidism, Graves' disease, antithyroid drugs, carbimazole, agranulocytosis*

## INTRODUCTION

The incidence of autoimmune thyroid disease is approximately 12% in Australia, with a greater prevalence in women. Graves' disease and Hashimoto's thyroiditis are the most common forms of autoimmune thyroid disease.[1]

Autoimmune thyroid disease can involve one or more types of thyroid antibodies. These include the thyroid stimulating hormone (TSH) receptor antibodies, which can be divided into stimulating or blocking types. The former is thought to be the cause of Graves' disease. Additionally, thyroid peroxidase antibody and thyroglobulin antibody are thyroid-specific antibodies commonly found in thyroid autoimmunity.[2]

It is well known that Graves' thyrotoxicosis may be followed by hypothyroidism. However, development of Graves' thyrotoxicosis after a period of hypothyroidism is not a common phenomenon.[3]

The treatment for Graves' disease involves the use of antithyroid drugs such as carbimazole, methimazole and propylthiouracil. These medications are associated with several side effects, including pancytopenia and agranulocytosis. While the incidence and management of agranulocytosis is well documented, there are no clear evidence-based guidelines on the immediate management of Graves' disease if agranulocytosis occurs. A recent study employed the use of Lugol's solution with beta blockers to prepare patients for thyroidectomy with Graves' disease and found this was effective.[4] In this paper, we report a case of a man who developed agranulocytosis due to carbimazole to treat Graves' disease after long-standing primary hypothyroidism.

## CASE

A 51-year-old Caucasian male, was diagnosed by his General Practitioner with subclinical hypothyroidism in 2010 based on an elevated thyroid stimulating hormone level [10.7 mU/L, normal reference (NR) 0.40-3.50], normal FT4 and FT3 levels, and elevated thyroid peroxidase antibodies (604 IU/mL, NR 0-35).

His other medical conditions included hypertension, thalassemia minor, impaired glucose tolerance and cholecystitis. The patient was started on thyroxine 50 mcg daily (0.52 mcg/kg/day), and his TSH decreased to 4.09 mU/L after 6 months and then normalized to 2.99 mU/L. After an intervening normal TSH level, indicating adequate thyroxine replacement, the patient reported weight loss and restlessness in July 2016. His biochemistry was in keeping with hyperthyroidism with suppressed TSH (<0.005 mU/L) and elevated FT4 (18.8 pmol/L, NR 9-19) and FT3 (30.5 pmol/L, NR 2.6-6 ). His thyroxine dose was reduced before being totally discontinued by his General Practitioner. Thyroid function tests at this time showed TSH <0.005 mU/L (0.40-3.50), FT4 30.5 pmol/L (NR 9-19) and FT3 19.2 pmol/L (NR 2.6-6).

After 6 months there was little change in his thyroid function tests and he was commenced on propranolol 20 mg daily and referred to a local endocrinologist. On examination, he had a diffuse, mobile goiter, blood pressure of 135/80 mm Hg and a heart rate of 75 bpm with a weight of 95 kg with a BMI of 29.3. He appeared clinically euthyroid with no signs of dermopathy, acropachy, proximal myopathy or ophthalmopathy. A thyroid ultrasound revealed heterogenous echogenicity and increased vascularity (Figure 1). A pertechnetate uptake scan showed elevated

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thyroid uptake, consistent with Graves' disease (Figure 2). TSH receptor antibody (TRAb) titer was elevated at 15.3 IU/L (NR <2 ). Anti TPO at this time was 407.

He was given advice on precautions regarding agranulocytosis and commenced on carbimazole 15 mg daily. After 6 weeks of treatment with carbimazole, his thyroid function tests continued to show suppressed TSH of <0.005 mU/L with raised FT4 and FT3 of 26.4 pmol/L and 12.2 pmol/L, respectively. His total daily dose of carbimazole was then increased to 25 mg. However, he was subsequently admitted to the local hospital with agranulocytosis and fever of unknown origin twenty six days after the dose of carbimazole was increased. Blood tests on admission showed white cell count (WCC) of 1.2 x$10^9$/L and neutrophils of 0 x $10^9$/L. carbimazole was stopped and he was initially treated with filgrastim 300 mcg daily injections, intravenous cefepime 2 g QID for five days and a once-only dose of gentamicin 400 mg. Due to ongoing fever he was also commenced on vancomycin 1.5 g BID for three days concurrently. At this same time his dose of propranolol was increased to 20 mg BID. Subsequently, his neutrophil count improved on day 5. Finally, he was administered Lugol's iodine BID for 10 days and then underwent total thyroidectomy. Histological diagnosis was Graves' disease (Figure 3). Further analysis revealed chronic lymphocytic thyroiditis and oncocytic metaplasia (Figure 4). He is currently on thyroxine 150 mcg daily.

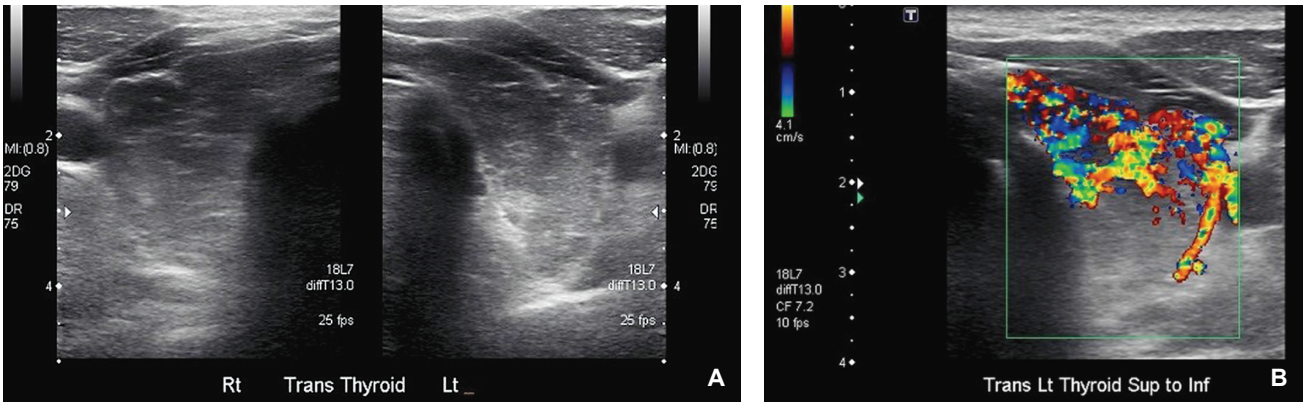


**Figure 1.** Ultrasound of the thyroid gland showing heterogenous echogenicity of the tissue parenchyma **(A)** and increased vascularity **(B)**.

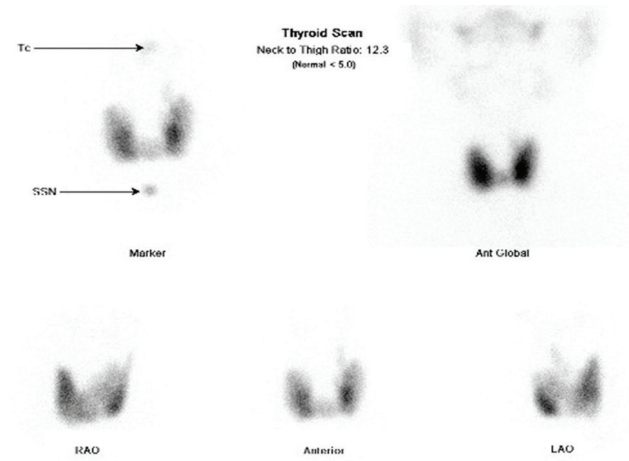


**Figure 2.** Thyroid scan showing increased pertechnetate uptake.

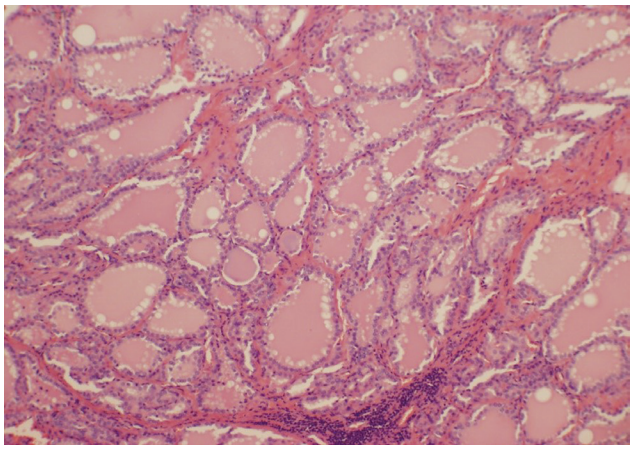

**Figure 3.** Histopathologic examination of the excised thyroid showed diffuse hyperplasia characterized by prominent scalloping in the thyroid follicles (H&E, 10x).

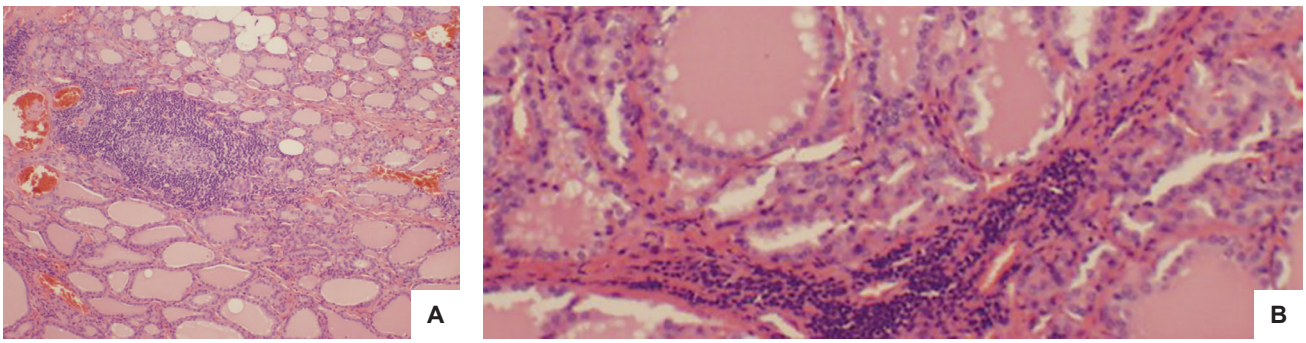


**Figure 4.** Histopathologic examination of the thyroid further revealed a background of chronic lymphocytic thyroiditis with lymphoid aggregates complete with germinal centres (H&E, 10x) **(A)** and oncocytic metaplasia with thyroiditis (H&E, 200x) **(B)**.

## DISCUSSION

In this case report, the patient had been on thyroxine replacement for approximately 6 years. During this period, thyroid antibodies were positive, although TSH receptor antibodies were not tested until early 2017. Our patient then went on to develop Graves' disease. He subsequently developed agranulocytosis secondary to carbimazole, requiring treatment with Lugol's iodine before undergoing total thyroidectomy.

The conversion of Hashimoto's thyroiditis to Graves' disease is documented in literature, but such cases are rare and are postulated to be due to a combination of atypical destructive thyroiditis and the development of antibodies associated with Graves' disease.[5] Several reports have suggested that Graves' disease can follow thyroid gland destruction.[5-8] One author postulated that autoimmune destruction initially produced a hypothyroid state, but the stimulatory effect of thyrotropin receptor stimulating antibodies (TSAb) and thyroid destruction may alter and subsequently create a hyperthyroid state.[5] There were also 2 studies that looked at several cases and proposed that the damage to thyroid tissue acted as the triggering factor for Graves' disease. This also involved the production of TSH receptor antibodies which changed effects from blocking to stimulating to produce a state of hyperthyroidism.[6-8] Another older proposed mechanism is that damage to thyroid epithelial cells leads to thyroid hormone leakage, which stimulates microsomal antigens and subsequently helper T cells to induce the production of thyroid antibodies.[7]

It is important to note that treatment with thyroxine can lead to an increase in ongoing antibody action or induce the production of TSAb in patients who may or may not have thyrotropin receptor blocking antibodies (TBAb).[9] It has been proposed that this could be due to a rise in serum T4 with replacement therapy, leading to an increased expression of stimulatory molecules that initiate antibody production. Alternatively, TBAb activity falls below the activity of TSAb, and a 'switch' occurs, often mediated by diminishing thyroid autoantibody levels secondary to antithyroid medications.[9]

It is well-documented in literature that the incidence rate of agranulocytosis with thionamides is 0.1-0.5%.[10] Thionamides remain the first-line treatment option for hyperthyroidism, and their mechanism of action involves inhibiting the thyroid peroxidase enzyme which decrease the production of T3 and T4.[2] The mechanism of agranulocytosis is poorly understood, with the consensus suggesting that the production of antibodies leads to an interaction with a granulocyte antigen, or causes depression of myelopoiesis.[10]

Two studies that looked at HLA profiles in the Asian population and one study in white European people concluded that some HLA genotypes were associated with antithyroid drug-induced agranulocytosis, and suggested individuals identified as carriers could potentially be offered alternative treatment at an earlier stage.[11-13] The cross-reactivity between methimazole and propylthiouracil is documented in literature, so that the use of a second antithyroid medication is contraindicated if the first antithyroid caused agranulocytosis.[14]

Most cases of agranulocytosis occur within 90 days of commencing antithyroid treatment but can occur when treatment is recommenced in the event of a relapse of hyperthyroidism.[14] The management of agranulocytosis that is induced by antithyroid medications is supportive therapy with antibiotics and G-CSF.[10]

The 3 current acceptable modalities for the treatment of hyperthyroidism are antithyroid medications, radioactive iodine and total thyroidectomy. Radioactive iodine was not selected for this patient because it can take up to 6 months before the full effect is achieved. Also, the patient was not well-controlled biochemically, even when he was taking carbimazole. The decision to undertake an urgent thyroidectomy was based on his clinical and biochemical instability. The patient was involved in this decision-making process.

One of the weaknesses in this case is that obtaining a TSAb level was not indicated at the time of diagnosis of hypothyroidism when the General Practitioner commenced thyroxine based on current guidelines of elevated thyroid peroxidase and TSH level >10 mU/L.

This case report illustrates a rare conversion of autoimmune subclinical hypothyroidism after 6 years of stable treatment with thyroxine to severe Graves' disease. While it is unclear if TRAb was positive early in the primary hypothyroidism state, it is evident that some cases of Graves' disease are preceded by states of hypothyroidism with TRAb present. Additionally, this case demonstrated the difficulty of treating a patient with hyperthyroidism complicated by agranulocytosis secondary to carbimazole. Further studies are required to investigate cross-reactions between antithyroid medications when agranulocytosis occurs, and other potential curative measures for hyperthyroidism following a primary hypothyroid state.

## CONCLUSION

Clinicians need be aware that, albeit rare, cases of Hashimoto's thyroiditis and hypothyroidism can convert to Graves' thyrotoxicosis. Antithyroid drugs remain the first-line treatment option for Graves' disease. Treatment options for thyrotoxicosis when agranulocytosis develops will need to be selected on a case-by-case basis. An experienced surgeon and an urgent thyroidectomy after a brief blockade with Lugol's iodine was selected in our patient. This resulted in a rapid cure, in the context of clinical and biochemical instability.

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

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

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Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

# Osteonecrosis of the Jaw and Bilateral Atypical Femoral Fracture Both Occurring During Treatment for Osteoporosis: A Case Report

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**Abstract**

Osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) are rare potential adverse effects of bisphosphonates and RANKL antibody therapy. The pathogenic mechanisms of both conditions are known to be independent of each other. Here, we report both conditions sequentially occurring in the same patient.

An 81-year-old, obese, diabetic, female was admitted due to hypertensive urgency and persistent jaw pain after tooth extraction. The patient has postmenopausal osteoporosis for fourteen years and was on intermittent, unsupervised treatment with alendronate, denosumab and ibandronate. Upon presentation, the patient was noted with tenderness intraorally of tooth number 35 periapical region. This was associated with elevated erythrocyte sedimentation rate and C-reactive protein. Imaging study showed presence of bony sclerosis which represent a sequestrum in the molar area of the left hemi-mandible. Antibiotic infusion and excision and debridement of left posterior mandible were done. Histopathologic finding was consistent with a diagnosis of osteonecrosis of the jaw. The same patient, upon review, had suffered sequential fracture of both femurs during the eighth and eleventh year of treatment with antiresorptive agents. The fractures were transverse, non-comminuted, at the proximal femoral shaft. Each occurred after a minor trauma and was managed with open reduction and internal fixation. Both fractures were consistent with atypical femoral fractures.

ONJ and AFF can occur both in the same patient during prolonged treatment with bisphosphonates and denosumab and may suggest a common pathogenic mechanism.

*Key words: osteonecrosis of the jaw, subtrochanteric fracture, osteoporosis*

## INTRODUCTION

Osteoporosis is being recognized as a growing health problem due to the aging population. Oral nitrogen-containing bisphosphonates such as alendronate and ibandronate, and human monoclonal antibody to the receptor activator of nuclear kappa B ligand (RANKL), denosumab are pharmacologic therapies for osteoporosis. Both agents have been shown to reduce the incidence of vertebral and non-vertebral (except ibandronate) fracture in patients with osteoporosis.[1] These drugs affect osteoclast function and formation and therefore are powerful inhibitors of bone resorption. Clinical trials have shown favorable safety and benefit profile of these antiresorptive agents.[2,3] The use of bisphosphonates and denosumab, however, has been linked to cases of osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF).

AFF and ONJ are individually recognized as rare serious adverse complications of antiresorptive therapy. The incidence of ONJ in patients with osteoporosis is estimated to be between 1/10,000 and 1/100,000.[4] Atypical femoral fracture, on the other hand, occurs in 1.8/100,000 person-years in patients treated with bisphosphonates for two years and up to 113/100,000 years when treatment is extended to 8-9.9 years.[5] The pathogenic mechanisms of both conditions are known to be independent of each other. We report a case of postmenopausal osteoporosis treatment complicated by both bilateral AFF and ONJ.

## CASE

An 81-year-old, Asian, female presented with persistent jaw pain after tooth extraction in 2016. The patient was a diagnosed case of postmenopausal osteoporosis since 2002, with a lumbar bone densitometry T score of -3.7. She had been on intermittent treatment with alendronate in 2002, 2007 and 2009-2013. Thereafter, she was given denosumab every 6 months from 2014-2016 and unknown to the primary physician, she also took ibandronic acid once a month for the past five months prior to presentation as prescribed by another physician.

For the past two years prior to her admission, the patient had intermittent toothache in the left inferior molar described as boring in character. She was previously advised to have tooth extraction by her dentist but did not consent and resolved with analgesics and antibiotics. Two weeks prior to admission, however, the patient had severe toothache prompting her to undergo tooth extraction. A week after, she developed more severe pain on the affected area now associated with swelling and lymphadenopathy.

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The same patient suffered fracture of both femurs on two separate occasions. First femoral fracture occurred in 2010 after patient accidentally slipped. The fracture was closed complete displaced at the proximal, mid femoral shaft, left (Figure 1). The second fracture occurred three years after (2013), also after a similar trauma. This was described as complete, closed, displaced on the proximal third of the right (Figure 2). Both fractures were managed with open reduction and internal fixation with intramedullary nailing of the femur.

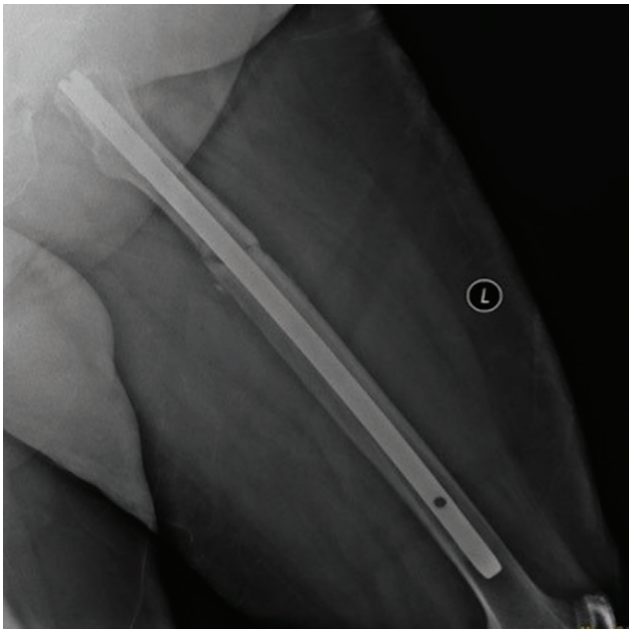


**Figure 1.** Radiograph of the first fracture of the patient on the left femur taken one year after open reduction and internal fixation.

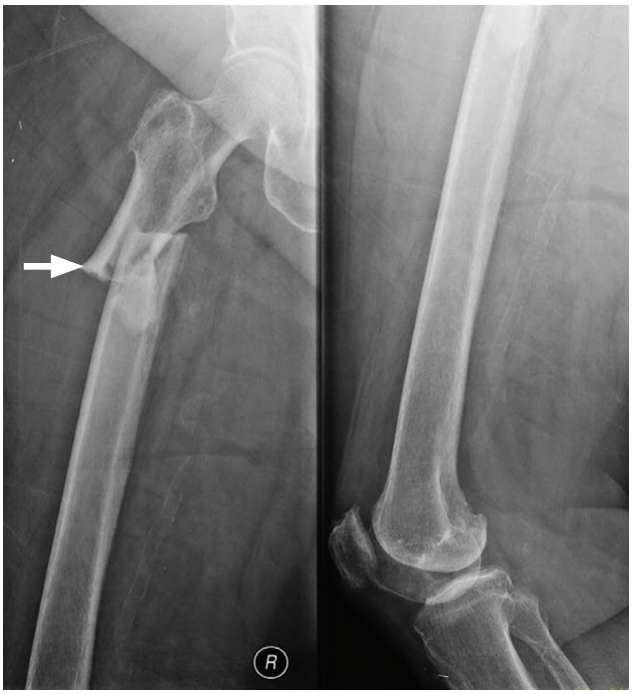


**Figure 2.** Radiograph of right femoral fracture, the second fracture of the patient, showing transverse fracture of the proximal femoral shaft. Also shown is the "beaking" (arrow) of lateral cortex at the fracture site as well as cortical thickening.

Other comorbidities of the patient include hypertension for more than 10 years, type 2 diabetes mellitus for 10 years, fairly controlled with glycosylated hemoglobin of 7.1%, and chronic kidney disease stage 3B secondary to DM nephropathy. Review of other medication of the patients include: aliskerin, verapamil, carvedilol, valsartan/HTCZ, spirinolactone, epoetin Beta, voglibose, sitagliptin, and insulin glargine. The patient was also previously on rosiglitazone and pioglitazone for five years until 2007. The patient's medications were prescribed by different physicians managing her comorbidities. The patient has no history of radiation therapy to the craniofacial region.

The patient was initially admitted due to hypertensive urgency with blood pressure of 200/100 mmHg, triggered by the severe toothache. She was obese with a body mass index of 31.2 kg/m$^2$. On examination, there was note of tenderness intraorally of tooth number 35 periapical region, palpable nodule periapical region tooth 35, no pus, no mandibular swelling (Figure 3). Other systemic findings were normal.

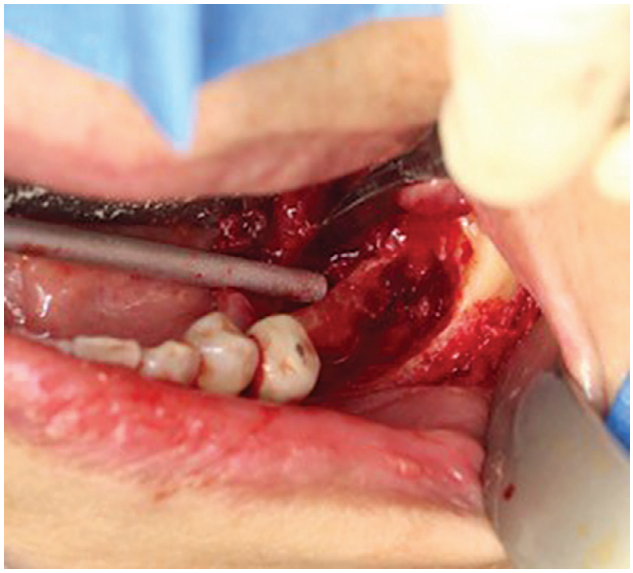

**Figure 3.** Preoperative photo of left mandibular area showing exposed bone, erythema and swelling of prior tooth extraction site.

On laboratory examination, the patient had normal complete blood count, elevated erythrocyte sedimentation rate (75 mm/hr, reference range: 0-30 mm/hr), high sensitivity C-reactive protein (14.4 mg/L, reference range: <5 mg/L), creatinine (264.32 umol/L, reference range: 49-90 umol/L), blood urea nitrogen (23.75 mmol/L, reference range: 3.5-7.2 mmol/L), intact PTH (10.12 pmol/L, reference range: <7.2 pmol/L), serum calcium (2.71 mmol/L, reference range: 2.10-2.55 mmol/L), and phosphorous (1.63 mmol/L, reference range: 0.74-1.52 mmol/L); serum 25-hydroxyvitamin D (25-OHD) was sufficient at 38.6 ng/mL (reference range >30 ng/mL).

Non-contrast computed tomography of the mandible showed presence of bony sclerosis seen in the molar area, medial to site of the recently extracted tooth in the left hemi-mandible, which represent a sequestrum (Figure 4).

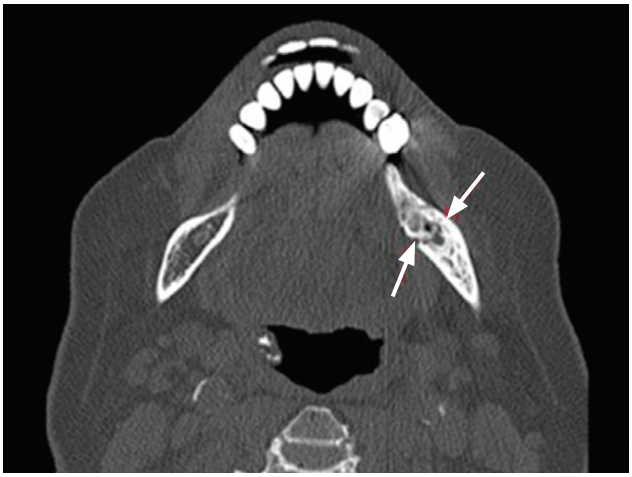

**Figure 4.** Non-contrast computed tomography scan (axial view) of the mandible. Bony sclerosis is seen in the molar area, medial to the site of the recently extracted tooth in the left hemimandible. Within the sclerosis, there is a lytic area (arrows) containing a focal osseous structure which may represent a sequestrum.

A multidisciplinary team including Oral and Maxillofacial Surgeon, Otorhinolaryngology and Head and Neck Surgeon, Endocrinologist, Cardiologist, Anesthesiologist, Infectious Disease Specialist and Nephrologist managed the patient. The blood pressure, blood glucose and pain of the patient were controlled medically. The patient was also given intravenous antibiotics. Excision and debridement of left posterior mandible were done with a finding of necrotic bone, described as dark in color. Histopathology reported acute and chronic inflammatory cells around necrotic bone fragments mixed with colonies of bacteria. The patient tolerated the procedure well and was discharged on the fourth post-operative day. She was placed on a drug holiday.

## DISCUSSION

The American Society of Bone and Mineral Research (ASBMR) revised the diagnostic criteria for AFF in a published report in 2014.[5] AFF can be recognized if the fracture is located at femoral diaphysis between distal part of the lesser trochanter and proximal part of the supracondylar flare and satisfies at least four of five major features (Table 1). AFFs appear to be more common in patients who have been exposed to long-term bisphosphonates, usually more than three years, while risk for AFFs decline with cessation of bisphosphonate treatment.[5] Additional risk factors recognized but not consistent in studies were prior low-energy fracture, glucocorticoid therapy for more than six months, active rheumatoid arthritis, serum 25-hydroxyvitamin D (25-OHD) concentration below 16 ng/mL, female gender, younger age, diabetes and use of proton-pump inhibitor.[5,6] The pathogenesis of AFF is also still not fully understood but is also thought to be related to altered bone remodeling by antiresorptive agents which is supposed to repair microcracks formed by mechanical stresses. Long-term decrease in bone turnover also leads to deterioration of mechanical properties of bone tissue.

The femoral fractures reported in the case satisfied all the major criteria for AFF by ASBMR (Table 1) and most of the minor criteria including generalized increase in cortical thickness of the femoral diaphysis, bilateral complete femoral diaphysis fractures and delayed fracture healing. The first AFF of the patient occurred after intermittent use of alendronate for five years. Given the high-risk for occurrence of osteoporosis-related fracture, bisphosphonate treatment was continued until the second fracture being now recognized as AFF and a complication of bisphosphonate. The earliest atypical femoral fracture reported with bisphosphonate use for osteoporosis was after 1.5 years with risk increases with longer duration of treatment.[7] Aside from bisphosphonate use, additional risk factors for AFF present in the patient are female gender and diabetes. There is also note of increase incidence of AFF among Asians.[7] Treatment recommendation by ASBMR for AFF includes discontinuation of bisphosphonates, adequate calcium and vitamin D supplementation, limitation of weight-bearing through the use of crutches or a walker for patients with minimal pain, prophylactic nail fixation and therapy with teriparatide.[6]

ONJ is characterized by an exposed necrotic bone in the maxillofacial region persisting for at least eight weeks despite appropriate therapy in a patient with exposure to potent antiresorptive or anti-angiogenic agents with no history of radiation therapy to craniofacial region.[4] Although the pathogenesis of ONJ is still unclear, it is thought that the antiresorptive agents by altering bone remodeling as well as by their antiangiogenic property, in combination with trauma such as a tooth extraction or inflammation/infection from periodontal or periapical disease can lead to bone necrosis.[4]

**Table 1.** American Society for Bone and Mineral Research (ASBMR) Task Force 2013 Revised Case Definition of Atypical Femoral Fractures (AFFs)[5]

| | |
|---|---|
| To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five Major Features must be present. None of the minor features is required but have sometimes been associated with these fractures | |
| Major features[a] | • The fracture is associated with minimal or no trauma, as in a fall from a standing height or less<br>• The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur<br>• Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex<br>• The fracture is noncomminuted or minimally comminuted<br>• Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”) |
| Minor features | • Generalized increase in cortical thickness of the femoral diaphyses<br>• Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh<br>• Bilateral incomplete or complete femoral diaphysis fractures<br>• Delayed fracture healing |

[a] Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (e.g., Paget’s disease, fibrous dysplasia).

The risk of ONJ among osteoporotic patients exposed to bisphosphonates or denosumab is very low, but significantly increases over time to 0.21% from a baseline of 0.1% after four years or more of exposure to bisphosphonates.[4] Dentoalveolar surgery is a major risk factor for developing medication-related ONJ. Other risk factors include dentures, preexisting dental disease, corticosteroid use and co-morbidities such as anemia and diabetes.[4] Risk factors for the development of ONJ in the patient include at least nine years of treatment with antiresorptive agents as well as dental extraction.

Diabetes was also reported to be 58% prevalent among patients with medication-related ONJ with presence of diabetic nephropathy even increasing the risk further.[8] The presence of pain, swelling, presence of sequestrum on radiograph further strengthen the diagnosis of ONJ. Surgical resection of necrotic bone, antibiotic therapy and pain control were in congruence with the recommended stage-specific treatment strategies by the American Association of Oral and Maxillofacial Surgeons.[4] Hyperbaric oxygen as adjunct to treatment of ONJ has been shown to improve healing but there is not enough evidence to recommend this treatment modality.[4] Discontinuation of antiresorptive therapy until soft tissue closure has occurred should also be considered, though there is limited data to support this. Preventive measures against ONJ in patients on antiresorptive therapy involves maintenance of excellent oral hygiene and cessation of smoking and should be emphasized.[4] Invasive dental procedures such as dental extractions or implants should be avoided, if possible.

Although the pathogenic mechanisms of ONJ and AFF differ, a common pathogenesis for both explains that the jaw bone and lateral cortex of subtrochanteric area of femur endure more mechanical stress compared to other bones and therefore may be prone to damage and demand repair through bone remodeling. Bisphosphonates and denosumab by inhibiting osteoclast function and bone resorption, impair this bone remodeling process.[7] Occurrence of one of the two serious complications of antiresorptive therapy should prompt reconsideration of the risks and benefits of further antiresorptive treatment. Drug holiday should also be observed to minimize side effects in long-term treatments. Most experts and guidelines recommend a drug holiday after 4-5 years of treatment with bisphosphonates in patients at moderate risk of fracture, and after 10 years for high-risk patients.[1] Bisphosphonates accumulate in bone with some persistent anti-fracture efficacy after therapy is stopped. In contrast, the anti-resorptive effect of denosumab wears off rapidly after it is stopped, hence, drug holiday for this agent has not been defined.

The occurrence of both ONJ and AFF in one patient is very rare. In our literature search, this is only the fifth published report of ONJ and AFF occurring in the same patient. Of the previous four cases reported, three were Oriental women[9-11] and one Caucasian woman.[12]

Another important lesson learned from this case is that all doctors must do regular review of medications. Our patient was prescribed with two antiresorptive medications at the same time, which could have increased the risk for the side effect of the treatment particularly the ONJ. Open and complete communication among health care professionals and between the patient and health care professionals must be maintained. The patient should be warned about the possible side effects of treatment but be assured that proper screening and follow up can minimize his/her risk. Early dental consultation and dental preventive measures prior to initiation of antiresorptive therapy is recommended.[4]

## CONCLUSION

ONJ and AFF can both occur in the same patient during prolonged treatment with bisphosphonates and RANK-L inhibitor and may suggest a common pathogenic mechanism. Occurrence of any of these two complications should prompt reconsideration of the risks and benefits of further antiresorptive therapy. Patient education and vigilance on the occurrence of symptoms and risk factors such as thigh pain, trauma, dental extraction as well as emphasis on follow up care should be observed in all patients receiving long-term antiresorptive drugs. This case further emphasized that bisphosphonates should be given for a limited period to avoid these consequences, particularly in patients with additional risk factors.

**Ethical Consideration**
The authors submitted a letter of permission from the Makati Medical Center Institutional Review Board (MMCIRB) to publish the case.

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

**Author Disclosure**
The authors declared no conflict of interest.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

# Case Report of an Adult Female with Neglected Congenital Adrenal Hyperplasia (CAH)

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**Abstract**

An apparently well 27-year-old phenotypically male adult was seen at the endocrine clinic for gender assignment. Patient had been raised as a male and identifies as such. Abdominal CT scan showed a unilateral left adrenal mass and karyotyping revealed 46 XX female karyotype. She was diagnosed to have simple virilizing CAH and needed thorough counselling with subsequent management by a multidisciplinary team.

*Key words: Congenital Adrenal Hyperplasia (CAH), 17-hydroxyprogesterone, gender assignment*

## INTRODUCTION

Congenital Adrenal Hyperplasia is an autosomal recessive disorder with 21-hydroxylase deficiency accounting for most cases.[1] Hydrocortisone is the treatment of choice in children but management of the adult patient remains controversial.[1] Few doctors are trained to manage adults with rare genetic conditions like CAH.[2] Adrenocortical tumors in CAH are not rare but are mostly benign.[3] This case report highlights the challenges in both physical and psychological management of an adult female with neglected CAH who has been raised as a male.

## CASE

A 27-year-old patient was referred to the adult endocrine team for gender assignment as the National Registration Department (NRD) required this information when she needed an identification card to apply for a driving licence. Patient was diagnosed with ambiguous genitalia at birth but was subsequently lost to follow-up. Antenatal period was uneventful and she remained relatively well thereafter, having no reason to seek medical attention. In primary school, she was the tallest in class, but shortest when in secondary school. Academic performance was average. She is the 6th of 7 siblings from a consanguineous marriage and had a brother who died suddenly at 2 months of age. She is 143 cm tall with mid-parental height of 154 cm. She exhibits external male body habitus and has a high pitched voice. Pubic hair was Tanner 4 with marked clitoromegaly measuring 3.5 cm, prominent labia majora and no palpable testes. She had never experienced vaginal bleeding and was not sexually active. Blood investigations revealed FSH-8.2 IU/L (1.79-22.5), LH-6.4 IU/L (2.12-12.86), testosterone-7.6 nmol/L (0.3-2.1), progesterone-32.1 nmol/L (<5-60), estradiol-448 pmol/L (84-1068), TSH-1.82 mIU/ml (0.4-4.0) and cortisol-138.2 nmol/L (193-772). Serum 17-OH progesterone level was >60.6 nmol/L (0.9-7.58) and cytogenetic analysis showed 46,XX apparently normal female karyotype. Abdominal CT scan showed a 4.1 x 4.7cm left adrenal mass, 39-42 HU on plain scan that enhanced with contrast (Figure 1A and B). The right

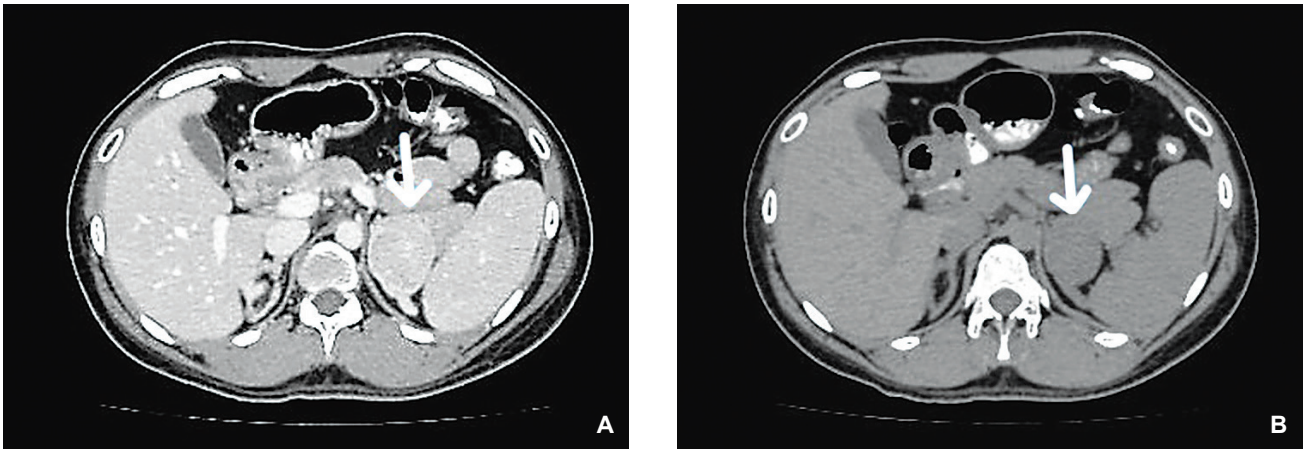


**Figure 1A and B.** Abdominal CT scan of the patient [**(A)** plain and **(B)** with contrast]. Arrows show a left adrenal mass.

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adrenal gland appeared normal. Bilateral ovaries and a small uterus were seen. After detailed assessment and discussion including consultation with the local religious authority, patient was assigned male gender given his upbringing and own preference.

## DISCUSSION

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder with 21-hydroxylase deficiency accounting for up to 95% of cases.[1] The clinical phenotype of CAH is typically classified into three, namely; classic salt losing, classic non salt losing (simple virilizing) and nonclassic forms. Although the same gene, CYP21A2, is involved, genetic mutations in the milder forms only partially impair 21-hydroxylase activity.[1] Treatment is aimed at replacing cortisol and aldosterone and controlling hyperandrogenism. Treatment of CAH especially in the adult patient, remains controversial.[1]

Our patient's history suggests the simple virilizing form of CAH. She was lost to follow-up in early childhood leading to sub-optimal treatment, posing unique challenges in management as an adult. She has been well for the past 27 years with no hospital admissions; suggesting she never experienced adrenal crisis. A CT scan of the abdomen showed unilateral left adrenal hyperplasia with a left adrenal mass. She has been brought up as a male all her life and identifies as such given that she phenotypically exhibits a male body habitus. This raises the following issues; (i) the role of steroids, (ii) management of the adrenal mass and (iii) gender identification. We will address this in turn.

Androgen excess is always a problem for women with simple virilizing CAH, but the degree and clinical consequences vary.[2] At minimum, all affected women must receive physiological replacement doses of glucocorticoids.[2] Some patients, like ours, may do well for years without replacement dose glucocorticoids, but this predisposes them to life threatening adrenal crisis should they experience significant stress.[2] Higher doses of steroids are used to address hyperandrogenism if it is a concern.[2] Our patient was not troubled by the virilization and self identifies as a male. Physiological dose of steroids is recommended but treatment aimed at reducing hyperandrogenism may paradoxically cause more distress.

Chronic adrenal gland enlargement in CAH is associated with increased prevalence of adrenal tumors, including myelolipomas, especially if CAH is poorly controlled. It is believed to be due to chronic adrenocorticotropic hormone (ACTH) stimulation leading to adrenocortical cell metaplasia.[3] Reported prevalence rates of adrenocortical masses in homozygote patients are up to 83%. Adrenocortical masses may be bilateral or unilateral.[4] Majority are benign but adrenal carcinoma has been described previously in four cases with CAH.[4] Adrenal tumors in patients with CAH should be managed similarly to those without CAH. Our patient would need a detailed adrenal CT and possible surgical intervention should the mass be suspicious. However, despite every effort to convince her, she is not willing to undergo further tests or interventions as she feels well. This poses a challenge in the prognostication of the adrenal mass.

A major clinical manifestation of CAH is disorder of sex development (DSD), characterized by difficulty identifying gender from external genitalia as was the case with our patient. Gender identity is a sensitive issue carrying social, psychological and religious implications. Gender identity refers to an individual's subjective internal sense of being a male or a female.[5] There are differing opinions about the time of gender assignment of a child with DSD; some psychologists suggest postponing it until after puberty and then to act according to the desire of the patient while other authors say it should be done according to the grade of virilization whereby a girl with more severe virilization should be raised as a boy.[6] A study by Maryam et al., in 2017 among patients with CAH suggested that karyotype did not have a role in gender identity. Hormonal disposition after birth had more effect on gender identity than intrauterine hormones and chromosomal parameters.[6] In cases of delayed presentation as with our patient, a meticulous discussion with the patient in the presence of a multi-disciplinary team should be undertaken. Gender assignment should ultimately be decided based on the patient's perception and preference.[7] Continuous effort should be made in helping the patient through psycho-social and legal challenges that may be faced. Genital reconstruction surgery should be offered if appropriate. Our patient should have undergone thorough psychosocial assessment and counselling but this was no longer pursued due to her reluctance to attend further clinic visits.

## CONCLUSION

Delayed diagnosis and the subsequent management of CAH present a unique set of challenges that needs to be addressed on an individual basis.

**Ethical Consideration**
The authors submitted a letter of permission from the Head of the Department of Medicine of Hospital Raja Perempuan Zainab II to publish the case.

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

**Author Disclosure**
All the authors declared no conflict of interest.

**Funding Source**
None.

**References**
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# PRINCIPLES OF TRANSPARENCY

## & Best Practice in Scholarly Publishing

**Committee on Publication Ethics (COPE),** the **Directory of Open Access Journals (DOAJ),** the **Open Access Scholarly Publishers Association (OASPA),** and the **World Association of Medical Editors (WAME)** are scholarly organizations. All have seen increases in the number, and range in quality, of membership applications. Our organizations have collaborated to identify **Principles of Transparency & Best Practice for Scholarly Publications.** These principles form the basis of the criteria by which suitability for membership is assessed by **COPE, DOAJ** and **OASPA,** and part of the criteria on which membership applications are evaluated by **WAME.**

### WEBSITE

**A Journal's website, including the text that it contains, shall demonstrate that care has been taken to ensure high ethical and professional standards.**

**It should:**

– contain an 'Aims & Scope' statement and the readership clearly defined.

– include a statement on what a journal will consider for publication including authorship criteria e.g. not multiple submissions, redundant publications)

– ISSNs displayed clearly (separate for print and electronic).

**It must not:**

– contain information that might mislead readers or authors.

– attempt to mimic another journal/ publisher's site.

### NAME OF JOURNAL

**The Journal name shall be unique.**

**It must not:**

– be one that is easily confused with another journal.

– mislead potential authors and readers about the Journal's origin or association with other journals.

### PEER REVIEW PROCESS

**Journal content must be clearly marked as whether peer reviewed or not. Peer review is defined as obtaining advice on individual manuscripts from reviewers expert in the field who are not part of the journal's editorial staff.**

**The journal's website should:**

– clearly describe this process, as well as any policies related to the journal's peer review procedures including the method of peer review used.

**The journal's website should not:**

– guarantee manuscript acceptance or very short peer review times.

### OWNERSHIP AND MANAGEMENT

**Information about the ownership and/or management of a journal shall be clearly indicated on the journal's website.**

**Publishers should not:**

– use organizational or journal names that would mislead potential authors and editors about the nature of the journal's owner.

### GOVERNING BODY

**Journals shall have editorial boards or other governing bodies whose members are recognized experts in the subject areas included within the journal's scope.**

**The journal's website should:**

– show full names and affiliations of the journal's editorial board or other governing body.

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**Journals shall provide the full names and affiliations of the journal's editors on the journal website as well as contact information for the editorial office, including a full address.**

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**The policy for copyright shall be clearly stated in the author guidelines and the copyright holder named on all published articles.**

**The journal's website should:**

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### AUTHOR FEES

**Any fees or charges that are required for manuscript processing and/or publishing materials in the journal shall be clearly stated.**

**This must be:**

– in a place that is easy for potential authors to find prior to submitting their manuscripts for review

OR

– explained to authors before they begin preparing their manuscript for submission.

– if no such fees are charged that should also be stated.

*Each organization also has their own, additional criteria which are used when evaluating applications. The organizations will not share lists of publishers or journals that failed to demonstrate that they met the criteria for transparency and best practice. This is the third version of a work in progress (published January 2018); the first version was posted on the **COPE** website on January 2014 and a second version in June 2015. We encourage its wide dissemination and continue to welcome feedback on the general principles and the specific criteria.*

publicationethics.org doaj.org oaspa.org wame.org

In the event that a member organization is found to have violated these best practices, or other specific requirements of the organization, **OASPA/DOAJ/COPE/WAME** shall in the first instance try to work with them in order to address any concerns that have been raised. In the event that the member organization is unable or unwilling to address these concerns, their membership in the organization may be suspended or terminated. All of the member organizations have procedures for dealing with concerns raised about member journals.

## ALLEGATIONS OF RESEARCH MISCONDUCT

**Publishers and editors shall take reasonable steps to identify and prevent the publication of papers where research misconduct has occurred.**

**This includes but not limited to:**

– plagiarism
– citation
– manipulation
– data falsification/fabrication

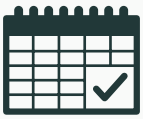
In no case shall a journal or its editors encourage such misconduct, or knowingly allow such misconduct to take place. In the event that a journal's publisher or editors are made aware of any allegation of research misconduct relating to a published article in their journal, the publisher or editor shall follow **COPE's** guidelines (or equivalent).

## PUBLICATION ETHICS

**A journal should have policies on publishing ethics. These should be clearly visible on its website, and should refer to:**

– journal policies on authorship and contributorship
– how the journal will handle complaints and appeals
– journal policies on conflicts of interest/competing interests
– journal policies on data sharing and reproducibility
– journal's policy on ethical oversight
– journal's policy on intellectual property
– journal's options for post-publication discussions and corrections.

## PUBLISHING SCHEDULE



**The periodicity at which a journal publishes shall be clearly indicated.**

## ACCESS

**The way(s) in which the journal and individual articles are available to readers and whether there are associated subscription or pay per view fees shall be stated.**

## ARCHIVING

**A journal's plan for electronic backup and preservation of access to the journal content shall be clearly indicated (for example, access to main articles via CLOCKSS or PubMedCentral).**

**This is in the event that a journal is no longer published.**

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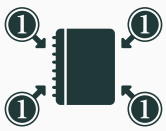

**Business models or revenue sources shall be clearly stated or otherwise evident on the journal's website.**

**For example:**

– author fees
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– institutional support
– organizational support

Publishing fees or waiver status should not influence editorial decision making.

## ADVERTISING

**Journals shall state their advertising policy if relevant including:**

– what types of adverts will be considered
– who makes decisions regarding accepting adverts
– (online only) whether they are linked to content or reader behavior or are displayed at random.

Advertisements should not be related in any way to editorial decision making and shall be kept separate from the published content.

## DIRECT MARKETING

**Any direct marketing activities, including solicitation of manuscripts that are conducted on behalf of the journal, shall be appropriate, well targeted, and unobtrusive.**

Information provided about the publisher or journal is expected to be truthful and not misleading for readers or authors.

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

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

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## ARTICLE TYPES

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

## COVER LETTER

UPDATE

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

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

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

## AUTHOR FORM

UPDATE

For submission to the JAFES to be accepted, all authors must read and sign the **JAFES AUTHOR FORM** consisting of: (1) the Authorship Certification, (2) the Author Declaration, and (3) the Statement of Copyright Transfer. Aside from certifying that all undersigned authors have qualified for authorship, the authors are obliged to specify their specific contributions to the manuscript in terms of: conception and design of the work, data analysis and interpretation, writing the article, critical revision of the article for important intellectual content, final approval of the version to be published, data collection, provision of materials, patients, resources, statistical analysis, obtain funding, literature search and accountability of all aspects of the work. The completely accomplished JAFES Author Form shall be scanned and submitted along with the manuscript. No manuscript shall be received without the JAFES Author Form.

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

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

UPDATE

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

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

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

## ETHICS REVIEW APPROVAL

UPDATE

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

## INFORMED CONSENT

UPDATE

For Case Reports, Images in Endocrinology and Clinical Case Seminars, authors are required to submit scanned soft copy of signed informed consent for publication from the involved subject/s ("Patient Consent Form"); otherwise, an appropriate ethical clearance should be obtained from the institutional review board.

## GENERAL GUIDELINES

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

**Title Page**

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

**Abstract**

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

**Keywords**

At least 3 keywords but no more than 6, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

**Text**

1. Generally, the text should be organized consecutively as follows: Introduction, Methodology, Results and Discussion, and Conclusion (IMRAD format).
2. All references, tables, figures and illustrations should be cited in the text, in numerical order.
3. All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the long names.
4. All measurements and weights should preferably be in System International (SI) units.
5. If appropriate, information should be provided on institutional review board/ethics committee approval.
6. Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

**References**

1. References in the text should be identified by Arabic Numerals in superscript on the same line as the preceding sentence.
2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
3. All references should provide inclusive page numbers.
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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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Padua FR, Paspe MG. Antinuclear antibody in the rheumatic and non-rheumatic diseases among Filipinos. Acta Med Philippina. 1990; 26(2):81-85.

***One to Six Authors (Commentary, Online)***

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

Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. JTranslational Med. January 20, 2004;2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the US. JAMA. 2001;286(10):1195-1200.

***More than Six Authors***

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

***Authors Representing a Group***

Moher D, Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-1991.

***Book***

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

***World Wide Web***

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

**Tables**

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

**Figures and Graphs**

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

**Illustrations and Photographs**

1. Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as.jpeg or.gif files).
2. For photomicrographs, the stain used (e.g., H&E) and magnification (e.g., X400) should be included in the description.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn or printed on good quality laser printers. Photocopies are not acceptable.
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**N.B.:** For tables, figures, graphs, illustrations and photographs that have been previously published in another journal or book, a note must be placed under the specific item stating that such has been adapted or lifted from the original publication. This should also be referenced in the **References** portion.

**PROCESS**

1. Upon receipt of the manuscript, the Editor shall review the submission, check if it has met aforementioned criteria and consult with members of the Editorial Board to decide whether it shall be considered for publication or not.
2. Within one (1) week of submission, authors shall be notified through e-mail that their manuscript either (a) has been sent to referees for peer-review or (b) has been declined without review.
3. The JAFES implements a strict double blind peer review policy. For manuscripts that are reviewed, authors can expect an initial decision within forty five (45) days after submission. There may be instances when decisions can take longer than 45 days, in such cases, the editorial assistant shall inform the authors. The editorial decision for such manuscripts shall be one of the following: (a) acceptance without further revision, (b) acceptance with minor revisions, or (c) major manuscript revision and resubmission.
4. Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal.

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

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

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

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

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

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

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

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

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

| Checklist Guide for Submission of Manuscripts to JAFES | |
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| **Instructions to Authors** | ☐ Review manuscript submission guidelines |
| **Cover Letter** | ☐ Include cover letter as an attachment<br>☐ Indicate in the letter the title of the work<br>☐ Indicate all the authors (complete names, affiliations, ORCID iD, specific role/s in writing the manuscript and email address)<br>☐ Indicate in the letter the corresponding author and provide complete contact information (post address, telephone, fax number, e-mail address) |
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## Instructions

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

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This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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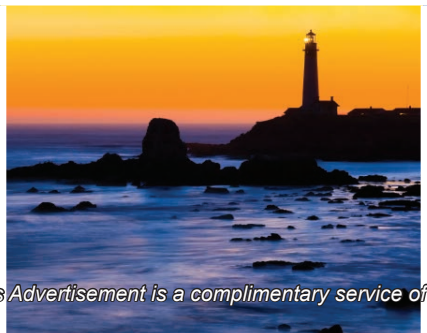

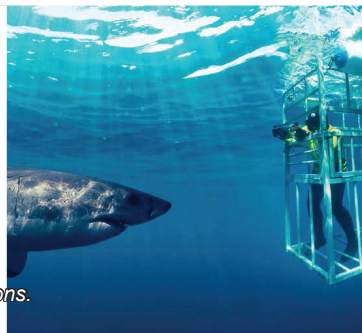

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