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JAFES

Journal of the
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JAFES

# Crossroad

For the recent 12 years, JAFES has maintained a nurturing approach for its authors, valuing manuscript acceptance over rejection, exerting as much assistance to authors as possible, seeing scientific merit beyond language barriers, and transforming submitted drafts into papers fully worthy of publication. Through the support of its member societies under the AFES banner, the journal has been able to survive and thrive for another decade and two, proudly showcasing Southeast Asian research on endocrinology.

You have been a witness to the steady growth of JAFES, incorporating international standards and best practices along the way, to be indexed in Scopus, Clarivate Analytics (formerly Thomson Reuters), and PubMed Central. The journal is constantly evolving for the better, and we in the Editorial Team have been hopeful that the improvements in policies, peer review, and manuscript production, will translate to more new submissions. However, the road is far from fully paved: given that JAFES *is for AFES,* we have yet to see the even increase in the number of articles received from all of our member country societies.

We continue to implement our society-funded Open Access model, such that article processing charges are 100% subsidized through the support of the AFES societies, and not to impose charges to authors. We look at this as a way of giving back to the society members and to encourage submissions from all the Southeast Asian countries. This financial model may need to be revisited by AFES in the context of sustainability.

The Philippine endocrinologists, especially those in fellowship training, through the society, continue to patronize JAFES as their journal-of-choice, and this is reflected in the number of articles published by the country. While Malaysia, Indonesia, and Myanmar are able to publish more articles in JAFES over the years, the growth is still modest in submissions and journal metrics (which are computed based on citation data of published articles). Metrics, as a measure of journal quality, are very much a reality in the academic or scientific world: JAFES would actually need more years of publication, and more citation data, to be able to achieve a level of metrics that would entice more authors to select it as their publication pathway.

Meanwhile we are attempting to enhance engagement further, through our visual abstract team, and by tapping into social media. This year we plan to hold a visual abstract workshop for interested researchers from the region to be able to summarize their manuscripts' key findings in one graphic, as a way of promoting the journal among readers. Perhaps, it is also time to consider more marketing strategies, given the sheer number of journals competing for researchers' attention.

Thanks to digital technology, we in the Editorial Team have been allowed to directly reach out to each country society, and ask them their individual needs and concerns, and their take on the future of JAFES. Mutually we are glad to be able to meet, discuss these important administrative matters, and, more importantly, to affirm our continuing commitment to quality and ethical publication.

There is a continuing journey ahead of us, but at this point JAFES has come to another crossroad. This year, 2022, there will be an AFES Congress. Although still virtual, this will still give us a chance to reconnect with our colleagues from across the region. It is our hope that the leadership of AFES, our publisher, will be able to set the direction and light the way once more for JAFES.

Elizabeth Paz-Pacheco
Editor-in-Chief

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

# Comparison of Modified Rose Method of Thyroid Palpation Versus Other Methods for the Detection of Retrosternal and Nodular Goitre

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**Abstract**

Objectives. This is a diagnostic test research study to evaluate the various existing methods of thyroid examination and their comparison with the novel modified Rose method. It also aims to measure inter-examiner variation in clinical findings based on the level of education and training, as compared to ultrasonography.

Methodology. This cross-sectional study was conducted at a tertiary care hospital with 83 patients presenting to surgery OPD with neck swelling. Each patient was examined by one trained Junior Resident and a Surgery Consultant with all the four methods and with ultrasonography. Data was analysed by Stata-14, agreement between the two categorical variables was assessed by Kappa. In case of continuous variable agreement was assessed by Intra class correlation and Bland-Altman plot.

Results. Modified Rose method by the consultant has the highest sensitivity (98%) and diagnostic odds (210) as compared to others but its specificity ranges from 46.7-91.1% to diagnose retro-sternal extension of a goiter. It has 93.98% agreement for identification of nodules. It has a high specificity (Consultant - 100%, Resident - 95.5%) with relatively lower sensitivity (Consultant - 94%, Resident - 86.8%) to diagnose solitary thyroid nodule (STN) but the sensitivity and specificity for diagnosing a multinodular goitre (MNG) was high. However, the highest sensitivity to diagnose STN was highest with Crile's method, but specificity was low. Lahey's method was a better clinical method to palpate lymph nodes compared to the other three.

Conclusion. Examination in modified Rose's position is a better method of clinical examination of thyroid especially in patients with occult substernal extension. Lahey's method is a better method to examine cervical lymph nodes.

*Key words: clinical thyroid examination, modified Rose position, modified Rose method, Kappa statistic, retro-sternal extension*

## INTRODUCTION

The burden of thyroid diseases is on the rise including both benign and malignant conditions.[1] Thirty percent of Indians suffer from a thyroid disorder.[1] The clinical spectrum is wide but the most common presentation is thyroid swelling.[2,3] Improvement in imaging techniques pick up small nonpalpable nodules in its incipient stage causing increase in the incidence.[4]

Periodic neck sonogram is ideal but does not happen, especially once the patient knows that the swelling is not malignant. Follow up surveillance with ultrasound and/or cytology for initially nodules is individualized based on sonographic features.[5] In low-income countries, the ultrasound (US) and computerized tomography (CT) of the thyroid are expensive, limiting the evaluation to the physical examination of thyroid abnormalities. Some of the previous methods of thyroid physical examination are still largely insensitive or non-specific with lack of evidence of their accuracy.

One grey zone of clinical examination of thyroid swelling is the palpability of the lower border which comes in handy for ruling out retrosternal goitre. A retrosternal goitre is defined when 50% of the mass is in the mediastinum.[6] Ultrasonography cannot comment on the intrathoracic extension and fine needle aspiration cytology (FNAC) is not feasible. CT/magnetic resonance imagining (MRI) is required to rule it out. Due to the high cost of these imaging

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modalities, patients need to be segregated into those who absolutely need them from those who do not.

The purpose of this study is to evaluate the diagnostic indices of different methods of physical examination and to comment on the inter-examiner variation in the physical findings of various clinical methods with training as compared to ultrasonography, which is the gold standard.

## METHODOLOGY

This cross-sectional observational study was conducted at the Department of Surgery of a tertiary care University teaching hospital after ethical clearance. Patients with neck swellings over the front of the neck region moving with deglutition, who attended the outpatient Department of Surgery and Endocrinology, were enrolled after an informed consent was taken. Patients who had either received prior interventions (core needle, incisional biopsy, and surgical intervention) or refused for consent were excluded from study.

### Sample size

Sample size for the study was computed to estimate sensitivity and specificity of lower border visibility of thyroid swelling based on the following assumptions: Both sensitivity and specificity of any of the four tests as 90%; absolute precision as 10% and 95% confidence level. We required thirty-five patients having visible lower boundaries and thirty-five patients with lower boundaries that are not visible. Assuming that in 50% of the patients with goiter, the lower boundaries would be visible, we needed to enroll seventy patients. However, considering potential missing values, we enrolled eighty-three patients in the study.

### Details of clinical examination

Detailed examination of neck region in sitting and lying position was conducted in good light both from front and side of the neck. Inspection was followed by different methods of physical examination: Lahey's, Pizzilo's, and Crile's method and modified Rose method. Crile's method of examination was performed in patients having comparatively smaller swelling so only fifty-two patients were examined with this method by the consultant and fifty-six patients by the resident.

### Examination in Modified Rose Method

Patient was asked to lie down. A pillow was placed below the shoulder blade with 10-12 cm elevation while extending the head and neck**.** A head support is placed behind the occiput of the patient (Figure 1)**.** Patient's discomforts should be assessed at this stage for breathing difficulty, pain over the neck. Begin the examination as follows (Figure 2A-2H):


**Figure 1.** Positioning the patient for Modified Rose's Method. The yellow arrow shows the hyperextended neck, and the black double arrow shows the necessary elevation of shoulder blades should be 10-12 cm. This can be achieved by a shoulder roll or a pillow.

1. The palpation of swelling was performed with both hands to note any rise in temperature, tenderness, and consistency of the swelling(s). Any fixation to the skin and deep structure was also noted. Trachea, thyroid cartilage, cricoid cartilage was palpated to ascertain any deviation/compression of the airway.
2. First examine the isthmus part of the gland by placing examiner's thumb below the lower border of cricoid cartilage and over first two tracheal rings. Nodularity in its substance can be appreciated by gently holding it between thumb and the fingers.
3. To palpate the lateral lobes, the patient's chin should be turned slightly to the side intended to be examined, relaxing the SCM muscle on that side.
4. Palpation of the right lobe was done with the examiner's right hand, while pressing the opposite lobe towards midline by the left hand to make the right lobe more prominent.
5. Now the examiner gently insinuates the fingers of his palpating hand along the anterior border of the sternocleidomastoid muscle deep into the posterior surface of the thyroid gland, keeping the thumb over the lateral surface of the lower portion of the thyroid cartilage.
6. The examiner gently grasps the gland between his fingers and thumb to appreciate the surface, consistency, and presence of nodule(s). The patient is requested to swallow and the examiner assesses for mobility and defines the upper and lower margins of the gland (Figure 2F).
7. Caution should be exercised not to mistake the belly of the SCM as part of the thyroid gland (Figure 2H).
8. This method should be avoided in patients with any kind of cervical spine disease or with large goiter leading to tracheal instability signs (stridor, breathing distress).

Two investigators performed the physical examination independently. One investigator was a postgraduate resident, and another investigator was a faculty member

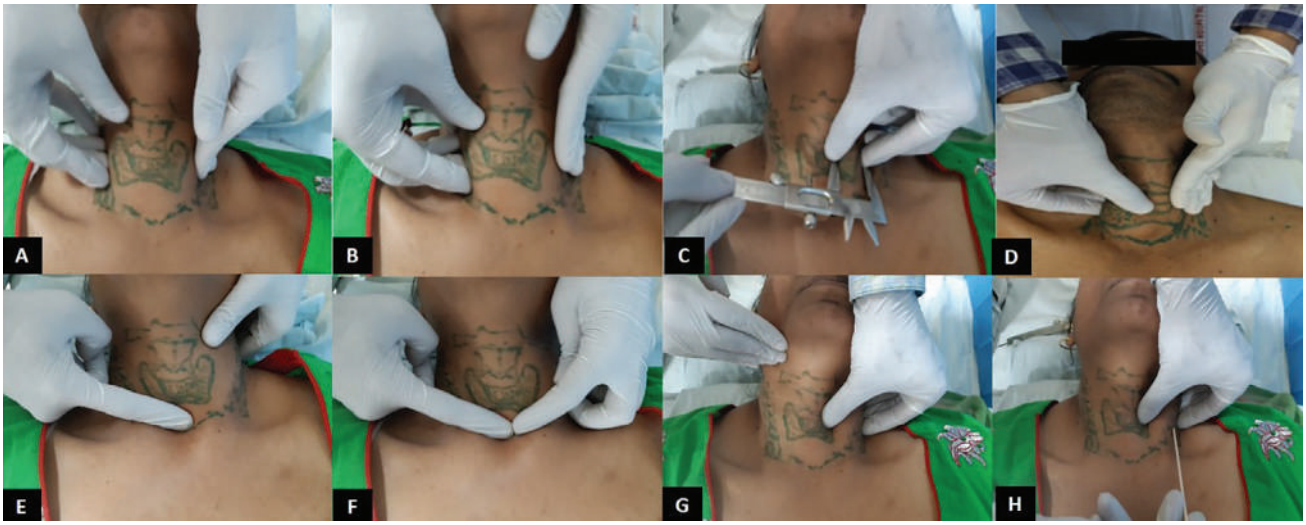


**Figure 2.** Examination by Modified Rose's method for a solitary thyroid nodule. **(A)** Head is turned to the side of palpation; **(B)** palpating the right lobe; **(C)** measurement by Vernier callipers; **(D)** palpating the left lobe; **(E)** palpating the lower border; **(F)** palpating the lower border on swallowing. Caution while palpating **(G)** thyroid gland, (H) sternocleidomastoid muscle may be mistaken as thyroid gland substance.

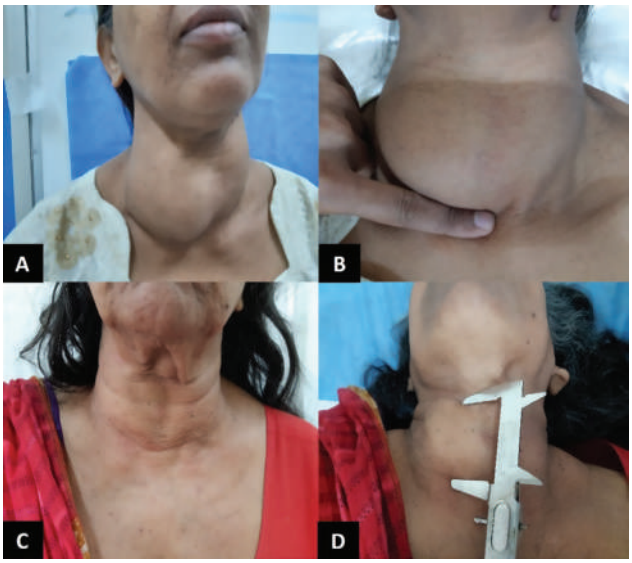


**Figure 3.** Examination by Modified Rose method. **(A)** A multinodular goitre seen on standing position; **(B)** examined in the modified rose position with palpation of the lower border; **(C)** faintly visible swelling on standing position; **(D)** the same swelling became prominent when examined in this position.

from the Department of Surgical Disciplines. Investigators recorded the finding without conferring with each other. The resident was trained by the Professor of Surgery in performing the various physical examination methods till Cohen's kappa statistics attained a value of '0.9.' This junior resident started the recordings of finding only after his training. The thyroid swellings were examined using four methods: Lahey's, Crile's, Prizzilo's and modified Rose (Appendix 1) in this sequence and the findings noted (Appendix 2). The duration of examination was somewhere between 10-15 minutes. Ultrasound (USG) of neck was performed in all the patients and considered the gold standard for certain parameters. We computed different diagnostic indices for various parameters by different methods. We considered following parameters for thyroid examination: nodularity, consistency of nodule, palpability of lower border, size in cranio-caudal dimension and tracheal deviation. The presence of cervical lymphadenopathy was also noted. The agreement between clinical examination and ultrasound scan findings for different parameters was computed. For retrosternal extension, CT scan of the neck and thorax was considered the gold standard.

### Statistical analysis

Data was analysed by Stata-14 and presented in Mean, Standard Deviation, and frequency percentages. Agreement between the two categorical variables was assessed by Kappa. In case of continuous variable agreement was assessed by ICC (intra class correlation) and Bland-Altman plot. Interpretation of Cohen's kappa values is, below 0 is no agreement, 0-0.2 is slight agreement, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1 as almost perfect agreement based on the guidelines by Landis and Koch.[7] The sensitivity, specificity NPV, PPV with 95% CI was assessed for diagnostic methods in comparison to gold standard. The association between two categorical variables was tested using either Chi square test or Fischer's exact test.

## RESULTS

A total of 83 patients with thyroid enlargements were enrolled for study. Majority of patients were females, 69 (83%) and remaining 14 (17%) were male patients. The predominant age group was 36-50 years in 31% patients followed by 26-35 years (29%). The chief complaint leading to consultation at the Surgery OPD was thyroid

enlargement (91.50%). Breathing difficulty was seen in 18 (21.70%) patients. Thirteen (15.60%) patients presented with voice changes. Difficulty in swallowing was seen in 14 (16.87%) patients. No patient had history of radiation exposure. There were 7 incidentally detected thyroid nodule cases (8.4%, 4 picked up on CT on 3 on USG).

### Agreement for nodularity

The USG examination revealed that 1 (1.20%) patient had a normal thyroid gland, 2 (2.41%) patients had a non-thyroidal swelling, 38 (45.78%) patients had a STN, and 42 (50.60%) patients had presented with an multinodular goitre (MNG). Modified Rose method showed 93.98% (kappa – 0.91, excellent agreement in identification of nodule in thyroid swelling followed by Crile's method 86.54% (kappa – 0.79), Pizzilo's method 81.93% (kappa – 0.75) and Lahey's method 80.72% (kappa – 0.73). The agreement for the resident was good using modified Rose and moderate in others (Table 1). All these agreements were statistically significant.

### Agreement for consistency of nodule

Modified Rose method when performed by the consultant and resident showed fair agreement at 59.50% and 37% respectively (kappa - 0.40), to identify consistency of nodule. Crile's method showed least agreement 17% and 19% respectively (kappa – 0.079). These are depicted in Table 1. All agreements were statistically significant.

### Agreement for finding lymph nodes

Lahey's and Pizzilo's method showed better agreement at 90.36% in both (kappa – 0.58 each) followed by Crile's method at 88.46% (kappa – 0.55). Least agreement was seen with modified Rose method at 87.95% with kappa of 0.5 (when performed by a consultant). When this was done by a resident, Lahey's method showed highest agreement at 92.77% (kappa – 0.70) followed by modified Rose method at 90.36% (kappa – 0.61). These findings were statistically significant. Therefore, it was interpreted that Lahey's method was the best clinical method among the four to palpate lymph nodes (Table 1).

### Mean of vertical dimension

The mean of vertical dimension measured by a consultant in the modified Rose method was comparatively higher than in other methods as shown by the difference of means in Table 2. Mean differences measured between Lahey's vs modified Rose/ Pizzilo's vs modified Rose/ Crile's vs modified Rose were all in negative value with an excellent ICC value (>0.9). It is consistent with the logic that in the modified Rose position, due to greater neck extension, some occult part of the substernal goiter comes out and becomes palpable. Similar results were reflected when measured by resident.

### Bland Altman Plot for dimensions

The Bland Altman Plot was drawn for agreement between craniocaudal dimension of enlarged lobe measured by Lahey's method and modified Rose method. Most of the measurements lies within 95% limits of agreement. There were only 4 out of 59 (6.78%) outside the limit of agreement (Figure 4A). The 95% confidence interval varies from -1.7 cm to 0.8 cm which is slightly larger than the pre-set value of plus minus 1 cm. The values outside the agreement range were within the acceptable limit of 10%. Modified Rose method measures the size more accurately as compared to Lahey's method. The other Bland Altman plot was drawn for agreement between craniocaudal dimension of the enlarged lobe measured by Pizzilo's method versus modified Rose method. The confidence interval varies from -1.4 cm to 0.9 cm which is slightly larger than the expected interval but narrower than the interval between the previous comparison. The values outside the agreement were acceptable at 4 out of 59 (6.78%) (Figure 4B).The mean of the difference of craniocaudal measurements by the two methods was 0.43 cm between Lahey's and Rose as compared to a narrower difference between Pizzilo and Rose at 0.25 cm. Another trend noted was that as the size of the nodule increased and the more inferior is the location of the lower border, the greater is the discrepancy. This could be explained by the non-palpability of the lower border. Thus, to measure the craniocaudal dimension the most accurate method is modified Rose followed by Pizillo and Lahey's respectively.

**Table 1.** Agreement for various parameters between USG and clinical methods; Consultant (C) and Resident (R)

| Parameter Assessed | | Lahey's (n=83) | | Pizzilo's (n=83) | | Crile's (n=52 C & n=56 R) | | Modified Rose (n=83) | |
|---|---|---|---|---|---|---|---|---|---|
| | | C | R | C | R | C | R | C | R |
| Nodularity | Agreement % | 80.72% | 77.10% | 81.93% | 78.31% | 86.54% | 83.98% | 93.98% | 86.75% |
| | Cohen's Kappa (95% CI) | 0.73 (0.60-0.85) | 0.68 (0.56-0.79) | 0.75 (0.63-0.87) | 0.70 (0.57-0.82) | 0.79 (0.62-0.95) | 0.76 (0.60-0.91) | 0.91 (0.78-1.03) | 0.81 (0.68-0.93) |
| | P value | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Consistency | Agreement % | 26.90% | 44.30% | 26% | 40% | 17% | 19% | 59.50% | 37% |
| | Cohen's Kappa (95% CI) | 0.20 (0.10-0.30) | 0.23 (0.12-0.34) | 0.21 (0.11-0.31) | 0.20 (0.10-0.30) | 0.08 (0.02-0.18) | 0.11 (0.01-0.21) | 0.40 (0.20-0.57) | 0.49 (0.36-0.62) |
| | P value | <0.001 | <0.001 | <0.001 | <0.001 | 0.05 | 0.01 | <0.001 | <0.001 |
| Lymph Node palpability | Agreement % | 90.36% | 92.77% | 90.36% | 90.30% | 88.46% | 90.09% | 87.95% | 90.36% |
| | Cohen's Kappa (95% CI) | 0.58 (0.43-0.73) | 0.70 (0.55-0.84) | 0.58 (0.43-0.73) | 0.58 (0.43-0.72) | 0.55 (0.35-0.74) | 0.58 (0.39-0.76) | 0.50 (0.35-0.65) | 0.61 (0.45-0.74) |
| | P value | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

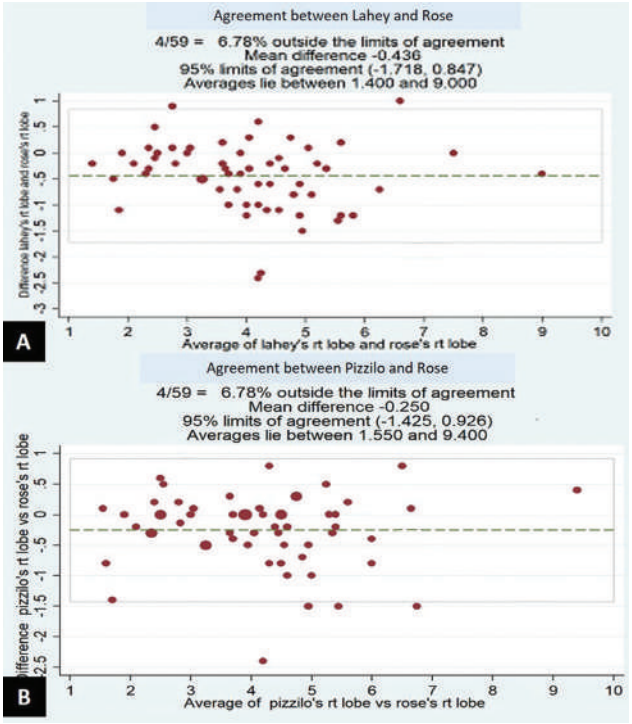


**Figure 4.** Bland-Altman plot for agreement between craniocaudal dimension measured by the consultant using the **(A)** Lahey's method vs Modified Rose's method; **(B)** Pizzilo's method and Modified Rose's method.

### Diagnostic test indices for finding Solitary Thyroid Nodule (STN) and multinodular goitre (MNG)

The sensitivity to identify STN was seen highest (Consultant – 97%, Resident – 100%) with Crile's method but specificity was low (Consultant – 75%, Resident – 70%). Modified Rose method had high sensitivity and specificity for the Consultant at 94% and 100% compared to that of Resident at 86.80% and 95.50%, respectively. Lahey's and Pizzilo's method were moderately sensitive and specific (Table 3). The sensitivity to identify multinodular goitre (MNG) by modified Rose method was high (Consultant – 100%, Resident – 86%). The other 3 methods were moderately sensitive. The specificity of all methods to identify MNG was good (Table 4). The agreement of modified Rose was highest, excellent with consultant examination.

### Diagnostic test indices for palpability of lower border

It was observed that modified Rose method by consultant has the highest sensitivity (98%) and diagnostic odds (210) as compared to other conventional methods of thyroid examination but its specificity ranges from 46.7 to 91.1 (75%). A CT of the neck and thorax was taken as the gold standard to rule out retrosternal extension. The level of agreement for modified Rose is good as compared to fair agreement by all other methods (Table 5).

**Table 2.** Mean difference of size (vertical dimension) by various methods and intraclass correlation by consultant and resident

| Cranio-caudal Dimensions (Mean±SD cm) | | Consultant | | Resident | |
|---|---|---|---|---|---|
| | | Right Lobe (n=66) | Left Lobe (n=47) | Right Lobe (n=66) | Left Lobe (n=47) |
| Lahey's | | 3.82±1.42 | 3.45±1.78 | 4.01±1.84 | 3.53±1.89 |
| Pizzilo's | | 3.9±1.48 | 3.66±1.75 | 4.1±1.89 | 3.73±1.77 |
| Crile's | | 3.75±1.32 (n=34) | 3.66±1.85 (n=18) | 3.54±1.41 (n=36) | 3.73±2.05 (n=26) |
| Modified Rose | | 4.31±1.76 | 3.74±1.78 | 4.47±2.0 | 3.95±1.96 |
| Lahey-Rose | Difference of mean (95% CI) | -0.46 (-0.69, -0.24) | -0.51 (-0.80, -0.23) | -0.46 (-0.69, -0.24) | -0.61 (-0.92, -0.31) |
| | ICC | 0.94 | 0.95 | 0.94 | 0.93 |
| Pizzilo-Rose | Difference of mean (95% CI) | -0.24 (-0.40, -0.09) | -0.32 (-0.54, -0.11) | -0.29 (-0.49, -0.08) | -0.41 (-0.62, -0.19) |
| | ICC | 0.96 | 0.96 | 0.94 | 0.95 |
| Crile-Rose | Difference of mean (95% CI) | -0.25 (-0.39, -0.10) | -0.22 (-0.46, 0.02) | -0.27 (-0.54, 0.01) | -0.33 (-0.55, -0.11) |
| | ICC | 0.96 | 0.98 | 0.91 | 0.97 |

**Table 3.** Diagnostic test indices for finding Solitary Thyroid Nodule (STN) with USG as a gold standard for Consultant (C) and Resident (R)

| STN | Lahey's (n=83) | | Pizzilo's (n=83) | | Crile's (n=52 C & n=56 R) | | Modified Rose (n=83) | |
|---|---|---|---|---|---|---|---|---|
| | C | R | C | R | C | R | C | R |
| Sensitivity (95% CI) | 94% (82.70-98.50) | 92.10% (79.20-97.20) | 94% (82.70-98.54) | 94.70% (82.70-98.50) | 97% (85.80-99.50) | 100% (90.30-100) | 94% (82.70-98.50) | 86.80% (72.60-94.20) |
| Specificity (95% CI) | 84% (71.20-92.20) | 82.20 (68.70-90.70) | 86% (73.80-93.70) | 80% (66.10-89.10) | 75% (50.50-89.80) | 70% (48-85.45) | 100% (92.10-100) | 95.50% (85.10-98.70) |
| PPV (95% CI) | 83% (70-91.80) | 81.40% (67.30-90.20) | 85% (72.10-93.20) | 80% (66.10-89.10) | 89% (76.40-95.90) | 85.7% (72.10-93.20) | 100% (90.30-100) | 94.20% (81.30-98.40) |
| NPV (95% CI) | 95% (83.50-98.60) | 92.50% (80.14-97.42) | 95% (83.80-98.60) | 94.70% (82.70-98.50) | 92% (66.60-98.60) | 100% (78.40-100) | 95% (85.70-98.80) | 89.50% (77.80-95.40) |
| Diagnostic Accuracy (95% CI) | 89% (80.60-94.10) | 86.70% (77.80-92.40) | 90% (82.10-95) | 86.70% (77.80-92.40) | 90% (79.30-95.80) | 89.2% (78.50-95) | 97% (91.60-99.30) | 91.50% (83.60-95.80) |
| Diagnostic Odds (95% CI) | 97 (19-501) | 53.9 (13.20-219.90) | 117 (22-617) | 72 (14.50-365) | 105 (10.60-1034) | Not defined | Not defined | 141 (25.80-777) |
| Cohen's kappa (95% CI) | 0.78 (0.57-0.99) | 0.73 (0.52-0.94) | 0.80 (0.59-1.00) | 0.73 (0.52-0.94) | 0.76 (0.49-1.00) | 0.75 (0.49-1.00) | 0.95 (0.73-1.00) | 0.82 (0.61-1.00) |
| P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

**Table 4.** Diagnostic test indices for finding Multinodular Goitre (MNG) with USG as a gold standard for Consultant (C) and Resident (R)

| MNG | Lahey's (n=83) | | Pizzilo's (n=83) | | Crile's (n=52 C & n=56 R) | | Modified Rose (n=83) | |
|---|---|---|---|---|---|---|---|---|
| | C | R | C | R | C | R | C | R |
| Sensitivity (95% CI) | 66% (49.60-80.20) | 60.60% (43.60-75.30) | 69% (52.60-82.60) | 60.60% (43.60-75.30) | 66% (39-86.10) | 56.20% (33.10-76.90) | 100% (89.50-100) | 90.90% (76.40-96.80) |
| Specificity (95% CI) | 100% (92.80-100) | 98% (89.50-99.60) | 100% (92.80-100) | 96% (86.50-98.90) | 97% (87.10-99.50) | 100% (91.80-100%) | 96% (86.50-98.90) | 94% (83.70-97.90) |
| PPV (95% CI) | 100% (85.10-100) | 95.20% (77.30-99.10) | 100% (85.60-100) | 90.90% (72.10-97.40) | 88% (56.50-90) | 100% (70-100) | 94% (81.30-98.40) | 90.90% (76.40-96.80) |
| NPV (95% CI) | 81% (70.50-89.60) | 79% (67.30-87.30) | 83% (71.90-90.60) | 78.60% (66.80-87.10) | 90% (79.30-95.80) | 86% (73.80-93) | 100% (92.50-100) | 94% (83.70-97.90) |
| Diagnostic Accuracy (95% CI) | 86% (77.80-92.40) | 83.10% (73.60-89.60) | 87% (79.20-93.30) | 81.90% (72.30-88.70) | 90% (79.30-95.82) | 88.10% (77.40-94.10) | 97% (91.60-99.30) | 92.70% (85.10-96.60) |
| Diagnostic Odds (95% CI) | Not defined | 75.30% (9.20-615) | Not defined | 36.90 (7.60-178) | 78 (7.60-793) | Not defined | Not defined | 156 (29.60-827) |
| Cohen's kappa (95% CI) | 0.70 (0.50-0.91) | 0.62 (0.42-0.82) | 0.73 (0.52-0.94) | 0.60 (0.39-0.80) | 0.70 (0.43-0.97) | 0.65 (0.41-0.89) | 0.95 (0.73-1.00) | 0.84 (0.63-1.00) |
| P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

**Table 5.** Diagnostic test indices for palpability of lower border with CT as gold standard for Consultant (C) and Resident (R)

| Lower Border | Lahey's (n=83) | | Pizzilo's (n=83) | | Crile's (n=52 C & n=56 R) | | Modified Rose (n=83) | |
|---|---|---|---|---|---|---|---|---|
| | C | R | C | R | C | R | C | R |
| Sensitivity (95% CI) | 77% (66.40-85.60) | 76% (64.90-84.80) | 87% (77.60-93.20) | 85% (75.90-92.00) | 77% (63.40-86.60) | 82% (69.20-90.20) | 98% (92.40-99.70) | 98% (92.40-99.70) |
| Specificity (95% CI) | 83% (55.20-95.30) | 83% (55.20-95.30) | 58% (31.90-80.60) | 75% (46.70-91.10) | 75% (30.06-95.44) | 80% (37.50-96.30) | 75% (46.70-91.10) | 66% (39.00-86.19) |
| PPV (95% CI) | 38% (22.40-57.40) | 37% (21.50-55.70) | 43% (23.10-66.80) | 47% (27.30-68.20) | 21% (7.57-47.50) | 30% (12.60-57.60) | 90% (59.50-98.20) | 88% (56.50-98.10) |
| NPV (95% CI) | 96% (88-99.30) | 96% (87.80-99) | 92% (83.60-96.70) | 95% (87.10-98.30) | 97% (86.50-99.50) | 97% (87.60-99.50) | 95% (88.26-98.10) | 94% (86.90-97.80) |
| LR+ (95% CI) | 4.64 (1.73-12.50) | 4.50 (1.69-12.30) | 2.09 (1.41-3.11) | 3.40 (1.70- 6.66) | 3.08 (0.43- 22.24) | 4.10 (0.57-29.4) | 3.94 (2.05-7.50) | 2.95 (1.81-4.83) |
| LR- (95% CI) | 0.27 (0.23-0.32) | 0.28 (0.24-0.35) | 0.21 (0.19-0.24) | 0.18 (0.14-0.24) | 0.30 (0.21-0.45) | 0.22 (0.16-0.31) | 0.02 (0.01-0.14) | 0.02 (0.01-0.17) |
| Diagnostic odds (95% CI) | 17 (3.41-86.60) | 15 (3.16-79.70) | 9 (2.52-36.90) | 18 (4.20-79.40) | 10 (0.95-107) | 18 (1.81- 183) | 210 (19.6- 2240) | 140 (13.90-1411) |
| Diagnostic Accuracy (95% CI) | 78% (68.30-85.60) | 77% (66.90-84.80) | 83% (73.60-89.60) | 84% (74.10-90.40) | 76% (63.8-86.28) | 81% (72.80-87.20) | 95% (88.20-98.10) | 95% (88.20-98.10) |
| Cohen's Kappa (95% CI) | 0.41 (0.22-0.60) | 0.39 (0.20-0.58) | 0.40 (0.19-0.61) | 0.49 (0.28-0.69) | 0.24 (0.03-0.45) | 0.36 (0.13-0.58) | 0.79 (0.57-1.00) | 0.72 (0.52-0.94) |
| P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

### Association between sub-sternal extension by clinical methods and Pemberton's sign

If Pemberton's sign positive, physical examination by Lahey's, Pizzilo's and modified Rose method shows probability of substernal extension in 78%, 56% and 78% respectively, when examined by the Consultant. With a negative Pemberton's sign, the probability of getting false positive finding of substernal extension was 26%, 15% and 4% respectively. When examined by the Resident, there was lower probability of getting false positive finding with modified Rose method (*p*-value <0.001).

## DISCUSSION

The thyroid gland weighs 10-20 grams in a normal adult, is not usually palpable in health due to its relatively soft consistency and the coverage provided by the strap muscles. There are very few studies in the literature describing the appropriate physical examination of thyroid region swelling. With the improvement in techniques of imaging, the importance of thyroid examination has been overshadowed by unreasonable reliance on these modalities. A narrow differential diagnosis can be established by a simple physical examination of the thyroid gland by an experienced clinician.[8] The evaluation of thyroid swelling must begin with a proper clinical examination followed by imaging and cytology studies. Many methods have been described in literature for examination of thyroid swellings like Lahey's, Pizzilo's and Crile's methods.[9]

Thorough characterization of the interobserver variation on ultrasound of the thyroid is important. Knudsen et al., studied the interobserver variation of the ultrasound examination of thyroid in 25 patients.[10] They compared findings of postmortem ultrasonography of the thyroid with finding after autopsy. Echogenicity and echo pattern showed less agreement but good correlation and agreement between observers was found for thyroid volume (r = 0.98) and prevalence of thyroid nodules (kappa = 0.72). The correlation of thyroid volume by ultrasonography to autopsy results was satisfactory (r = 0.93), but the

volume was slightly underestimated.[11-13] The ACR TI-RADS (Thyroid Imaging Reporting and Data System) assess thyroid nodules under 5 categories: composition, echogenicity, shape, margin and echogenic foci; and based on total combine score assign a risk level that ranges from TR1 to TR5. The risk of malignancy is TR1 (0.3%), TR2 (1.5%), TR3 (4.8%), TR4 (9.1%), TR5 (35%).[14] The goal of this surveillance is detecting the missed thyroid malignancies on the initial assessment.[15]

Lahey's method was described by Frank H Lahey in 1926. It gives information about the anterior surface of the thyroid nodule and increases the prominence of lateral lobes, thus highlighting the small nodules.[9] It also allows for assessment of the consistency of the nodule. Contrary to this, our study highlighted that Lahey's method had the least agreement for assessing the nodularity, consistency and craniocaudal dimensions but had the highest agreement for the lymph node assessment. The sensitivity of Lahey's method to identify a solitary nodule was comparable to the other three methods. The sensitivity to identify multinodular goiter and the palpability of the lower border was the lowest among these four methods.

Pizzillo's method was described to facilitate the examination of the thyroid region in obese individuals with short neck. The neck is extended to better appreciate the nodules. Our study revealed that the agreement levels were comparable for assessing the nodularity and lymph node status but poor for consistency. It was almost as accurate as the Rose method to measure the cranio-caudal dimension of the nodule. The sensitivity to identify the solitary nodule was comparable to the others, however, the sensitivity for multinodular goiter was very low. The sensitivity to palpate the lower border was higher than all the other methods except the Rose method. This was primarily because of the extension of the neck which was not done in the Lahey's and Crile's method.

Crile's method was described for palpation of smaller nodules. This was confirmed by our study by the high sensitivity to identify the solitary nodule and the lowest sensitivity for multinodular goiter and palpation of the lower border. The agreement to measure the nodularity and lymph nodes was high, but it was poorest for the consistency.

In the classic Rose position described by Professor Edmund Rose, Trendelenburg position was recommended.[16] This was proposed for the patients undergoing head and neck surgeries and the position was achieved on the operation theatre table. But to practice this clinically in the out-patient as well as the ward setup, modification was needed. So, the modified Rose position was devised, in which the patient lies flat with elevation of shoulder blades with a pillow and extension at the neck joints. This is feasible in the examination rooms where the modular operating tables (OT) tables are not encountered routinely. The anatomic advantages offered by this position is because the neck extension causes the laryngo-pharyngeal unit to be pulled cranially towards the skull base. This makes the swelling more discernable for palpation. This also allows for the palpation of the lower border of the swelling which in sitting position dips behind the sterno-clavicular joint and the clavicle. Our study confirmed that the agreement for nodularity, consistency and the cranio-caudal dimension was highest with this method. The agreement for lymph nodes was second to the Lahey's method. This is the most sensitive method to identify the solitary nodule, multinodular goiter and the palpation of the lower border of the swelling. It also has the highest specificity, positive likelihood ratio and the best diagnostic odds for these characteristics. Thus, modified Rose emerges as the single best method to assess all the features of the thyroid enlargement for a superior diagnostic yield.

The palpability of the lower border of thyroid sounds less important but has a great bearing to the evaluation. As per various textbooks a retrosternal goitre is one that has 50% of the mass in the mediastinum. Ultrasonography cannot comment on the intrathoracic part and FNAC is not feasible. So, for diagnosis of retrosternal extension, CT/MRI is required.[17] So, for a resource limited setting like ours, a clinical method should be devised which can guide the necessity to do CT to rule out the extension.

We found in our study that the new method "Modified Rose's Method" has the highest sensitivity and diagnostic odds as compared to other conventional methods of thyroid examination, but its specificity is moderate. Hence, the modified Rose technique and its findings should guide decision making in performing USG and CT as well. It is expected that use of this method would clearly prioritise those patients who need CT for further assessment, optimising the use of limited resource in low-middle income class countries.

This is the first study in literature which has compared 4 different methods of clinical examination of thyroid enlargement. It was found that modified Rose's method has high sensitivity and specificity to identify solitary thyroid nodule when compared to neck ultrasound as gold standard. The sensitivity to identify multinodular goiter was also high. The other advantages of this method were that inspection, palpation and auscultation could be performed in one position. So, it was time saving especially in the busy environment of the Out-Patient Clinic (OPD).

A major disadvantage of this method is its inapplicability to be used in patient with exceptionally large goiter (stridor, breathing distress) and patients with cervical spine disease (trauma, instability, disc prolapse). Lahey's method is a relatively better clinical method to palpate lymph nodes. Perhaps it is the extension causes the bilateral sternocleidomastoid (SCM) muscles to be taut. It would be difficult to palpate cervical lymph nodes when the SCM is less relaxed.

Another interesting trend highlighted throughout the study is that the diagnostic indices of the Consultant were superior to those of the Resident in almost all the scenarios. This is an expected finding as clinical examination improves by experience.

### Strengths

This is the first study available in English literature to have compared all methods of clinical thyroid examination in living human patients. The study consistently shows modified Rose's method was superior to others. The study also emphasizes the importance of thoroughness in clinical examination of thyroid. The study also demonstrates reproducibility of the results as performed by two different examiners with varying level of experience.

### Limitations

The study was done at a single centre with limited number of patients. As the study was done for a limited period, a strict inclusion criterion could not be followed, and a sample of convenience was taken. The number of patients examined by all the methods were not equal due to the size differences of the goiters.

## CONCLUSION

Modified Rose's position is the best method of clinical examination of thyroid swellings especially in patients with occult substernal extension. Lahey's method is better for the examination of cervical lymph nodes. Considering the better diagnostic indices that we got in our patients, this method can be used in field studies to screen thyroid swelling in at-risk population.

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

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

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## APPENDICES

**Appendix 1.** Standard steps of examination followed in the study

| |
|---|
| **Lahey's method[9]** |
| 1. Patient is examined in the sitting position with the examiner in front of the patient.<br>2. Elevate the patient's chin ensuring the movement of patient's larynx and trachea forward. This maneuver increases the prominence of the lateral lobes.<br>3. With the neck in forward position, the chin is rotated slightly towards the side on which the lobe of the thyroid to be palpated, relaxing the ipsilateral sternocleidomastoid.<br>4. Then using the pulp of the thumb against the lower lateral portion of the thyroid cartilage and upper two rings of trachea. The trachea is to be dislocated laterally with gentle pressure from opposite site as far as possible without causing choking.<br>5. Then using the fingers of the opposite hand press deeply inward behind the sternomastoid and behind the thyroid lobe, and the thumb of that hand is brought over the anterior surface of the gland anterior to the sternomastoid. The dislocated lobe may then be palpated between the two.<br>6. Patient is asked to swallow to confirm the palpated structure is thyroid. |
| **Pizzilo's method** |
| 1. Patient is examined in the sitting position with the head resting on the clasped hands at the occiput. The patient is asked to push the head backwards.<br>2. The examiner stands behind the patient to examine the gland.<br>3. With the pulp of the index, middle and ring finger the lobes of the gland are palpated on both the sides followed by palpation of the isthmus. The flexion should be at the metacarpophalangeal joint and should not poke the patient.<br>4. The patient is then asked to swallow to assess the lower border of the swelling as well as the retrosternal extension.<br>5. This method is usually employed for examining obese patients with shorter neck as neck extension ensures better access to the thyroid gland. |
| **Crile's method** |
| 1. The patient is examined in the sitting position with head in normal position. The examiner stands in front of the patient. This method was described for small solitary thyroid swellings.<br>2. Pulp of the thumb of the examiner is used to palpate the gland for any abnormality. The examiner uses his/her left thumb to palpate the left side of the gland and vice versa.<br>3. The isthmus can be palpated with either hand of the examiner.<br>4. Patient is asked to swallow to visualise the lower border and rule out retrosternal extension |
| **Modified Rose method** |
| *-Described in the main text-* |

**Appendix 2.** Case Record Form

Participant Identification Number: .....
Name: ..... Age: ..... Gender: ... M / F ...
UHID No.: ..... Unit: ..... Ward: ..... Bed: .....
Address: ..... Phone No: .....

**HISTORY:**

| *Symptoms* | | *Duration* |
|---|---|---|
| • Thyroid Swelling (Self detection, physician) | Yes/No | |
| • Palpable cervical lymph nodes | Yes/No | |
| • Dysphagia | Yes/No | |
| • Dysphonia | Yes/No | |
| • Dyspnoea | Yes/No | |
| • Pain | Yes/No | |
| • Others | Yes/No | |
| • History of any radiation exposure in past | Yes/No | |
| • History of thyroid malignancy in family | Yes/No | |

| *History of any hyperthyroidism symptoms* | | *Duration* |
|---|---|---|
| • Insomnia | Yes/No | |
| • Diarrhoea | Yes/No | |
| • Palpitations | Yes/No | |
| • Heat intolerance | Yes/No | |
| • Sweating | Yes/No | |
| • Nervousness | Yes/No | |
| • Tremors | Yes/No | |
| • Vision changes | Yes/No | |
| • Hair loss | Yes/No | |

| *History of any hypothyroidism symptoms* | |
|---|---|
| • Fatigue and lethargy | Yes/No |
| • Muscular weakness | Yes/No |
| • Weight gain | Yes/No |
| • Constipation | Yes/No |
| • Voice changes | Yes/No |
| • Myxoedema | Yes/No |
| • Cold intolerance | Yes/No |

**CLINICAL EXAMINATION:**

| *(S. No.) Methods* | *Findings* |
|---|---|
| **(1) Lahey's method** | |
| Right lobe enlargement | Yes/No |
| Left lobe enlargement | Yes/No |
| Diffuse enlargement | Yes/No |
| Cervical Lymph node Enlargement | Yes/No |
| Retrosternal Extension | Yes/No |
| Tracheal Shift | Yes/No |
| Stridor on compression | Yes/No |
| Engorged neck veins | Yes/No |
| Size (by Vernier calliper) – | |
| Consistency – Soft/Firm/Hard | |
| Mobility – Mobile/Restricted/Fixed | |
| **(2) Pizzilo's method** | |
| Right lobe enlargement | Yes/No |
| Left lobe enlargement | Yes/No |
| Diffuse enlargement | Yes/No |
| Cervical Lymph node Enlargement | Yes/No |
| Retrosternal Extension | Yes/No |
| Tracheal Shift | Yes/No |
| Stridor on compression | Yes/No |
| Engorged neck veins | Yes/No |
| Size (by Vernier calliper) – | |
| Consistency – Soft/Firm/Hard | |
| Mobility – Mobile/Restricted/Fixed | |
| **(3) Crile's method** | |
| Right lobe enlargement | Yes/No |
| Left lobe enlargement | Yes/No |
| Diffuse enlargement | Yes/No |
| Cervical Lymph node Enlargement | Yes/No |
| Retrosternal Extension | Yes/No |
| Tracheal Shift | Yes/No |
| Stridor on compression | Yes/No |
| Engorged neck veins | Yes/No |
| Size (by Vernier calliper) – | |
| Consistency – Soft/Firm/Hard | |
| Mobility – Mobile/Restricted/Fixed | |
| **(4) Modified Rose method** | |
| Right lobe enlargement | Yes/No |
| Left lobe enlargement | Yes/No |
| Diffuse enlargement | Yes/No |
| Cervical Lymph node Enlargement | Yes/No |
| Retrosternal Extension | Yes/No |
| Tracheal Shift | Yes/No |
| Stridor on compression | Yes/No |
| Engorged neck veins | Yes/No |
| Size (by Vernier calliper) – | |
| Consistency – Soft/Firm/Hard | |
| Mobility – Mobile/Restricted/Fixed | |

**INVESTIGATIONS:**

S. Calcium
- Value ..... (mg/dL. mEq/dL)
- Total/Ionized
- Serum Phosphate:
- Serum Albumin:

Thyroid Function Test
- Free T3
- Free T4
- TSH

USG thyroid
- Right lobe
- Left lobe

Size of Tumour ..... cm side Left/Right
- Cervical Lymph nodes:
  - Ipsilateral II/III/IV/V/V/VI
  - Contralateral II/III/IV/V/V/VI

NCCT thyroid
- Right lobe
- Left lobe

Size of Tumour ..... cm side Left/Right
- Cervical Lymph nodes:
  - Ipsilateral II/III/IV/V/V/VI
  - Contralateral II/III/IV/V/V/VI

Retrosternal extension

FNAC
- Accession No. & Date
- Report:
- Bethesda Category

Operative Findings

Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

# The Development of a Protocol for Critical Illness-Related Corticosteroid Insufficiency (CIRCI) at a Tertiary Hospital

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**Abstract**

Objectives. The diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) remains a challenge. This initiative aimed to develop a protocol for the diagnosis and management of CIRCI which will facilitate informed decision-making among clinicians through consensus-building among a multi-disciplinary team.

Methodology. This was a single-center, qualitative study which utilized the modified Delphi method, consisting of a sequential iterative process with two rounds of voting. A cut-off value of 70% was set as the threshold for reaching consensus.

Results. The protocol on the diagnosis and management of CIRCI was approved after two rounds of voting, with all the components reaching 83.3%-100% agreement. This protocol on CIRCI provided a framework for the clinical approach to refractory shock. It was advocated that all cases of probable CIRCI should immediately be started on hydrocortisone at 200 mg/day. The definitive diagnosis of CIRCI is established through a random serum cortisol <10 mcg/dL or increase in cortisol of <9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test in patients with indeterminate random cortisol levels.

Conclusion. The presence of refractory shock unresponsive to fluid resuscitation and vasopressors should warrant the clinical suspicion for the existence of CIRCI and should trigger a cascade of management strategies.

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

## INTRODUCTION

Critical illness-related corticosteroid insufficiency or CIRCI, which refers to an inadequate and blunted corticosteroid response to the level of stress, is an underrecognized condition in the critical care arena.[1] It occurs in about 30-70% of critically ill patients[2] and can be as high as 77% in patients with sepsis.[3] The clinical presentation of CIRCI is ominous, commonly manifesting with shock refractory to fluid resuscitation and vasopressors. Hypoglycemia, metabolic acidosis and eosinophilia may also be signs of relative adrenal insufficiency.[4] Indeed, CIRCI is a challenging disease plaguing critically ill patients.

To this day, the diagnosis of CIRCI remains a challenge. Guidelines from various societies differ in terms of the proposed criteria for diagnosis. The Society of Critical Care Medicine and the European Society of Intensive Care Medicine recommended in their consensus statements that in patients with putative signs and symptoms of CIRCI such as refractory shock that is unresponsive to catecholamines, a random cortisol level of less than 10 mcg/dl or a delta cortisol at 60 minutes of less than 9 mcg/dl after administration of 250 mcg cosyntropin or ACTH may be utilized by physicians to diagnose CIRCI.[4] On the other hand, local sepsis guidelines advocate that the use of random cortisol is not a prerequisite to diagnosing CIRCI, that the presence of shock refractory to fluid resuscitation and the finding of increasing vasopressor requirements are enough to establish the diagnosis.[5] This lack of consensus underscores the need to formulate a protocol that can be adapted to the local setting, and which can guide clinicians in managing critically ill patients.

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Practice variation is an important issue to be reckoned with in managing CIRCI. Such differences in clinical practice likely stem from differences in local and international guidelines. For instance, in a tertiary care center, the presence of CIRCI was investigated in only 58% of patients with refractory shock, and among these patients, only 47% received corticosteroids.[6]

This trend in clinical practice is also seen locally. In a study done at the Medical Intensive Care Unit of the Philippine General Hospital, less than half (46.6%) of the non-survivors and 60% of the survivors with adrenal insufficiency were given glucocorticoids, which is the cornerstone of management of patients with CIRCI,[7] hence the exigency to improve its recognition and timely management.

A protocol in the clinical setting refers to a recommended course of action for a particular situation and serves as a guide for healthcare providers. The protocol is formulated based on updated evidence-based research to facilitate better health service delivery.[8] An important component is a clinical algorithm, which consists of a series of steps involved in clinical decision-making. Algorithms help to standardize practice when it comes to important clinical scenarios and are a product of expert consensus.[9] These algorithms facilitate the provision of optimal high-quality care when a clinical pathway responsive to the health problem is activated upon contact with the healthcare system, and provides guidance for decision-making that is evidence-based.[10] Deming's quality improvement theory illustrates a strong basis for the creation and implementation of clinical pathway algorithms. These pathways enable standardization of clinical processes and reliable measurement of clinical outcomes.[11]

Consensus-building is an integral aspect of protocol development. The Delphi method, originally proposed by Dalkey and Helmer, is a validated means for arriving at a consensus in clinical settings.[10] It has been used in many studies which involve the development of clinical pathway algorithms. The Delphi method is iterative and the participants, who are experts in the field, engage in several rounds of voting to arrive at a consensus. In the modified Delphi method, experts vote to agree or disagree on a set of statements communicated through email questionnaires. Similar to the original Delphi method in terms of its objective, the modification refers to initiating the discussion with set issues from literature review.[12] This modified method is appropriate in situations where the evidence surrounding disease management is inconclusive, and expert opinion to adjudicate the current pool of literature is paramount,[10] such as in the case of CIRCI.

The lack of local guidance on the diagnosis and management of CIRCI needs to be urgently addressed with a clinical pathway in the care of critically ill patients with refractory shock. A tertiary hospital, which is a national referral center for patients warranting intensive care, is a suitable location to initiate a vital protocol that will shape clinical practice.

This research aims to develop a protocol for the diagnosis and management of critical illness-related corticosteroid insufficiency through consensus-building among a multi-disciplinary team of experts. To date, this is the first initiative of its kind on this topic in the country.

## METHODOLOGY

### Identification of key issues

The authors identified pressing inquiries on the diagnosis and management of CIRCI that need to be addressed. These questions were deemed pertinent for the identification of patients with CIRCI in whom treatment is indicated. Such questions reflect processes that entail crucial decision-making. The following key issues in the diagnosis and management of CIRCI were identified:

1. When should CIRCI be suspected?
2. How should cases of probable CIRCI be managed?
3. How should patients be managed after the initiation of steroids for probable CIRCI?
4. How long should corticosteroids be given for patients with CIRCI?
5. How should steroids be tapered for patients with CIRCI?
6. What blood glucose levels should be maintained for patients on steroids?
7. How is the definitive diagnosis of CIRCI made?
8. How should patients be managed after the cessation of steroid therapy?
9. Do you approve of this algorithm for the initiation and use of corticosteroids for patients admitted with shock at this tertiary hospital?

### Formulation of recommendations

The authors reviewed published literature and existing guidelines on critical illness-related corticosteroid insufficiency and key clinical trials were identified. The following selection criteria were applied to determine inclusion of the literature for creating recommendations: validity, feasibility, and adaptability.[13] Seminal works on CIRCI were also included. [1,4,6,14-20]

Since septic shock is the most common etiology of shock among patients with CIRCI,[14] recommendations for managing patients with sepsis were also critically appraised. From this review of evidence, responses to the inquiries were constructed by the authors to serve as recommendations for the diagnosis and management of CIRCI. The authors, who belong to different fields (two authors from Endocrinology, one author from Pulmonology and Critical Care, and one author from Infectious Diseases), independently examined and approved all the recommendations that they formulated from the systematic

review of literature. These recommendations were then forwarded to the experts for consensus-building to develop a protocol for the diagnosis and management of CIRCI.

### Selection of experts

A multi-specialty panel of clinicians directly involved in managing patients with refractory shock was formed. These experts have a wide range of knowledge and clinical experience that can contribute to the decision-making process. They also fulfill the criteria for panel selection of being able to implement the recommendations of the body.[21] Deemed as content experts, the participants in the consensus-building process were clinicians from the Divisions of Endocrinology, Diabetes, and Metabolism (18 participants), Pulmonary Medicine and Critical Care (1 participant), Infectious Disease (1 participant) and Cardiology (1 participant). All stages of the study involved participants from various specialties, ensuring that diverse inputs were reflected in all the processes. A letter detailing the objectives and nature of the procedure was sent to all the invited experts.

There has been substantial variation in the panel size for the Delphi method. Several protocols advocate that about 5-10 experts are sufficient for consensus-building.[10] A minimum of 12 respondents is considered adequate for the Delphi method.[22] For the development of a protocol for CIRCI, more than 20 experts were invited, which exceeded the minimum required number of participants for the Delphi method. The expected dropout rate is around 20% based from previous studies.[22] Because the number of participants invited exceeded the number of participants required, the validity of the consensus-building procedure was unlikely to be affected by drop-outs. The number of experts in this study enabled us to reach saturation point.

### Modified Delphi Method

A sequential process consisting of two rounds of voting was instigated for the development of a protocol for the diagnosis and management of CIRCI. Informed consent was obtained from the invited experts. Upon signifying their consent to join the consensus-building process, the first set of recommendations for the diagnosis and management of CIRCI was sent through electronic mail to the participants' encrypted institutional webmail address for all the exchanges about the consensus-building process to ensure data privacy.

The online tool utilized in this modified Delphi method was Google forms, which had secure sockets layer (SSL) encryption, which guaranteed that the transmitted data were secure. Since this study was conducted in 2020 during the surge of the COVID-19 pandemic, the modified Delphi method was done virtually through this secure online tool because face-to-face meetings were discouraged to ensure the participant's safety. The Google forms questionnaire was checked by the investigators before every Delphi round to ascertain its operability to a diverse pool of participants.

For the first round of voting, the experts were asked to indicate if they "agree or disagree" with the stipulated provisions and were instructed to submit any comments and suggestions through the free-text response feature on Google forms. After the first round of voting, the feedback was incorporated and the recommendations revised.

During the second round of voting, the experts were asked to scrutinize the recommendations and indicate "agree," "disagree with minor modifications," and "disagree with major modifications," and "redo algorithm." Both rounds of voting utilized a Likert-type scale to gauge the expert responses and level of agreement and was deemed sufficient to determine which components of the protocol should be retained, discarded or modified.[23] The protocol for the diagnosis and management of CIRCI was modified after the second round of voting.

This amended protocol was again disseminated to the experts. A third round of voting was only reserved for any major disagreements that would arise in the second round of voting. This strategy is compliant with the recommended two to three rounds for Delphi procedures.[24] Reminders were regularly sent to experts to improve response time.

The method for establishing consensus that was applied for this study was based on the proportion of experts showing agreement with the recommendations. A cut-off value of 70% was set as the threshold for reaching consensus, the same level of agreement used in a large number of studies.[22,25,26]

### Data analysis

Pooled results from all the experts were generated after every round. Descriptive statistics were employed based on the level of agreement set at 70% for establishing consensus. The stability of the consensus was assessed if there was variation after each round of voting in just 10% or less of the statements. For each statement, the investigators produced a statistical representation of the viewpoints of the experts.[23] Based on the feedback for every recommendation stipulated in the free text response, qualitative content analysis[27] was pursued. The responses of the experts were categorized by themes, which addressed the various aspects of the diagnosis and management of CIRCI.

### Protocol development

The results acquired from all the rounds of voting were synthesized. A statistical representation of all the responses of the experts and the feedback of all the experts were sent

to all the participants after every round. All statements that reached consensus were incorporated in the final form.

The protocol format for the diagnosis and management of CIRCI was a set of key inquiries followed by responses, accompanied by the evidence that served as the basis for such recommendations. An algorithm for CIRCI among patients with refractory shock was presented at the end of the protocol. The experts received a copy of the protocol prior to dissemination so that they could corroborate the recommendations made in the final form.

### Dissemination

This protocol, which was a product of a thorough consensus-building process, was disseminated to trainees and consultants of the Department of Medicine, who are the main users of this clinical pathway. The document, accompanied by a cover letter, was submitted to the Department Chair and Assistant Vice-Chair for Patient Services for review. Upon approval, the protocol on the diagnosis and management of CIRCI was disseminated. A consultation session to reinforce awareness about the protocol and to address inquiries about the recommendations was attended by the residents of the Department of Medicine.

### Ethical considerations

The protocol development phase was a component of the mixed methods study entitled, "The Development and Pilot Testing of a Protocol for the Initiation and Use of Corticosteroids for Critical Illness-Related Corticosteroid Insufficiency for Patients Admitted with Shock at the Philippine General Hospital," approved by the University of the Philippines Manila Research Ethics Review Board with the UPMREB code 2019-505-01. For the consensus-building procedure, participation was voluntary and informed consent was obtained.

## RESULTS

### Consensus-building

To initiate the development of a protocol for CIRCI, twenty-seven experts from the Divisions of Endocrinology, Infectious Disease, Pulmonology and Critical Care and Cardiology were invited to participate in the consensus-building process. Out of the 27 experts invited, 21 experts participated. This corresponds to a 78% response rate, which was satisfactory because this was more than the minimum target number of participants. In an earlier study, a 61% response rate was already considered sufficient for a Delphi consensus.[28] The consensus-building process for the diagnosis and management of CIRCI consisted of two modified Delphi rounds, and all experts participated in both rounds, thereby corresponding to a 100% response rate in the second round. There were no dropouts during the entire consensus-building process.

Inclusivity of the consensus-building process was upheld. Detailed instructions and reminders on the modified Delphi rounds were disseminated and all experts were given an adequate time to respond. For the first round of voting, the experts were given 21 days to evaluate the proposed recommendations on the diagnosis and management of CIRCI. The average response time was 2.1 days, with the shortest turnaround time of less than one day, and the longest turnaround time of 19 days. The feedback from all the participants were synthesized and circulated among the participants. A revised version of the protocol was sent. Another 21 days were allotted to assess the revisions. This three-week period for evaluation for each round is sufficient for reviewing the protocol, the recommended length of time of modified Delphi rounds is at least 10 days and up to 10 weeks.[13]

Consensus building was facilitated through two rounds of voting using the modified Delphi method. Participants were asked to give their responses on each component of the protocol. During the first round of voting, the participants indicated "agree" or "disagree" for each component of the protocol and indicated their reasons for doing so. There was an 84.2%-100% agreement for all the components of the proposed protocol.

The expert's feedback were consolidated and the following revisions in the protocol were made: 1) Simplified the algorithm for benefit of the user; 2) Clarified the timing of the ACTH stimulation testing; 3) Included hydrocortisone infusion as a means of administering steroids for CIRCI; and 4) Incorporated a protocol for tapering steroids. This proposed protocol for CIRCI was also reviewed for consistency with local and international sepsis guidelines.

During the second round of voting, the respondents were asked to evaluate each component of the protocol by indicating "agree," or "disagree–minor modification needed," "disagree–major modification needed, redo algorithm." All the components of the protocol reached 83.3%-100% agreement, exceeding the threshold of at least 70% agreement among participants. No disagreement calling for major modification of the algorithm was encountered during the second round of voting. All experts gave feedback on the proposed modifications. The process of consensus-building was completed after the second round because a convergence on viewpoints was achieved.[23] Both rounds also showed no significant difference in the level of consensus.[24] A table detailing the level of agreement for every recommendation in the protocol for both rounds is found in Appendix 1.

The protocol on the diagnosis and management of CIRCI, a product of consensus-building among experts from different fields, was approved by the Department of Medicine, which served as a form of external validation. It was then disseminated to all residents, fellows and consultants of the Department of Medicine prior to pilot testing and implementation.

## Final form of the protocol

Presented below is the final form of the protocol on the diagnosis and management of CIRCI:

### *Protocol for the Initiation and Use of Corticosteroids for Critical Illness-Related Corticosteroid Insufficiency (CIRCI) for Patients Admitted with Shock at a Tertiary Hospital*

*When should Critical Illness-Related Corticosteroid Insufficiency (CIRCI) be suspected ?*

All patients aged 19-years-old and above with an admitting diagnosis of refractory shock or developed **refractory hypotension or shock** during the admission should be managed as a case of **probable CIRCI**. Refractory shock is defined as any of the following:

- **Systolic blood pressure of persistently <90 mm Hg after hypovolemia is addressed through adequate fluid resuscitation (at least 30 ml/kg if without signs of congestion)**[5] **for at least 30 minutes** with a need for a vasopressor to maintain adequate organ perfusion, accompanied by signs of hypoperfusion such as tachycardia, altered mental status, confusion or encephalopathy, cold extremities, oliguria, or blood lactate > 2mmol/L[15] or
- requiring **at least 0.2 mcg/kg/min of norepinephrine** (or any other vasopressor)[29] or
- with **increasing vasopressor requirement**[29] or
- **requiring a second vasopressor to maintain MAP of ≥65 mm Hg).**[5]
- Adequate fluid resuscitation, of at least 30 ml/kg of fluid (if the patient is not at risk of pulmonary congestion), should have been administered and the patient should have been assessed for other etiologies of shock (hypovolemic, septic, cardiogenic) and adequate management (i.e., antibiotics for septic shock, inotrope such as dobutamine for cardiogenic shock) should already have been initiated for the patient.

*How should cases of probable CIRCI be managed?*

**As soon as CIRCI is suspected, prior to initiating steroids, obtain a blood sample for random serum cortisol** (at least 4 ml of blood sample in a red top vial).* **Subsequently, immediately start hydrocortisone as 100 mg intravenous (IV) loading dose followed by 50 mg IV every 6 hours or a 200 mg continuous infusion in isotonic saline to run for 24 hours** even if the result of the random cortisol is not yet available.[5,16] Treat a case of probable CIRCI even prior to establishing a definitive diagnosis based on the laboratory result. Testing should not cause any delay in the delivery of appropriate, life-saving management in the form of steroids.

*How should patients be managed after the initiation of steroids for probable CIRCI?*

**Continue hydrocortisone** at a dose of 200 mg/day for at least 72 hours and up to 7 days for patients:

- whose norepinephrine or vasopressor requirement are reduced by ≥50% within 72 hours of initiating hydrocortisone or
- have a random serum cortisol of <10 mcg/dL or <275.9 nmol/L[4] or
- with septic shock[5]

**Discontinue hydrocortisone** for patients who have random serum cortisol of >34 mcg/dL or >938.06 nmol/L or an increase in cortisol of at least 9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test[4]** unless given for other indications [e.g., Acute Respiratory Distress Syndrome (ARDS) or Chronic Obstructive Pulmonary Disease (COPD) in Acute Exacerbation or autoimmune disease].

*How long should corticosteroids be given for patients with CIRCI?*

Hydrocortisone at 200 mg/day should be given for **at least 72 hours and up to 7 days**, to have significant benefit.[4,5]

*How should steroids be tapered for patients with CIRCI?*

Steroids may be tapered in the following instances:

- Vasopressor requirements decrease by at least 50% for at least 72 hours[30] or
- Patient is off vasopressors for at least 72 hours,[30] and
- There are no other indications for maintaining patient on corticosteroids (i.e. ARDS, COPD or bronchial asthma in exacerbation, autoimmune disease, etc.)

**Hydrocortisone may be tapered as follows: decrease dose to 50 mg IV every 8 hours for one day, then 50 mg IV every 12 hours the next day, then may discontinue the following day.**[30]

*What blood glucose levels should be maintained for patients on steroids?*

Target blood glucose at **140-180 mg/dl**, which is the recommended range for critically ill patients,[31] with or without underlying diabetes mellitus. Refer to Endocrinology for difficulty in managing diabetes mellitus or steroid-induced hyperglycemia.

*How is the definitive diagnosis of CIRCI made?*

CIRCI is likely to be present if **random serum cortisol <10 mcg/dL or <275.9 nmol/L.**[4] Thus, patient is likely to benefit from corticosteroids.

For patients with an **indeterminate result of random cortisol (random cortisol of 11-34 mcg/dl or 304.49-938.06 nmol/L)** but with clinical features of CIRCI, an adrenocorticotrophic hormone (ACTH) stimulation test using high dose ACTH (250 mcg) with determination

** At least 4 ml of blood in a red top vial is needed for random serum cortisol. The test must be submitted to a laboratory for radioimmunoassay. If the test cannot be submitted on the same day of collection, the sample must be stored in the refrigerator (at 4°C for up to 72 hours) and brought to the laboratory once it is open.*

*** Unlikely to be CIRCI, therefore, corticosteroids are not proven to be of benefit in such cases.*

of the baseline cortisol, and peak cortisol response at 60 minutes after ACTH administration should be undertaken. An **increase in cortisol of <9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test** is indicative of CIRCI.[4]*** This test should be done 24-hours after the last dose of hydrocortisone.

***How should patients be managed after the cessation of steroid therapy?***

A random cortisol should be drawn 24-hours after the last dose of hydrocortisone. If the results still meet the criteria for CIRCI (random serum cortisol <10 mcg/dL or <275.9 nmol/L), a low dose oral steroid should be initiated in the form of prednisone tablet at 5-7.5 mg/day, which is equivalent to the physiologic dose of hydrocortisone at 10-12 mg per square meter of body surface area for clinically stable patients.[17]

For patients who remain critically ill, maintain the corticosteroid dose at least twice as high as the physiologic dose, which is about 40-60 mg of hydrocortisone or 10-15 mg of prednisone while optimizing work-up and management of the underlying conditions (i.e., adequate hydration, microbiologic diagnosis and source control for sepsis, two-dimensional echocardiography with cardiac index for cardiac dysfunction, initiation of work-up for causes of primary or secondary adrenal insufficiency if indicated****).

The clinical algorithm for the initiation and use of corticosteroids for patients admitted with shock is found in Figure 1.

## DISCUSSION

The pressing need to address both practice variations in treating critical illness and the lack of local guidance on this condition fueled the development of the protocol for the diagnosis and management of CIRCI. Through the modified Delphi method, a consensus among experts from different fields was achieved and divergent points in international and local guidelines on both CIRCI and sepsis were reconciled to increase adaptability in the local setting.

All recommendations were evaluated through a rigorous process through the modified Delphi method, subscribing to the CREDES (Conducting and Reporting for Delphi Studies) standards.[13] The modified Delphi method is a reliable method that upholds shared responsibility among the experts[27] in the development of a clinical pathway. This initiative featured a highly motivated set of experts who analyzed the current body of literature and screened the proposed clinical pathway and algorithm for CIRCI for validity and clarity.

### Setting the criteria for diagnosis

This protocol on CIRCI provides a framework for the clinical approach to refractory shock, which will aid in the management of critically ill patients in the local setting. The definition of refractory shock was comprehensive and specific, incorporating key components of the Surviving Sepsis guidelines and the Philippine Society of Microbiology and Infectious Diseases (PSMID) guidelines.[5,33] Indeed, a large number of studies have shown that CIRCI is likely present in patients with refractory shock, with patients in septic shock comprising a significant proportion of these cohorts.[18]

A major contribution of this protocol is the emphasis on the utility of random cortisol as a vital tool in diagnosing CIRCI. During critical illness, the circadian rhythm of cortisol production is lost, therefore, random serum cortisol is the appropriate laboratory examination to diagnose CIRCI.[19] Assays for serum cortisol are more accessible in local diagnostic centers than plasma cortisol and both methods for determining cortisol levels are comparable. There is also no advantage in utilizing free cortisol levels to detect relative adrenal insufficiency in the clinical setting.[34] Though random cortisol is an important tool for diagnosis, its value should not be used to decide whether corticosteroids should be given or not.[18] Patients afflicted with refractory shock with a clinical setting for relative adrenal insufficiency should immediately be started on corticosteroids. The pool of experts emphasize that awaiting the cortisol result is not a reason to delay treatment.

The role of ACTH stimulation testing was also stipulated in this protocol. It is an important adjunct in the diagnosis of CIRCI and it is also useful in guiding subsequent management after the acute phase. For patients with indeterminate result of random serum cortisol (11-34 mcg/dl), an incremental increase in serum cortisol of less than 9 mcg/dl after administration of 250 mcg ACTH is indicative of CIRCI, thus warranting further treatment with corticosteroids. The use of the high dose 250 mcg ACTH, rather than the low dose 1 mcg ACTH, for definitive testing for adrenal insufficiency, has been validated among critically ill patients.[20] Once the patient has been stabilized, ACTH stimulation testing facilitates a definitive diagnosis if the relative adrenal insufficiency has already been reversed. For critically ill patients, the absolute increase in cortisol levels is used rather than the peak cortisol level, for the latter is more appropriately used in non-critically ill patients.[35]

*** *Refer to Endocrinology for administration of the standard ACTH stimulation test. Clinicians may also refer patients with probable CIRCI for guidance in optimizing diagnostics and management, even if the patient is not a candidate for ACTH stimulation testing. The standard ACTH stimulation test with 250 mcg ACTH (the optimal dose that overcomes ACTH resistance) is done by first obtaining a baseline serum cortisol level, then administering 1 ampule containing 250 mcg of ACTH in the form of tetracosactrin (Synacthen) intramuscularly or intravenously, and then drawing blood again for serum cortisol after 60 minutes.[32] An increase in serum cortisol of <9 mcg/dl is highly indicative of CIRCI.[4] This test will be done 24-hours after the last dose of hydrocortisone for patients with an indeterminate random cortisol result.*

**** *Refer to Endocrinology for assessment for possible primary or secondary adrenal insufficiency.*

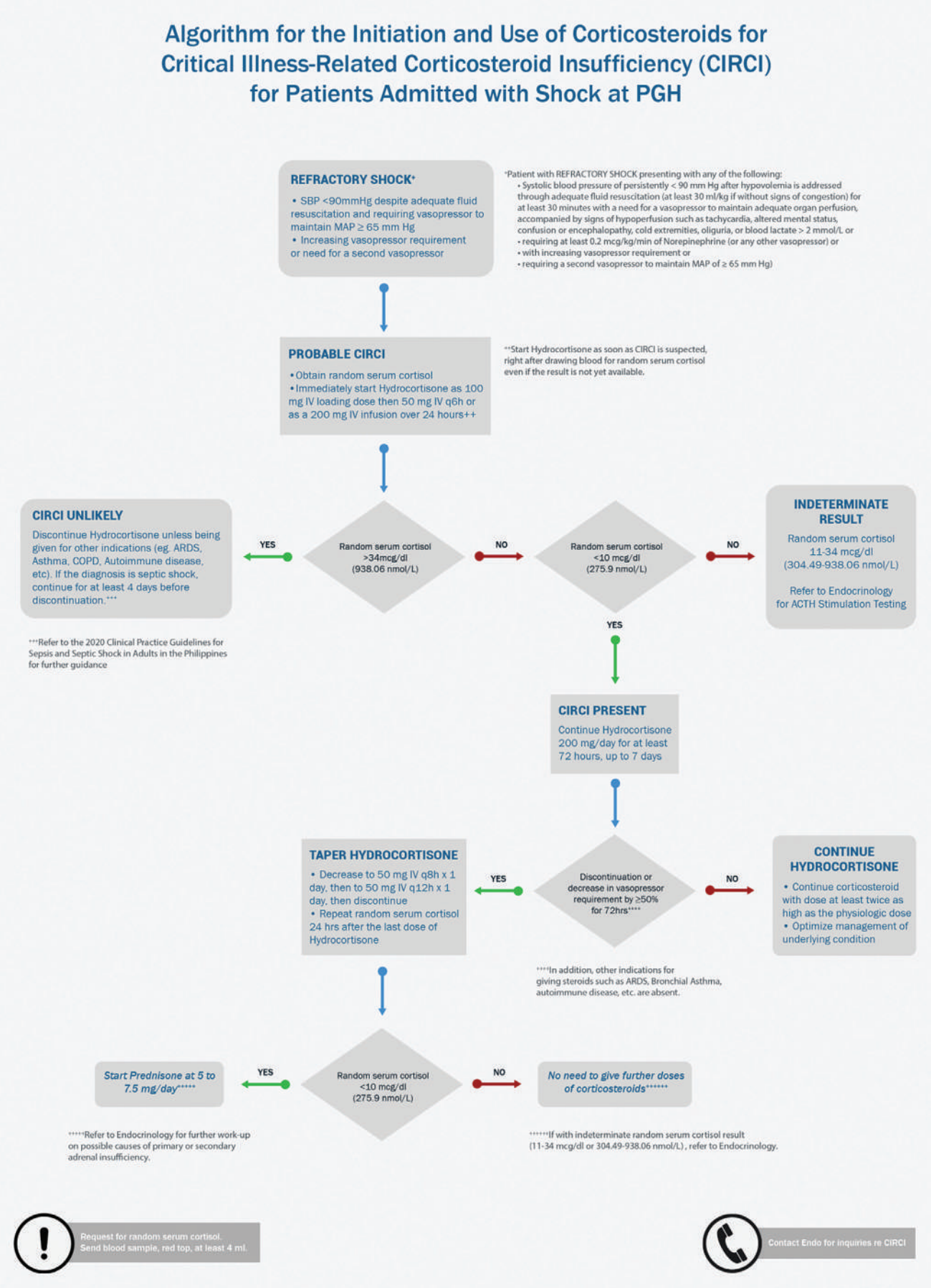


**Figure 1.** Algorithm for the diagnosis and management of CIRCI.

The experts also advocate for the use of a modified protocol for ACTH stimulation testing, which involves obtaining the serum cortisol at baseline and 60 minutes after ACTH stimulation because this methodology is adequate to diagnose CIRCI, even for late responders,[20] and is more adaptable in the local, resource-limited setting.

### Addressing management issues

A comprehensive approach to management, incorporating the appropriate treatment regimen is a key component of this protocol. The optimal dose of hydrocortisone was set at 200 mg/day, in line with the recommendations of various societies of critical care and infectious diseases.[4,20] This stress dose did not lead to increased risk of infections and other adverse events such as hypernatremia and hypercoagulability, as seen in several trials such as the HYPOLYTE study.[18,36] Higher doses exceeding 200 mg/day, on the other hand, did not result in better patient outcomes.[18]

Pertinent issues in the management of CIRCI were also addressed in this clinical pathway. The criteria for the discontinuation of steroids, specifically those used to ascertain clinical improvement, are included to guide clinicians in the initiation and maintenance of the corticosteroid dose. A tapering protocol was incorporated in this clinical pathway to reduce the risk of hypotension and rebound inflammation.[18]

### Future challenges

A standardized approach to the diagnosis and management of CIRCI was forwarded by this protocol. The institution of this clinical pathway underscores the need to evaluate the impact of this protocol on patient outcomes and in optimizing the care of critically ill patients in the local setting.

## CONCLUSION

Using the modified Delphi method, a systematic and validated tool for consensus-building, we were able to create a protocol for the diagnosis and management of CIRCI. The presence of refractory shock unresponsive to fluid resuscitation and vasopressors should warrant the clinical suspicion for the existence of CIRCI and should trigger a cascade of management strategies. This stepwise clinical pathway and algorithm aids in the prompt recognition of CIRCI. The timely initiation of corticosteroids is paramount. This clinical pathway, tailored for the local setting, provides guidance on the management of a challenging condition afflicting critically ill patients.

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**Statement of Authorship**
All the authors fulfilled the ICJME criteria for authorship.

**Author Disclosure**
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## APPENDIX

**Appendix 1.** Levels of Agreement per Recommendation

| Recommendation | Round 1 Percent Agreement | Round 2 Percent Agreement |
|---|---|---|
| ***When should CIRCI be suspected?***<br>All patients aged 19 years old and above with an admitting diagnosis of shock or developed refractory hypotension during the admission (i.e. requiring at least 0.2 mcg/kg/min of norepinephrine or its equivalent dose with another vasopressor or with increasing vasopressor requirement) should be managed as a case of probable CIRCI. | 94.7% | 94.4% |
| ***How should cases of probable CIRCI be managed?***<br>Prior to initiating steroids, obtain a blood sample for random serum cortisol. Immediately start hydrocortisone (as soon after blood sample is drawn, even if result is not yet available) as 100 mg intravenous (IV) loading dose followed by 50 mg IV every 6 hours for at least 72 hours, but not longer than 7 days. | 84.2% | 94.4% |
| ***How should patients be managed after the initiation of steroids for probable CIRCI?***<br>Continue hydrocortisone for patients whose norepinephrine or vasopressor requirement are reduced by more than 50% or have a random serum cortisol of < 10 mcg/dL or < 275.9 nmol/L. | 100% | 100% |
| ***How should patients be managed after the initiation of steroids for probable CIRCI?***<br>Discontinue corticosteroids for patients whose vasopressor requirements are not decreasing or have random serum cortisol of > 34 mcg/dL or > 938.06 nmol/L or a peak cortisol at 60 minutes of > 18 mcg/dL unless given for other indications (ex. Acute Respiratory Distress Syndrome (ARDS) or Chronic Obstructive Pulmonary Disease (COPD) in Acute Exacerbation). | 94.7% | 94.4% |
| ***How long should corticosteroids be given for patients with CIRCI?***<br>Hydrocortisone should be given for at least 72 hours, to have significant benefit, but not longer than 7 days. | 100% | 94.4% |
| ***How should steroids be tapered for patients with CIRCI?***<br>Steroids may be tapered in the following instances:<br>• Vasopressor requirements decrease by at least 50% for at least 72 hours, or<br>• Patient is not on vasopressors anymore for at least 72 hours, and<br>• there are no other indications for maintaining patient on corticosteroids (i.e. ARDS, COPD or Bronchial Asthma in exacerbation, autoimmune disease, etc.)<br><br>Hydrocortisone may be tapered as follows: decrease dose to 50 mg IV every 8 hours for one day, then 50 mg IV every 12 hours the next day, then may discontinue the following day. | 94.7% | 100% |
| ***At what levels should blood glucose be maintained for patients started on steroids?***<br>Target blood glucose 140-180 mg/dl, which are the recommended levels for critically ill patients. | 94.7% | 100% |
| ***How is the definitive diagnosis of CIRCI made?***<br>CIRCI is likely to be present if random serum cortisol < 10 mcg/dL or < 275.9 nmol/L. Thus, patient is likely to draw benefit from corticosteroids.<br>For patients with indeterminate result of random cortisol (random cortisol of 11-34 mcg/dl or 304.49-938.06 nmol/L) but with clinical features of CIRCI, an adrenocorticotrophic hormone (ACTH) stimulation test using high dose ACTH (250 mcg) with determination of the baseline cortisol, and peak cortisol response at 60 minutes after ACTH administration should be employed. An increase in cortisol of < 9 mcg/dL at 60 minutes after a 250 mcg ACTH stimulation test is indicative of CIRCI. This test will be done at 24 hours after the last dose of hydrocortisone. | 100% | 100% |
| ***How should patients be managed after the cessation of steroid therapy?***<br>A random cortisol test will be performed after the cessation of the steroid therapy. If the results still meet the criteria for CIRCI (random serum cortisol < 10 mcg/dL or <275.9 nmol/L), a low dose oral steroid should be resumed in the form of prednisone tab at 5-7.5 mg/day. | 84.2% | 94.4% |
| ***Algorithm*** | 84.2% | 83.3% |

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ORIGINAL ARTICLE

# Prevalence of Metabolic Syndrome and its Associated Risk Factors in Pediatric Obesity

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**Abstract**

Objective. We aimed to study the prevalence of metabolic syndrome (MetS) and the factors associated with metabolic syndrome among obese children.

Methodology. We recruited 175 subjects, aged 7 to 18 years old, referred for obesity. We studied their demography (age, gender, ethnicity, family background), performed clinical/auxological examinations [weight, height, body mass index (BMI), waist circumference (WC), blood pressure (BP)], and analyzed their biochemical risks associated with metabolic syndrome [fasting plasma glucose (FPG), fasting lipid profile (FLP), fasting insulin, liver function tests (LFT)]. MetS was identified according to the criteria proposed by the International Diabetes Federation (IDF) for pediatric obesity. Multiple logistic regression models were used to examine the associations between risk variables and MetS.

Results. The prevalence of metabolic syndrome among children with obesity was 56% (95% CI: 48.6 to 63.4%), with a mean age of 11.3 ± 2.73 years. Multiple logistic regression analysis showed age [adjusted odds ratio (OR) 1.27, 95% CI: 1.15 to 1.45] and sedentary lifestyle (adjusted OR 3.57, 95% CI: 1.48 to 8.59) were the significant factors associated with metabolic syndrome among obese children.

Conclusion. The prevalence of metabolic syndrome among obese children referred to our centers was 56%. Older age group, male gender, birth weight, sedentary lifestyle, puberty and maternal history of gestational diabetes mellitus (GDM) were found to be associated with MetS. However, older age group and sedentary lifestyle were the only significant predictors for metabolic syndrome.

*Key words: prevalence, metabolic syndrome, risk factors, obese children*

## INTRODUCTION

Obesity is one of the major public health problems in both developed and developing countries. Over 340 million children and adolescents age 5 to 19 years were overweight or obese in 2016, according to the World Health Organization (WHO).[1] An estimated 38.2 million children under the age of 5 years old were either overweight or obese. Half of the estimated children with obesity were from Asia.[1] The prevalence of obesity in South America was as high as 41.8% in Mexico, 19.3% in Argentina and 22% in Brazil.[2] In the Asia-Pacific region, the prevalence of obesity among children and adolescents was 16.3% in New Zealand, 14.1% in Brunei Darussalam, and 12.7% in Malaysia.[3] The estimated prevalence of obesity in the United States was 19.3% or about 14.4 million children and adolescents.[4] The high prevalence of obesity is most often related to excessive consumption of a high-calorie diet and poor lifestyle.[5] More important, it is reported that a third of obese children and 80% of obese adolescents remain obese when they reach adulthood.[6]

Obesity is associated with multiple co-morbidities/complications. The most serious endocrine complication is metabolic syndrome.[7,8] In the National Health Survey in China (2002), the prevalence of MetS among adolescents was 3.7%, and the prevalence rates of obesity, overweight and normal weight in children were 35.2%, 23.4% and 2.3%, respectively.[2] The prevalence of MetS among Turkish students with obesity was ten times more than lean students (21% versus 2%).[2] MetS prevalence was as high as 36% among children with obesity in Bolivia compared to children in South Korea, with a prevalence of only 9.1%.[2]

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There are numerous publications related to pediatric obesity in Malaysia. In 2011, the South-East Asia Nutrition Survey (SEANUTS) revealed that the prevalence of overweight and obesity in children six months to 12 years of age was 21.6%.[9] The 2015 National Health and Morbidity Survey (NHMS) reported that the prevalence of obesity among children age 10 to 14 years in Malaysia was 14.4%.[10] The study by Fadzlina et al., showed a 16.0% and 9.4% prevalence of overweight and obese status among 13-year-old adolescents respectively.[11] The MyBreakfast study found that the prevalence of overweight and obesity in Malaysian children age 6 to 12 years was 14.7 %.[12] Compared to other Southeast Asian countries such as the Philippines, Thailand and Vietnam, there are more overweight and obese Malaysian adolescents.[13-15]

Metabolic syndrome is defined as the clustering of risk factors of dyslipidemia, abnormal glucose metabolism and high blood pressure. If left untreated, the syndrome would result in cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).[16,17] According to Andrabi et al., the prevalence of MetS among children and adolescents was 3.8%, with obese subjects having the highest proportion of MetS compared with those at risk for overweight and average weight (30.7% vs. 2.5% and 0.5%, respectively).[18] A review of MetS research in Malaysia by Lim et al., using the IDF criteria found the prevalence of metabolic syndrome among overweight and obese children was 1.3% to 5.3%.[19,20] Using the same criteria, Fadzlina and colleagues found a 10% prevalence of metabolic syndrome among 280 overweight and obese 13-year old school children.[11] None of those with average weight had metabolic syndrome.

Despite the increasing prevalence of pediatric obesity in Malaysia, there are few studies on the factors associated with MetS. Most of them are mainly population-based studies among school children with a much lower prevalence of metabolic syndrome. In contrast, ours is a hospital-based study which sought to identify risk factors for MetS that will be essential to prevent the consequent CVD and T2DM among at-risk patients. This study aimed to determine the prevalence of MetS and to identify risk factors associated with MetS among recruited and referred obese children in a hospital-based setting.

## METHODOLOGY

### Study design and setting

This is a cross-sectional study conducted from May 2019 to August 2021 at the Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZII). The study was approved by the Human Research Ethics Committee USM (reference: USM/JEPeM/18120807) and Medical Research and Ethics Committee Kementerian Kesihatan Malaysia (NMRR-20-3213-56314 (IIR).

### Patients and procedures

The study involved 175 patients using consecutive sampling method from the two study sites. The inclusion criteria included the following: age 7 to 18 years; waist circumference more than 90$^{th}$ percentile; diagnosis of exogenous or primary obesity, defined as BMI more than 95$^{th}$ percentile according to age and gender; and with assent to join the study. Patients with secondary causes of obesity (monogenic disorders, syndromic forms of obesity, neurogenic, endocrine and drug-induced) were excluded.

All subjects underwent measurements of height, weight, BMI, WC and BP. Waist circumference was measured over the skin midway between the tenth rib and iliac crest at the end of normal expiration, using the same measuring tape. Body weight was recorded to the nearest 0.1 kg, measured using a standard weighing scale while the subject was barefoot and clad in light clothes. Height was measured to the nearest 0.5 cm in a standing position without shoes using a standard stadiometer. Blood pressure was measured with a digital BP monitoring device and an aneroid sphygmomanometer. Each device was calibrated regularly. Doctors evaluated pubertal maturation according to standardized Tanner staging.

BMI was expressed in kg/m$^2$. Obesity was defined as BMI >95$^{th}$ percentile of the standard WHO BMI. The diagnosis of MetS was based on the 2007 IDF pediatric definition: WC ≥90$^{th}$ percentile and at least two components above or under a single cut-off point (triglyceride ≥1.7 mmol/L; high-density lipoprotein cholesterol <1.03 mmol/L; fasting plasma glucose ≥5.6 mmol/L; and systolic or diastolic BP ≥130 or ≥85 mmHg, respectively).For biochemical measurements, a 10 mL venous blood sample was obtained in the morning using standard venipuncture after an overnight fast by trained health staff. Blood was analysed for fasting plasma glucose, fasting lipid profile, fasting insulin, liver function tests and renal profile.

A questionnaire on age, gender, race, birth weight, feeding history, family history of diabetes mellitus or GDM, hypertension, cardiovascular disease, physical activity, and sedentary lifestyle was provided on enrollment in the study. According to the WHO recommendation, a sedentary lifestyle was defined as more than 2 hours of screen time and less than 60 minutes of moderate to vigorous physical activity per day.[1] The questionnaire took 15-20 minutes to complete, and was answered by the parents of children less than 13 years old; older subjects answered together with their parents.

The recruited participants were then followed up at the Endocrine Clinics every three months.

### Sample size estimation

The sample size was calculated using a single proportion formula for the estimation of the proportion and prevalence

odds ratios for the factors considered in the study. The largest sample size obtained was for breastfeeding as one of the factors associated with metabolic syndrome. The information used for the sample size computation using Power and Sample Size Program were as follows: (a) 37% of pediatric patients with metabolic syndrome were breastfed based on the study by Sangun and colleagues, (b) the expected prevalence difference was 25% (since proportion with metabolic syndrome was assumed to be higher among patients who were not breastfed), (c) the level of significance was set at 5%, (d) the power of the test was set at 80%, and (e) the ratio between patients with metabolic syndrome to those without metabolic syndrome in the sample was set at 3.[6] This resulted in a minimum sample size of 165 patients. Anticipating a non-response rate of 10% among prospective respondents, the sample size was adjusted to 182 obese patients.

### Statistical analysis

All categorical variables were presented as frequencies and percentages. For numerical (quantitative) variables, the distribution was evaluated by examining the skewness and kurtosis values as well as the histogram with overlaid normal curve and the box whisker plot. Numerical variables with normal distribution were presented as mean and standard deviation (SD). Non-normally distributed numerical variables were presented as median and inter-quartile range (IQR). The point and 95% confidence interval estimates of the prevalence of MetS among obese pediatric patients were calculated.

Logistic regression analysis was used to determine factors associated with MetS. Simple logistic regression analysis was used to identify factors to be included in the multiple regression analysis. Cut-off was set at $p<0.25$ in determining variables to be included in the full model. The forward selection method was used for the variable selection procedure. Probability to enter the model was set at $p<0.05$. All the assumptions of the test were examined. The fitness of the model was assessed using the Hosmer-Lemeshow test. Outlier and influential observations were examined using Cook's influential statistics, while linearity was examined using the Box-Tidwell procedure. The factors that remained in the final model were presented using a table with its corresponding adjusted odds ratio, 95% CI, and $p$ value. Data were analyzed using IBM® SPSS® Statistics 26.0.

## RESULTS

Baseline characteristics are summarized in Table 1. There were 98 (56%) male patients and 77 (44%) female patients. The predominant race was Malay (n=172, 98%). The subject's mean age was 11.3 years (SD 2.73): 96 patients (54.9%) were between 7 to 11 years old, and 79 (45.1%) were between 12 to 18 years. The mean birth weight of the subjects was 2.9 kg (SD 0.43). Of the 175 children, 104 (59.4%) received exclusive breastfeeding until the age of 6 months, 55 (31.4%) were fed with milk formula during infancy, and 16 (9.1%) were given mixed feeding. A total of 170 subjects (97.1%) had a sedentary lifestyle.

**Table 1.** Sociodemographic, clinical and biochemical characteristics

| Variables | n (%) |
|---|---|
| Gender | |
| Male | 98 (56.0) |
| Female | 77 (44.0) |
| Age, year | 11.3 ± 2.73[a] |
| 7 to 11 | 96 (54.9) |
| 12 to 18 | 79 (45.1) |
| Race | |
| Malay | 172 (98.0) |
| Chinese | 2 (1.1) |
| Indian | 1 (0.6) |
| Birth weight, kg | 2.9 ± 0.43[a] |
| Feeding | |
| Breastfeeding | 104 (59.4) |
| Formula milk | 55 (31.4) |
| Mixed | 16 (9.1) |
| Lifestyle | |
| Active | 5 (2.9) |
| Sedentary | 170 (97.1) |
| Family history of obesity | |
| Yes | 170 (97.1) |
| No | 5 (2.9) |
| Family history of medical illness | |
| None | 4 (2.3) |
| Diabetes | 68 (38.9) |
| Hypertension | 19 (10.9) |
| Heart disease | 6 (3.4) |
| Hypertension + diabetes | 66 (37.7) |
| Hypertension + diabetes + heart disease | 12 (6.9) |
| Gestational diabetes mellitus | |
| Yes | 130 (74.3) |
| No | 45 (25.7) |
| Weight, kg | 62.0 ± 21.89[a] |
| Height, cm | 139.1 ± 21.75[a] |
| Body mass index, kg/m$^2$ | 30.2 ± 4.00[b] |
| Waist circumference, cm | 89.6 ± 13.65[a] |
| Fasting plasma glucose, mmol/L | 4.9 ± 1.20[b] |
| Triglycerides, mmol/L | 1.5 ± 0.60[b] |
| High-density lipoprotein cholesterol, mmol/L | 1.0 ± 0.36[b] |
| Aspartate aminotransferase, IU/L | 26.0 ± 15.00[b] |
| Alanine aminotransferase, IU/L | 36.0 ± 30.00[b] |

[a] Age, birth weight, weight, height and waist circumference are normally distributed and presented as mean ± standard deviation (SD)
[b] Body mass index, fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol, aspartate aminotransferase and alanine amino-transferase are non-normally distributed and presented as median ± interquartile range (IQR)

The majority of the subjects had a family history of obesity (n=170, 97.1%). In this study, 130 subjects (74.3%) were born to a mother with gestational diabetes mellitus (GDM). Almost all children had a family history of chronic illnesses; 68 (38.9%) had a family history of diabetes, 66 (37.7%) had family history of diabetes and hypertension, 19 (10.9%) had hypertension alone, six (3.4%) had ischemic heart disease, and 12 (6.9%) reported diabetes, hypertension and ischemic heart disease in their family. Four subjects (2.3%) reported no family history of chronic illnesses.

The mean weight and height were 62.0 kg (SD 21.89) and 139 cm (SD 21.75), respectively. The median BMI was

**Table 2.** Simple and multiple logistic regression analyses to determine factors associated with metabolic syndrome

| Variables | Crude OR (95% CI) | *p* value | Adjusted OR (95% CI) | *p* value |
|---|---|---|---|---|
| Age in years | 1.30 (1.15 to 1.48) | <0.001 | 1.27 (1.15 to 1.45) | <0.001 |
| Age category in years | | | | |
| 7 to 11 | 1.00 | | | |
| 12 to 18 | 2.09 (1.13 to 3.86) | 0.018 | | |
| Gender | | | | |
| Female | 1.00 | | | |
| Male | 1.62 (0.88 to 2.96) | 0.117 | | |
| Birth weight in kg | 1.80 (0.88 to 3.70) | 0.107 | | |
| Sedentary lifestyle | | | | |
| Active | 1.00 | | 1.00 | |
| Sedentary | 4.48 (1.94 to 10.35) | <0.001 | 3.57 (1.48 to 8.59) | 0.005 |
| Puberty | | | | |
| No | 1.00 | | | |
| Yes | 2.85 (1.42 to 5.70) | 0.003 | | |
| Gestational diabetes mellitus | | | | |
| Yes | 1.00 | | | |
| No | 0.47 (0.23 to 0.93) | 0.030 | | |

OR, odds ratio
Forward LR variable selection method applied.
$R^2$ = 0.198, classification table = 68.0% overall percentage of correct prediction, Hosmer and Lemeshow Test $\chi^2$ (7) = 5.00, $p$ = 0.660,
Area under ROC curve = 72.8% (95% CI: 65.3 to 80.3%)
No multicollinearity and no interaction were found between age and sedentary lifestyle status
A linear relationship was found between age and the logit transformation of the dependent variable as assessed by the Box-Tidwell procedure
Cook's influential statistics indicate no significant outliers, high leverage points or highly influential points

30.2 kg/m$^2$ (QR 4.00) and the mean WC was 89.6 cm (SD 13.65). In our cohort study, the prevalence of metabolic syndrome among children with obesity was 56% (95% CI: 48.6% to 63.4%).

On simple logistic regression analysis, age, older age group (12 to 18 years), male gender, birth weight, sedentary lifestyle, puberty, and maternal GDM were the important factors associated with metabolic syndrome among obese children. However, multiple logistic regression analysis revealed only age (adjusted OR 1.27, 95% CI: 1.15 to 1.45) and sedentary lifestyle (adjusted OR 3.57, 95% CI: 1.48 to 8.59) to be significant factors (Table 2).

## DISCUSSION

Our study recruited 175 obese children who attended the endocrine clinic in tertiary hospitals in Kota Bharu, Kelantan (HUSM and HRPZII). We analyzed the prevalence of metabolic syndrome in obese children aged 7 to 18 years old. Using the 2007 IDF criteria, the prevalence of MetS in our cohort was 56%. The prevalence of MetS has been reported to be higher in severely obese (49.7%) than moderately obese children (38.7%); none of the overweight or normal-weight children had MetS.[20] This is consistent with the results of Simunovic et al., which showed that the risk of MetS increases with obesity.[22] Compared to our findings, there were lower prevalence rates of MetS in other groups of obese children in previous studies by Fadzlina et al., (10%) and Wee et al. (5.3%).[11,20]

Most pediatric obesity studies in Malaysia were mainly population-based studies on school children. Our study had a higher prevalence of MetS since we recruited only obese subjects referred to our hospitals. Majority of our subjects had BMI consistent with morbid obesity or BMI >30 kg/m$^2$. A higher BMI increases the likelihood of MetS as a metabolic complication of obesity.

Friend et al., analyzed 85 pediatric obesity studies in a systematic review: 63 applied the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) variants, 26 used the International Diabetes Federation (IDF) criteria, and 15 adopted WHO criteria. The study found that the median (range) prevalence of MetS in the whole population was 3.3% (0% to 19.2%), 11.9% (2.85 to 29.3%) in overweight and 29.9% (10.0% to 66.0%) in obese subjects.[23] The authors concluded that the prevalence of MetS varies considerably depending on the criteria used. Prevalence rates were higher when age-specific criteria were applied to children compared to adult criteria. Childhood prevalence differed when childhood and adolescent criteria were applied.[23]

Metabolic syndrome was present in 30.7% of obese subjects based on the modified ATP III criteria among 8- to 18-year old school-going children of Srinagar city of Kashmir, India.[18] In one Myanmar hospital-based study, the MetS prevalence was 39.1% among the obese group using IDF criteria.[24] The prevalence of MetS was also different when other definitions were applied to the same population: the rate was 66.2% based on NCEP ATP III criteria and 42.5% using the definition by Weiss et al.[25] In China, the prevalence of MetS in all moderately and severely obese children and adolescents was 10.3%, and 22.1%, respectively, using ATP III criteria.[26] The overall prevalence of MetS in hospital-based studies varied between 18% to 66.2% using the IDF criteria (2007).[22,24,26-30]

Our present study showed that most obese children were male (56%). A study done by Caceres et al., demonstrated that the prevalence of MetS was 36%, with a higher rate

among males (40%) than females (32.2%) ($p$=0.599).[31] The odds of developing MetS in females were nearly 70% lower than the odds among males in 354 overweight and obese school-aged adolescents (age 10 to 19 years) in the city of Piracicaba, Brazil.[32] Male sex was a significant predictor of metabolic syndrome (adjusted OR 2.338, 95% CI: 1.204 to 4.540).[33] More significant abdominal fat deposition in males than females may be one of the contributing factors for increased MetS.[34] An increase in visceral adiposity would lead to a higher rate of free fatty acid influx into the liver, resulting in increased production of very low-density lipoproteins (VLDL). Under normal circumstances, insulin inhibits the secretion of VLDL into the systemic circulation. In the setting of insulin resistance, an increased influx of free fatty acids into the liver increases hepatic triglyceride synthesis.[35]

Sangun et al., reported that the prevalence of MetS was significantly higher in children with a family of diabetes, hypertension, coronary artery disease and hyperlipidemia.[6] The risk of MetS was 2.4 times higher in children with a family history of chronic medical problems.[36] Our study population had family members with diabetes (38.9%); a combination of diabetes and hypertension (37.7%); hypertension alone (10.9%); a combination of hypertension, diabetes and coronary artery disease (6.9%); and coronary artery disease (3.4%). Only 2.3% had no family history of chronic illnesses. Among the 175 subjects, 97.1% had a family history of obesity. This observation may indicate the interplay of genes with environmental risk factors. A patient with a family history carries some potential genes which would be expressed with poor lifestyle choices and unhealthy diets.

The other risk factor of metabolic syndrome in children was a history of maternal gestational diabetes mellitus. Tam et al., reported that maternal GDM increases cardiometabolic risk in children who had significantly higher systolic and diastolic blood pressure values and lower high-density lipoprotein cholesterol levels.[37] *In utero* hyperinsulinemia is an independent predictor of abnormal glucose tolerance in childhood.[37] A similar study by Boney et al., showed that infants of mothers with diabetes were at significant risk of developing MetS in childhood.[38] Our study showed that 74.3% of the children were born by mothers with GDM. Those without a history of GDM had 53% reduced odds of having metabolic syndrome compared to those with GDM mothers.

There were only two significant predictors for MetS from the multiple logistic regression analyses: older age and sedentary lifestyle. Obese children in the older age range had 1.27 times higher odds to have MetS. Those with sedentary lifestyles had 3.57 times higher odds of having metabolic syndrome than those who were non-sedentary. Our findings were similar to other studies. Wee et al., found that children in the older age group were more likely to have metabolic syndrome compared to those in the younger age group (OR 2.8, 95% CI: 0.7 to 10.6).[20] This is most likely related to hormonal changes associated with puberty. The levels of sex hormones, growth hormone and insulin-like growth factor-1 (IGF-1) are higher during puberty than in the prepubertal period because of hypothalamic-pituitary-gonadal and -IGF-1 axes activation. Sex hormones work synergistically with growth hormones. Pubertal growth spurts coincide with peak secretion of growth hormone, leading to worsening insulin resistance.[39-41] It is estimated that there is a 25-50% decline in insulin sensitivity which recovers upon completion of pubertal development.[42,43]

Dejavitte et al., found that insufficient physical activity was associated increased odds of MetS compared to those who were active (OR 4.60, 95% CI: 1.01 to 20.96).[32] A study in Thailand by Siwarom et al., showed that increased duration of physical activity was associated with decreased odds of MetS (OR 0.96, 95% CI: 0.92 to 0.99).[44] The Third Korea National Health and Nutrition Examination Survey concluded that screen time for more than 2 hours a day was associated with increased odds of having MetS (adjusted OR 2.001, 95% CI: 1.008 to 3.972).[33]

A possible mechanism for this relationship is due to exercise-induced mitochondrial biogenesis in skeletal muscle, representing about 80 to 90% of all insulin-sensitive tissues and accounting for approximately 50% of basal metabolic rate.[45] Increased mitochondrial biogenesis by increased volume and functional capacity is of fundamental importance. It leads to greater rates of oxidative phosphorylation and an improved ability to utilize fatty acids during submaximal exercise.[46] Additionally, physical activity also directly improves insulin sensitivity by facilitating substrate uptake in muscle and adipose tissue.

This study found a significant prevalence of metabolic syndrome among obese children referred to our centers. With more than half of them with MetS at a mean age of 11 years, they already have the most serious complication of obesity. This is a serious public health issue, as untreated MetS may progress to cardiovascular and metabolic diseases such as hypertension, dyslipidemia and type 2 diabetes. More efforts are needed to educate the public about healthy lifestyles to prevent obesity and its complications.

### Limitations of the Study

Our study has a few limitations. The selection of cases was limited to referrals to our hospital, which might not be truly representative of the pediatric population in our state. In the future, we may need to include more hospitals in the state to obtain a more accurate representation. Movement restrictions associated with the COVID-19 pandemic may have resulted to fewer referrals from other district hospitals. The short-term design of the study was also a limitation. It would be ideal to have a longer study duration designed to evaluate the effectiveness of the hospital-based weight reduction program.

## CONCLUSION

The prevalence of metabolic syndrome among obese children referred to our centers was 56%. The factors associated with MetS included older age group, male gender, birth weight, sedentary lifestyle, puberty and maternal history of gestational diabetes mellitus. However, older age group and sedentary lifestyle were the only significant predictors for MetS.

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ORIGINAL ARTICLE

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# Accuracy and Cost-effectiveness of the Diabetic Foot Screen Proforma in Detection of Diabetic Peripheral Neuropathy in Myanmar

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**Abstract**

Objective. Proper foot assessment is important for early detection and treatment of diabetic peripheral neuropathy (DPN), the main cause of diabetic foot ulcers (DFUs). This study aimed to determine the accuracy and cost-effectiveness of the locally developed Diabetic Foot Screen (DFS) proforma in detecting DPN among diabetic patients at 10 selected clinics in Yangon, Myanmar.

Methodology. The study included 625 type 2 diabetics from 10 primary care clinics who participated in the diagnostic accuracy and cost-effectiveness analysis. They were assessed with DFS proforma and biothesiometry by two examiners independently. The cost-effectiveness analysis was conducted based on available data in the local primary care setting.

Results. The overall accuracy of the DFS proforma assessment was 74.76% (95% CI: 70.46%- 79.06%). The optimal cut-off DFS score was ≥1.5 (sensitivity 62%; specificity 76%) in detecting DPN. Compared to biothesiometry, the cost-effectiveness of DFS proforma assessment in DPN detection was 41.79 USD per DPN case detected.

Conclusion. This study supported the use of DFS proforma for DPN detection in primary care clinics. It also provided new information on the estimated costs per patient with DPN detected in Myanmar.

*Key words: foot screening, diabetic peripheral neuropathy, biothesiometry, cost-effectiveness, Myanmar primary care*

## INTRODUCTION

The global prevalence of diabetes mellitus (DM) has been increasing exponentially, from 422 million people in 2014 to 463 million people in 2019.[1,2] In Myanmar, the estimated prevalence of DM was 6.6% of the total population in 2016[3] and its prevalence among adults aged 25- 64 years in Yangon region was 18% in 2014.[4] The escalating rise of global and local DM prevalence rates reflects the increasing number of people who are susceptible to diabetic complications annually.

Among individuals with diabetes, the lifetime risk of developing non-traumatic foot ulcers is approximately 15%.[5] Foot ulcers secondary to diabetes are commonly associated with increased morbidity and mortality and are a financial burden to healthcare systems.[6] Among several causes for diabetic foot ulcers (DFUs), peripheral neuropathy is the most important.[6]

Diabetic peripheral neuropathy (DPN) can affect up to 50% of diabetic patients.[7] The prevalence of DPN is around 33.7% in Myanmar.[8] Despite its high prevalence, DPN often remains undiagnosed by healthcare professionals,[2] especially at primary care clinics in Myanmar. The early detection of DPN is recommended for all diabetic patients.[9]

Diabetic foot examination is essential for the primary prevention of neuropathy-related foot complications, and the secondary prevention of neuropathic foot ulcers and amputations. As the comprehensive foot exam requires a detailed investigation of the lower limb by a specialist, it is not feasible in resource-limited primary care clinics in Myanmar.[10] In clinical practice, only a few primary care physicians provide regular foot screening for DM patients, using a 10-gram monofilament to test for DPN. Hence, the Diabetic Foot Screen (DFS) proforma was developed by the Myanmar Ministry of Health and Sports, in collaboration with the World Diabetes Foundation (WDF), as a clinical tool to screen for risk factors for foot ulceration among DM patients. Its initial implementation was at the launch of the Myanmar Diabetic Foot Care Program in 2016.[11]

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The DFS proforma includes focused history taking, foot examination, and three bedside tests: 10-gram monofilament test, ankle reflex, and vibration perception test (VPT) by a 128-Hz tuning fork. It contains a scoring system for each item except for background data, history taking and checking of foot pulses. Although the DFS proforma has already been used in out-patient clinics of a few government hospitals, it has not yet been widely introduced to Myanmar primary care physicians.

As the three bedside tests of the DFS proforma can be done with relatively low expense, it can be useful as a screening tool to detect DPN in primary care. However, its accuracy and cost-effectiveness in the diagnosis of DPN are not known, and need to be studied especially in a primary care setting.

## METHODOLOGY

### Subjects, materials and methods

This study was aimed to determine the diagnostic accuracy and cost-effectiveness of the DFS proforma in the detection of DPN among diabetic patients at primary care clinics in Yangon, Myanmar. The first part of the study was the cross-sectional study for diagnostic accuracy of the DFS proforma (which was a one-time assessment without repetition) and the second part was the cost-effectiveness analysis.

### Study subjects

For the diagnostic accuracy study, 10 private primary care clinics of the members of the General Practitioners' Society located in Yangon were first selected. Participants were then selected by purposive sampling. Previously diagnosed diabetic patients, 18 years and above, who came to the selected clinics at least once during the data collection period, were included. Diabetic patients who were previously diagnosed with any kind of neuropathy other than diabetic peripheral neuropathy and those with peripheral vascular disease and unhealed foot ulcers were excluded. The sample size calculated using the formula for ROC analysis [n = $((Z_{\alpha/2}))^2$ V((AUC) ^ ))/ ($d^2$)] was 184, while sample size calculated by using the formula for the cross-sectional diagnostic study was 620 [$n = p(1-p)/d^2*(Z_{\alpha/2})^2$]. This study was approved by the Research Ethics Board of the University of the Philippines Manila (UPMREB 2020-254-01) in May 2020 and by the Institutional Review Board of the University of Public Health (UPHIRB 2020/Research/13), Myanmar, in July 2020.

### Data collection procedure

All eligible participants from the ten clinics were continuously recruited through their respective doctors from July 12, 2020, to January 17, 2021. Detailed information about the study was provided to the participants in the Burmese language and written informed consent was taken.

Before data collection, the primary investigator (PI) and his research assistant (RA) received training from a footcare specialist for biothesiometry and the DFS proforma assessment using the standardized procedures, respectively. The results of biothesiometry reported by the PI were compared with the results reported by the footcare specialist to test the inter-rater reliability.

All participants were assessed with the DFS proforma by the RA and with a biothesiometry test by the PI independently. The results of one examiner were blinded to the other while they were assessing the patients. The DFS proforma assessment was done according to the standard procedures in the guideline of the Myanmar Diabetic Foot Care Program.[11]

Biothesiometry assessment was used as the reference-standard test in this study because there were several limitations to referring the patients to hospitals for nerve conduction studies during the time of coronavirus 2019 (COVID-19) pandemic. The vibration perception threshold (VPT) of each patient was assessed with Vibrasens - a portable digital biothesiometer (Mediko Foot Care, India) according to the standard procedure for biothesiometry.

The cost-effectiveness analysis of the DFS proforma assessment in DPN detection was done based on the available data from the selected clinics. The primary care physicians were asked to collect the cost-related data for the DFS proforma test and the mean of 10 different costs was taken as the estimated cost for the DFS proforma test per patient.

In the cost-effectiveness analysis, only the direct costs related to the DFS proforma test and biothesiometry were considered. Cost estimations were done for local primary care settings from the patients' perspective. Indirect costs due to transportation and loss of productivity were not included because of the lack of a standardized way to measure such costs in the local context.

### Data processing and analysis

Background characteristics of the patients were analyzed as mean and standard deviation (SD) for quantitative variables and numbers with percentages for qualitative variables. The sensitivity, specificity and likelihood ratios of the DFS proforma assessment with different cut-off scores in detecting DPN were obtained from the receiver operating characteristics (ROC) curve analysis by using Stata 15.0. From ROC analysis and Youden's index, the receiver operator cut-off score of the DFS proforma, with the optimal sensitivity and specificity, was determined.

The cost-effectiveness analysis included 2 hypothetical groups of 1000 diabetic patients: the DFS group, assessed with the DFS proforma and the biothesiometry group. Theanalysis was done by comparing the cost and the number of DPN cases detected in the DFS group, with

the cost of biothesiometry and the number of DPN cases detected in the biothesiometry group. The effect of false positive and false negative test results was considered in analyzing the cost-effectiveness. Sensitivity analysis was done by using the different costs of the DFS proforma test and biothesiometry and the estimated number of DPN cases detected for the DFS group and biothesiometry group. All cost estimations were done in local currency, Myanmar kyat (MMK), which were converted to the equivalent US dollar (USD) at the time of data analysis.

## RESULTS

### Diagnostic accuracy study

The diagnostic accuracy study consisted of 625 diabetic patients from 10 selected primary care clinics located in seven townships of Yangon, Myanmar. The baseline characteristics of the participants are summarized in Table 1.

The majority of the participants were female (71.4%), with a mean age of 57.8 years. The average height, weight and body mass index (BMI) of the participants were 156.9 cm, 65.4 kg, and 26.5 kg/m$^2$, respectively. All had type 2 diabetes with a mean diabetes duration of 6.2 years. Majority of the participants were non-smokers (77.9%); 81.6% did not drink alcoholic beverages. Only 231 participants had hemoglobin A1c (HbA1c) results tested within the previous 6 months. Their mean HbA1c value was 7.9% (63 mmol/mol).

### Results of the DFS proforma assessment

All participants received both the DFS proforma assessment (Figure 1) and biothesiometry during their respective visits at 10 selected clinics. The flow of participants throughout the study is described in Figure 2.

**Table 1.** Baseline characteristics of the study participants

| Characteristics | | |
|---|---|---|
| Female gender | Frequency (%) | 446 (71.4%) |
| Age (years) | Mean (SD) | 57.8 (10.09) |
| BMI (kg/m$^2$) | Mean (SD) | 26.5 (4.69) |
| Duration of diabetes (years) | Mean (SD) | 6.2 (5.97) |
| Smoking status | Frequency (%) | |
| Non-smoker | | 487 (77.9%) |
| Current smoker | | 57 (9.1%) |
| Ex-smoker | | 81 (13.0%) |
| Alcohol drinking status | Frequency (%) | |
| Non-drinker | | 510 (81.6%) |
| Current | | 54 (8.6%) |
| Ex-drinker | | 61 (9.8%) |
| HbA1c results (%)* | Mean (SD) | 7.9 (2.01)* |

*Only 231 participants had HbA1c results; SD: standard deviation

The DFS proforma assessment found that 48.3% (302/625) of patients had neuropathic symptoms (tingling, numbness, or altered sensation). The majority did not have intermittent claudication (95.7%), rest pain (99%), or previous foot ulcers (96.8%). The foot examination revealed that: 89.6% (560/625) of participants did not have any sign of infection on either foot; 31.7% (198/625) had callus and/or dry skin; and 58 patients had foot deformities. None of the participants had a foot ulcer at the time of examination.

The results of the monofilament test were scored as 'all present' (score-0), '>2 points absent' (score-0.5), or 'all absent' (score-1) for each foot. We found 511 patients (81.8%) had protective sensation in all 10 points tested on each foot; 34 had a loss of protective sensation (LOPS) in >2 points on one foot, and 59 had LOPS in >2 points on both feet.

Ankle reflex was present in all but two of the study participants (623, 99.7%). The results of the 128-Hz tuning fork test were scored as 'present' (score-0), 'reduced' (score-0.5), or 'absent' (score-1) for each foot. Vibration perception was present on both feet in 435 patients (69.6%); reduced on both feet in 19 patients (3%), and absent on both feet in 61 patients (9.8%). The remaining 17.6% had reduced and/or absent vibration perception on one or both feet.

The overall result of the DFS proforma assessment was described as the DFS score, the sum of the scores from the foot examination and the three bedside tests. A DFS score of less than 1.5 was found in 64.8% (405/625) of the participants, while the rest scored between 1.5 to 8.

### Results of the biothesiometry

During biothesiometry training, the inter-rater reliability was checked as follows: the footcare specialist and PI independently assessed 10 DM patients. The overall agreement on VPT values between the two assessors was 80%. Due to constraints in getting appointments with the same foot-care specialist for the inter-rater reliability test, it involved only 10 patients. However, the PI strictly followed the specialist's guidance and the standard procedure for biothesiometry during data collection.

In the diagnostic accuracy study, 185 patients (29.6%) with the average VPT value of >25 V on one or both feet were diagnosed with DPN (DPN-positive). On the other hand, 440 patients (70.4%) with the average VPT ≤25 V were not diagnosed with DPN (DPN-negative).

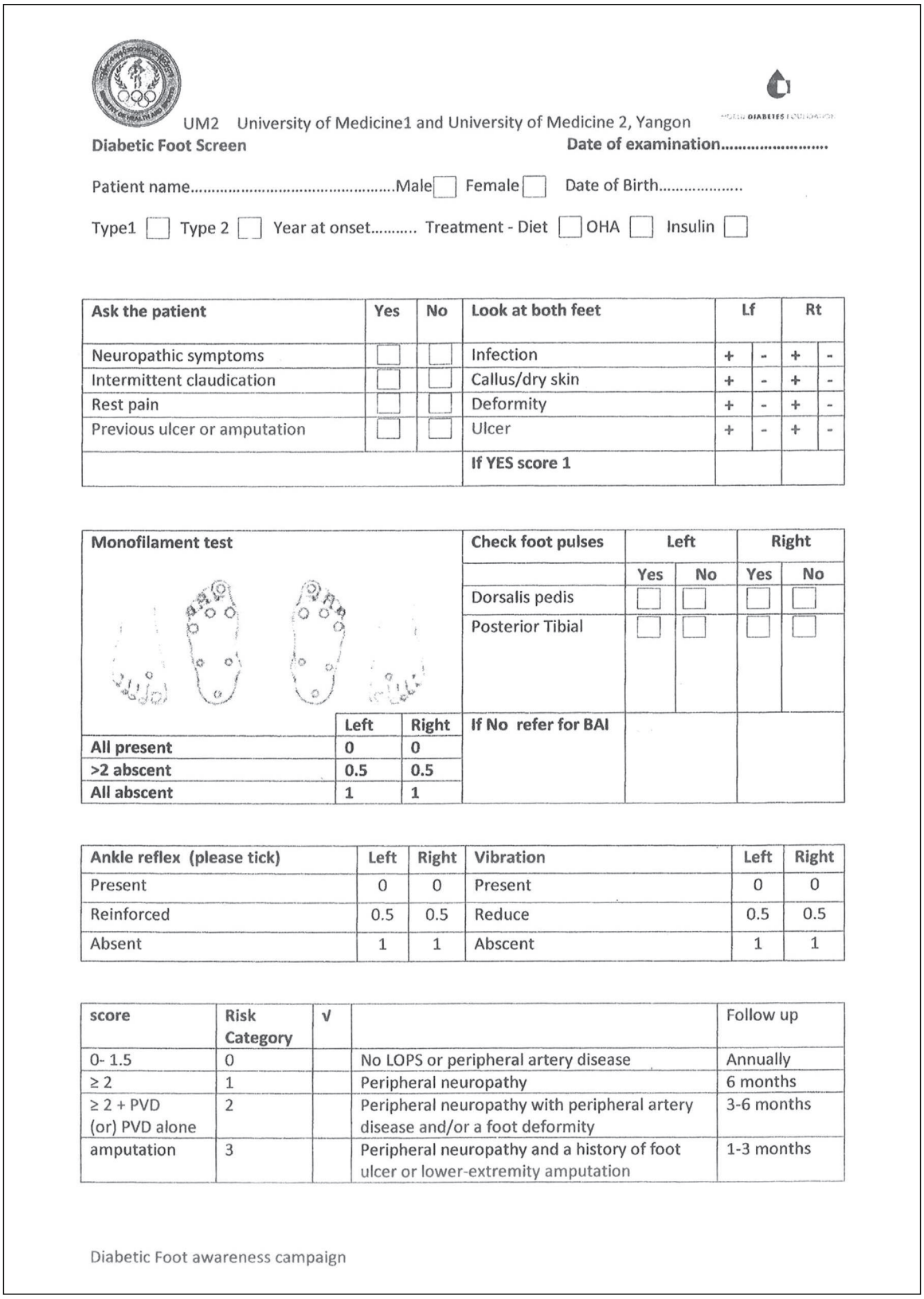
**Table 2.** Direct cost and estimated number of patients with DPN detected per group

| Name of the groups | The direct cost of the test per group in USD (min.- max.) | Estimated number of patients with DPN detected (n; 95% CI) |
|---|---|---|
| DFS group | 3080 (1337.1 - 6685.4) | 184 (160 - 208) |
| Biothesiometry group | 7760 (6016.8 - 11365.2) | 296 (268 - 324) |

n: point estimate; 95%CI: 95% confidence interval; min.-max.: minimum – maximum

### Results of the ROC analysis

The area under the curve (AUC) was defined as the measure of overall diagnostic accuracy, which reflected the probability of correctly diagnosing a DM patient with DPN by using the DFS proforma. From the ROC analysis (Figure 3), the overall accuracy (AUC) of the DFS proforma assessment in detecting DPN was 74.76% with a 95% confidence interval (CI) of 70.46% - 79.06%. The DFS score of ≥1.5 was determined as the receiver operator cut-off score, with the optimal sensitivity of 62.2% (95% CI: 55.17%- 69.15%), and specificity of 76.1% (95% CI:



UM2 University of Medicine1 and University of Medicine 2, Yangon

**Diabetic Foot Screen** **Date of examination**.....

Patient name.....Male☐ Female☐ Date of Birth.....

Type1 ☐ Type 2 ☐ Year at onset..... Treatment - Diet ☐ OHA ☐ Insulin ☐

| Ask the patient | Yes | No | Look at both feet | Lf | | Rt | |
|---|---|---|---|---|---|---|---|
| Neuropathic symptoms | ☐ | ☐ | Infection | + | - | + | - |
| Intermittent claudication | ☐ | ☐ | Callus/dry skin | + | - | + | - |
| Rest pain | ☐ | ☐ | Deformity | + | - | + | - |
| Previous ulcer or amputation | ☐ | ☐ | Ulcer | + | - | + | - |
| | | | **If YES score 1** | | | | |

**Monofilament test**

| | Left | Right |
|---|---|---|
| **All present** | **0** | **0** |
| **>2 abscent** | **0.5** | **0.5** |
| **All abscent** | **1** | **1** |

| Check foot pulses | Left | | Right | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| Dorsalis pedis | ☐ | ☐ | ☐ | ☐ |
| Posterior Tibial | ☐ | ☐ | ☐ | ☐ |
| **If No refer for BAI** | | | | |

| Ankle reflex (please tick) | Left | Right | Vibration | Left | Right |
|---|---|---|---|---|---|
| Present | 0 | 0 | Present | 0 | 0 |
| Reinforced | 0.5 | 0.5 | Reduce | 0.5 | 0.5 |
| Absent | 1 | 1 | Abscent | 1 | 1 |

| score | Risk Category | √ | | Follow up |
|---|---|---|---|---|
| 0- 1.5 | 0 | | No LOPS or peripheral artery disease | Annually |
| ≥ 2 | 1 | | Peripheral neuropathy | 6 months |
| ≥ 2 + PVD (or) PVD alone | 2 | | Peripheral neuropathy with peripheral artery disease and/or a foot deformity | 3-6 months |
| amputation | 3 | | Peripheral neuropathy and a history of foot ulcer or lower-extremity amputation | 1-3 months |

Diabetic Foot awareness campaign

**Figure 1.** The Diabetic Foot Screen Proforma.

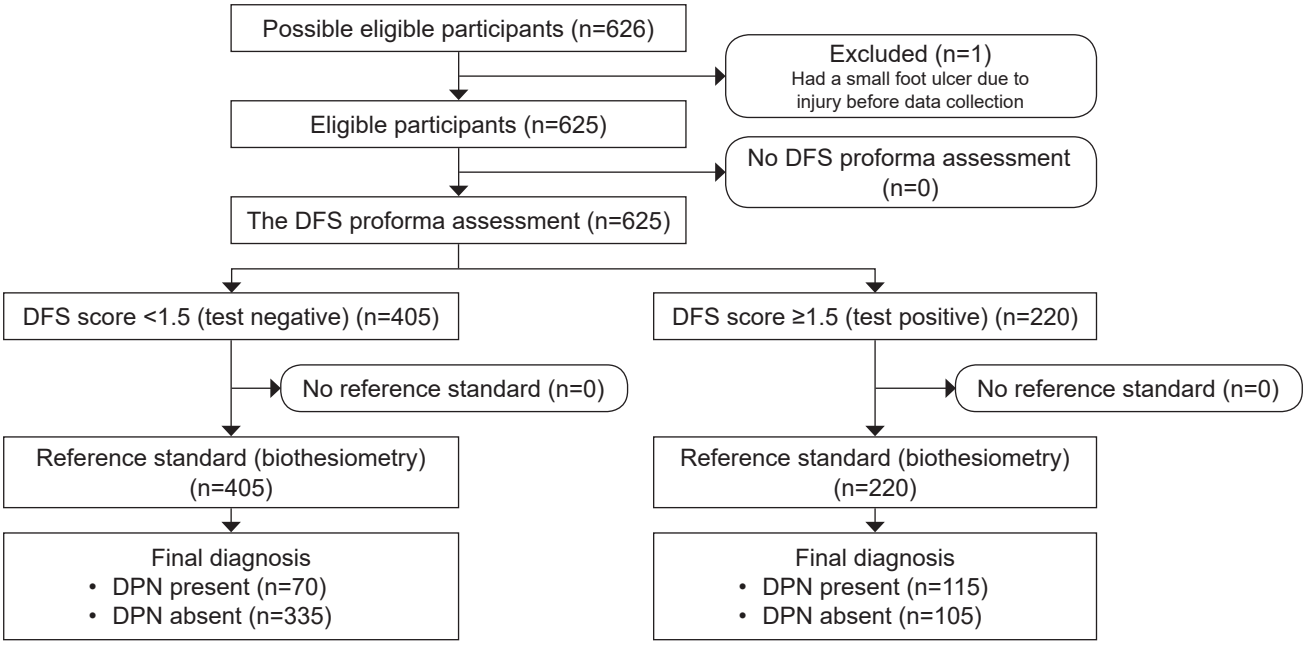



**Figure 2.** Diagram showing the flow of participants throughout the diagnostic study.

72.15%- 80.12%). The Youden's index (*J*) of the cut-off score ≥1.5 was 0.383. For the cut-off score ≥1.5, the positive predictive value was 52.3% (95% CI: 45.67%- 58.87%), negative predictive value was 82.7% (95% CI: 79.03%- 86.39%), likelihood ratio for a positive test was 2.6 (95% CI: 2.13- 3.19), and likelihood ratio for a negative test was 0.5 (95% CI: 0.41- 0.60).

### Cost-effectiveness analysis

The results of the cost-effectiveness analysis included the following: the direct costs of the DFS proforma and biothesiometry assessments, the number of patients with DPN (DPN cases) detected by the DFS proforma test, the number of DPN cases detected by biothesiometry, and the cost-effectiveness of the DFS proforma assessment compared to biothesiometry in the detection of DPN.

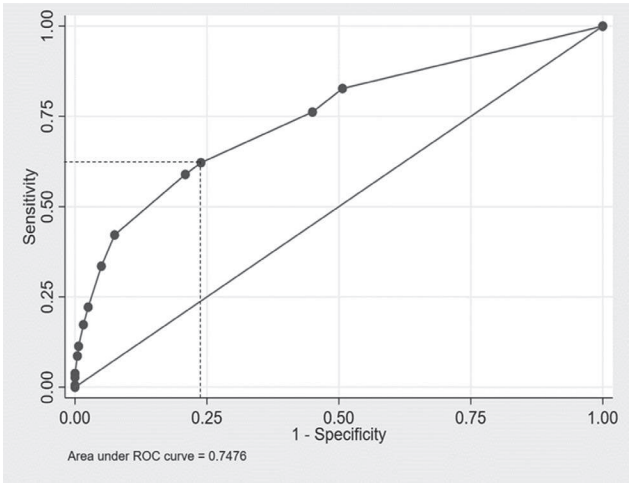



**Figure 3.** ROC curve of the DFS proforma assessment with different cut-off DFS scores.

### Direct costs of the DFS proforma and biothesiometry assessments

In Myanmar private GP clinics, the consultation fees and service fees are fees charged to individual patients for each clinic visit. Doctors do not usually charge additional fees for simple bedside tests (such as monofilament test, ankle reflex test, and 128-Hz tuning fork test) which can be done as part of a physical examination. Among the 10 clinics, the mean consultation and service fee was USD 3.08 per patient. The DFS proforma assessment could be done during the consultation, and the investment costs of the required instruments (monofilament, 128-Hz tuning fork and reflex hammer) per patient were negligible (<USD 0.05). Therefore, the direct cost for each patient was taken as the mean of consultation fees and service fees totaling USD 3.08.

Similarly, the direct cost of biothesiometry for each patient was calculated by adding the average of consultation and service fees (mentioned above) with an extra charge for each biothesiometry assessment. The additional extra charge (MMK 7000 or USD 4.68) covered the cost of the biothesiometer device. The direct cost of biothesiometry was approximately USD 7.76 per patient.

### Estimation of the number of patients with DPN

Based on the results of the diagnostic study, the proportion of diabetic patients with DPN detected by the DFS proforma test was calculated for a group of 1000 DM patients as follows:

Proportion of DM patients with DFS score ≥1.5 x positive predictive value x 1000 patients = 0.352 x 0.523 (PPV) x 1000 = 184 patients

From the above calculation, the number of patients with DPN detected by the DFS proforma assessment was 184 out of 1000 DM patients ($N_{DFS}$).

Similarly, the proportion of diabetic patients with DPN detected by biothesiometry was determined in the diagnostic study as 29.6%. Hence, the number of patients with DPN detected by the biothesiometry assessment was 296 out of 1000 DM patients ($N_{Bio}$).

### Results of sensitivity analysis on the cost of tests and number of DPN cases detected

By doing the sensitivity analysis, the minimum and maximum direct costs of the DFS proforma test and biothesiometry were found for each hypothetical cohort of 1000 diabetic patients (the DFS group and the biothesiometry group). The 95% confidence interval for the number of DPN cases detected in each group was also determined. The results of the sensitivity analysis are summarized in Table 2.

### Cost-effectiveness of the DFS proforma

Compared to biothesiometry, the cost-effectiveness (CE) of the DFS proforma test in DPN detection was determined by dividing the difference in the direct costs of the DFS proforma test and biothesiometry test with the difference in the number of DPN cases detected in the DFS group and the biothesiometry group. The calculation was done as follows:

$$\text{Cost-effectiveness ratio (DFS vs Bio)} = \frac{C_{Bio} - C_{DFS}}{N_{Bio} - N_{DFS}}$$

Where, $C_{Bio}$ = direct cost of biothesiometry (7760 USD), $C_{DFS}$ = direct cost of the DFS proforma test (3080 USD), $N_{Bio}$ = 296 patients, $N_{DFS}$ = 184 patients, CE ratio (DFS vs Bio) = 4680/112 = 41.79 USD per DPN case detected.

Thus, the cost-effectiveness of the DFS proforma assessment in DPN detection was USD 41.79 per DPN case detected.

## DISCUSSION

This study is the first of its kind to determine the accuracy of the DFS proforma in detecting DPN among diabetic patients in Yangon, Myanmar. The background characteristics of participants showed that the results could apply to a similar population of patients with Type 2 DM consulting in primary care clinics in Yangon.

The mean BMI of participants (26.5 kg/m$^2$) was higher than the average BMI of the adult population in Myanmar (22.3 kg/m$^2$).[4] Comparing the smoking and drinking status of participants were to that of the general adult population, the proportions of smokers (9.1%) and drinkers (18.4%) among participants were lower than that of smokers (26.1%) and drinkers (31.2%) among Myanmar adults.[4]

Only 37% of patients had HbA1c rechecked within six months which could partly be due to stay-at-home regulations and fear of visiting healthcare centers during the COVID-19 pandemic.

According to International Diabetes Federation, more than two-thirds of physicians can miss signs and symptoms of DPN.[2] An Indonesian study found that most physicians rely on history taking alone to screen for DPN.[12] In this study, only 120 out of 302 patients (39.7%) with neuropathic symptoms were diagnosed with DPN. It is clear DPN should not be diagnosed with history taking alone.

This study also showed that the monofilament test had low sensitivity (44.3%) and high specificity (92.7%) in detecting DPN. A systematic review on the accuracy of the monofilament test recommended using it with the 128-Hz tuning fork test, ankle reflex test, and pinprick test.[13] Based on our results, the monofilament test should be used together with other neurological tests for DPN screening in daily practice.

We also found that nearly all participants (99.7%) had a normal ankle reflex. In a study by Jayaprakash et al., the accuracy of the ankle reflex test was 62.3%.[14] Therefore, the ankle reflex test should also not be used alone to diagnose DPN. One study reported that the DPN detection rates of the 128-Hz tuning fork test (32.6%) and 10-gram monofilament test (31.4%) were similar while both rates were higher than that of the ankle reflex test (23.1%).[15] In our study, the 128-Hz tuning fork test showed a relatively higher sensitivity (59.5%) and lower specificity (81.8%) than the monofilament test. So, the 10-gram monofilament, ankle reflex and 128-Hz tuning fork tests should be used together for better DPN detection.

The Michigan Neuropathy Screening Instrument (MNSI) cut-off of 2 had 65% sensitivity and 83% specificity whereas the DFS cut-off score of 1.5 had 59% sensitivity and 79% specificity. The accuracy of the DFS proforma with a cut-off score ≥1.5 (72%) is comparable to that of the MNSI with cut-off ≥2 (76%).[16]

This study also determined the cost-effectiveness of the DFS proforma in the detection of DPN. We estimated the proportion of patients with DPN among DM patients in the primary care setting but our findings do not apply to diabetic patients who are not treatment compliant or who are consulting in public hospitals because the prevalence of DPN may be higher in those patient groups.

Primary care physicians play an important role in the early detection and treatment of DPN since they care for the majority of DM patients in the community. One clinical review mentioned that the prevention of DFUs should begin with DPN screening in primary care settings. While screening, doctors can simultaneously provide patient education to reduce the risks for DFUs.[6]

As the reported costs were estimated from March to April 2021, the costs are liable to change later, responding to inflation. This study reported that there would be an additional cost of nearly USD 42 (MMK 62,824) for one patient with DPN detected if the biothesiometry test is used, instead of the DFS proforma test. DFS proforma assessment

was less costly but less accurate than the biothesiometry test in diagnosing DPN among diabetic patients. Despite this, the DFS proforma test can be easily done by any healthcare professional trained to fill up and calculate the scores of the proforma and how to do three bedside tests (monofilament test, tuning fork test, and ankle reflex test). In addition to requiring electricity, biothesiometry entails advanced hands-on training by a foot care specialist or an experienced operator of biothesiometer devices which are not widely available in Myanmar. Thus, the DFS proforma test may be more feasible and applicable for DPN detection in the resource-limited primary care setting.

Although there is no cost-effectiveness threshold for diagnostic tests to detect diabetic complications in Myanmar, the direct cost of the DFS proforma test per DPN case detected is less than 3% of the local gross domestic product (GDP) per capita (USD 1407).[17] The assessment is cost-effective and affordable for most DM patients consulting at Myanmar primary care clinics.

### Limitations of the study

The main limitation of the diagnostic study is the use of biothesiometry as an alternative reference standard test. Due to the use of purposive sampling, the generalizability of the results is relatively limited. However, the results would still apply to patients of similar background characteristics in the primary healthcare setting. In the cost-effectiveness analysis, the indirect costs for the two diagnostic tests were not included because of the lack of a standardized way to measure such costs in Myanmar.

## CONCLUSION

In conclusion, the results of this study supported the use of the DFS proforma as a screening tool for DPN and provided valuable information for primary care physicians and health authorities about the estimated costs of using the DFS proforma compared to biothesiometry. The use of the DFS proforma should be promoted among physicians in the resource-limited primary care setting of Myanmar.

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All authors certified fulfillment of ICMJE authorship criteria.

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ORIGINAL ARTICLE

# Adaptation and Validation of the Vietnamese Translated Diabetes Knowledge Questionnaire

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**Abstract**

Objectives. There is no existing Vietnamese diabetes knowledge questionnaire. This impedes assessment of patient knowledge that will be helpful in providing effective diabetes intervention. We aimed to validate the Vietnamese Translated Diabetes Knowledge Questionnaire (DKQ).

Methodology. Translation and adaptation strictly followed the guidelines of Beaton et al. Internal consistency was assessed by Cronbach's alpha coefficient, test-retest reliability was assessed by Fleiss' Kappa coefficient, and validity value was determined among type 2 diabetes patients in a general hospital.

Results. The Vietnamese version of the DKQ had good internal consistency (Cronbach's alpha for all items = 0.898) and stability (Kappa coefficient >0.600). The average score for all equivalence criteria was 1.00, demonstrating good equivalence to the original. The significant difference between knowledge score and education level ($p$ <0.001) confirmed construct validity.

Conclusion. Our study provided a reliable Vietnamese version of the DKQ. Future studies may apply the version in different regions in Vietnam to determine external validity.

*Key words: diabetes, diabetes knowledge questionnaire, translation, Vietnamese*

## INTRODUCTION

Diabetes is one of the most prevalent non-communicable diseases in the world.[1-3] In 2021, the International Diabetes Federation (IDF) estimated that there were 537 million people with diabetes worldwide, and this was predicted to increase to 783 million by 2045.[4] It was estimated that over 3.5 million Vietnamese people were living with diabetes in 2015, and this increased to approximately 5.76 million in 2020.[5,6] According to the World Health Organization (WHO), more than half of people with diabetes in Vietnam are unaware of their disease, delaying early diagnosis and management.[7]

Disease knowledge is considered the foundation for diabetes self-management. Patients with good disease knowledge have fewer misconceptions and better understanding of the consequences of diabetes, which improves adherence to medications and a better lifestyle.[8-12] Patients with diabetes (PWD) need lifelong self-management to prevent or delay acute and chronic complications. The American Diabetes Association guideline emphasizes that all patients should receive diabetes self-management and support.[13] Studies show that diabetes self-management interventions improved knowledge, self-care behavior, and reduced HBA1c.[13-16]

An appropriate diabetes knowledge assessment questionnaire is essential to conducting diabetes self-management support and intervention. However, most assessment questionnaires either consist of too many options or are too long, making it difficult to assess and manage diabetes patients in developing countries with low education levels, including Vietnam. For example, the Diabetes Self-Care Knowledge by Adibe et al., may be too long with 30 sentences; while the Michigan Diabetes Knowledge Test by Fitzgerald et al., may be difficult for Vietnamese to answer due to cultural differences.[17,18] To illustrate, one question about high-carbohydrate food is correctly answered with "baked chicken/Swiss cheese/baked potato/peanut butter," which are uncommon food in Vietnam.[18]

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In 2019, the proportion of collegiate or equivalent educational attainment of the population aged 25 years and above in Vietnam was 10.2%. This was relatively low compared to 15.6% in Thailand, 32.4% in Singapore and 46.6% in the United Arab Emirates.[19] The mean score of the English Proficiency Index of Vietnamese was 473/800 in 2020, listed under the low-proficiency category.[20] This suggests that most Vietnamese patients could merely engage in short and simple conversation, and may be unable to under-stand and complete a diabetes knowledge questionnaire in the English language. Thus, developing a simple, culturally suitable and valid knowledge questionnaire for Vietnamese patients with diabetes is crucial.

The Diabetes Knowledge Questionnaire (DKQ) developed by Garcia et al. is a set of questions that assess diabetes knowledge.[21] It consists of 24 questions answerable by one of three choices: "yes", "no" or "I don't know." Each correct answer is equivalent to one point. Overall, the Cronbach's alpha value of the 24 questions is 0.78. The structural value expressed through the mean knowledge score of patients participating in a diabetes education program is higher than that of patients not participating ($p$<0.001), and the relationship between knowledge score and education level is significant ($p$<0.001). The questionnaire has been translated and adjusted into many different languages.[22] The DKQ may be a more appropriate and effective questionnaire for use in Vietnam because its content about diabetes knowledge is adequate and suitable for all patients, including those with low education levels in developing countries. It is an easy and quick tool for assessing diabetes knowledge for clinical and research purposes.

The DKQ has not been translated and adapted for use in Vietnam. In this study, we conducted translation, cultural adaptation and validation of the first Vietnamese version DKQ for future assessment of patient knowledge on diabetes.

## METHODOLOGY

### Study design and population

We conducted a study on outpatients with type 2 diabetes mellitus consulting at Hau Giang General Hospital, Vietnam. A pilot study involving 30 participants was conducted from January 2 to 6, 2020, while questionnaire validation involving 87 participants was conducted from January 7 to February 29, 2020.

Eligible patients were 18 years old or older, and treated with at least one diabetes medicine for at least 6 months, to ensure that participants had similar baseline knowledge on diabetes.

Patients were excluded if they were pregnant, foreigners or they did not consent to participate in the study. We also excluded those who failed to complete at least one question set/study scale. Patients who participated in a diabetes knowledge study within the past year were also excluded because they may have higher baseline diabetes knowledge which may result in higher DKQ scores.

### Ethics approval

The study was approved by the Ethical Council of Ho Chi Minh City Medicine and Pharmacy University. All information of study participants was encrypted, securely kept and used only for research purposes.

### Translation, adaptation, and validation

We translated and adapted the DKQ according to a five-step process described by Beaton et al.[23,24]

#### *Step 1: Initial translation*

The DKQ was translated from English to Vietnamese by two independent Vietnamese translators who were fluent in English. The first had clinical background and knowledge about research concepts, while the second had no medical background and was not informed of the research objectives. We obtained two translations referred to as T1 and T2.

#### *Step 2: Translation synthesis*

The two translations were synthesized by another translator experienced in methodology, resulting in the T12 translation.

#### *Step 3: Back-translation*

Two translators without medical expertise who did not know the research objectives and the original questionnaire worked independently to translate the T12 translation into English, obtaining the BT1 and BT2 translations.

#### *Step 4: Expert committee evaluation*

A committee including eight members (five translators from the above steps, two doctors with research expertise, and an expert in research methods) worked independently to compare all the DKQ versions translated from the above stages with the original version. The evaluation criteria were: (a) semantic equivalence, pertaining to the equivalence of meaning or multiple meanings of the words, and grammar when translating; (b) idiomatic equivalence, defined as the equivalent expression when translating idioms; (c) experiential equivalence, relating to the equivalence of adjusting to adapt to the target culture when translating daily task expressions; and (d) conceptual equivalence, referring to the equivalence of adjusting to adapt the different meanings of specific word expressions of different cultures.

Experts gave 1 point if there was an equivalent and 0 if there was no equivalent for each item. Items that failed to

achieve absolute equivalence (8/8) for all four criteria were gathered and adjusted to increase equivalence. The consensus was reached when all experts agreed on the same point. Following discussion, the experts reached a consensus on the pre-final wording of the Vietnamese version.

***Step 5: Tests of the adapted version***

*Stage 1: Pilot study*

This step evaluated the clarity and comprehensibility of the DKQ. Thirty patients were recruited by convenience sampling method and were interviewed face-to-face. Participants evaluated the wording of each item of the pre-final version on a scale from 0 (very confusing expression) to 10 (very clearly and easily understandable expression). Items with a mean score of less than or equal to 9 were then adjusted by the expert committee.

*Stage 2: Questionnaire validation study*

We conducted a cross-sectional study on 87 patients. This was based on the recommendation of a sample size of at least 50 patients to evaluate a questionnaire from Terwee et al.[25] Each patient was interviewed twice, two weeks apart.

During the first interview, eligible patients were interviewed face-to-face at the Internal Medicine clinic of the Outpatient Department at Hau Giang General Hospital. The second interview was conducted via phone. The patients rated the wording of each item in the trial version on a scale of 0 (very difficult to understand) to 10 (very clear and easy to understand). The expert committee reviewed and adjusted items with an average score of ≤9 to form a complete version. The author of the study was in charge of conducting the interviews. The purpose of this step was to evaluate the reliability and validity of the questionnaire.

**Statistical analysis**

Data were collected and processed using IBM® SPSS® 20.0 and Microsoft Excel 2013 software. Continuous variables with a normal distribution were represented by mean and standard deviation.

Qualitative variables were represented by frequency and percentages. Mann-Whitney and Kruskal-Wallis tests were used to determine the differences in the median knowledge scores of gender, age group, insulin use, illness duration, comorbidities, and education level. A $P$ value <0.05 was considered statistically significant.

We tested the reliability of the Vietnamese version through internal consistency and test-retest. Internal consistency was based on Cronbach's alpha coefficients. Test-retest was assessed by the Fleiss' kappa coefficient, based on the repeatability of the results of the first and second interviews.

The validity of the version was evaluated through content and construct validity. Content validity was measured based on the consensus of the experts on the equivalence between the translation and the original version. Construct validity was evaluated by identifying whether the relationship between the items and scale content was compatible with the hypothesis of the study about the score outcomes of different populations. The questionnaire would achieve construct validity if a significant difference between diabetes knowledge and patient characteristics was found. Construct validity was investigated based on the significant differences of first response questionnaire results according to different patient characteristics (gender, age, insulin use, illness duration, comorbidities and education level).

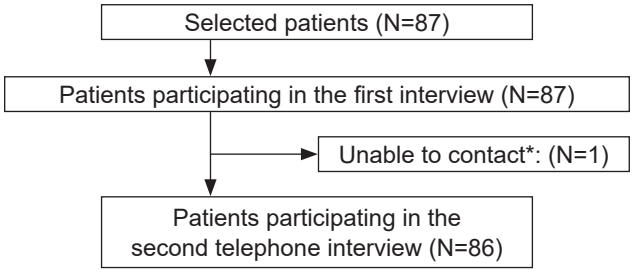


**Figure 1.** Study population flowchart.

* One patient was counted as "unable to contact" after seven failed contact attempts (first day, 3 times, 30 minutes apart; and 4 consecutive days thereafter, once daily).

## RESULTS

**Population characteristics**

A total of 30 patients with mean age of 62.50 ± 11.77 years were included in the pilot study. Majority of the participants were male (n=19, 63.3%) and had comorbidities (86.6%) (Table 1).

We conducted two interviews for the questionnaire validation process,. The first interview had 87 participants with a mean age of 66.87 ± 9.93 years, 51.7% of whom were male (Table 2). The second interview had 86 participants (Figure 1).

**Validity evaluation**

Content validity is the ability to appropriately measure and comprehensively evaluate research issues, assessed by the consensus of experts. After the expert committee consensus, the equivalence assessment score was 1.00 for all four equivalence criteria, which was considered as high equivalence to the original (Table 3).

In the pilot study, the clarity and comprehension score of the 24 questions was 9.98 ± 0.03 (Table 4). The main discrepancies between the original and the Vietnamese version of the DKQ questionnaire from the initial translation (Step 1) to the pilot test of the adapted version (Stage 1 of Step 5) are presented in Table 5. After the pilot study, we formulated a complete Vietnamese version (Table 6).

**Table 1.** Patient characteristics of the pilot study

| Patient characteristics | n (%) (N=30) |
|---|---|
| Gender | |
| Male | 11 (36.7) |
| Female | 19 (63.3) |
| Age, year | 62.5 ± 11.77[a] |
| Age group | |
| <65 years | 14 (46.7) |
| ≥65 years | 16 (53.3) |
| Illness duration | |
| <5 years | 8 (26.7) |
| 5-10 years | 6 (20.0) |
| >10 years | 16 (53.3) |
| Comorbidities | |
| 0 | 4 (13.4) |
| 1 disease | 19 (63.3) |
| ≥2 diseases | 7 (23.3) |
| Educational level | |
| Primary school | 15 (50.0) |
| Junior high school | 8 (26.7) |
| High school and higher | 7 (23.3) |

[a]Age presented as mean ± standard deviation

**Table 2.** Patient characteristics of the validation study

| Patient characteristics | n (%) (N=87) | *p* value |
|---|---|---|
| Gender | | 0.008 |
| Male | 42 (48.3) | |
| Female | 45 (51.7) | |
| Age, year | 66.87 ± 9.93[a] | |
| Age group | | 0.105 |
| <65 years | 33 (37.9) | |
| ≥65 years | 54 (62.1) | |
| Illness duration | | 0.552 |
| <5 years | 13 (14.9) | |
| 5-10 years | 24 (27.6) | |
| >10 years | 50 (57.5) | |
| Comorbidities | | 0.175 |
| 0 | 11 (12.7) | |
| 1 disease | 57 (65.5) | |
| ≥2 diseases | 19 (21.8) | |
| Educational level | | <0.001 |
| Primary school | 38 (43.7) | |
| Junior high school | 33 (37.9) | |
| High school and higher | 16 (18.4) | |
| Insulin use | | 0.255 |
| Yes | 29 (33.3) | |
| No | 58 (66.7) | |

[a]Age presented as mean ± standard deviation

**Table 3.** Equivalence assessment by the expert committee

| Item | Semantic equivalence | Idiomatic equivalence | Experiential equivalence | Conceptual equivalence |
|---|---|---|---|---|
| A1* | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| A2* | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 1 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 2 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 3 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 4 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 5 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 6 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 7 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 8 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 9 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 10 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 11 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 12 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 13 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 14 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 15 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 16 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 17 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 18 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 19 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 20 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 21 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 22 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 23 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| 24 | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) | 1.0 (8/8) |
| Mean | 1.0 | 1.0 | 1.0 | 1.0 |

*A1 and A2 are the instructions to answering the questionnaire.

**Table 4.** Comprehensive score of the items rated by participants in the pilot study

| Item | Semantic equivalence |
|---|---|
| A1* | 10.00 ± 0.00 |
| A2* | 10.00 ± 0.00 |
| 1 | 10.00 ± 0.00 |
| 2 | 10.00 ± 0.00 |
| 3 | 10.00 ± 0.00 |
| 4 | 10.00 ± 0.00 |
| 5 | 10.00 ± 0.00 |
| 6 | 10.00 ± 0.00 |
| 7 | 10.00 ± 0.00 |
| 8 | 10.00 ± 0.00 |
| 9 | 10.00 ± 0.00 |
| 10 | 10.00 ± 0.00 |
| 11 | 10.00 ± 0.00 |
| 12 | 9.53 ± 0.68 |
| 13 | 10.00 ± 0.00 |
| 14 | 10.00 ± 0.00 |
| 15 | 10.00 ± 0.00 |
| 16 | 10.00 ± 0.00 |
| 17 | 10.00 ± 0.00 |
| 18 | 10.00 ± 0.00 |
| 19 | 10.00 ± 0.00 |
| 20 | 10.00 ± 0.00 |
| 21 | 10.00 ± 0.00 |
| 22 | 10.00 ± 0.00 |
| 23 | 10.00 ± 0.00 |
| 24 | 10.00 ± 0.00 |
| Mean Score | 9.98 ± 0.03 |

[a] A1 and A2 are the instructions to answering the questionnaire.
[b] SD, standard deviation

**Table 5.** Main adjustments and discrepancies between the original and the Vietnamese versions

| Item | Discrepancy | Solution |
|---|---|---|
| 3. Diabetes is caused by failure of the kidneys to keep sugar out of the urine. | The expression of “failure of the kidneys” is unnatural in Vietnamese. | We translated “by failure of the kidneys to keep sugar out of the urine” into “due to decreased ability of the kidneys to retain sugar (made sugar migrate into urine)” in Vietnamese. |
| 12. An insulin reaction is caused by too much food. | The expression of "insulin reaction" seems unnatural and academic in Vietnamese and made it difficult for participants to understand. | We translated “An insulin reaction is caused” into “Insulin is secreted” in Vietnamese. |

**Table 6.** Original and Vietnamese diabetes knowledge questionnaires

| Item | Original version | Vietnamese version |
|---|---|---|
| 1 | Eating too much sugar and other sweet foods is a cause of diabetes. | Ăn quá nhiều đường và các loại thực phẩm ngọt là nguyên nhân của bệnh đái tháo đường |
| 2 | The usual cause of diabetes is lack of effective insulin in the body. | Nguyên nhân thường gặp của đái tháo đường là insulin hoạt động không hiệu quả trong cơ thể |
| 3 | Diabetes is caused by failure of the kidneys to keep sugar out of the urine. | Bệnh đái tháo đường là do khả năng giữ lại đường của thận bị giảm (làm cho đường vào nước tiểu) |
| 4 | Kidneys produce insulin. | Thận sản xuất ra insulin |
| 5 | In untreated diabetes, the amount of sugar in the blood usually increases. | Khi bệnh đái tháo đường không được điều trị, đường huyết thường tăng |
| 6 | If I am diabetic, my children have a higher chance of being diabetic. | Nếu ông/bà mắc bệnh đái tháo đường, các con của ông/bà có nguy cơ mắc bệnh đái tháo đường cao so với bình thường |
| 7 | Diabetes can be cured. | Bệnh đái tháo đường có thể được chữa khỏi |
| 8 | A fasting blood sugar level of 210 is too high. | Mức đường huyết đói bằng 210 mg/dl (= 11,55 mmol/L) là quá cao |
| 9 | The best way to check my diabetes is by testing my urine. | Cách tốt nhất để kiểm tra bệnh đái tháo đường là xét nghiệm nước tiểu |
| 10 | Regular exercise will increase the need for insulin or other diabetic medication. | Tập thể dục thường xuyên sẽ làm tăng nhu cầu về insulin hoặc các thuốc điều trị đái tháo đường |
| 11 | There are two main types of diabetes: type 1 (insulin-dependent) and type 2 (non-insulin dependent). | Bệnh đái tháo đường có 2 type chính: type 1 (phụ thuộc insulin) và type 2 (không phụ thuộc insulin) |
| 12 | An insulin reaction is caused by too much food. | Insulin được tiết ra sau khi ăn quá nhiều |
| 13 | Medication is more important than diet and exercise to control my diabetes. | Để kiểm soát bệnh đái tháo đường thì việc dùng thuốc quan trọng hơn chế độ ăn uống và luyện tập |
| 14 | Diabetes often causes poor circulation. | Bệnh đái tháo đường thường dẫn đến tuần hoàn máu kém |
| 15 | Cuts and abrasions on diabetics heal more slowly. | Đối với các bệnh nhân bị đái tháo đường, các vết thương hay trầy xước lâu lành hơn |
| 16 | Diabetics should take extra care when cutting their toenails. | Bệnh nhân đái tháo đường nên cẩn thận hơn khi cắt móng tay chân |
| 17 | A person with diabetes should cleanse a cut with iodine and alcohol. | Người bị đái tháo đường nên rửa sạch vết thương bằng iốt và cồn |
| 18 | The way I prepare my food is as important as the foods I eat. | Cách ông/bà chế biến thức ăn cũng quan trọng như những thực phẩm ông/bà ăn |
| 19 | Diabetes can damage my kidneys. | Bệnh đái tháo đường có thể làm hỏng thận của ông/bà |
| 20 | Diabetes can cause loss of feeling in my hands, fingers, and feet. | Bệnh đái tháo đường có thể gây mất cảm giác ở tay, ngón tay và bàn chân của ông/bà |
| 21 | Shaking and sweating are signs of high blood sugar. | Run và đổ mồ hôi là dấu hiệu của đường huyết cao |
| 22 | Frequent urination and thirst are signs of low blood sugar. | Đi tiểu thường xuyên và hay khát nước là dấu hiệu của đường huyết thấp |
| 23 | Tight elastic hose or socks are not bad for diabetics. | Vớ/tất áp lực không gây hại cho bệnh nhân đái tháo đường |
| 24 | A diabetic diet consists mostly of special foods. | Một chế độ ăn kiêng cho bệnh nhân đái tháo đường chủ yếu bao gồm các loại thực phẩm đặc biệt |

**Table 7.** Results of the DKQ questionnaire according to patient characteristics

| Patient characteristics | n (%) (N=87) | Average questionnaire score | *p* value |
|---|---|---|---|
| Gender | 66.87 ± 9.93 | | |
| Male | | | 0.105[b] |
| Female | 33 (37.9) | 14.12 ± 5.92 | |
| Age, year | 54 (62.1) | 12.30 ± 5.37 | |
| Age group | | | 0.008[b] |
| <65 years | 42 (48.3) | 14.55 ± 6.03 | |
| ≥65 years | 45 (51.7) | 11.53 ± 4.83 | |
| Illness duration | | | 0.175[c] |
| <5 years | 11 (12.7) | 14.45 ± 5.20 | |
| 5-10 years | 57 (65.5) | 13.39 ± 6.14 | |
| >10 years | 19 (21.8) | 10.95 ± 3.52 | |
| Comorbidities | | | 0.552[c] |
| 0 | 13 (14.9) | 11.85 ± 6.07 | |
| 1 disease | 24 (27.6) | 13.42 ± 5.68 | |
| ≥2 diseases | 50 (57.5) | 13.08 ± 5.55 | |
| Educational level | | | <0.001[c] |
| Primary school | 38 (43.7) | 7.97 ± 2.98 | |
| Junior high school | 33 (37.9) | 14.76 ± 2.64 | |
| High school and higher | 16 (18.4) | 21.25 ± 0.93 | |
| Insulin use | | | 0.255[b] |
| Yes | 29 (33.3) | 14.03 ± 6.15 | |
| No | 58 (66.7) | 12.47 ± 5.31 | |

[a]Age presented as mean ± standard deviation
[b]Mann-Whitney test
[c]Kruskal-Wallis test

Construct validity, defined as the possibility of finding a difference between different population groups, was assessed by the differences in the median knowledge scores according to participants' characteristics in the first interview of the questionnaire validation study. The average patient knowledge score in the study was 12.99 ± 5.62 points. There was a significant difference in diabetes knowledge scores between different education levels. Patients who received high school or higher education had better diabetes knowledge than patients with lower education levels ($p$<0.001). There was a significant difference in the median knowledge scores between males and females. Male patients had higher knowledge scores compared to female patients ($p$=0.008) (Table 7).

### Reliability validation

Cronbach's alpha coefficient of all questionnaire items was 0.898 was assessed in 87 patients. The total variable correlation coefficient of all items was >0.3 (Table 8).

We assessed questionnaire stability based on the repeatability of the first and second responses of 86 patients. All items of the Vietnamese version had a kappa coefficient greater than 0.600 (Table 9).

**Table 8.** Cronbach's alpha values of the questionnaire

| Item | Total variable correlation coefficients | Cronbach's alpha coefficients if the item is removed |
|---|---|---|
| 1 | 0.420 | 0.895 |
| 2 | 0.670 | 0.889 |
| 3 | 0.589 | 0.892 |
| 4 | 0.519 | 0.893 |
| 5 | 0.481 | 0.894 |
| 6 | 0.414 | 0.896 |
| 7 | 0.483 | 0.894 |
| 8 | 0.508 | 0.893 |
| 9 | 0.599 | 0.891 |
| 10 | 0.610 | 0.891 |
| 11 | 0.390 | 0.896 |
| 12 | 0.366 | 0.896 |
| 13 | 0.394 | 0.896 |
| 14 | 0.692 | 0.888 |
| 15 | 0.301 | 0.897 |
| 16 | 0.362 | 0.896 |
| 17 | 0.325 | 0.897 |
| 18 | 0.424 | 0.895 |
| 19 | 0.403 | 0.896 |
| 20 | 0.530 | 0.893 |
| 21 | 0.743 | 0.887 |
| 22 | 0.743 | 0.887 |
| 23 | 0.325 | 0.897 |
| 24 | 0.371 | 0.897 |
| Cronbach's alpha coefficient of all items | | 0.898 |

**Table 9.** Kappa coefficient of the questionnaire

| Item | Kappa coefficient | *p* value |
|---|---|---|
| 1 | 0.945 | <0.001 |
| 2 | 0.930 | <0.001 |
| 3 | 1,000 | <0.001 |
| 4 | 0.731 | <0.001 |
| 5 | 0.849 | <0.001 |
| 6 | 0.861 | <0.001 |
| 7 | 0.728 | <0.001 |
| 8 | 0.873 | <0.001 |
| 9 | 0.782 | <0.001 |
| 10 | 0.917 | <0.001 |
| 11 | 0.639 | <0.001 |
| 12 | 0.838 | <0.001 |
| 13 | 0.858 | <0.001 |
| 14 | 1.000 | <0.001 |
| 15 | 0.845 | <0.001 |
| 16 | 0.882 | <0.001 |
| 17 | 0.829 | <0.001 |
| 18 | 0.839 | <0.001 |
| 19 | 1.000 | <0.001 |
| 20 | 0.930 | <0.001 |
| 21 | 1.000 | <0.001 |
| 22 | 1.000 | <0.001 |
| 23 | 0.830 | <0.001 |
| 24 | 1.000 | <0.001 |

### Mean duration to complete the validated version

The mean time needed to complete the questionnaire was calculated in the first interview of 87 patients. The results showed that patients took 5 to 12 minutes, with an average of 9.43 ± 1.79 minutes, to complete the questionnaire.

## DISCUSSION

The pilot survey's clarity and comprehension score for the 24 questions was 9.98 ± 0.03, demonstrating a clear and easily understandable question expression. Two items of the DKQ questionnaire were difficult to translate. The significant challenges were linguistic and expression differences. For example, the expression "failure of the kidney" in item 3 is translated as "the lack of success of the kidney" in Vietnamese, which made the information confusing.

Cronbach's alpha coefficient for all questions was 0.898, which indicated good consistency. The result was higher than the original (0.780).[21] The reason may be because Cronbach's alpha is specific to the survey population. Differences between patient characteristics, such as age, education level and comorbidities, in two studies conducted on two different countries and populations affected knowledge score results. Other questionnaire translation and validation studies also showed different Cronbach's alpha coefficients compared to the original. For example, Cronbach's alpha in Bukhsh et al's DKQ translation and adaptation into Urdu study was 0.702.[22]

The total variable correlation coefficients of the questionnaire ranged from 0.301 to 0.743, and all question values were above 0.3. This showed that all the questions contributed to assessing diabetes knowledge.[26]

All items of the Vietnamese version achieved a good kappa coefficient (>0.600), indicating questionnaire stability.[27] Four questions had good correlation between the first and second interviews (kappa coefficient ranged from 0.600 to 0.800,) and 14 questions had very good correlation between the 2 interviews (kappa coefficient >0.800). For questions number 3, 14, 19, 21, 22 and 24, the second-interview answers perfectly coincided with the first-interview answers (kappa coefficient = 1.000).

There was a relationship between educational level and knowledge score, showing the structural value of the questionnaire. Patients who received high school or higher education had better diabetes knowledge than patients with lower education levels ($p$<0.001). This result was similar to many other diabetes patient knowledge studies.[21,22] This result suggested that more attention should be given to providing disease information to patients, especially among those with low education levels, to improve their knowledge and achieve better treatment efficacy.

There was a difference in scores between the two genders. Male patients had higher knowledge scores than females ($p$=0.008) (Table 8). Bukhsh et al., reported different results: the scores of the two gender groups were not statistically significant ($p$=0.11), possibly due to differences in survey populations.[22] Additionally, outcomes may be influenced by educational levels between male and female patients. Almost 67% of male patients in our study received junior

high school or higher education, compared to only 46.7% of females, affecting knowledge scores.

Our study was pioneering in its translation of the DKQ into Vietnamese. To increase the reliability and validity value of the Vietnamese version, we conducted a translation and adaptation process that strictly followed the recommendations of Beaton et al.[23,24] This guideline comprehensively assesses the questionnaire translation and adaptation process, and is widely used and applied in research.[28-32] The translation phases consisted of multiple steps from forward to backward translation and obtaining expert committee evaluation. Our Vietnamese questionnaire version was also adjusted to be simple and easily understood to suit various patient characteristics in Vietnam, including those with low education levels.

Our study also had several limitations. Being the first to translate the DKQ into Vietnamese, there were no other Vietnamese versions for comparison and evaluation of criterion validity. Furthermore, bias from missing data in our validation study might affect internal validity results. To prevent bias from missing data, future studies should give clear instructions to respondents and emphasize the need to answer the questionnaire as completely as possible, get assistance from the investigators during data collection, and follow-up patients to complete the questionnaire. In addition, the DKQ author (Ms. Alexandra A. Garcia, RN, MS) could not participate in the expert committee in our study.

Our study aimed to develop a knowledge assessment tool for the majority of patients, excluding special population groups such as pregnant women and patients with dementia. Future studies should be conducted in these special population groups as well.

## CONCLUSION

Our study created a validated Vietnamese version of the DKQ with high equivalence to the original. All questions are simple, easy to understand, and suitable for a survey on Vietnamese patients with a high average score of clarity and comprehension of all items. The Vietnamese questionnaire version can assess patient knowledge and may help identify the relationship between patient knowledge and medication adherence or treatment outcomes. It may also be used as a knowledge assessment tool to design appropriate diabetes self-management programs and interventions. Further studies could apply the questionnaire version in different regions and populations in Vietnam to verify consistency, stability and validity in these specific regions and populations.

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

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ORIGINAL ARTICLE

# Development of a Validated Diabetes Risk Chart as a Simple Tool to Predict the Onset of Diabetes in Bogor, Indonesia

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**Abstract**

Objective. To develop a simple, non-invasive tool for predicting the onset of type 2 diabetes mellitus (T2DM).

Methodology. A total of 4418 nondiabetic respondents living in Bogor were included in this cohort study. Their ages ranged from 25 to 60 years old and were followed for 6 years with interviews, physical examinations and laboratory tests. The investigators used logistic regression to create a tool for diabetes risk determination.

Results. The cumulative incidence of T2DM was 17.9%. Risk factors significantly associated with T2DM included age, obesity, central obesity, hypertension and lack of physical activity. The Bogor Diabetes Risk Prediction (BDRP) chart had a cut-off of 0.128, with sensitivity of 76.6% and specificity of 50.3%. The Positive Predictive Value (PPV) was 21.6% and Negative Predictive Value (NPV) was 92.3%. The Area under the Curve (AUC) was 0.70 with a 95% confidence interval ranging from 0.675-0.721.

Conclusion. The BDRP chart is a simple and non-invasive tool to predict T2DM. In addition, the BDRP chart is reliable and can be easily used in primary health care.

*Key words: diabetes screening, risk factors, diabetes, cohort study, Bogor*

## INTRODUCTION

Diabetes Mellitus (DM) is an increasingly prevalent global chronic disease that can have serious complications. Data from the International Diabetes Federation (IDF) shows that Indonesia is among the top 10 countries with the highest prevalence of DM among individuals aged 20 to 79 years. In 2019, it was projected that the number of patients with diabetes would increase from 10.7 to 13.7 million by 2030.[1] In a nationwide community-based survey known as RISKESDAS conducted under the Ministry of Health of the Republic of Indonesia, the diabetes prevalence in individuals younger than 15 years old was noted to continue to increase every year. RISKESDAS (2018) showed that the cases of undiagnosed Diabetes Mellitus (UDD) increased from 6.9% in 2013 to 8.5% in 2018. On the other hand, diagnosed Diabetes (DD) cases increased from 1.5% in 2013 to 2.0 % in 2018. Noticeably, the prevalence of UDD was higher than that of DD.[2-4]

The increasing incidence of diabetes must be curtailed since the subsequent development of micro- and macrovascular events is a socioeconomic burden on the patient's family. Risk factor control and early T2DM detection are crucial to reduce diabetes complication rates. In addition, counseling with regard to self-assessment of diabetes risk is important to raise public awareness about their health conditions. Models for diabetes risk assessment have been developed in several countries mostly in America, Europe and China through cross-sectional or cohort studies that used questionnaires and blood tests.[5,6]

There are fewer studies from Korea, Hong Kong and Thailand, with observation times ranging from 4 to 12 years. The results indicate that the risk factors for T2DM are generally similar across the different ethnic groups with age, family history of DM, obesity and hypertension as the most common.[7,8]

Some studies, included other variables depending on the conditions of the country or region. The Finnish FINRISK study, included these additional variables: antihypertensive drug intake, antidiabetic drug intake and consumption of fruits and vegetables.[9] Furthermore, a study from Korea included smoking and HbA1c levels as risk variables; while a study in Zhanang (China) included

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frequent tea-drinking habits, hypertriglyceridemia and fasting plasma glucose (FPG).[7,10] Subsequently, excess meat consumption was found to be a risk factor in a study in Daqiang, China, while total sleep time and waist circumference were included in other studies. Non-invasive models from these risk factors showed a fair value with means an AUC of 0.7-0.8 for predicted diabetes.[11,12]

Similar studies among Indonesians are rare. Hence, we developed a simple and non-invasive diabetes risk prediction model based on the data obtained from the Bogor Cohort Study of the Risk Factors of Non-Communicable Diseases (BCSRFNCD).[7,10-12] The result of this prediction model is presented in chart form to make it easier to apply in the community. Utilizing this model, we aim to develop a screening tool for the prediction of T2DM among adults in Indonesia, and that this self-assessment tool can be used to determine the risk of developing T2DM in the community.

## METHODOLOGY

### Participants

This analysis is part of the BCSRFNCD that was conducted by the National Institute of Health Research and Development (NIHRD) under the Ministry of Health of the Republic of Indonesia in 5 villages located in the Central Bogor District, Bogor City. Subject recruitment took place in three stages in 2011, 2012,and 2015. A total of 5690 respondents aged 25-60 years were included and were followed biennially for six years. A total of 4418 non-diabetic stage 1 and 2 subjects were eventually enrolled and underwent complete laboratory examination.

The reasons for failure to follow-up (dropout) included pregnancy, change of residence, and work-related. Figure 1 illustrates the methodology flow chart.

### Ethics committee approval

This research was approved by the Ethics Commission of the National Institute of Health Research and Development (NIHRD).

### Interview and physical examination

Data were collected using the WHO STEPS method. Informed consent was obtained before blood sampling. Interviews were conducted to determine each patient's sociodemographic characteristics, diagnoses, symptoms and efforts to prevent and treat diabetes.[12] Trained health workers measured the subjects' body weight, height, abdominal circumference and blood pressure using standardized tools.

According to the recommendation of the MHRI, obesity was defined as a body mass index (BMI) ≥25.0 kg/m$^2$. Abdominal circumference ≥90 cm in men or ≥80 cm in women was categorized as central obesity. Abdominal circumference was obtained by placing a measuring-tape around the most prominent part of the abdomen, which is usually located midway between the lower ribs and the iliac crests. Respondents were asked to wear light clothes and stand straight with their feet together. Hypertension was determined based on a history of antihypertensive drug intake, a measured systolic blood pressure ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg. Blood pressure measurement with a digital sphygmomanometer was performed while the individual was in a sitting position with the cuff placed on the right arm at the level of the heart. Blood pressure measurement was carried out twice within approximately 3 minutes. If there was a difference of greater than 10 mmHg between the two measurements in both the systolic and diastolic pressure, it was retaken after a 10-minute rest.[13]

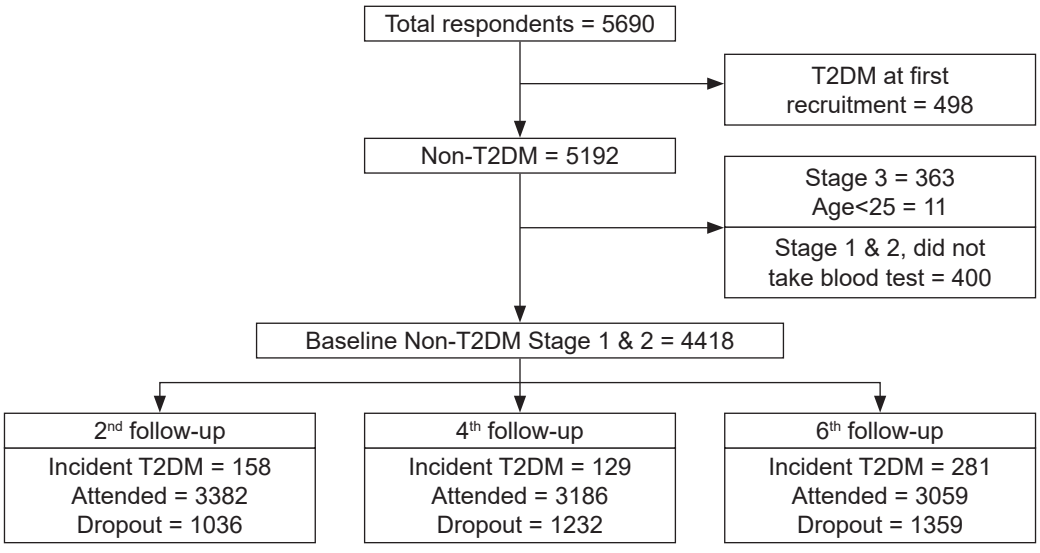


**Figure 1.** The flow of determining respondents of The Bogor Cohort Study of the Risk Factors of Non-Communicable Diseases (BCSRFNCD).

### Laboratory examination

Approximately 8 ml of venous blood was taken from each respondent after a 10- to 12-hour fast for analysis of the fasting plasma glucose (FPG) and lipid profile which includes total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides. Blood extractions were carried out at the Bogor "cohort house" by experienced laboratory personnel. After samples for fasting blood sugar were obtained, the respondents were given a drink containing 75 grams of glucose. Blood samples for glucose (~ 3ml) were taken 2 hours after the glucose load. FPG and 2-hour 75-g oral glucose tolerance test (OGTT) were measured using the glucose hexokinase II (GLUH) method. Total cholesterol was measured enzymatically. Serum LDL and HDL were measured using the homogeneous method. Serum triglycerides were measured using the glycerol-3-phosphate oxidase (GPO) method. The following blood results were considered as abnormal: total cholesterol ≥200 mg/dl, triglycerides ≥150 mg/dl, LDL ≥100 mg/dl, HDL ≤40 mg/dl in men and ≤50 mg/dl in women.[13]

A diagnosis of diabetes was given if the subject fulfilled the American Diabetes Association (ADA) criteria (FPG ≥126 mg/dl, 2-hour 75-g OGTT ≥200 mg/dl).[14,15] Respondents were further classified as either "Diagnosed Diabetes Mellitus" (DDM) if they were previously diagnosed by a physician, or "Undiagnosed Diabetes Mellitus" (UDD) if they were not previously diagnosed.

### Statistical analyses

Data analyses were carried out in stages including data exploration (univariate), simple relationship analysis (bivariate), and multivariable. Logistic regression was used in multivariate analysis to assess the relationship between risk factors and the incidence of T2DM and eventual modeling. Variables that had a *p*-value of less than 0.25 in the bivariate analysis were included in the multivariate analysis to obtain the results of the T2DM risk-fit model. Cut-off point, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) using the receiver operating curve (ROC) graph were also determined. Plasma glucose results served as the reference standard for the diagnosis of diabetes (ADA criteria).[16–18]

The predictive finest cut-off value of BCSFRNCD was compared with the ADA questionnaire scoring in the same population. The ADA questionnaire was chosen because it has been widely used in many countries and has proved to be useful. In the ADA questionnaire, age was categorized into four groups: 25-39, 40-49, 50-59, and ≥60 years old. SPSS v.21 (IBM, New York, Chicago) was used for the analyses.

## RESULTS

Majority of the 4418 respondents were women between the ages of 25 and 39 years. Only 13.9% of the respondents had a family history of diabetes. Based on BMI, 50% of the respondents were obese. The majority of respondents did not have central obesity or hypertension. Most of the respondents have high total cholesterol and LDL levels. Regarding glucose status, 5.3% had impaired fasting glucose (IFG), while 21.6% had impaired glucose tolerance (IGT). On the second year, 158 out of 3382 respondents who followed-up were diagnosed with DM. On the fourth year, 129 out of 3186 returning respondents developed DM. On the sixth year, 281 out of the 3059 subjects developed DM. Within 2 to 6 years of follow-up, the proportion of the cohort with hypertension, obesity, central obesity, hypercholesterolemia and hypertriglyceridemia increased. The cumulative 6-year incidence of T2DM in the 5 villages of Central Bogor was 17.9 % (n = 568), with majority having UDD as shown in Table 1.

The results of the multivariate analysis showed that age, obesity, hypertension, central obesity and lack of physical activity increased the risk of developing T2DM (Table 2). A cut-off point of the Bogor Diabetes Risk Prediction (BDRP) was obtained using the ROC graph with cumulative incidence of DM (on year 6) as the dependent variable and plasma glucose levels as the reference standard. Using a cut-off point of 0.128, the risk prediction model has a sensitivity of 76.6%, specificity of 50.3%, PPV of 21.6%, and NPV of 92.3%. The AUC was 0.70 (95% confidence interval 0.675-0.721). The accuracy of the BDRP in predicting T2DM compares favorably with the ADA questionnaire which has a sensitivity of 70.4%, specificity of 58.5%, PPV of 20.0%, NPV of 93.0%, and AUC of 0.70 (Figure 2).

After data analysis, the identified risk factors for diabetes were converted into a chart called the BDRP Chart as shown in Figure 3. At a cut-off point of 0.128, the probabilities of developing T2DM among those above 60 years old and those 50-59 years old were similar, hence, they were combined into one chart. The presence of 2 or more risk factors in a respondent who is at least 46 years old

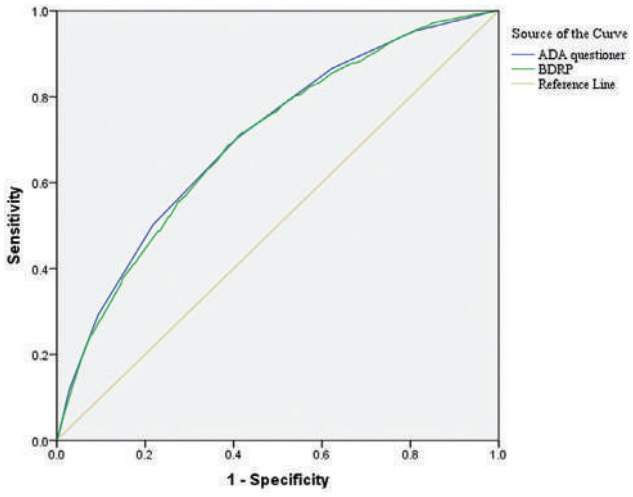


**Figure 2.** ROC analysis of the BDRP and the ADA questioner of The Bogor Cohort Study of the Risk Factors of Non-Communicable Diseases (BCSRFNCD) respondents.

**Table 1.** Characteristics of non-T2DM respondents in the Cohort Study Risk Factors of NCDs

| Characteristics | baseline (n=4418) | | 2nd FU (n=3382) | | 4th FU (n=3186) | | 6th FU (n=3059) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Gender | | | | | | | | |
| Men | 1548 | 35 | 1030 | 30.5 | 942 | 29.6 | 889 | 29.1 |
| Women | 2870 | 65 | 2352 | 69.5 | 2244 | 70.4 | 2170 | 70.9 |
| Age | | | | | | | | |
| 25-39 | 1655 | 37.5 | 982 | 29.0 | 730 | 22.9 | 555 | 18.1 |
| 40-49 | 1402 | 31.7 | 1137 | 33.6 | 1082 | 34.0 | 976 | 31.9 |
| 50-59 | 1063 | 24.0 | 920 | 27.2 | 926 | 29.1 | 939 | 30.7 |
| ≥60 | 298 | 6.7 | 343 | 10.1 | 448 | 14.1 | 589 | 19.3 |
| Family history of diabetes | | | | | | | | |
| No | 3804 | 86.1 | 2643 | 78.1 | 2463 | 77.3 | 2380 | 77.8 |
| Yes | 614 | 13.9 | 739 | 21.9 | 723 | 22.7 | 679 | 22.2 |
| Hypertension* | | | | | | | | |
| No | 3134 | 70.9 | 2376 | 70.3 | 2270 | 71.2 | 1905 | 62.3 |
| Yes | 1284 | 29.1 | 1006 | 29.7 | 916 | 28.8 | 1154 | 37.7 |
| Obese** | | | | | | | | |
| No | 2471 | 55.9 | 1677 | 49.6 | 1535 | 48.2 | 1370 | 44.8 |
| Yes | 1947 | 44.1 | 1706 | 50.4 | 1649 | 51.8 | 1687 | 55.2 |
| Central obesity*** | | | | | | | | |
| No | 2663 | 60.3 | 1675 | 49.9 | 1361 | 41.3 | 1139 | 37.3 |
| Yes | 1755 | 39.7 | 1685 | 50.1 | 1868 | 58.7 | 1918 | 62.7 |
| Physical activity**** | | | | | | | | |
| appropriate | 2265 | 51.3 | 1330 | 39.3 | 1718 | 53.9 | 2082 | 68.1 |
| not appropriate | 2153 | 48.7 | 2052 | 60.7 | 1468 | 46.1 | 977 | 31.9 |
| Total Cholesterol***** | | | | | | | | |
| Normal | 2238 | 50.7 | 1862 | 55.1 | 1589 | 49.9 | 1160 | 38.1 |
| Risk | 2180 | 49.3 | 1520 | 44.9 | 1597 | 50.1 | 1886 | 61.9 |
| LDL-chol***** | | | | | | | | |
| Normal | 781 | 17.7 | 613 | 18.1 | 582 | 18.3 | 489 | 16.1 |
| Risk | 3637 | 82.3 | 2769 | 81.9 | 2604 | 81.7 | 2557 | 83.7 |
| HDL-chol***** | | | | | | | | |
| Normal | 2688 | 60.8 | 2074 | 61.3 | 2124 | 66.7 | 1755 | 57.4 |
| Risk | 1730 | 39.2 | 1308 | 38.7 | 1062 | 33.3 | 1304 | 42.6 |
| Triglycerides***** | | | | | | | | |
| Normal | 3657 | 82.8 | 2749 | 81.3 | 2552 | 80.1 | 2271 | 74.2 |
| Risk | 761 | 17.2 | 633 | 18.7 | 634 | 19.9 | 788 | 25.8 |
| T2DM****** | | | | | | | | |
| No | 4418 | 100.0 | 3224 | 95.3 | 3057 | 96.0 | 2778 | 90.8 |
| Yes | | | 158 | 4.7 | 129 | 4.0 | 281 | 9.2 |
| -DDM | | | 29 | 18.4 | 34 | 26.4 | 12 | 4.3 |
| -UDD | | | 129 | 81.6 | 95 | 73.6 | 269 | 95.7 |

*Hypertensive: if systolic ≥140 mmHg and/or diastolic ≥90 mmHg (JNC VII)
**Obese: BMI ≥25 kg/m$^2$
***Central obesity: if the abdominal circumference is ≥90 cm (men), ≥80 cm (women)
****inadequate physical activity: if <600 Meq
*****Risk of total cholesterol ≥200 mg/dL, triglycerides ≥150 mg/dL, LDL ≥100 mg/dL, HDL ≤40 mg/dL (men) and ≤50 mg / dL (women).
******T2DM: if FPG ≥126 mg/dL or post 75g-OGTT ≥200 mg/dL (ADA criteria)

predicts T2DM. Among respondents between 25-39 years old, having 3 risk factors was predictive of T2DM. In contrast, having only one risk factor was not predictive with a sensitivity of 76.6%.

## DISCUSSION

The 6-year cumulative incidence of T2DM in the 5 sub-districts of Bogor City was quite high at 17.9% and prevalence 23.4% (include diabetes patients at baseline). This is very concerning since the majority of the population (70 to 95%) did not realize that their blood glucose levels were high (UDD). This is considerably higher compared to the national diabetes prevalence of 8.5% and the West Java Province prevalence from RISKESDAS result of 2.05%.[3,4] This finding is similar to a Thai study which revealed that 13.5% of 2,677 respondents in the 35–55 age group had T2DM after a 12-year follow-up.[19] An Israeli study showed that 13.7 % of the 1,894 respondents in an Arab community aged 21 years and above had T2DM.[8] This result was lower than the study in Saudi Arabia, where 25.1% of the 872 respondents had T2DM.[20] Thus, the increasing prevalence of T2DM, particularly UDD, requires more intensive prevention efforts by early identification of the risk factors. Furthermore, it is necessary to increase public awareness and to conduct self-assessment of diabetes risk routinely.

Risk factors that predicted the occurrence of T2DM among the respondents of the Bogor Cohort Study were age, obesity, central obesity, hypertension, and lack of physical activity. The BDRP model had a fairly good sensitivity, specificity and AUC. Furthermore, monitoring of bodyweight, abdominal circumference, blood pressure, and physical activity is easy to carry out in the community.

**Table 2.** The result of the multivariate analysis for T2DM prediction for the Cohort Study Risk Factors of NCDs

| Variables | β | p | RR | CI 95% | |
|---|---|---|---|---|---|
| | | | | lower | upper |
| Age group | | | | | |
| 25-39 | - | - | ref | - | - |
| 40-49 | 0.393 | 0.013 | 1.481 | 1.088 | 2.016 |
| 50-59 | 0.662 | 0.001 | 1.940 | 1.435 | 2.622 |
| ≥60 | 0.816 | 0.001 | 2.261 | 1.635 | 3.126 |
| Obese** | | | | | |
| No | - | - | ref | - | - |
| Yes | 0.600 | 0.001 | 1.822 | 1.402 | 2.368 |
| Hypertensive* | | | | | |
| No | - | - | ref | - | - |
| Risk | 0.574 | 0.001 | 1.775 | 1.466 | 2.148 |
| Central obesity*** | | | | | |
| No | - | - | ref | - | - |
| Yes | 0.518 | 0.001 | 1.679 | 1.272 | 2.215 |
| Physical activity**** | | | | | |
| No | - | - | ref | - | - |
| Risk | 0.459 | 0.001 | 1.582 | 1.310 | 1.909 |
| Constant | -3.388 | 0.001 | - | - | - |

*Hypertensive: if systolic ≥140 mmHg and/or diastolic ≥90 mmHg (JNC VII)
**Obese: if BMI ≥25 kg/m$^2$
***Central obesity: if abdominal circumference ≥90 cm (in men), ≥80 cm (in women)
**** inadequate physical activity: if <600 Meq

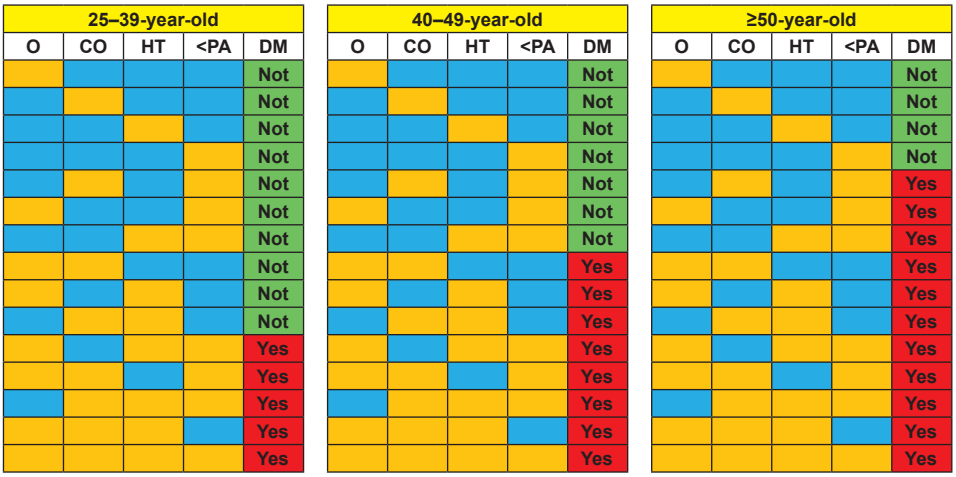


**Figure 3.** The Bogor Diabetes Risk Prediction (BDRP) Chart.

The Ministry of Health has an Integrated Services Post for Non-Communicable Diseases (NCD) program called "*Posbindu*" that performs these checks every month and records the results in the NCD Cohort Book for each individual. The development of the BDRP Chart from the BDRP model aims to simplify interpretation, with the hope that it can be used for T2DM self-assessment and screening. Compared to other studies with scoring systems, this chart differs in the prediction of T2DM. However, researches in America, Australia, Europe and Asia have almost the same variables.

Similar to our findings, various studies in America also showed that age, gender, family history of diabetes mellitus, history of hypertension, obesity and physical activity are risk factors for diabetes.[21] An Australian study showed that the risk factors for T2DM are a history of high plasma glucose, antihypertensive drug intake, and smoking.[22] Age, gender, history of high plasma glucose, antihypertensive drug intake, obesity, central obesity, physical activity, and fruit and vegetable consumption were included in the prediction models from studies conducted in Finland and Denmark.[9,23] Cross-sectional studies among Israeli-Arabs, Saudi Arabians, Indians, Omanis and Thais show that age, family history of diabetes, obesity, central obesity and physical activity are all associated with T2DM.[8-21,24] Hypertriglyceridemia and high FPG were shown to predict T2DM occurrence in a 6-year prospective cohort study in China.[10] This finding was attributed to the frequent intake of tea. The difference in the variables included in this predictive model could be due to variations in habits such as diet.

The BDRP Chart had a higher sensitivity but lower specificity compared to the results of a cohort study in China which had a sensitivity of 69,63%, specificity of 75.56% and AUC of 0.791.[10] Our results are nearly identical to the Thai cohort which had a sensitivity of 77%, specificity of 60%, and AUC of 0.74.[19] These results were better than other Chinese studies among respondents aged 20-74 years old, which showed an AUC of 67.3 % at 95 % CI (64.9-69.7).[25] Similar with research in India from the Chennai Urban Rural Epidemiology Study (CURES) used the Indian Diabetic Risk Score (IDRS) and obtained an AUC of 0.698 using 95% CI ranging from 0.663-0.733.[26]

The BDRP chart was compared to the ADA risk score questionnaire which is widely used in many countries.[27] Results showed that the BDRP had diagnostic values that are nearly identical to the ADA questionnaire. A tool with high sensitivity can be used as a screening tool. The BCSFRNCD respondents found it easier to provide data using the BDRP chart than the ADA questionnaire because, particularly for those living in urban communities, most were unable to provide an accurate information regarding their family history. The majority of the respondents were immigrants who did not live close to their parents, hence, they are uncertain of their health status. Moreover, since medical records have not yet been integrated into a single health system, recording of the health history of the Indonesian population has not been properly implemented. In addition, the colours displayed on the BDRP chart are easier to understand.

Without question, this chart can be applied to Indonesian women. The lack of knowledge about gestational diabetes among Indonesian women is difficult to overcome due to lack of public awareness, and limited knowledge of pregnant women about the management of gestational diabetes.[28]

### Limitations of the study

The multivariate analysis uses only non-invasive risk factors variables. The study population has fewer male than female respondents and, hence, may not reflect the general population of Bogor. Further validation in a larger population is warranted.

## CONCLUSION

The cumulative incidence of T2DM in Bogor is 17.9%. The risk factors that predict its occurrence are age, obesity, central obesity, hypertension and lack of physical activity. The BDRP Chart fared well when compared to the ADA questionnaire in terms of predicting who will develop T2DM among the BCSRFNCD population. The BDRP Chart is a simple, non-invasive and easy-to-use screening tool that can be employed in "*Posbindu*" and primary healthcare. Moreover, the BDRP chart colour stresses the importance of adopting a healthy lifestyle.

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

**Author Disclosure**
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ORIGINAL ARTICLE

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# Metabolic Profile of People Living with HIV in a Treatment Hub in Manila, Philippines: A Pre- and Post-Antiretroviral Analysis*

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**Abstract**

Objectives. People living with HIV (PLHIV) are susceptible to develop dyslipidemia and hyperglycemia. This study aims to determine the prevalence of these metabolic derangements among Filipino PLHIV.

Methodology. We reviewed 635 medical records in a treatment hub in Manila, Philippines from January 2004 to July 2016. Logistic regression analysis was done to determine factors associated with dyslipidemia and hyperglycemia pre- and post-ART.

Results. Among 635 PLHIV, 97.3% were males with mean age of 30 years and median CD4 count of 207 cells/mm$^3$. Pre-ART, prevalence of dyslipidemia was 65.4% and hyperglycemia was 10.4%. Risk factors for dyslipidemia include hyperglycemia (AOR 3.8, *p* 0.001) and >320 days delay in ART initiation from HIV confirmation (AOR 1.5, *p* 0.032), while dyslipidemia was associated with hyperglycemia (AOR 3.1, *p* 0.001). Post-ART, prevalence of dyslipidemia was 48.6% and hyperglycemia was 15.6%. Risk factors for post-ART dyslipidemia include being WHO stage 4 (AOR 2.1, *p* 0.021), hyperglycemia (AOR 16.1, *p*<0.001), >36 months ART duration (AOR 8.7, *p*<0.001) and efavirenz-based ART (AOR 2.8, *p*<0.001). Low CD4 count post-ART had a negative correlation with dyslipidemia (AOR 0.5, *p* 0.005). Post-ART hyperglycemia was associated with age >30 years (AOR 2.1, *p* 0.004), being overweight (AOR 1.8, *p* 0.023), dyslipidemia (AOR 17.8, *p*<0.001) and zidovudine-based ART (AOR 1.4, *p* 0.051).

Conclusion. Dyslipidemia and hyperglycemia prevalence was high in Filipino PLHIV. Traditional, HIV and treatment related factors contributed to its development. Intensive monitoring and initiation of appropriate treatment is recommended.

*Key words: HIV, AIDS, dyslipidemia, hyperglycemia, antiretroviral therapy*

## INTRODUCTION

Antiretroviral therapy (ART) improves survival and has made Human Immunodeficiency Virus (HIV) infection a chronic, controllable disease.[1] As such, there is increasing interest among experts on the long-term complications of HIV and ART use.

HIV infection induces immune activation making patients susceptible to metabolic abnormalities.[2] In addition, prolonged ART use is linked to the increasing prevalence of dyslipidemia and hyperglycemia.[1,3] Like the non-HIV infected population, traditional risk factors (e.g., smoking, obesity) also contribute to its development.[4]

Multi-center, cross-sectional studies from both developed and resource limited settings reported an alarming rate of dyslipidemia between 54-81%,[5,6] while hyperglycemia was present in 32% of PLHIV.[7] A 2013 study investigated the role of ethnicity in the development of dyslipidemia and hyperglycemia. African Americans with cluster of differentiation 4 (CD4) <300 cells/mm$^3$ and Hispanics with CD4 >300 cells/mm$^3$ were at risk to develop these metabolic abnormalities,[8] however Asians were not represented in

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this study. On the other hand, a Malaysian cross-sectional study reported dyslipidemia rate at 82.3% (1318/1583 subjects) among ART experienced PLHIV.[9]

In the Philippines, ART previously consisted of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) with or without protease inhibitors (PIs).[10] Until recently, integrase strand transfer inhibitors (INSTIs) were included as part of the first line ART regimen as recommended by World Health Organization.[11] PIs have been identified as a risk factor for dyslipidemia and hyperglycemia.[3,9-12] However, recent studies have demonstrated an increased risk in developing dyslipidemia and hyperglycemia even on NRTI/NNRTI combinations.[5] The NRTI stavudine (d4T) and zidovudine (AZT), and the NNRTI efavirenz (EFV) has been linked to dyslipidemia[12,13] which often occurs after prolonged use.[14] On the other hand, INSTIs are less likely to produce lipid derangements.[11,15]

Insulin resistance (IR) and type 2 diabetes mellitus (T2DM) are increasingly recognized in PLHIV, particularly among those on ART.[16,17] IR is said to precede weight loss and is implicated in the pathogenesis of T2DM in PLHIV.[18] Glucose abnormalities were seen after 66 months of ART use.[19]

These HIV and ART induced metabolic derangements overlap with the components of metabolic syndrome, making PLHIV at high risk for cardiovascular diseases (CVD).[20,21] Various multicenter studies have shown that metabolic syndrome is present in 1.8% among ART naïve and 14-45.4% among ART experienced patients.[22]

Despite the HIV epidemic, these metabolic consequences have not been reported in the Philippine setting. We conducted a retrospective cohort study to determine the prevalence and risk factors for dyslipidemia and hyperglycemia pre- and post-ART exposure.

## METHODOLOGY

### Study Design and Setting

This is a retrospective cohort study conducted at a government-run treatment hub in the University of the Philippines-Philippine General Hospital (UP-PGH). The study was approved by the Research Ethics Board of the University of the Philippines Manila. The Research Ethics Board waived the need for patient's informed consent since the study will only involve analysis of existing database, has minimal risk, and the risk and welfare of the participants are not adversely affected.

### Study population and patient selection

We reviewed all patient records from January 2004 to July 2016. All adult patients confirmed to have HIV infection were included in the study. Patients who died and those who were lost to follow up during the study period were excluded. Patients without any serum lipid profile or fasting blood glucose determination from the time of clinic enrollment and subsequent follow up were also excluded from the study (Figure 1). A total of 635 PLHIV were included in the study.

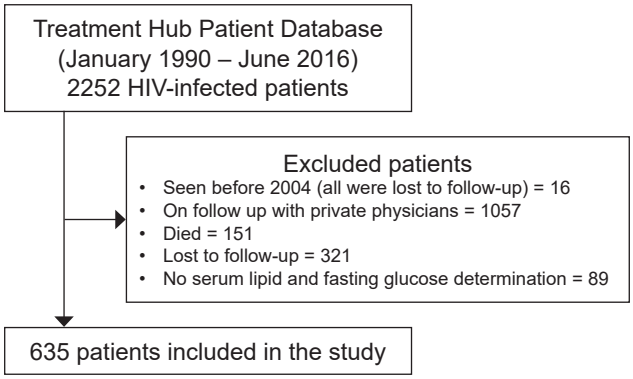


**Figure 1.** Schematic diagram of patient inclusion and exclusion in the study.

### Sample size computation

The sample size requirement for each study objective pre- and post-ART was computed. Estimating the prevalence of dyslipidemia and hyperglycemia required the largest sample size. Consequently, a minimum sample size of 382 PLHIV was needed to estimate the prevalence of dyslipidemia and 334 PLHIV to estimate prevalence of hyperglycemia among Filipino PLHIV in a treatment hub in Manila, Philippines. The formula for sample size for estimating the population proportion was used in this computation. The information used in the computation were: 1) Expected prevalence of dyslipidemia is 54%[5] and for hyperglycemia is 32%,[7] 2) Margin of error set at 5%, and 3) Confidence interval set at 95%. A logistic regression of a binary response (dyslipidemia) on a binary independent variable (ART) with a sample size of 215 PLHIV achieves 80% power at a 0.05 significance level. Appropriate adjustment was done since an $R^2$ of 0.03 was obtained in the multiple regression of independent variable on other variables in the final logistic regression model. Power Analysis & Sample Size (PASS-NCSS) software was used in the sample size computation.

### Definition of terms

Dyslipidemia is defined by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) as presence of one of the following: Total cholesterol (TC) >5.2 mmol/L, triglyceride (TG) >1.7 mmol/L, low density lipoprotein cholesterol (LDL-C) >2.6 mmol/L, high density lipoprotein cholesterol (HDL-C) <1.0 mmol/L. Hyperglycemia is defined by the American Diabetes Association (ADA) as presence of Type 2 Diabetes Mellitus (T2DM) and/or Impaired Fasting Glucose (IFG). Type 2 Diabetes Mellitus is defined as fasting blood glucose

(FBG) level ≥7.0 mmol/L. Impaired Fasting Glucose (IFG) is defined as FBG 5.6-6.9 mmol/L. Metabolic syndrome is defined as per NCEP-ATP III as having met any three of the five criteria: waist circumference 40 inches in men / 35 inches in women; FBG ≥5.6 mmol/L or on medications; TG >1.7 mmol/L, HDL-C<1.0 mmol/L or on medications; and blood pressure of >130 mmHg systolic or >85 mmHg diastolic or on medications for hypertension.

### Data collection

The clinic database was reviewed for relevant clinical and laboratory data from the date of enrollment until last follow up. To determine factors associated with dyslipidemia and hyperglycemia pre- and post-ART, the following variables were obtained from the records: age, sex, baseline, nadir and subsequent CD4 counts, baseline and subsequent height and weight, co-morbidities, smoking history, alcohol intake, type and duration of ART and intake of other medications. Serum lipid parameters and fasting blood glucose levels were determined using the Vitros DT60 II (Vitros 5.1) chemistry analyzer (Ortho Clinical Diagnostics, New Jersey, United States of America).

### Statistical analysis

Descriptive statistics were used to present patient demographics. Quantitative data were reported using means and medians for normally distributed and non-normally distributed data, respectively. Qualitative variables were reported using frequencies and percentages. Point and 95% confidence interval estimates of the prevalence of dyslipidemia and hyperglycemia were computed. Chi-square test was used to compare categorical variables. Continuous variables with normal and non-normal distribution were compared using T-test and Mann Whitney U test, respectively. To determine the factors associated with dyslipidemia and hyperglycemia, univariate and stepwise multivariate logistic regression analysis was done. Variables found to be significant ($p$<0.25) in the univariate logistic regression analysis and other variables of known clinical relevance to the outcomes were included in the multivariate logistic regression model for dyslipidemia and hyperglycemia. The final model of the stepwise logistic regression analysis performed was used to identify factors that are significantly associated with dyslipidemia and hyperglycemia. Significance level was set at $\alpha$=0.05. Data was analyzed using STATA version 13 (Stata Corp, College Station, Texas, USA).

## RESULTS

We reviewed and included 635 medical charts in this study. Majority of the participants were males (618/635, 97.3%) with a mean age of 30 years (SD 7.5). Median baseline CD4 count is at 213 cells/mm$^3$ (SD 195.9) and a BMI of 21.5 (SD 3.8). Demographic and clinical characteristics of participants are summarized in Tables 1 and 2.

### Metabolic abnormalities pre-ART exposure

Prior to the initiation of ART, the initial mean lipid profile was as follows: TC of 4.5 mmol/L (SD 1.2), TG of 1.63 mmol/L (SD 1.0), LDL-C of 2.76 mmol/L (SD 0.90), HDL-C of 1.1 mmol/L (SD 0.75). The median FBG was at 4.97 mmol/L (SD 0.84) (Table 3). No participants were diagnosed with dyslipidemia prior to HIV diagnosis.

The prevalence of dyslipidemia was at 65.4% (95% CI: 59.2, 71.9) and was documented within 415 days from the time of HIV diagnosis. The most common lipid derangement is low HDL-C (74.7%) followed by elevated LDL-C (53%), elevated TG (35.2%) and elevated TC (20.5%). The most common pattern of dyslipidemia noted were as follows: isolated low HDL-C (28.3%), high LDL-C/low HDL-C (14%), and high TG/low HDL-C (14%). The prevalence of hyperglycemia before ART was 10.4% (95% CI: 8.0, 13.2) and was documented within 615 days from the time of HIV diagnosis. Majority had FBG within the IFG levels (92.4%). Two patients self-reported to be diagnosed with IFG prior to HIV diagnosis; one patient is on metformin. Dyslipidemia and hyperglycemia were both observed in 8.8% (95% CI: 6.7, 11.45) of the cohort. Among those patients diagnosed with both dyslipidemia and hyperglycemia before ART initiation, 28.6% fulfilled the criteria for metabolic syndrome.

After adjusting for age, sex, CD4 count, BMI, comorbidities (hypertension and hyperglycemia), time of delay in ART initiation, prophylactic antibiotic use (cotrimoxazole, azithromycin, dapsone), oral corticosteroid use and statin/fibrates use the logistic regression analysis confirmed the following factors were associated with dyslipidemia: concurrent hyperglycemia (AOR 3.8, 95% CI: 2.7, 7.4) and delay of ART initiation for >320 days from HIV diagnosis (AOR 1.5, 95% CI: 1.1, 2.3). Early initiation of ART had a protective effect on dyslipidemia (AOR 0.3, 95% CI: 0.1, 0.7). For hyperglycemia, after adjusting for age, sex, CD4 count, BMI, comorbidities (hypertension), time of delay in ART initiation, prophylactic antibiotic use (cotrimoxazole, azithromycin, dapsone), use of TB medications and OHAs, it showed that concurrent dyslipidemia was an associated factor (AOR 3.1, 95% CI: 1.4, 5.8) (Table 4).

Initiation of appropriate interventions for dyslipidemia were documented in 26.9% (112/415). Lifestyle modification is the only intervention prescribed in 54.5% (61/112). Pharmaceutical intervention which includes use of statins and fibrates were started in 19.6% (22/112) and 7.1% (8/112), respectively. On the other hand, both lifestyle modification and use of medications were advised in 18.8% (21/112).

Interventions for hyperglycemia were only documented in 10.6% (7/66). Lifestyle modification alone was advised in three participants while four participants were started on oral hypoglycemic agents (OHAs).

**Table 1.** Demographic, clinical and laboratory characteristics of 635 Filipino PLHIV with and without dyslipidemia

| Demographics | Pre-ART | | | Post-ART | | |
|---|---|---|---|---|---|---|
| | Dyslipidemic (n=415) | Non-dyslipidemic (n=220) | P | Dyslipidemic (n=309) | Non-dyslipidemic (n=326) | P |
| Mean age; SD (years) | 29; 7.4 | 30; 7.5 | 0.180 | 33; 10.3 | 33; 10.2 | 0.183 |
| Age ≥30 | 181 (43.6%) | 88 (40%) | 0.380 | 141 (45.6%) | 128 (39.2%) | 0.185 |
| Male sex | 408 (98.3%) | 210 (95.5%) | 0.030 | 299 (96.8%) | 319 (97.9%) | 0.395 |
| Median CD4; IQR (cells/mm$^3$) | 207; 196.3 | 206; 195.8 | 0.190 | 343; 223.1 | 343; 223.3 | 0.120 |
| Median Nadir CD4; IQR (cells/mm$^3$) | 161; 296 | 160;293 | 0.241 | - | - | - |
| CD4 <200 cells/mm$^3$ | 207 (49.9%) | 140 (63.6%) | 0.002 | 57 (18.4%) | 122 (37.4%) | 0.030 |
| WHO stage | | | 0.153 | | | 0.267 |
| 1 | 169 (40.7%) | 76 (34.5%) | | 111 (35.9%) | 134 (41.1%) | |
| 2 | 49 (11.8%) | 22 (10.0%) | | 38 (12.3%) | 33 (10.1%) | |
| 3 | 92 (22.2%) | 46 (21.0%) | | 63 (20.4%) | 75 (23.0%) | |
| 4 | 105 (25.3%) | 76 (34.5%) | | 97 (31.4%) | 84 (25.8%) | |
| Mean BMI; SD (kg/m$^2$) | 21.5; 3.9 | 21.5; 3.8 | 0.682 | 23.1; 3.9 | 23.2; 3.9 | 0.686 |
| BMI classification: | | | 0.671 | | | 0.178 |
| Normal | 232 (55.9%) | 125 (56.8%) | | 135 (43.7%) | 153 (46.9%) | |
| Underweight | 45 (10.8%) | 29 (13.2%) | | 11 (3.6%) | 17 (5.2%) | |
| Overweight | 106 (25.5%) | 48 (21.8%) | | 121(39.5%) | 103 (31.6%) | |
| Obese | 19 (4.6%) | 8 (3.6%) | | 31 (10%) | 23 (7.1%) | |
| Co-morbidities: | | | | | | |
| Hypertension | 15 (3.6%) | 3 (1.3%) | 0.104 | 9 (2.9%) | 9 (2.8%) | 0.178 |
| Asthma/Allergy | 42 (10.1%) | 24 (10.9%) | 0.181 | 29 (9.4%) | 36 (11.04%) | 0.202 |
| Smoker, mean; SD (pack/years) | 153 (36.9%),1.7; 5.2 | 69 (31.4%),1.7; 5.3 | 0.166,0.551 | 99 (32.0%), 1.7; 5.2 | 123 (37.7%), 1.7; 5.3 | 0.133,0.590 |
| Alcohol beverage drinker | 66 (15.9%) | 29 (13.18%) | 0.360 | 36 (11.6%) | 59 (18.1%) | 0.023 |
| Delay in ART initiation; SD (days) | 259; 384 | 421; 2591 | 0.038 | - | - | |
| 0-320 days | 266 (64.1%) | 167 (75.9%) | 0.002 | - | - | |
| >320 days | 66 (15.9%) | 37 (16.8%) | | - | - | |
| Duration of ART use | | | | | | <0.001 |
| 0-36 months | - | - | | 246 (79.6%) | 296 (90.8%) | |
| ≥ 36 months | - | - | | 63 (20.4%) | 30 (9.2%) | |
| OI Prophylaxis / Other Medications | | | | | | |
| Cotrimoxazole | 196 (47.2%) | 124 (56.4%) | 0.028 | - | - | |
| Azithromycin | 148 (35.7%) | 99 (45.0%) | 0.022 | - | - | |
| Isoniazid | 58 (13.9%) | 25 (11.4%) | 0.353 | - | - | |
| Fluconazole | 45 (10.8%) | 21 (9.5%) | 0.610 | - | - | |
| Anti-TB medications | 79 (19.0%) | 41 (18.6%) | 0.903 | - | - | |
| Dapsone | 23 (5.5%) | 19 (8.6%) | 0.135 | - | - | |
| Corticosteroid | 9 (2.2%) | 11 (5%) | 0.052 | - | - | <0.001 |
| ART regimen | | | | | | |
| NRTI: AZT based | - | - | | 133 (43%) | 62 (19 %) | |
| Non-AZT based | - | - | | 176 (57%) | 264 (81 %) | |
| NNRTI: | | | | | | |
| EFV-based | - | - | | 278 (90%) | 253 (77.6%) | <0.001 |
| Non-EFV based | - | - | | 31 (10%) | 73 (22.4%) | |
| NVP based | - | - | | 57 (18.4%) | 26 (8%) | <0.001 |
| Non-NVP based | - | - | | 252 (81.6%) | 300 (92%) | |
| PI based | - | - | | 22 (7.1%) | 15 (4.6%) | 0.176 |
| Non PI based | - | - | | 287 (92.9%) | 311 (95.4%) | |

ART – antiretroviral, SD – standard deviation, CD4 – cluster of differentiation 4, WHO – World Health Organization, BMI – Body Mass Index, WB – Western Blot, OI – opportunistic infection, TB – Tuberculosis, NRTI – nucleoside reverse transcriptase inhibitor, AZT – zidovudine, NNRTI – non-nucleoside reverse transcriptase inhibitor, EFV – efavirenz, NVP – nevirapine, PI – protease inhibitor

### Metabolic abnormalities post-ART exposure

The mean duration of ART use was 978 days (SD 670). The mean lipid and fasting blood glucose level increased after ART initiation with TC at 4.9 mmol/L (SD 1.0), TG at 1.78 mmol/L (SD 1.1), LDL-C at 2.96 mmol/L (SD 0.87), HDL-C at 1.20 mmol/L (SD 0.39) and FBG at 5.2 mmol/L (SD 0.79) (Table 3).

Dyslipidemia was noted in 48.7% (95% CI 43.4, 54.4) of the study population and majority was observed within the first 36 months (79.3%). Majority had high LDL-C at 81.5%, high TC at 58.6%, high TG at 57.9% and low HDL-C at 52.1%. On the other hand, the most common dyslipidemia pattern was high TC/high TG/high LDL-C/low HDL-C in 21% followed by high TC/high TG/high LDL-C in 15.5%. The prevalence of hyperglycemia after ART was 15.6% (95% CI: 12.7, 19.0) with the majority (89.9%) falling within the IFG level. Dyslipidemia and hyperglycemia were both observed in 14.6% (95% CI: 11.8, 17.9) of the cohort after ART initiation. Among these, 43% fulfilled the criteria for metabolic syndrome.

After adjusting for age, sex, CD4 count, WHO stage, BMI, comorbidities, alcohol consumption and smoking history, duration of ART initiation and ART regimen and statins/fibrates use, logistic regression analysis confirmed the following factors associated with dyslipidemia: WHO stage 4 (AOR 2.1, 95% CI: 1.3, 3.7), hyperglycemia (AOR 16.1, 95% CI: 6.5, 35.7), >36 months of ART use (AOR 8.7, 95% CI: 6.4, 14.2) and EFV based ART (AOR 2.8, 95% CI: 1.3, 4.4). Low CD4 count was protective against dyslipidemia (AOR 0.5, 95% CI: 0.2, 0.8). Adjusting for age, sex, CD4 count, WHO stage, BMI, comorbidities, alcohol consumption and smoking history, duration of ART initiation and ART regimen, and OHAs use logistic regression analysis showed that age ≥30 (AOR 2.1, 95% CI: 1.7, 3.4), dyslipidemia (AOR 17.8, 95% CI: 7.6, 36.1), being

**Table 2.** Demographic and clinical characteristics of 635 Filipino PLHIV with and without hyperglycemia

| Demographics | Pre-ART | | | Post-ART | | |
|---|---|---|---|---|---|---|
| | Hyperglycemic (n=66) | Non-hyperglycemic (n=569) | P | Hyperglycemic (n=99) | Non-hyperglycemic (n=536) | P |
| Mean age; SD (years) | 29; 7.5 | 30; 7.5 | 0.710 | 35; 11.6 | 35; 11.4 | 0.990 |
| Age ≥30 | 29 (43.9%) | 240 (42.2%) | 0.784 | 56 (56.6%) | 213 (39.7%) | 0.002 |
| Male sex | 64 (97%) | 544 (95.6%) | 0.851 | 97 (98.0%) | 521 (97.2%) | 0.659 |
| Median CD4 count; IQR (cells/mm$^3$) | 206; 196.1 | 207; 195.9 | 0.292 | 346; 223.4 | 342; 223.0 | 0.055 |
| Median Nadir CD4; IQR (cells/mm$^3$) | 160;296 | 160;293 | 0.364 | - | - | - |
| CD4 <200 cells/mm$^3$ | 32 (48.5%) | 315 (55.4%) | 0.420 | 20 (20.2%) | 159 (29.7%) | 0.172 |
| WHO stage | | | 0.818 | | | 0.544 |
| 1 | 29 (43.9%) | 216 (38.0%) | | 34 (34.3%) | 211 (39.3%) | |
| 2 | 7 (10.6%) | 63 (11.1%) | | 8 (8.0%) | 62 (11.6%) | |
| 3 | 11 (16.7%) | 127 (22.3%) | | 26 (26.3%) | 112 (20.9%) | |
| 4 | 19 (28.8%) | 162 (28.4%) | | 31 (31.4%) | 150 (27.9%) | |
| Mean BMI; SD (kg/m$^2$) | 21.3; 3.8 | 22.8; 3.7 | 0.003 | 23.1; 4.0 | 23.2; 4.0 | 0.06 |
| BMI classification: | | | 0.169 | | | 0.084 |
| Normal | 36 (54.5%) | 321 (56.4%) | | 36 (36.4%) | 252 (47.0%) | |
| Underweight | 3 (4.5%) | 71 (12.5%) | | 4 (4.0%) | 24 (4.5%) | |
| Overweight | 18 (27.3%) | 136 (23.9%) | | 47 (47.5%) | 177 (33.0%) | |
| Obese | 5 (7.6%) | 22 (3.9%) | | 8 (8.1%) | 46 (8.6%) | |
| Co-morbidities: | | | | | | |
| Hypertension | 3 (4.5%) | 15 (2.6%) | 0.376 | 4 (4.0%) | 14 (2.6%) | 0.431 |
| Asthma/Allergy | 8 (12.1%) | 57 (1.0%) | 0.176 | 10 (10.1%) | 54 (10.0%) | 0.466 |
| Smoker, mean; SD (pack/years) | 23 (34.8%),1.7; 5.3 | 199 (35.0%),1.7; 5.3 | 0.984,0.412 | 28 (28.3%), 1.7; 5.2 | 194 (36.2%),1.7; 5.3 | 0.129,0.607 |
| Alcohol beverage drinker | 7 (10.6%) | 88 (15.5%) | 0.295 | 8 (8.0%) | 87 (16.2%) | 0.037 |
| Delay in ART initiation; SD (days) | 250; 312 | 327; 1691 | 0.999 | - | - | |
| 0-320 days | 44 (66.7%) | 389 (68.4%) | 0.849 | - | - | |
| >320 days | 12 (18.2%) | 106 (18.6%) | | - | - | |
| Duration of ART use | | | | | | <0.001 |
| 0-66 months | - | - | | 94 (95.0%) | 526 (98.1%) | |
| ≥ 66 months | - | - | | 5 (5.0%) | 10 (1.9%) | |
| OI Prophylaxis / Other Medications | | | | | | |
| Cotrimoxazole | 25 (37.9%) | 295 (51.8%) | 0.032 | - | - | |
| Azithromycin | 16 (24.2%) | 231 (40.6%) | 0.010 | - | - | |
| Isoniazid | 11 (16.7%) | 72 (12.7%) | 0.360 | - | - | |
| Fluconazole | 7 (10.6%) | 59 (10.4%) | 0.952 | - | - | |
| Anti-TB medications | 9 (13.6%) | 111 (19.5%) | 0.249 | - | - | |
| Dapsone | 1 (1.5%) | 41 (7.2%) | 0.078 | - | - | |
| Corticosteroid | 2 (3.0%) | 18 (3.2%) | 0.953 | - | - | |
| ART regimen | | | | | | <0.001 |
| NRTI: AZT based | - | - | | 50 (50.5%) | 145 (27.0%) | |
| Non-AZT based | - | - | | 49 (49.5%) | 391 (73.0 %) | |
| NNRTI: | | | | | | |
| EFV based | - | - | | 91 (91.9%) | 440 (82.1%) | 0.015 |
| Non-EFV based | - | - | | 8 (8.1%) | 96 (17.9%) | |
| NVP based | - | - | | 17 (17.2%) | 66 (12.3%) | 0.188 |
| Non-NVP based | - | - | | 82 (82.8%) | 470 (87.7%) | |
| PI based | - | - | | 8 (8.1%) | 29 (5.4%) | 0.297 |
| Non PI based | - | - | | 91 (91.9%) | 507 (94.6%) | |

ART – antiretroviral, SD – standard deviation, CD4 – cluster of differentiation 4, WHO – World Health Organization, BMI – Body Mass Index, WB – Western Blot, OI – opportunistic infection, TB – Tuberculosis, NRTI – nucleoside reverse transcriptase inhibitor, AZT – zidovudine, NNRTI – non-nucleoside reverse transcriptase inhibitor, EFV – efavirenz, NVP – nevirapine, PI – protease inhibitor

**Table 3.** Laboratory characteristics of 635 Filipino PLHIV pre- and post-antiretroviral exposure

| Laboratory Parameters | Pre-ART | 95% CI | Post ART | 95% CI | p |
|---|---|---|---|---|---|
| TC; SD (mmol/L) | 4.5; 1.1 | 4.4, 4.7 | 4.9;1.0 | 4.8, 5.1 | <0.001 |
| TG; SD (mmol/L) | 1.6; 1.0 | 1.5, 1.8 | 1.8;1.1 | 1.7, 1.9 | 0.024 |
| LDL-C; SD (mmol/L) | 2.8; 0.1 | 2.7, 2.9 | 2.9;0.1 | 2.9, 3.1 | <0.001 |
| HDL-C; SD (mmol/L) | 1.1; 0.5 | 1.0, 1.1 | 1.2;0.4 | 1.2, 1.3 | <0.001 |
| FBG; SD (mmol/L) | 4.9; 0.8 | 4.9, 5.1 | 5.2;0.8 | 5.1, 5.3 | <0.001 |

overweight (AOR 1.8, 95% CI: 1.3, 2.9) and AZT based ART (AOR 1.4, 95% CI: 1.3, 2.9) were the identified associated factors for hyperglycemia (Table 4).

Dyslipidemia and hyperglycemia were both present in 14.6% (93/635). In this cohort, 23.9% of the participants were already noted to have dyslipidemia before ART and remained to be dyslipidemic after initiation. Meanwhile, only 2% of the participants were hyperglycemic before ART and remained to be after ART.

Intervention for these metabolic abnormalities is lacking. Initiation of interventions for dyslipidemia were documented in 44.3% (137/309). Lifestyle modification alone was advised in 46.7% (64/137), statins and fibrate use were at 18.9% (26/137) and 6.6% (9/137), respectively. Both lifestyle modification and anti-dyslipidemia medications were started in 27.8% (38/137). For hyperglycemia, initiation of intervention is at 14.1% (14/99). Ten participants were advised lifestyle modification only while 4 were started on OHAs.

**Table 4.** Multivariate analysis of the factors associated with Dyslipidemia and Hyperglycemia pre- and post-ART initiation (N=635)

| Dyslipidemia | | | | | |
|---|---|---|---|---|---|
| **Pre-ART** | | | **Post-ART** | | |
| **Factors** | **AOR (95%CI)** | **p** | **Factors** | **AOR (95%CI)** | **p** |
| Hyperglycemia before ART | 3.8 (2.71, 7.4) | 0.001 | WHO stage 4 | 2.1 (1.3, 3.7) | 0.021 |
| Delay of ART initiation from WB: > 320 days | 1.5 (1.12, 2.31) | 0.032 | Hyperglycemia after ART | 16.1 (6.5, 35.7) | <0.001 |
| ART started before WB diagnosis | 0.3 (0.18, 0.65) | 0.011 | ART duration > 36 months | 8.7 (6.4, 4.2) | <0.001 |
| | | | Latest CD4 count <200 | 0.5 (0.2, 0.8) | 0.005 |
| | | | EFV-based regimen | 2.8 (1.3, 4.4) | <0.001 |
| **Hyperglycemia** | | | | | |
| **Pre-ART** | | | **Post-ART** | | |
| **Factors** | **AOR (95%CI)** | **p** | **Factors** | **AOR (95%CI)** | **p** |
| Dyslipidemia before ART | 3.1 (1.4, 5.8) | 0.001 | Age ≥ 30 | 2.1 (1.7, 3.4) | 0.004 |
| | | | Dyslipidemia after ART | 17.8 (7.6, 36.1) | <0.001 |
| | | | Overweight | 1.8 (1.3, 2.9) | 0.023 |
| | | | AZT-based regimen | 1.4 (1.1, 3.2) | 0.051 |

ART – antiretroviral, OR – odds ratio, AOR – adjusted odds ratio, CD4 – cluster of differentiation 4, WHO – World Health Organization, WB – Western Blot, AZT – zidovudine, EFV – efavirenz

## DISCUSSION

Dyslipidemia and hyperglycemia were evident among Filipino PLHIV. We report a dyslipidemia prevalence of 65% prior to ART exposure. This prevalence is similar to previous studies.[5,6,23] Low HDL-C and the combination of low HDL-C and high TG were the two most common patterns of dyslipidemia observed among ART-naïve individuals and agrees with the patterns observed in prior studies of dyslipidemia among ART naïve regardless of race.[23-27]

Our study showed a high prevalence of patients with high LDL-C level (53%) and a low prevalence of high TC (20.5%). Prior studies showed trends towards lower TC level[24,26-28] but other studies did not show this effect.[29] Conflicting results are also evident on the pattern of LDL-C.[25,30] Previous studies have shown that HIV infection initially affects the TC, followed by other components.[31] One study reported that a low CD4 count increased the odds of dyslipidemia by eleven times.[32] Although low CD4 count did not reach statistical significance in our study, we hypothesize that the risk of dyslipidemia was mitigated by the presence of malnutrition, debilitation, malabsorption, or hepatic dysfunction.[33,34] Our results however, support the association between the progressive decline in HDL-C and the increase in TG level with worsening immunosuppression.[24-28,30]

Our study reports a 10.4% hyperglycemia prevalence before ART initiation. This is higher than the 2.6% prevalence of DM among ART-naïve individuals in an American study but is similar to the 11.7% hyperglycemia prevalence in a study done in Thailand.[35,36] Our result is consistent with literature demonstrating increased rates of IFG and DM among Asians compared to Caucasians adjusting for the same BMI.[37] Among our patients with hyperglycemia, an overwhelming majority (92.4%) met criteria for IFG, consistent with a prior study.[36] These figures are consistent with the pathophysiology of hyperglycemia in PLHIV, where IFG and impaired glucose tolerance (IGT) precede weight loss and progress to the development of DM.[18]

Among those patients diagnosed with both dyslipidemia and hyperglycemia before ART initiation, 28.6% (16/56) fulfilled the criteria for metabolic syndrome. Its manifestation cannot be completely attributed to traditional risk factors for metabolic syndrome, such as age and BMI, and might be complicated by the duration of HIV infection and prolonged immune activation. The co-existence of both dyslipidemia and hyperglycemia in 8.8% of the ART-naïve individuals is a testament to the shared risk factors in the etiogenesis of both diseases. This is strengthened by the fact that dyslipidemia was the only significant risk factor for hyperglycemia after multivariate logistic regression.

It is interesting that our study showed 1.5 times increased odds of developing dyslipidemia with a significant delay in ART initiation (e.g, more than 320 days) from time of HIV diagnosis. On the other hand, high risk patients who were started on ART prior to HIV confirmation, had a 70% decreased risk of developing dyslipidemia when compared to those who were started after the delay in HIV diagnosis. These findings suggest that prolonged, uncontrolled HIV infection itself somehow promotes the dyslipidemic state. This association was not observed for hyperglycemia.

In this study, the proportion of dyslipidemic subjects' post-ART is lower compared to the proportion pre-ART despite an increase in BMI. This finding might be due to the institution of non-pharmacologic and pharmacologic intervention for dyslipidemia before ART and continued post-ART. Although a low number received intervention, they likely helped to correct metabolic abnormalies. In addition, the initiation of ART may have reduced the inflammatory HIV milieu linked to the development of dyslipidemia.

Despite this finding, our data found a greater proportion of subjects fulfilled the criteria for metabolic syndrome

after ART initiation. This supports the combined effect of HIV infection and its treatment to the development of lipid abnormalities (elevated TG and decreased HDL), hyperglycemia and central obesity.[17-19]

In our study, the most common lipid derangements post-ART are elevated TC and LDL-C. Their role as the main driver for the development of metabolic syndrome in our cohort needs further investigation. Dyslipidemia in metabolic syndrome was brought about by increased tumor necrosis factor alpha (TNF-$\alpha$) and interleukin-6 (IL-6), downregulation of tyrosine kinase Ron while insulin resistance (IR) is due to increased soluble urokinase plasminogen activator receptor (suPAR) and adipokine production from adipocytes.[19]

The level of the various lipid parameters and serum glucose level after ART initiation in our cohort was higher compared to a similar cohort on first-line ART.[23] This may be because of inflammation caused by other AIDS defining illnesses and co-infections.[32] After ART exposure, there was an increase in the proportion of dyslipidemic patients with elevated TC (58%) and elevated LDL-C (81%). Though the atherogenic index of plasma (AIP) was not computed in this study, the described lipid profile is recognized as an important risk factor for cardiovascular events.[38]

Patients who were classified under WHO stage 4 had almost a two-fold increased odds of dyslipidemia after ART initiation. This suggests there is greater immune activation among those with co-infections and severe immunosuppression even after ART initiation.[39,40] We found that the persistence of low CD4 count (<200 cells/mm$^3$) after ART exposure had a protective effect against dyslipidemia. This result is consistent with another multi-center study implicating the insufficient duration of ART exposure as the cause of the persistent low CD4 count and the low dyslipidemia risk.[41]

The duration of ART exposure is a well-known risk factor for dyslipidemia.[14] In this cohort, there was an eight-fold increased risk of dyslipidemia with ART exposure of more than 36 months. PIs are classically often linked to metabolic consequences, but this study failed to demonstrate this observation, likely because of the low number of patients on PIs in our cohort. However, this study strengthens the association of dyslipidemia and the use of EFV[3,13,42] which are postulated to affect the process of triglyceride–cholesteryl ester exchange.

The prevalence of hyperglycemia after ART showed a 5.2% increase compared to the pre-ART period. The risk for hyperglycemia exists but the degree of derangement was not as prominent as dyslipidemia.[43] In our study, traditional risk factors such as age ≥30, and weight gain after ART initiation[7,19] were also associated with the development of hyperglycemia. Whether the increase in weight was from improved nutrition or from ART-induced lipodystrophy is unclear. This study showed that being overweight is a risk factor for hyperglycemia, but the association was not observed among the obese due to the small number of patients in that category. This study also validated the association of AZT-based regimen with hyperglycemia.[3] These findings are linked to mitochondrial dysfunction from persistent HIV infection and ART related mitochondrial toxicity that perpetuates the high oxidative stress milieu.[44] Mitochondrial dysfunction affects fatty acid beta-oxidation which in turn causes accumulation of nonmetabolized fatty acids. This is also linked to HIV-associated lipodystrophy syndrome that is characterized by alterations in fat deposition coupled with metabolic complications like dyslipidemia, IR and lactic acidemia.[44] Moreover, chronic immune activation involving monocytes and macrophages contribute to phagocytosis of LDL-C forming foam cells (classical monocytes), secretion of pro-inflammatory cytokines and generate reactive oxygen species (intermediate monocytes) that is associated with occurrence of metabolic complications and disease progression.[45]

In general, lifestyle modification is the recommended initial intervention for the metabolic syndrome. However only 23% of dyslipidemic and 7.2% of hyperglycemic patients in this cohort were advised lifestyle modification. The low application of this recommendation might be due to poor medical chart documentation. In addition, laboratory results may not have been given clinical importance since most patients were relatively young.

Statins in the form of rosuvastatin, pravastatin and atorvastatin were used in only 14% and fibrates in only 3.7% of our study cohort. The low use of hypolipidemic agents might be due to fear of drug-drug interaction with medications (ART, rifampicin), or lack of awareness of guideline recommendations. The decision to start statins should depend on the patient's cardiovascular risk stratification and the benefit of reduction should outweigh the potential side effects and cost of treatment.

Similarly, OHAs were used only in a minority of patients since 90% of hyperglycemic subjects were diagnosed with IFG. IFG is initially managed with lifestyle modification before resorting to OHAs. Metformin is the initial OHA of choice in most patients with IFG or DM, but exercise caution regarding its use among PLHIV due to ART interactions, worsening cachexia, impaired appetite and increased hypoglycemia risk.[29] Insulin, which is recommended for severe DM, was not used in this cohort, but is devoid of ART interactions.[46]

The strengths of this study include an analysis of HIV and non-HIV related risk factors pre- and post-ART and the effect of delayed ART institution. However, the retrospective nature of the study prohibited us from calculating important variables such as waist-hip ratio, measures of visceral adiposity and plasma insulin levels. Other limitations of this study include the lack of documentation of metabolic derangements among those

who died, the scarcity of laboratory data to document diagnosis of dyslipidemia and hyperglycemia prior to HIV diagnosis and the uncertainty that all bloodwork were obtained as fasting.

## CONCLUSION

The prevalence of dyslipidemia and hyperglycemia is high in a relatively young cohort of Filipino PLHIV. However, pharmaceutical and non-pharmaceutical interventions remain to be low. Preventive strategies against these metabolic derangements should be integrated in the healthcare program for HIV. Strategies include early HIV diagnosis and immediate initiation of ART among new cases, frequent and intensive monitoring of these metabolic parameters while on ART, appropriate dietary modifications and prompt initiation of treatment.

The results of this study serve as a call to make INSTI-based ART the first line ART in the country because of fewer effects on these metabolic parameters,. These non-infectious complications should be given equal attention to reduce the burden to the overwhelmed healthcare system brought by the HIV epidemic.

A prospective cohort is recommended to consider changes in important variables like immune activation levels, other anthropometric measurements (waist-hip ratio, visceral adiposity) and inflammatory markers on activated monocytes and its relation to the development of these metabolic abnormalities. Future research should investigate the association of these metabolic derangements and the noted risk factors to the development of cardiovascular outcomes.

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All authors certified fulfillment of ICMJE authorship criteria.

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ORIGINAL ARTICLE

# Profile of Levothyroxine Replacement Therapy in Graves' Disease Patients with Hypothyroidism Post-Radioactive Iodine Ablation: Focus on Different Weight-Based Regimens

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**Abstract**

Objective. To evaluate the status of euthyroidism achieved among Thai patients with post-ablative hypothyroidism and to examine the difference between various weight-based daily levothyroxine (LT4) replacement regimens in these patients.

Methodology. We conducted a retrospective review of Thai patients with Graves' disease (GD) who developed hypothyroidism following radioactive iodine treatment from 2016 to 2020 at Theptarin hospital. Daily LT4 dose was calculated based on actual body weight (ABW), ideal body weight (IBW), and estimated lean body mass (LBM).

Results. We reviewed a total of 271 patient records. Of these, 81.2% were females with a mean age of 40.8±11.7 years, LT4 intake duration of 27.1±14.6 months, and LT4 dose/kg ABW of 1.4±0.5 μg/kg/day. At the final follow-up, 62.4% of patients achieved thyroid-stimulating hormone (TSH) levels within the reference interval, 15.5% had TSH levels over, and 22.1% had TSH levels under the reference range. Obese patients required a lower daily LT4 dose relative to ABW and higher daily LT4 dose relative to IBW to attain euthyroidism (ABW 1.1±0.4 μg/kg/day and IBW 2.0±0.8 μg/kg/day). Estimated daily LT4 dose based on LBM showed a constant dosage of 2.0 μg/kg/day in all BMI categories.

Conclusions. Suboptimum LT4 replacement therapy was found in almost half of hypothyroid patients with GD treated with radioactive iodine. Estimated LBM was a better indicator for dosing calculation in these patients compared with ABW and IBW.

*Key words: post-ablative, hypothyroidism, Graves' disease, in-range TSH, levothyroxine (LT4), lean body mass*

## INTRODUCTION

Hyperthyroid Graves' disease (GD) is managed by antithyroid drugs (ATD), radioactive iodine (RAI) or thyroidectomy. RAI is a favorable alternative in many patients who fail to achieve remission from ATD.[1]

In our institute, one-fifth of all GD patients have been treated with RAI over a period of 35 years.[2] Majority (97.1%) developed hypothyroidism due to prescription of a relatively high single fixed dose of RAI to aim for hypothyroidism.

The complexity and challenges of maintaining biochemical euthyroidism in patients with lifelong levothyroxine (LT4) replacement therapy cannot be underestimated given the narrow therapeutic range of LT4.[3-5] The level of TSH is an indicator for monitoring and adjusting the dose of LT4 therapy. Initial dosing can vary greatly depending on the amount of residual thyroid. Most adult patients with overt hypothyroidism are provided a simple weight-based dose of LT4 at 1.6 μg/kg/day (equivalent to approximately 100–125 μg/day).[6-7] Lower doses of LT4 were suggested from Thai and Singaporean studies, on average 1.1 μg/kg/day.[8-10] After LT4 dose modification, it is recommended to recheck the serum TSH level every 6-8 weeks.[1]

After achieving the optimum dose of LT4, TSH levels should be monitored every 6-12 months. Factors that may affect the dose of LT4 required to maintain euthyroidism include: a reduction in residual thyroid reserve, ageing, obesity, drugs and illnesses.[11-12] Therefore, long-term monitoring is necessary to maintain LT4 replacement therapy. The danger of under-replacement is well recognized but the risks of over-treatment with LT4 (iatrogenic thyrotoxicosis) cannot be overemphasized.[3,13] In patients with low-normal or suppressed serum TSH levels, several studies consistently confirmed an increased risk of atrial fibrillation, osteoporosis, fracture and over-all mortality especially in elderly patients with underlying cardiac conditions.[14-15]

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Initial prescription with estimated weight-based dose of LT4 should be followed by a careful dose adjustment and periodic review of drug timing, adherence and concomitant drugs/illnesses that can affect LT4 absorption.[16]

Previous studies from Western countries showed that up to 40% of patients with hypothyroidism from various causes had abnormal serum TSH levels while on LT4 treatment.[13,17-18] In Thailand, there is a paucity of data on the status of serum TSH levels and practice patterns in patients with post-ablative hypothyroidism. LBM was superior to actual body weight (ABW) as a predictor of weight-based dosage from active LT4 pharmacokinetics in the lean body compartment, not in adipose tissue.[19-21] Using ABW to determine a starting LT4 dose in obese patients could lead to supra-therapeutic doses.[22] Ideal body weight (IBW) using the Devine formula which is calculated based on height was also studied as an alternative dosing regimen.[23] However, further validations are warranted to apply estimated LBM or IBW dosing regimens in hypothyroid patients with post-ablative hypothyroidism from RAI ablation.

## OBJECTIVES

The main objective of our study was to evaluate the status of achieved euthyroidism among Thai GD patients with post-ablative hypothyroidism. It also aimed to evaluate the difference between various weight-based daily LT4 regimens (ABW, LBM, and IBW) according to body mass index (BMI) in patients with euthyroidism.

## METHODOLOGY

This was a retrospective study of RAI-treated hyperthyroid GD patients in Theptarin Hospital, Bangkok, Thailand from 2016 to 2020. Patients aged 15 years and above with primary hypothyroidism from RAI ablation were studied. Patients with transient hypothyroidism from RAI, repeated RAI treatment due to relapsed GD, pregnant women and lactating mothers, major illnesses which could affect LT4 absorption, changes in body weight ≥ 15% in the previous 6 months, and those receiving LT4 therapy less than 6 months were excluded from the study.

In our hospital, a fixed dose of RAI (10-30 mCi) based on estimated thyroid size was prescribed individually to aim for hypothyroidism.[2] In Thailand, there are two brands of LT4 medication available (Eltroxin®, GlaxoSmithKline, United Kingdom and Euthyrox®, Merck, Germany). Euthyrox® is available in 50 μg and 100 μg tablets. No generic drug of LT4 was used in our hospital during the study period. Serum TSH concentrations were measured by electro-chemiluminescent immunoassays (Roche Diagnostics, Indianapolis, USA) with a reference range of 0.3 to 4.2 mIU/L.

Serum TSH levels at the last follow-up visit were retrieved and classified as in-range if a serum TSH value was within the reference range of 0.3-4.2 mIU/L. The out-of-range TSH group was further divided as over-treatment if the serum TSH level was < 0.3 mIU/L and under-treatment if the serum TSH level was > 4.2 mIU/L. Self-reported compliance with LT4 therapy was retrieved from medical records and categorized into three groups: missed <5% dose in the last 1 month; missed ≥5% to <15% dose in the last 1 month; and missed ≥15% in the last 1 month. Patterns of LT4 prescription were also collected and categorized as daily dose, alternate day dose, or segmented weekend dose.

BMI was calculated by dividing weight in kilograms by height in meters squared. LBM was calculated based on ABW, height, and gender using the Hume formula[24] and IBW was calculated based on height using the Devine formula (Supplement Table 1).[25] The LT4 dose requirement was calculated as μg per kilogram ABW, LBM and IBW per day. This study was approved by the Institutional Review Board committee of Theptarin Hospital (EC No.02-2021).

### Statistical analyses

Continuous variables were summarized as mean ± standard deviation (SD) or median (interquartile range, IQR) while categorical variables were summarized using counts and percentages. The t-test or analysis of variance was applied to compare differences in means among groups. The Chi-squared test was used to compare differences in percentages between groups. Univariate analysis of variance (ANOVA) was performed to test for differences among demographic parameters in patients with optimal serum TSH levels, patients with over-treatment, and patients with under-treatment. The post-hoc analysis was performed using the Dunnett test. A p-value of <0.05 was considered statistically significant. All analyses were conducted using SPSS Statistical Package, version 20 (IBM Corp., Armonk, NY, USA).

## RESULTS

A total of 418 charts were reviewed and 271 patients met the inclusion criteria (Figure 1). The baseline demographic data and patterns of LT4 prescription are presented in Table 1. In the cohort, the mean age was 40.8 ±11.7 years (8.5% were ≥ 60 years of age); females comprised 81.2%; the mean BW was 60.9±12.6 kgs, the mean BMI was 24.4±4.2 kg/m$^2$ and the mean duration of LT4 treatment was 27.1 ± 14.6 months. The mean weekly LT4 dose was 620±222 μg/week. The mean daily LT4 dose/kg of ABW was 1.4±0.5 μg/kg/day; mean daily LT4 dose/kg of LBM was 2.0±0.7 μg/kg/day; and the mean daily LT4 dose/kg of IBW was 1.6±0.6 μg/kg/day. Three percent (3.3%) of all patients report missing LT4 dose ≥15% of LT4 in the last month.

Only 62.4% of the patients achieved normal serum TSH range at the last follow-up. Serum TSH levels were above the reference range (TSH > 4.2 mIU/L) in 15.5% and were under the reference range (TSH < 0.3 mIU/L) in 22.1%. The detailed distribution of thyroid status at the last visit

**Table 1.** Baseline characteristics of the study population

| Characteristics | Total (n = 271) | Optimal-treated group (n = 169) | Over-treated group (n = 60) | Under-treated group (n = 42) | *p*-value |
|---|---|---|---|---|---|
| Present age (years) | 40.8 ± 11.7 | 41.4 ± 11.7 | 39.5 ± 12.7 | 40.1 ± 10.4 | 0.527 |
| < 40 years | 52.0% | 51.6% | 51.7% | 54.8% | 0.994 |
| 40–59 years | 39.5% | 39.6% | 40.0% | 38.1% | |
| ≥ 60 years | 8.5% | 8.9% | 8.3% | 7.1% | |
| Gender | | | | | **0.046** |
| Male | 18.8% | 14.8% | 21.7% | 31.0% | |
| Female | 81.2% | 85.2% | 78.3% | 69.0% | |
| Body weight (kg) | 60.9 ± 12.6 | 60.0 ± 11.4 | 59.9 ± 12.9 | 66.3 ± 15.4 | **0.010** |
| Body mass index (kg/m$^2$) | 24.2 ± 4.2 | 24.3 ± 4.1 | 23.8 ± 3.9 | 25.6 ± 4.7 | 0.092 |
| < 18.5 | 3.0% | 3.6% | 3.3% | 0 % | 0.087 |
| 18.5 – 24.9 | 57.9% | 57.4% | 70.0% | 42.8 % | |
| 25.0 – 29.9 | 29.5% | 30.1% | 20.0% | 40.5 % | |
| ≥ 30.0 | 9.6% | 8.9% | 6.7% | 16.7 % | |
| Ideal Body Weight (kg) | 54.7 ± 8.2 | 54.3 ± 7.9 | 54.0 ± 8.7 | 57.3 ± 8.3 | 0.073 |
| Lean Body Mass (kg) | 42.7 ± 6.8 | 42.1 ± 6.2 | 42.0 ± 7.2 | 45.6 ± 8.0 | **0.009** |
| Duration of GD Before RAI (Months) | 45.7 ± 63.6 | 45.3 ± 60.4 | 54.2 ± 72.7 | 35.3 ± 62.2 | 0.335 |
| Dose of Radioactive Iodine (mCi) | 19.0 ± 5.8 | 18.8 ± 5.9 | 19.1 ± 5.5 | 19.5 ± 6.0 | 0.825 |
| Duration of Hypothyroidism before the start of LT4 therapy (months) | 1.4 ± 2.0 | 1.3 ± 1.5 | 1.8 ± 3.3 | 1.1 ± 1.0 | 0.140 |
| Nadir TSH before the start of LT4 therapy (uIU/mL) | 38.4 ± 34.2 | 34.7 ± 30.2 | 46.8 ± 40.7 | 40.4 ± 36.4 | 0.070 |
| Patterns of LT4 intake (%) | | | | | **0.038** |
| Same dose daily | 43.5% | 42.6% | 35.0% | 59.5% | |
| Alternate day dose | 14.1% | 14.8% | 10.0% | 16.7% | |
| Segmented weekend | 42.4% | 42.6% | 55.0% | 23.8% | |
| LT4 dosage (mcg/kg of ABW) | 1.4 ± 0.5 | 1.4 ± 0.4 | 1.4 ± 0.5 | 1.6 ± 0.5 | **0.045** |
| LT4 dosage (mcg/kg of IBW) | 1.6 ± 0.6 | 1.6 ± 0.5 | 1.5 ± 0.5 | 1.9 ± 0.6 | **0.004** |
| LT4 dosage (mcg/kg of LBM) | 2.0 ± 0.7 | 2.0 ± 0.6 | 1.9 ± 0.7 | 2.3 ± 0.7 | **0.010** |
| LT4 dosage per week (mcg) | 620.1 ± 221.6 | 605.9 ± 207.9 | 567.5 ± 185.1 | 752.4 ± 272.8 | **<0.001** |
| Duration of LT4 (months) | 27.1 ± 14.6 | 28.3 ± 14.8 | 25.7 ± 13.1 | 24.1 ± 15.1 | 0.165 |
| LT4 compliance | | | | | **<0.001** |
| Missed < 5% | 81.2% | 83.4% | 81.7% | 71.4% | |
| Missed 5-14 % | 15.5% | 15.4% | 16.7% | 14.3% | |
| Missed ≥ 15 % | 3.3% | 1.2% | 1.6% | 14.3% | |

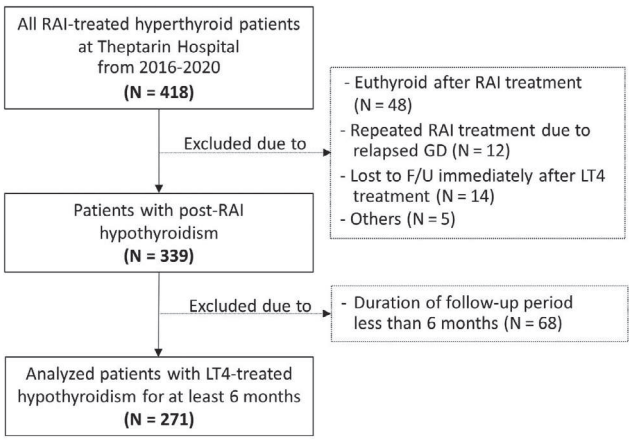


**Figure 1.** Flow diagram of patients in the present study.

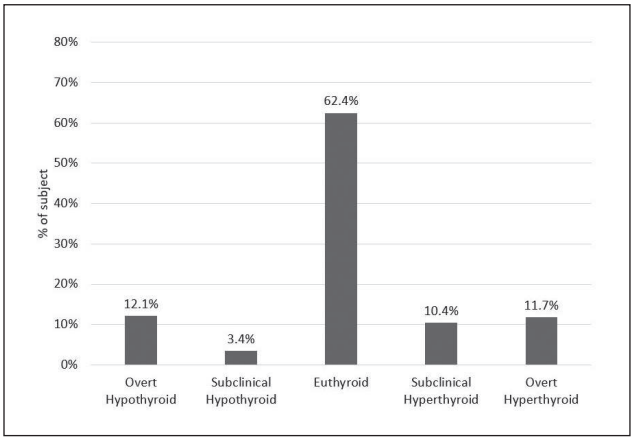


**Figure 2.** Thyroid status of studied patients at the last visit.

is summarized in Figure 2. The median serum TSH level in patients with optimal treatment was 1.45 mIU/L (0.79, 2.41), in the undertreated it was 7.02 mIU/L (5.43, 12.68), while in the overtreated it was 0.09 mIU/L (0.03, 0.19).

As shown in Table 1, 81.2% of patients adhered to their daily LT4 treatment in the last month. Regarding patterns of LT4 prescription, 43.5% were on the same daily LT4 dosing regimen; 42.4% were on the segmented weekend dosing regimen; while 14.1% were on the alternate daily dosing regimen. There was no statistical significance found between patterns of LT4 prescription and in-range serum TSH levels.

In the post-hoc analysis, the undertreated group was found to have a significantly lower actual body weight compared with the optimally-treated group ($p = 0.007$). Moreover, the undertreated group had a higher daily LT4 dose compared

**Table 2.** Baseline characteristics grouped by body mass index (BMI) in participants who achieved euthyroidism after LT4 replacement

| Characteristics | Body mass index (kg/m²) | | | | |
|---|---|---|---|---|---|
| | < 18.5 (n = 6) | 18.5 – 24.9 (n = 97) | 25.0 – 29.9 (n = 51) | ≥ 30.0 (n = 15) | *p*-value |
| Present age (years) | 31.2 ± 3.5 | 41.1 ± 11.1 | 43.1 ± 12.2 | 41.1 ± 14.6 | 0.010 |
| Gender | | | | | 0.606 |
| Male | 0.0% | 13.4% | 17.6% | 20.0% | |
| Female | 100.0% | 86.6% | 82.4% | 80.0% | |
| Body weight (kg) | 46.1 ± 3.9 | 54.9 ± 7.5 | 66.3 ± 9.2 | 76.7 ± 13.1 | <0.001 |
| Ideal Body Weight (kg) | 52.4 ± 6.8 | 54.3 ± 7.8 | 54.7 ± 8.4 | 53.8 ± 7.1 | 0.660 |
| Lean Body Mass (kg) | 37.1 ± 4.1 | 40.6 ± 5.4 | 44.2 ± 6.3 | 47.0 ± 6.7 | <0.001 |
| Duration of GD Before RAI (Months) | 17.0 ± 15.1 | 47.7 ± 67.1 | 46.1 ± 51.1 | 38.4 ± 55.1 | 0.624 |
| Dose of Radioactive Iodine (mCi) | 18.3 ± 2.6 | 18.6 ± 5.9 | 19.0 ± 6.1 | 19.7 ± 6.9 | 0.790 |
| Duration of Hypothyroidism before the start of LT4 therapy (months) | 0.8 ± 0.8 | 1.4 ± 1.6 | 1.2 ± 1.4 | 0.9 ± 1.0 | 0.211 |
| Nadir TSH before the start of LT4 therapy (uIU/mL) | 37.4 ± 32.1 | 31.4 ± 27.9 | 40.8 ± 34.4 | 35.9 ± 30.3 | 0.876 |
| Patterns of LT4 intake (%) | | | | | 0.800 |
| Same dose daily | 50.0% | 39.2% | 45.1% | 53.3% | |
| Alternate day dose | 0.0% | 14.4% | 17.6% | 13.4% | |
| Segmented weekend | 50.0% | 46.4% | 37.3% | 33.3% | |
| LT4 dosage (mcg/kg of ABW) | 1.8 ± 0.2 | 1.4 ± 0.3 | 1.3 ± 0.5 | 1.2 ± 0.5 | 0.002 |
| LT4 dosage (mcg/kg of IBW) | 1.6 ± 0.2 | 1.5 ± 0.3 | 1.7 ± 0.7 | 2.0 ± 0.8 | <0.001 |
| LT4 dosage (mcg/kg of LBM) | 2.2 ± 0.3 | 2.0 ± 0.4 | 2.0 ± 0.8 | 2.1 ± 0.9 | 0.397 |
| LT4 dosage per week (mcg) | 575.0 ± 74.2 | 572.6 ± 140.7 | 636.9 ± 271.2 | 728.3 ± 300.7 | <0.001 |
| Duration of LT4 (months) | 35.8 ± 18.7 | 29.6 ± 14.4 | 25.9 ± 15.6 | 25.6 ± 11.9 | 0.093 |

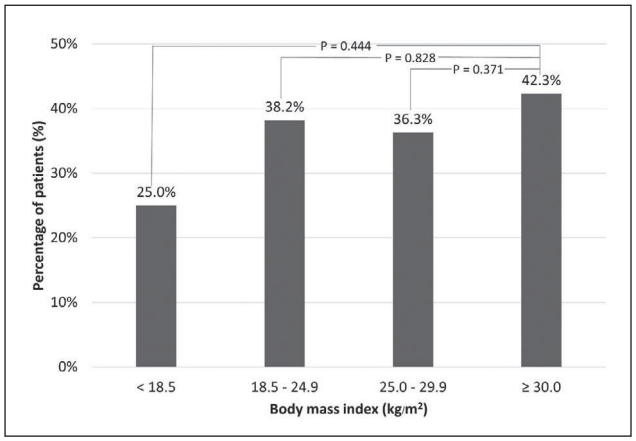


**Figure 3.** Percentage of out-of-reference range serum TSH values at the last visit in different BMI categories.

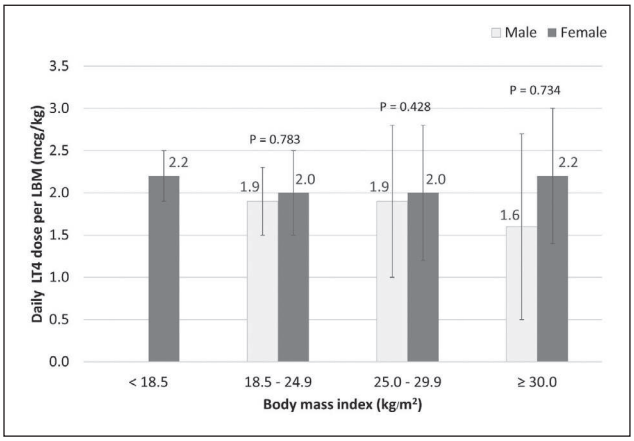


**Figure 4.** Comparison of gender differences in daily LT4 dose requirement based on lean body mass (LBM), stratified by BMI category.

with the optimally-treated group ($p < 0.05$) regardless of the weight-based regimen. The number of patients who missed LT4 ≥ 15% in the last month was also found to be higher in the undertreated compared with the optimally-treated group (14.3% vs. 1.2%, $p = 0.011$).

The comparisons of the percentages of patients with TSH levels out-of-reference range between BMI ≥30 kg/m² versus BMI 25-29.9 kg/m², BMI ≥30 kg/m² versus BMI 18.5-24.9 kg/m², and BMI ≥30 kg/m² versus BMI <18.5 kg/m² are shown in Figure 3. There was no statistically significant difference between percentages of serum TSH out of reference range between the two BMI categories. In obese patients with BMI ≥ 30 kg/m², 26.9% had TSH levels under the reference range while 15.4% had TSH levels lower than the reference range.

To determine the appropriate LT4 dosage in relation to the various categories of BMI, a subgroup analysis in patients with in-range serum TSH levels was performed (Table 2). Obese patients with BMI of ≥ 30 kg/m² had significantly lower daily LT4 dose per ABW and IBW but not per LBM compared with the other BMI categories ($p < 0.05$). Patients who were more obese had lower daily LT4 dose with the LT4 dosing strategy based on ABW. All patients with BMI ≥18.5 kg/m² ($p = 0.815$) had a constant daily dose of 2.0-2.2 μg/kg with the daily LT4 dosing strategy based on LBM. In contrast, obese patients required a higher daily LT4 dose with the LT4 dosing strategy based on IBW compared with lower BMI categories ($p < 0.05$). We found no gender difference in LT4 dose requirement based on LBM in each of the BMI stratum (Figure 4).

## DISCUSSION

While LT4 replacement therapy seems to be straightforward, its optimal use can be challenging. As LT4 is usually administered over a patient's lifetime, physicians need to understand the various factors that can affect LT4 dose and absorption. Apart from this, they will have to meticulously titrate the patient's LT4 dose to prevent adverse effects of suboptimum therapy. In this study, almost 40% of patients with RAI-treated hypothyroidism had suboptimum LT4 replacement. For initial dose estimation, lean body mass might be a better indicator for weight-based calculation in obese patients. No baseline parameter was found to be associated with in-range or out-of-range serum TSH levels. It is interesting that the percentage of over-replaced LT4 patients was greater than the percentage of under-replaced patients.

The main determining factors of LT4 requirement are the etiology of hypothyroidism, age, gender, body weight, and lean body mass.[3,5] Generally, hypothyroidism due to Hashimoto's thyroiditis or post-ablative treatment of GD require lower doses of LT4 compared to patients who completely lack thyroid tissue following total thyroidectomy. Unfortunately, most previous studies on dosing strategies did not specify the cause of hypothyroidism or selected only post-thyroidectomy patients. The optimal daily LT4 dose was suggested to be 1.5-1.8 μg/kg/day.[6] In 2005, the seminal study from Italy found that LBM was a better predictor of the daily LT4 requirement than total body weight in thyroid cancer patients who underwent thyroidectomy and RAI remnant ablation.[20]

The concept of LBM as a predictor of drug dosage has been studied much earlier where dual energy x-ray absorptiometry precisely evaluated body composition.[19] Recently, a study among Thai patients with various causes of hypothyroidism also demonstrated the usefulness of estimated LBM as calculated by the Hume formula in obese patients.[10] The daily LT4 dose of 2.3 μg/kg of LBM/day was suggested to shorten the time required to attain a stable LT4 dose. Our present study is aligned with this earlier one, but we provide more accurate dosing in GD patients with post-ablative hypothyroidism. Our study showed that a daily LT4 dose of 2.0 μg/kg of LBM/day achieved euthyroidism in patients with BMI of 18.5-29.9 kg/m$^2$. This dosage corresponded to a daily LT4 dose of 1.4 μg/kg of ABW, differing from the results of a previous study from Singapore (1.1 μg/kg of ABW)[9] and a previous European study (1.6 μg/kg of ABW).[7]

In many countries including Thailand, the limited available LT4 preparations pose a challenge to meticulous LT4 titration. Sophisticated regimens (alternate dosage or segmented weekend method) could be used in some patients but exercise caution with elderly patients or in those with polypharmacy. Moreover, both intrinsic and extrinsic factors which could affect LT4 dosage should be thoroughly reviewed before dose adjustment.

When prescribing initial LT4 replacement therapy, calculate BMI and LBM to guide the dose. In patients with BMI ≥ 25 kg/m$^2$, LBM is a better gauge to calculate daily LT4 dose than ABW or IBW. In patients requiring unusually high LT4 doses, investigate other factors apart from compliance and concomitant medications, including gastrointestinal tract malabsorption, concomitant food and drink, and *Helicobacter pylori* infection.[26-28]

LT4 dose requirements decrease with age due to decreased LBM, thus, elderly patients are specially vulnerable to adverse events from over-treatment.[29] Periodic monitoring is recommended in this particular age group with the aim of maintaining the serum TSH levels at the upper end of the reference range.

Our study had several limitations. First, the retrospective nature of data collection has inherent weaknesses. Several relevant data were missing from the medical records, including concomitant food and drink, over-the-counter medications, menstrual status and undocumented chronic illnesses. Second, self-reported compliance could not be ascertained by more objective medication adherence assessment such as electronic pill counter or validated questionnaire. Third, only the latest serum TSH levels were used as a marker for euthyroidism. This might not reflect the dynamic process of clinical practices to adjust LT4 dose based on serum TSH levels. However, our study selected the patients who received LT4 for at least 6 months after the initiation of LT4 replacement therapy and the duration of LT4 treatment was over 2 years. Also, our hospital provides only branded LT4 drugs to avoid the variable bioavailability of generic LT4 drugs.[30] Finally, estimated LBM was calculated using the Hume formula, which was introduced over 50 years before sophisticated imaging was available to analyze body composition.[24]

In conclusion, suboptimum LT4 replacement therapy was common in GD patients with post-ablative hypothyroidism. Our study showed that over-treatment of LT4 was more common than under-treatment. Estimated LBM was a better gauge to calculate doses compared with ABW and IBW. The complexity of maintaining biochemical and clinical euthyroidism in LT4-treated hypothyroid patients warrants more attention to dose adjustments, especially in populations at-risk for optimum therapy.

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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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## SUPPLEMENT TABLE 1

Lean body mass (LBM) was calculated based on actual body weight (ABW), height, and gender using the Hume formula[1]:

### Hume formula

Lean body mass (male) = ( (0.32810×BW,kg) + (0.33929×height,cm) ) – 29.5336
Lean body mass (female) = ( (0.29569×BW,kg) + (0.41813×height,cm) ) – 43.2933

Ideal body weight (IBW) was calculated based on height using the Devine formula[2]:

### Devine formula

Ideal BW (male) = 50.0kg + 0.9(height,cm – 152)kg
Ideal BW (female) = 45.5kg + 0.9(height,cm – 152)kg

### Sample cases

Female 40 yrs, height 160 cm, actual body weight 55 kg
Female 40 yrs, height 160 cm, actual body weight 65 kg
Female 40 yrs, height 160 cm, actual body weight 75 kg

| No. of Subject | Actual body weight (ABW) | Ideal body weight (IBW) | Lean body mass (LBM) |
|---|---|---|---|
| 1. | 55.0 | 52.7 | 39.9 |
| 2. | 65.0 | 52.7 | 42.8 |
| 3. | 75.0 | 52.7 | 45.8 |

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REVIEW ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

# Review of Literature on *Akkermansia muciniphila* and its Possible Role in the Etiopathogenesis and Therapy of Type 2 Diabetes Mellitus

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**Abstract**

*Akkermansia muciniphila* is a promising gut microbiota for the treatment of type 2 diabetes mellitus (T2DM). *A. muciniphila* stimulates intestinal wall integrity, is an anti-inflammatory agent, and reduces endoplasmic reticulum stress, lipogenesis and gluconeogenesis. These properties make *A. muciniphila* a potential treatment option for T2DM by reducing insulin resistance and increasing insulin sensitivity and glucose tolerance in different tissues. This article explores the possible role of *A. muciniphila* in T2DM management, along with the various methods known to modulate *A. muciniphila*.

*Key words: Akkermansia muciniphila, ER stress, gut microbiota, insulin resistance, probiotic, type 2 diabetes mellitus*

## INTRODUCTION

The complex etiopathogenesis of type 2 diabetes mellitus (T2DM) includes dysbiosis or the imbalance of gut microbiota composition as a contributory factor.[1] Dysbiosis may induce systemic low-grade inflammation which leads to insulin resistance.[2] An important gut microbiota in T2DM is *Akkermansia muciniphila* (*A. muciniphila),* a butyrate-producing microbiota which stimulates the secretion of incretin hormones, glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2) and peptide YY (PYY). Incretins stimulate insulin secretion from pancreatic beta cells.[3] Furthermore, *A. muciniphila* improves intestinal wall integrity and reduces endoplasmic reticulum (ER) stress, lipogenesis and gluconeogenesis.[4]

Management of T2DM currently focuses on controlling the symptoms and preventing complications through lifestyle intervention and administration of antidiabetic drugs. The modulation of *A. muciniphila* is a simple and potentially disease-modifying treatment of T2DM. This literature review will discuss the role of *A. muciniphila* in the treatment of T2DM to date and its prospects in the future.

## METHODOLOGY

We searched PubMed, Cochrane Database, Science Direct, and Google Scholar for relevant studies about *A. muciniphila* and T2DM that were published in English between the 2nd up to the 23rd of April 2020. The keywords included "*Akkermansia muciniphila*" AND "type 2 diabetes mellitus" OR "obese" OR "insulin resistance." Titles and abstracts were screened to avoid duplication, and reviews of the complete manuscripts were done to determine the appropriateness of the studies to be included. Additionally, the reference lists of the selected articles were reviewed to identify other relevant articles. Selected studies have met the inclusion and exclusion criteria of the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework. We included studies involving subjects with T2DM or metabolic syndrome who received intervention to increase *A. muciniphila* or improve metabolic parameters in comparison to a control group. The outcomes considered were the measured levels of *A. muciniphila* and/or improvement in other metabolic parameters. We excluded non-English-language studies, unavailable full texts, case reports and letters for this review article. Ultimately, 42 studies were included as references in the synthesis of this review article, and 9 were used for the methods of modulation of *A. muciniphila*.

### Gut microbiota and type 2 diabetes mellitus

T2DM is a multifactorial metabolic disease characterized by hyperglycemia. The factors that cause hyperglycemia are the egregious eleven, namely: pancreatic beta-cells failure to produce insulin; increased pancreatic alpha cell glucagon secretion; increased liver gluconeogenesis; impaired insulin action in skeletal muscles; increased lipolysis and free fatty acids from adipose tissue; intestinal GLP-1 deficiency; decreased gastric production of amylin; increased kidney reabsorption of glucose through sodium-glucose contransporters-2 (SGLT-2); low-grade systemic inflammation; neural stimulation to increase appetite due

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to high levels of insulin and changes in the composition of the gut microbiota.[2]

Alterations of the gut microbiota induce inflammation and play an important role in the complex pathogenesis of T2DM. Gut microbiota promote fermentation of undigested carbohydrates, stimulate insulin secretion, inhibit gluconeogenesis, increase insulin sensitivity and have anti-inflammatory effects. Gut microbiota convert undigested carbohydrates into short-chain fatty acids (SCFA),[5] metabolites which stimulate intestinal L cells to secrete incretin hormones (GLP-1, GLP-2 and PYY) that trigger pancreatic beta-cells to release insulin.[6] Dysbiosis decreases intestinal wall integrity and induces systemic low-grade inflammation. This metabolic endotoxemia state is precipitated by the dependent attachment of lipopolysaccharide (LPS) to the CD14 / toll-like receptor (TLR) 4 complex on the surface of intestinal cells leading to inflammation and subsequent insulin resistance.[7-9]

### *Akkermansia muciniphila*

*A. muciniphila* belongs to the *Verrucomicrobia* (phylum), *Verrucomicrobiae* (class), *Verrucomicrobiales* (order), *Verrucomicrobiacaea* (family), dan *Akkermansia* (genus) and is a microbiome that is abundant in the human intestine. It makes up 3% of the entire gut microbiota colony and is a butyrate-producing bacteria.[10] Derrien et al. discovered *A. muciniphila* in 2004 and it has since become a popular research field because of its potential as a probiotic.[11] It ferments mucin as a source of carbon, energy, and nitrogen, then releases sulfate after the mucin fermentation is complete.

*A. muciniphila* colonizes the mucosal lining of the intestine,[4] and various studies have shown that the amount of *A. muciniphila* in the intestines of healthy people is significantly greater than those who have diabetes and obesity.[12,13] Another study by Schneeberger et al. in 2015 also found an inversely proportional relationship between the number of *A. muciniphila* and body weight, inflammation and the metabolic syndrome.[14]

### The role of *Akkermansia muciniphila* in type 2 diabetes mellitus

*A. muciniphila* has a role in the pathogenesis of T2DM through several mechanisms (Figure 1). An increase in the number of bacterial colonies improves the integrity of the intestinal wall by colonizing the mucus layer of the cell surface and protects the cells from LPS, which attaches itself independently. The amount of *A. muciniphila* in the intestine also depends on the amount mucin – their energy source – present. In addition, the administration of *A. muciniphila* also enhances the expression of regenerating islet-derived protein (Reg3γ), a peptide that stimulates aggregation between microbiota in the intestinal epithelium.[15]

*A. muciniphila* improves insulin sensitivity and glucose tolerance through its anti-inflammatory mechanisms. The inflammatory process begins with the entry of LPS into the intestinal cell mucosa as an endotoxin, which then attaches to the lipopolysaccharide binding protein (LBP) which initiates activation of nuclear factor-KB (NF-KB) and Jun N-terminal Kinase (JNK).[16] *A. muciniphila* can reduce the amount of phosphor-JNK significantly and increases the NF-KB inhibitor protein and IKBA protein levels in the liver, indicating that the inactivation of the NFKB and JNK pathways results in an anti-inflammatory reaction. This is supported by an increase in the concentration of both α-tocopherol (an essential antioxidant and anti-inflammatory factor),[17] and β-sitosterol, which maintain

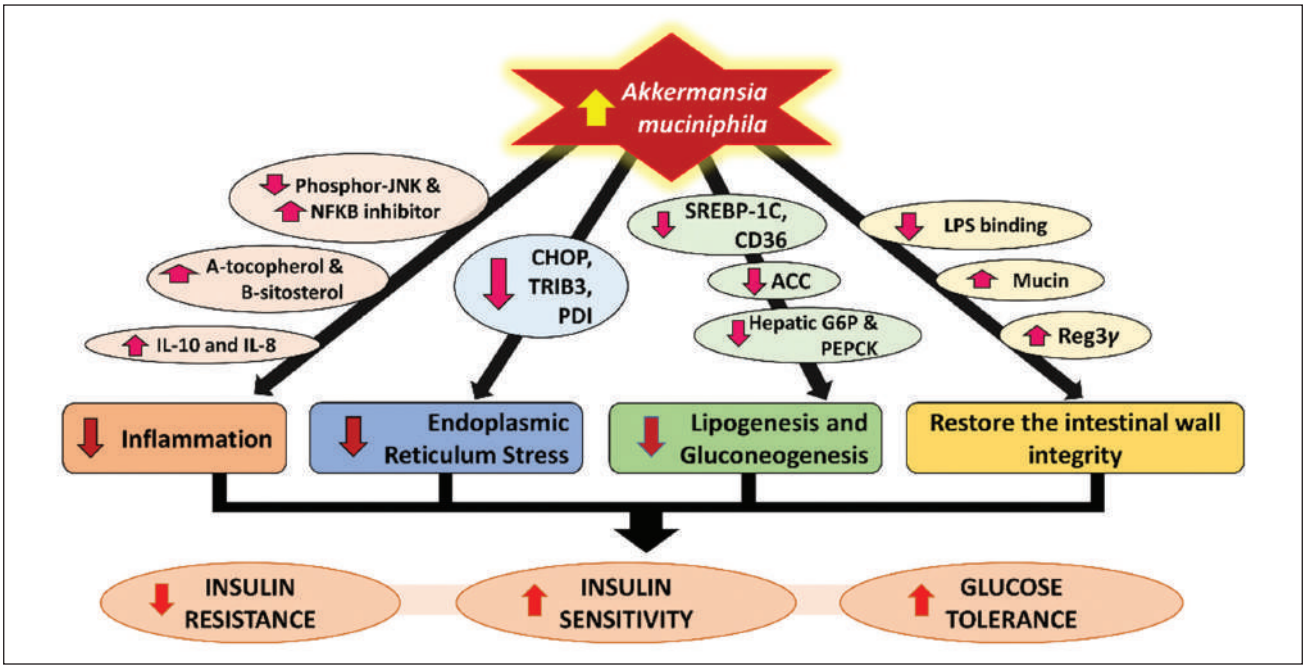


**Figure 1.** The role of *Akkermansia muciniphila* in type 2 diabetes mellitus.

the immune system and provide anti-inflammatory activity in the intestinal endothelial cells.[18] *A. muciniphila* also induces the release of anti-inflammatory cytokines, namely IL-10 and IL-8.[19]

The improvement in glucose tolerance is due to decreased lipotoxicity and ER stress. *A. muciniphila* reduces unfolded protein levels inside the cell – a marker of ER stress – such as immunoglobulin heavy chain-binding protein / glucose-regulated protein 78 (BiP / GRP78) and PKR-like ER kinase (PERK) in the liver and skeletal muscle. In addition, *A. muciniphila* decreases genes contributing to the ER stress process, namely, a decrease in the concentration of mRNA C / *EBP homologous protein* (CHOP) and *tribbles homolog 3* (TRB3) in the large intestine, and a decrease in mRNA of *protein disulfide isomerase* (PDI) in the jejunum. These genes activate the unfolded protein response, which triggers ER stress.[20] This mechanism suggests that *A. muciniphila* can reduce ER stress and interfere with the genetic process.

*A. muciniphila* also plays a role in the process of lipogenesis and gluconeogenesis. *A. muciniphila* supplementation significantly reduces the expression of genes that participate in lipogenesis, namely *sterol regulatory element-binding proteins* (SREBP1c) and *fatty acid translocase* (CD36) in the liver and muscles. A 2015 *in vivo* study by Schneeberger et al., found a low amount of *acetyl-CoA carboxylase* (ACCase) in muscle after *A. muciniphila* supplementation.[14] ACCase is an enzyme needed to form *malonyl-CoA* from acetyl-CoA as a substrate for fatty acid biosynthesis. The decrease in the amount of ACCase indicates that *A. muciniphila* decreases fat deposition in hepatic tissue and muscle, thereby increasing insulin sensitivity.[8]

In gluconeogenesis, *A. muciniphila* supplementation is known to deplete visceral fat mass and increase glucose tolerance based on an intraperitoneal glucose tolerance test (IPGTT). Its administration induces a rise in phosphorus AKT Ser473 in the liver and muscles a marker of increased insulin sensitivity in these tissues. *A. muciniphila* also depresses the expression of gluconeogenic enzymes hepatic glucose-6-phosphatase (G6P) and phosphoenolpyruvate carboxykinase (PEPCK). Normally, these enzymes are suppressed by insulin. A decrease in their levels indicates improved hepatic insulin sensitivity.[21]

## Current insights on *Akkermansia muciniphila* modulation as a therapeutic innovation for type 2 diabetes mellitus

The modulation of *A. muciniphila* can be done through several methods such as direct administration as a probiotic, administration of prebiotics and by other interventions like administration of metformin and through bariatric surgery (Table 1).

### Direct administration of probiotic *Akkermansia muciniphila*

*A. muciniphila* can be administered directly but the dose and viability of the bacteria require further investigation. The effective dose of *A. muciniphila* in humans is unknown,

**Table 1.** Modulation of intestinal *Akkermansia muciniphila*

| Author (year) | Intervention | Subjects | Findings | Ref |
|---|---|---|---|---|
| ***In vitro*** | | | | |
| Marcial-Coba et al. (2019) | Microencapsulation in xanthan and gellan gum matrix. Stored aerobically or anaerobically for 1 month at 4 °C or 25 °C. | *A. muciniphila* DSM22959 and *Lactobacillus plantarum subsp. plantarum* ATCC14917 as the comparator | Cryoprotectant solutions improved the survival of both strains (survival rate 64–76%; p < 0.001). Survivability of *A. muciniphila* was significantly better when stored anaerobically at 4 °C. | 22 |
| ***In vivo*** | | | | |
| Everard et al. (2011) | Prebiotic administration; oligofructose (0.3 g/mouse/day) for 5 weeks. | High-fat diet-induced obese mice | Increased in the abundance of *Akkermansia muciniphila* by ~100 fold. | 25 |
| Roopchand et al. (2015) | Grape polyphenols administration for 13 weeks | High-fat diet-induced obese mice | Increased in the abundance of *Akkermansia muciniphila*. (cecal sample: 6.2 ± 4.6% on control group, versus 49.1 ± 2.0% on intervention group; Fecal sample: 7.5 ± 4.7% on control group, versus 54.8 ± 2.5% on intervention group. | 26 |
| Tu et al. (2018) | Dietary black raspberry (*Rubus occidentalis*, BRB) for 7 weeks | Normal and specific-pathogen free C57BL/6 mice | *A. muciniphila* population increased by 157-fold in the intervention group compared to control group | 27 |
| Shin et al. (2014) | 300 mg/kg/day of metformin treatment by oral gavage for 6 weeks | Diet-induced obese mice (C57BL/6 mice, fed either a normal-chow diet or a high-fat diet) | Metformin treatment significantly improved the glycaemic profile of HFD-fed mice and increased the number of mucin-producing goblet cells (p<0.0001) | 30 |
| **Clinical** | | | | |
| Depommier et al. (2019) | Daily oral supplementation of $10^{10}$ *A. muciniphila* bacteria either live or pasteurized for three months. | Overweight/obese insulin-resistant volunteers | Pasteurized *A. muciniphila* improved insulin sensitivity (p = 0.002), reduced insulinemia (p = 0.006) and plasma total cholesterol (p = 0.02); slightly decreased body weight (p = 0.091), fat mass (p = 0.092) and hip circumference (p = 0.091) compared to placebo group | 24 |
| de la Cuesta-Zuluaga et al. (2016) | Metformin treatment | 459 participants (28 with diabetes, 14 taking Metformin, and 84 participants without diabetes) | Participants with metformin-taking diabetes had higher relative abundance of *Akkermansia muciniphila* compared with those without diabetes (p = 0.003, q value = 0.01) | 31 |
| Murphy et al. (2016) | RYGB compared to SG | 14 obese T2DM patients underwent laparoscopic SG (n = 7) or RYGB (n = 7) | RYGB resulted in increased *Firmicutes* and *Actinobacteria* phyla but decreased *Bacteroidetes* phyla. SG resulted in increased *Bacteroidetes* phyla. | 33 |
| Dao et al. (2019) | RYGB compared to GB | 65 women with severe obesity | A significant increase in *A. muciniphila* relative abundance after RYGB, but not correlated with metabolic improvement. | 37 |

Abbreviation: GB, gastric binding; GIT, gastrointestinal tract; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy

but the standard dose of probiotics is in the range $10^9$ to $10^{11}$ colony-forming units (CFU).[22]

One alternative to safely and effectively deliver *A. muciniphila* to the intestine is by microencapsulation.[23] An *in vitro* study simulated the administration of microencapsulated *A. muciniphila* through the digestive tract and showed its viability was reduced 2.01 log CFU $ml^{-1}$ under fasting conditions (pH 2) and by 0.3 log CFU $ml^{-1}$ at post-meal conditions (pH 4) with a survival rate of 0.97% and 49.76%, respectively. The unencapsulated cells had a more significant decrease in viability at fasting and post-meal of 3.12 log CFU $ml^{-1}$ and 1.53 log CFU $ml^{-1}$ respectively. This implies that microencapsulation effectively protects the bacteria to reach the intestine *in vitro*.[22] Administration of probiotics after meals is also the best way to maintain bacterial viability.[22,23]

A proof-of-concept randomized-controlled exploratory study was conducted by administering live and pasteurized *A. muciniphila* to 40 overweight/obese volunteers with insulin resistance. There were no significant changes in inflammatory markers associated with hematology, liver, kidney and muscle function. However, *A. muciniphila* increased insulin sensitivity and decreased total plasma cholesterol, body weight and fat mass.[24] This first human trial indicated that both live and pasteurized *A. muciniphila* was well-tolerated, safe and improves several metabolic parameters.

### Prebiotic as growth enhancing substance of intestinal *Akkermansia muciniphila*

The use of prebiotics together with the consumption of probiotics has become popular in recent years. Oligofructose, an oligosaccharide of short-chain inulin fragments, is a widely used prebiotic. In 2011, Everard et al., found that oral administration of oligofructose restored the level of *A. muciniphila* in high-fat- diet-fed (HFD) mice and those with genetic manipulation of leptin deficiency and obesity. Baseline *A. muciniphila* levels were 100 and 3300 times less than the control group, respectively.[25]

Polyphenol is another substance increasingly being used as prebiotic. It is derived from grapes and nourishes gut microbiota, stimulates growth, increases metabolic function and reduces inflammation.[26] This is seen as reductions in levels of tumor necrosis factor $\alpha$ (TNF-$\alpha$), bacterial LPS and the absence of serum IL-6. Roopchand et al., in 2015 compared clinical differences between a group of mice given polyphenol plus soy protein isolate (SPI) and a group given SPI alone. Mice given polyphenol-SPI had a lower body weight, liver mass and liver fat, and significantly higher glucose tolerance than the SPI-diet-alone group.[26] Moreover, a 2008 study by Tu et al., evaluated the administration of black raspberries containing polyphenol and oligosaccharide in normal mice. They showed an elevation in the proportion of *A. muciniphila* by as much as 157 times compared to normal mice without the intervention.[27] Apples are another rich source of this substance, with procyanidin as the dominant polyphenol. The procyanidin macromolecules in apples may suppress pro-inflammatory factors in the intestinal mucosa, inhibit weight gain and improve the *Firmicutes*/*Bacteroidetes* ratio, including *A. muciniphila*, as a trigger factor of intestinal barrier function repair.[28]

Roopchand et al., added that the relatively low absorption of polyphenol is vital to how it fights oxygen radicals. This study also found an increase in *A. muciniphila* on HFD mice fecal concentration from 7.5% to 54.8%.[26]

### The effect of metformin on *Akkermansia muciniphila* abundance in the intestine

Metformin is the most commonly prescribed drug in the management of T2DM.[29] Its accumulation in the intestine is approximately 300 times higher than in plasma, making the intestine the body's main reservoir of metformin.[23] A 2014 study by Shin et al., attempted to prove the effect of metformin on gut microbiota composition. The prevalence of *Verrucomicrobe* associated with *A. muciniphila* was significantly lower in mice given HFD than those who were on normal diet (ND). However, after metformin administration, *Verrucomicrobe* increased significantly in the HFD group, while no significant change was observed in the ND group. Metformin was also found to significantly increase goblet cells in the HFD and ND groups of mice, independent of the metabolic profile or diet. Furthermore, they found a positive correlation between the number of goblet cells and the availability of *A. muciniphila* in the intestine.[30]

A 2015 study by Forslund et al., showed that the abundance of *A. muciniphila* in the intestine of T2DM patients was similar to non-diabetic patients after metformin administration. Those who were treated with metformin also showed an increased production of propionate, a substance produced through mucin fermentation by *A. muciniphila*.[29] A recent study by De La Cuesta-Zuluaga et al., also revealed that T2DM patients treated with metformin had 3.4 times more *A. muciniphila* in their intestines than those who did not receive this therapy.[31] Metformin enhances the intestinal protective barrier which may work synergistically with *A. muciniphila* in maintaining the integrity of the mucus layer.[29] Although further investigation into other bacterial genus/species that may be involved in the metformin-induced improvement of metabolic parameters is required, these findings may suggest that an increase in *A. muciniphila* may contribute to the antidiabetic properties of metformin.

### Bariatric surgery and the improvement of intestinal microbiota composition

Bariatric surgery (BS) is an effective option in the management of obese patients and their complications.[32] One interesting outcome related to BS is the improvement

in the gut microbiota population and diversity after the procedure, despite no observed difference in the parameters of glucose homeostasis. In 2017, Murphy et al., report a significant increase in general gut microbiota diversity from baseline to 3 months post-Roux-en-Y Gastric Bypass (RYGB) and even up to 1-year post-treatment.[33]

Although BS improves gut microbiota composition, the mechanisms as to how are still not fully understood. Aside from modification of the digestive tract anatomy, there are several factors that can affect post-BS intestinal microbiota including post-surgery food preferences, reduced food consumption and nutritional malabsorption.[13,34,35]

A study by Ulker et al., in 2018 has shown that a difference in post-BS diet therapy options, namely a low-fat-high-carbohydrate diet compared to a high-carbohydrate-low-glycemic index diet affects the number of specific strains of the gut microbiota.[32] The second factor that affects the post-BS intestinal microbiota are hormonal changes in leptin and ghrelin. Circulating serum leptin levels are reported to positively impact the growth of *Mucispirillum, Lactococcus* and *Lachnospiraceae*.[36] Finally, the composition of the gut microbiota is influenced by the gastrointestinal pH. The pH level in each component of the gastrointestinal tract distal to the stomach becomes more basic after surgery due to the decrease in gastric acid production from its reduced volume.[32] Alterating the pH affects microbiota level to a significant extent. A study by Murphy et al., in 2017 demonstrated a decrease in *Bacteroidetes* and an increase in *Firmicutes* and *Actinobacteria* groups due to post-BS pH changes.[33]

A post RYGB study by Dao et al., in 2019 revealed an increase in the mean relative number of *A. muciniphila* after 3 months. By 1 year-post operative follow-up, *A. muciniphila* levels increased 200-fold, although the total number was still lower than non-obese subjects. Furthermore, patients with a relatively low level of *A. muciniphila* at baseline had the greatest increase in numbers regardless of the type of BS performed.[37] Hence, an improvement in the intestinal microbiota composition is one of the positive effects after any BS procedure.

### Future perspectives

*A. muciniphila* as a potential therapy for T2DM can be facilitated by fecal microbiota transplantion (FMT), already in use for *Clostridium difficile* infection and inflammatory bowel disease.[38,39] The complex interaction between patients and their gut microbiota should trigger further consideration regarding other factors that may influence the modulation of *A. muciniphila* and the intestines, in particular a comprehensive dietary review to maintain the homeostasis and efficiency of *A. muciniphila.* The mechanisms related to the gut microbiome and the selection between different strains require more data. Administration of probiotics has been noted to trigger disturbances in the horizontal transfer of genes between microbiota.[40] Several studies have found the occurrence of horizontal antibiotic-resistant gene transfer by lactic acid bacteria in fermented foods.[41,42] *A. muciniphila* is known to be related to increase insulin sensitivity and glucose tolerance. However, an actual reduction in the glucose parameters (Hba1c, fasting blood glucose) is still limited to be found. Thus, this gaps in knowledge should be further explored in the future researches.

## CONCLUSION

Alterations of the gut microbiota is one of the patho-physiologic changes that underlies the development of T2DM. The amount of *A. muciniphila* is inversely correlated with body weight, inflammation and the metabolic syndrome, and can be a potential intervention for T2DM by improving these parameters. Increasing the levels of *A. muciniphila* can be achieved through several modulations such as functional food or probiotic intake, metformin and bariatric surgery. However, clinical studies are still sparse and further research is needed to determine its definite role and safety among patients with T2DM.

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REVIEW ARTICLE

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# Medication Adherence of Persons with Type 2 Diabetes in Malaysia: A Scoping Review and Meta-Analysis

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**Abstract**

Objective. This is a scoping review of Malaysian scientific studies on medication adherence among persons with type 2 diabetes mellitus (T2DM).

Methodology. We conducted a bibliographic search of PubMed, Scopus and Google Scholar using the following keywords: "medication adherence," "drug compliance," "DMTAC" and "Malaysia." The search covered all publications up to 31 December 2021. Eligible articles were original studies conducted in Malaysia that measured or quantified medication adherence among persons with T2DM.

Results. We identified 64 eligible studies published between 2008 to 2021. Most studies included patients with T2DM in ambulatory facilities. Five studies were qualitative research. The quantitative research publications included clinical trials, and cross-sectional, validation, retrospective and prospective cohort studies. Thirty-eight studies used medication adherence scales. The Morisky Medication Adherence Scale (MMAS-8, used in 20 studies) and Malaysian Medication Adherence Scale (MALMAS, used in 6 studies) were the most commonly used tools. There were 6 validation studies with 4 medication adherence scales. A meta-analysis of 10 studies using MMAS-8 or MALMAS revealed that the pooled prevalence of low medication adherence is 34.2% (95% CI: 27.4 to 41.2, random effects model). Eighteen publications evaluated various aspects of the Diabetes Medication Therapy Adherence Clinics (DMTAC).

Conclusion. This scoping review documented extensive research on medication adherence among persons with diabetes in Malaysia. The quantitative meta-analysis showed a pooled low medication adherence rate.

*Key words: diabetes mellitus, medication adherence, Malaysia, scoping review*

## INTRODUCTION

Diabetes mellitus is a major health issue worldwide with an increasing incidence over the past few decades.[1] In Malaysia, the prevalence of diabetes escalated alarmingly from 11.2% in 2011, to 13.4% in 2015, and to 18.3% in 2019, affecting 3.9 million people aged 18 and above.[2] This increase is associated with the parallel rise in the prevalence of overweight and obese individuals.[3] As one of the major non-communicable diseases, type 2 diabetes mellitus poses a significant challenge to the Malaysian healthcare system, estimated to incur a total annual cost of MYR 2,484 million (USD 600 million) annually.[4]

Malaysia's healthcare system is composed of both public and private sectors. In the public health clinics where most patients with diabetes are treated, patient care is undertaken by a medical officer, who may refer selected patients to a Diabetes Medication Therapy Adherence Clinic (DMTAC). In Malaysia, DMTAC was started in 2004 by the Pharmaceutical Services as an ambulatory care service managed by the pharmacist for patients with diabetes to improve their medication adherence and glycemic control.[5] A recent systematic review of DMTAC studies from Southeast Asia conducted by Dwiputri et al., concluded that pharmacists can contribute to improve diabetes management in a variety of settings.[6] Of the 16 articles included in the above review, half (8 studies) came from Malaysia.[6]

Good glycemic control of diabetes is essential to prevent long-term microvascular and macrovascular complications. One component of self-management is medication adherence to pharmacologic regimens. Optimal medication adherence is associated with a lower risk of diabetes complications, lower health care costs and lower mortality rates.[7] While there are many studies on medication adherence in Malaysia, currently, there is no

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scoping review that provides a global picture of medication adherence among persons with diabetes and efforts to deal with it in the local context. The data generated from this scoping review can provide pointers for the planning of further research on diabetes medication adherence and DMTAC in Malaysia.

## METHODOLOGY

This scoping review aims to describe Malaysian scientific studies on the topic of medication adherence among patients with diabetes. We searched PubMed and Scopus using a combination of the search terms such as "diabetes mellitus," "medication adherence," "drug compliance," "DMTAC and "Malaysia," covering publications up to 31 December 2021. This was supplemented by a Google Scholar search using the same text words. The citations were processed using Endnote 20 citation manager.[8] Keywords of all citations were coded for study designs, study settings (primary or tertiary care) and any medication adherence data and its associated factors.

The inclusion criteria for eligible studies were:
1. Original research conducted in Malaysia;
2. Studies that measured or discussed medication adherence and associated factors;
3. Study participants must be patients diagnosed with both type 1 and type 2 diabetes mellitus.

We excluded the following types of publications: books, monographs, reports, case reports, conference abstracts, editorials, letters, comments, reviews (narrative or systematic), study protocols and theses or dissertations.

The full text of eligible studies were retrieved. Relevant data in the included studies were extracted by a pair of investigators. Meta-analysis of prevalence data on low medication adherence was performed using MedCalc® Statistical Software. Fixed effects model was selected if the study heterogeneity ($I^2$) were less than 50%; otherwise, random effects model was used.[9]

This review was prepared following the PRISMA guideline.[10] Quality assessment of the published studies was performed using a checklist for prevalence studies published by Joanna Briggs Institute (JBI).[11]

## RESULTS

### Search results

Of the 147 items retrieved from the bibliographic databases and internet search, 68 journal articles published between 2008 to 2021 were deemed eligible for qualitative analysis. However, only 64 articles were used for qualitative analysis as four articles found to be published in "predatory journals" were excluded. Ten publications that provide prevalence data on medication adherence were selected for quantitative analysis (Figure 1).[12-21]

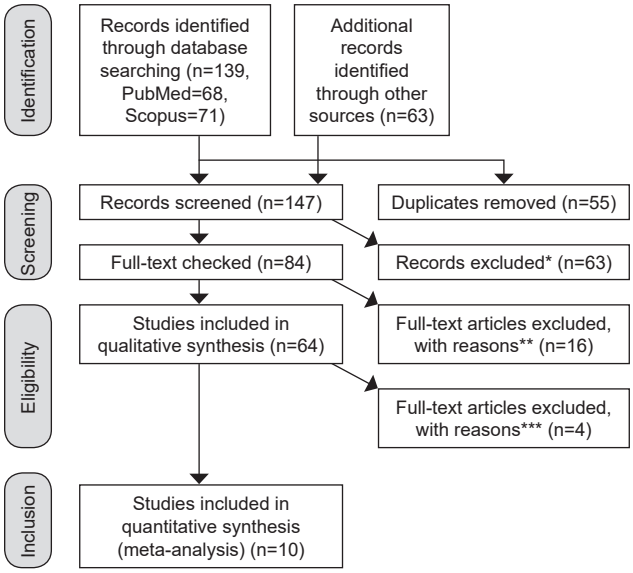


**Figure 1.** PRISMA flow diagram.

* conference abstract=12; non-journal=36 (monographs, reports, theses); non-Malaysian publication=14; case report=2; comment/letter=2; correction=1; review (narrative/systematic)=7; study protocol=3; retracted publication=1 [number added is more than 63 because some excluded publications are in several categories]

** no measurement or exploration of medication adherence=4; Not focused on general diabetes care in adults=12 (asthma, diet, hyperlipidemia, hypertension, telemonitoring, tuberculosis, validation); type 1 diabetes in children=1

*** published in predatory journals

### Qualitative assessment

#### *A. Study participants*

Most study participants had T2DM (59 studies). In 5 studies, both type 1 diabetes mellitus (T1DM) and T2DM patients were recruited.[22-26] However, 5 studies did not mention if the study participants had T1DM or T2DM.[27-31]

#### *B. Study site*

In 53 studies, the study site included an ambulatory clinic; in 32 of them, a primary care clinic was used. In 41 studies, the study took place in a hospital setting (wards, outpatient clinics or pharmacies). In one study, the study site was unclear.[27]

#### *C. Study design*

Out of the 64 included studies, 59 were quantitative research, while 5 were qualitative research.[29,32-35] Among the quantitative studies, we found 16 clinical trials, 6 validation studies, 7 retrospective studies and 2 prospective cohort studies, while the rest were cross-sectional studies.

#### *D. Measurement tool for medication adherence*

In 38 studies, a named medication adherence scale was used. The most commonly used was the Morisky Medication Adherence Scale (MMAS-8), seen in 20

studies.[12-17,19,20,23,24,36-45] Six studies used the Malaysian Medication Adherence Scale (MALMAS).[17,18,20,21,42,46,47] The other scales and the number of respective studies that utilized them were the Adherence to Refills and Medications Scale (ARMS, 2 studies),[48,49] the Medication Compliance Questionnaire (MCQ, 7 studies),[28,50-55] the Drug Attitude Inventory (DAI-10, 1 study),[56] the Malaysia Medication Adherence Assessment Tool (MyMAAT, 1 study),[57] the PATIENT-Medication Adherence Instrument (P-MAI, 1 study),[58] the Self-Efficacy for Appropriate Medication Use Scale (SEAMS, 2 studies),[57,59] and the Malay Elderly Diabetes Self-Care Questionnaire (MEDSCaQ, 1 study).[60] Medication adherence was measured using a self-developed questionnaire in 6 studies.[22,25,26,61-63] Three studies used pill count[30,64,65] and the medication dose, frequency, indication and time score (DFIT).[66]

### *E. Study objectives*

The objectives of the included studies can be categorized as:

1. Validation of medication adherence scales;
2. Prevalence and factors associated with medication adherence; and
3. Intervention to promote self-care and medication adherence.

### *F. Validation studies*

We identified 6 publications reporting psychometric data using four rating scales on medication adherence in Malaysia: MMAS-8, 2 studies;[23,36] MALMAS, 2 studies;[17,20] MyMAAT, 1 study;[57] and P-MAI, 1 study[58] (Table 1). We noted that both MMAS-8 and MALMAS had more extensive reliability and validity data, but as noted by Hatah et al., the use of these two copyrighted scales requires substantial payment.[57]

### *G. Prevalence and factors associated with low medication adherence*

#### *1. Prevalence of low medication adherence*

Many Malaysian studies measured medication adherence. We found 15 cross-sectional studies that used either MMAS-8 or MALMAS. In light of the comparability of prevalence data, a meta-analysis on low medication adherence was performed. After excluding studies where medication adherence data was not extractable or where the same dataset was used, we narrowed the list down to 10 studies. The MMAS-8 was more commonly used in measuring medication adherence (8 studies), followed by MALMAS (4 studies); 2 publications reported prevalence data using both scales.[12–21] The reported medication adherence rates varied from 11.7% to 44.8% (Table 2). All the included studies received a moderate to high quality rating in the JBI critical appraisal tool for prevalence study.

A meta-analysis of 10 studies[12-21] (N=2836) using MMAS-8 and MALMAS was performed. We felt that this synthesis was appropriate since MALMAS was developed based on MMAS-8 using the same definition for degrees of medication adherence. There was high heterogeneity. The random effects model showed the summative prevalence

**Table 1.** Malaysian validation studies on medication adherence scale in type 2 diabetes

| Study | Scale | Setting | Participants | Method | Data |
|---|---|---|---|---|---|
| Al-Abboud 2016[23] | MMAS-8[a] (Malay version) | Hospital clinic | 62 T1DM[b]/ T2DM[c] adults, mean age 47 years | MMAS-8[a] (and 2 other scales: PDSMS[d], MUSE[e]) translated to Malay. Reliability and correlation assessed using Partial Credit Rasch Model | Reliability and correlation of 24-item composite scale is produced. The person reliability (α=0.76) and item reliability (α=0.93) were good to excellent |
| Al-Qazaz 2010[14] | MMAS-8[a] (Malay version) | Hospital clinic | 223 T2DM[c] adults, mean age 61 years | MMAS-8[a] translated to Malay. Test re-test reliability done for 39 subjects. Correlation with MAS-4[f] and HbA1c[g]. | Cronbach's alpha: 0.675<br>MMAS-8[a] vs MAS-4[f] correlation: r=0.792<br>MMAS-8[a] categories vs HbA1c[g] categories: significant relationship |
| Chung 2015[17] | MALMAS[h] (English version) | Hospital clinic | 136 T2DM[c] adults, mean age 58 years | Test re-test reliability done 4 weeks later. Correlation with MMAS-8[a] Scale and HbA1c[g]. | Cronbach's alpha: 0.565<br>MALMAS[h] vs MMAS-8[a] correlation: rho=0.715<br>MALMAS[h] adherent group had lower HbA1c[g] |
| Goh 2020[58] | P-MAI[i] (English version) | Primary care clinic | 120 T2DM[c] adults | Developed using the nominal group technique. | Cronbach's alpha: 0.722 |
| Hatah 2020[57] | MyMAAT[j] (Malay version) | Both hospital clinic and primary care clinic | 495 T2DM[c] adults | Newly developed 12-item Malay questionnaire. Correlation with SEAMS[k] Scale and HbA1c[g]. | Cronbach's alpha: 0.910 |
| Lai 2020[20] | MALMAS[h] (Malay version) | Hospital clinic | 100 T2DM[c] adults | MALMAS[h] translated to Malay. Test re-test reliability done 4 weeks later. Correlation with MMAS-8[a] Scale and HbA1c[g]. | Cronbach's alpha: 0.654; Test-retest: no significant difference for any Item; correlation between MMAS-8[a]: Spearman's rho=0.797; HbA1c[g] higher in those with better adherence |

[a] MMAS-8: 8-item Morisky Medication Adherence Scale
[b] T1DM, type 1 diabetes mellitus
[c] T2DM, type 2 diabetes mellitus
[d] PDSMS, Perceived Diabetes Self-Management Scale
[e] MUSE, Medication Understanding and Use Self-Efficacy Scale
[f] MAS-4, 4-item Morisky Adherence Scale
[g] HbA1c, glycosylated hemoglobin
[h] MALMAS, Malaysian Medication Adherence Scale
[i] P-MAI, PATIENT-Medication Adherence Instrument
[j] MyMAAT, Malaysia Medication Adherence Assessment Tool
[k] SEAMS, Self-Efficacy for Appropriate Medication Use Scale

**Table 2.** Malaysian studies providing medication adherence data using rating scales in type 2 diabetes

| Study | Scale | Setting | Participants | JBI checklist score[a] | Medication adherence: high, moderate, low (%) | Risk factors for low adherence |
|---|---|---|---|---|---|---|
| Abu Bakar 2016[12] | MMAS-8[b] | Hospital clinic | 165 T2DM[b] adults, mean age not available | 6 | 26.1, 29.1, 44.8 | Younger age, male gender, lower education |
| Al-Amedy 2016[13] | MMAS-8[b] | Hospital clinic | 223 T2DM[b] adults, mean age 57.9 years | 7 | 1.3, 87.0, 11.7 | Not associated with socio-demographic factors, knowledge |
| Al-Qazaz 2010[14] | MMAS-8[b] | Hospital clinic | 223 T2DM[b] adults, mean age 61 years | 6 | 17.1, 44.5, 38.2 | Lower education, larger number of medications |
| Balasubramaniam 2019[15] | MMAS-8[b] | Hospital clinic | 384 T2DM[b] adults, mean age 58 years | 8 | 23.7, 36.2, 39.6 | NA[e] |
| Chew 2015[16] | MMAS-8[b] | Primary care clinic | 668 T2DM[b] adults, mean age not available | 8 | 0.1, 57.1, 42.8 | Younger age, Malay ethnicity, higher income, higher education, less exercise, lower HRQoL[f], higher diabetes distress depressive symptoms |
| Chung 2015[17] | MMAS-8[b] and MALMAS[d] | Hospital clinic | 136 T2DM[b] adults, mean age 58 years | 7 | 30.1, 43.4, 26.5 | NA[e] |
| Dhillon 2019[18] | MALMAS[d] | Primary care clinic | 150 T2DM[b] adults, mean age 59.4 years | 7 | 54.7, 16.7, 28.7 | NA[e] |
| Jannoo 2019[19] | MMAS-8[b] | Hospital clinic and primary care clinic | 497 T2DM[b] adults, mean age not available | 8 | 17.7, 37.6, 44.7 | Malay ethnicity, longer duration of diabetes, higher BMI[g] |
| Lai 2020[20] | MMAS-8[b] and MALMAS[d] | Hospital clinic | 100 T2DM[b] adults, mean age 64 years | 7 | 43.0, 33.0, 24.0 | NA[e] |
| Nini 2019[21] | MALMAS[d] | Primary care clinic | 338 T2DM[b] adults, mean age not available | 8 | 20.4, 37.0, 42.6 | NA[e] |

[a] JBI checklist score, Joanna Briggs Institute checklist score using critical appraisal tool for prevalence study
[b] MMAS-8, 8-item Morisky Medication Adherence Scale
[c] T2DM, type 2 diabetes mellitus
[d] MALMAS, Malaysian Medication Adherence Scale
[e] NA, not available
[f] HRQoL, health-related quality of life
[g] BMI, body mass index

| | n | % | 95% CI | Weight (%) | |
|---|---|---|---|---|---|
| | | | | Fixed | Random |
| Al-Almedy 2016 | 223 | 11.66 | 7.76 to 16.62 | 7.87 | 10.06 |
| Al-Qazaz 2010 | 175 | 38.29 | 31.05 to 45.92 | 6.18 | 9.84 |
| Balasubramaniam 2019 | 384 | 39.58 | 34.66 to 44.67 | 13.5 | 10.41 |
| Chew 2015 | 668 | 42.81 | 39.03 to 46.67 | 23.5 | 10.63 |
| Chung 2015 | 136 | 26.47 | 19.28 to 34.72 | 4.81 | 9.57 |
| Dhillon 2019 | 150 | 28.67 | 21.59 to 36.61 | 5.31 | 9.68 |
| Jannoo 2018 | 497 | 44.67 | 40.24 to 49.16 | 17.5 | 10.53 |
| Lai 2020 | 100 | 24.00 | 16.02 to 33.57 | 3.55 | 9.15 |
| Nini 2019 | 338 | 42.60 | 37.27 to 48.07 | 11.9 | 10.34 |
| Total (fixed effects) | 2836 | 37.48 | 35.69 to 39.29 | 100 | 100 |
| Total (random effects) | 2836 | 34.15 | 27.43 to 41.20 | 100 | 100 |

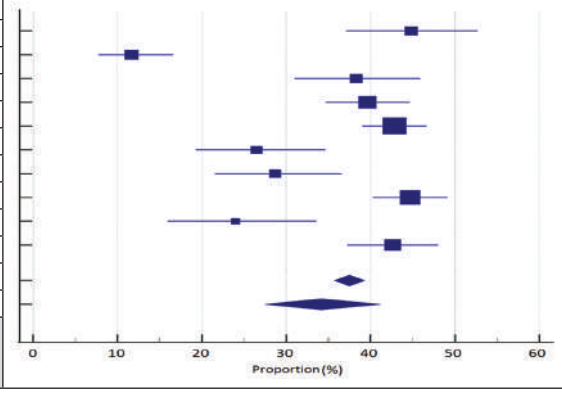


**Figure 2.** Meta-analysis of studies on medication adherence.

of low medication adherence to be 34.2% (95% CI: 27.4 to 41.2) (Figure 2). The prevalence of low medication adherence in primary care and hospital-based studies were 37.5% (95% CI: 31.3 to 43.9) and 32.3% (22.8 to 42.6), respectively.

### 2. Risk factors for low medication adherence

Data on risk factors for low medication adherence was available in five studies (Table 2). The factors associated with medication adherence were somewhat conflicting. These studies were not originally designed to investigate risk factors for low medication adherence and the type and definition of risk factors assessed were not standardized.

### *H. Diabetes medication therapy adherence clinic*

Eighteen publications on DMTAC were retrieved (Table 3).[12,24,28,29,31,37,44,45,65-74] The study designs included 1 qualitative research,[29] 3 cross-sectional studies,[12,28,31] 6 retrospective studies[24,44,45,65,70,73] and 8 randomized controlled trials (RCTs).[37,66-69,71,72,74] The retrospective studies reported an HbA1c reduction between 1.0 to 1.7% (end of study versus baseline) after 4 to 8 DMTAC consultations done on top of usual care. All RCTs, except that of Butt et al.,[37] showed reduction of HbA1c at the end of the study. Drop-outs from the RCTs were substantial, varying between 9.6 to 26.5%. Iqbal et al., and Khan et al., published 5 RCTs based on a single project and showed a statistically significant reduction of HbA1c and apparent reduction of symptoms attributable to diabetes complications within

**Table 3.** Malaysian studies providing data on diabetes medication adherence therapy clinic (DMTAC) in type 2 diabetes

| Study | Study design | Participants | Methods | Findings |
|---|---|---|---|---|
| Abu Bakar 2016[12] | Cross-sectional study | Hospital clinic 165 T2DM[a] adults, mean age ? | Patients recruited over three months. They had attended at least one visit in the DMTAC[b]. | 87% of patients reported satisfied with DMTAC[b] service. HbA1c[c] change not reported. |
| Alison 2020[66] | Randomized controlled trial | Primary care clinic 100 T2DM[a] adults, mean age 52 years | Patients randomized to receive treatment at DMTAC[b] in addition to usual care vs usual care alone. Intervention group received at least four DMTAC[b] consultation. | HbA1c[c] reduction at one year: intervention group 1.58%, control group 0.48% (p<0.05). Drop-out 14%. |
| Azmi 2020[53] | Cross-sectional study | Hospital and primary care clinics 275 T2DM[a] adults | Controls were patients who were not managed in DMTAC[b] (n=144). Intervention group had attended at least four visits in the DMTAC[b] (n=131). Medication adherence was assessed using Medication Compliance Questionnaire. | Thirty (10.9%) patients were non-adherent in the control group while 15 (5.5%) patients were non-adherent in the intervention group. |
| Butt 2016[37] | Randomized controlled trial | Hospital clinic 73 T2DM[a] adults | Patients randomized to receive treatment at DMTAC[b] in addition to usual care vs usual care alone. Intervention group received three DMTAC[b] consultation. | No statistically significant difference in HbA1c[c] at six months between intervention and control group. Drop-out 9.6%. |
| Iqbal 2021* | Randomized controlled trial | Hospital clinic 400 T2DM[a] adults | Patients randomized to receive treatment at DMTAC[b] vs usual care alone. After baseline evaluation, intervention group received two DMTAC[b] consultation. | Baseline HbA1c[c] 11.15 % (control) and 11.69% (intervention); end of study HbA1c 9.72% (control) and 8.87% (intervention). Drop-out 26.5%. |
| Karunagaran 2018[70] | Retrospective study | Hospital clinic 213 T2DM[a] adults | Retrospective review of medical record. Intervention group received up to seven DMTAC[b] consultation. | Reduction of HbA1c[c] was achieved, results reported graphically (mean change in HbA1c[c] cannot be extracted). Drop-out not reported. |
| Lau 2018[73] | Retrospective cohort study | Hospital clinic 58 T2DM[a] adults | Comparison of one-year outcome in patients followed up by pharmacist vs usual medical care | Pharmacist group: Baseline HbA1c[c] 11.16%, end of study HbA1c[c] 9.57% Usual medical care: Baseline HbA1c[c] 9.26%, end of study HbA1c[c] 9.09%. |
| You 2015[44] | Retrospective study | Primary care clinic 56 T2DM[a] adults | Retrospective review of medical record. Intervention group received four DMTAC[b] consultation. | Reduction of HbA1c[c] achieved (mean change 1.0%). |
| Lim 2010[24] | Retrospective study | Hospital clinic 76 T2DM[a] adults | Retrospective review of medical record. Intervention group received eight DMTAC[b] consultation | Reduction of HbA1c[c] achieved (mean change 1.7%). |
| Lim 2016[74] | Randomized controlled trial | Hospital clinic 120 T2DM[a] adults | Patients randomized to receive treatment at DMTAC[b] in addition to usual care vs usual care alone. Intervention group received eight DMTAC[b] consultation. | HbA1c[c] reduction at one year: intervention group 0.9%, control group 0.08% (p<0.05). Drop-out 24%. |
| Sim 2021[31] | Cross-sectional study | Hospital clinic 37 T2DM[a] adults | Patient satisfaction of 148 patients (37 had diabetes) followed up in medication therapy adherence clinic. | No HbA1c[c] outcome data. Patient satisfaction data not extractable for diabetes patients. |
| Tai 2016[45] | Retrospective study | Primary care clinic 100 T2DM[a] adults | Retrospective review of medical record. Intervention group received four or more DMTAC[b] consultation. | Reduction of HbA1c[c] achieved (mean change 1.0%). |
| Tey 2020[65] | Retrospective study | Primary care clinic 80 T2DM[a] adults | Retrospective review of medical record. Intervention group received four or more DMTAC[b] consultation. | Reduction of HbA1c[c] achieved (mean change 1.0%). |

[a] T2DM, type 2 diabetes mellitus
[b] DMTAC, Diabetes Medication Therapy Adherence Clinics
[c] HbA1c, glycosylated hemoglobin
* There are five randomized controlled trial published by this group, all apparently coming from one single project [same ethics approval number: KKM/NIHSEC/P18-1307(13)]. See references 71-73,75,76.

one year, which is a surprising finding.[67-69,71,72] Only 6 out of 18 DMTAC studies measured medication adherence; 5 of them used MMAS-8,[12,24,28,37,44,45] and 1 used the MCQ.[28]

### Qualitative studies

We identified 5 qualitative studies;[29,32-35] 2 were based on the same population of 21 physically disabled T2DM patients.[33,34] The study of Al-Qazaz et al.,[32] involved 12 T2DM adults who were mostly university staff, while that of Saidi et al.,[35] included 18 T2DM patients. Selvadurai et al., interviewed 10 pharmacists to explore pharmacist-patient active engagement during DMTAC consultation.[29] All the qualitative studies cited employed semi-structured interviews and provided insights into patients' views about their health conditions, especially regarding self-care and medication adherence.

## DISCUSSION

Medication adherence is a critical determinant of outcomes in persons with diabetes. To our knowledge, this is the first scoping review that maps the published studies on medication adherence among persons with diabetes in Malaysia. We identified 64 Malaysian studies published in the past 13 years that examined medication adherence among persons with diabetes in Malaysia; they all included T2DM patients and a minority also included T1DM patients. As expected, the included studies covered a broad scope, with the nature of the studies ranging from estimation of prevalence of low medication adherence and associated factors, validation of measurement tools for medication adherence, qualitative research and various interventional studies.

We found 6 studies assessing the psychometric properties of 4 rating scales on medication adherence in Malaysian adult patients with diabetes. While MMAS-8 and MALMAS have more comprehensive reliability and validity data, the need for payment for their application may restrict their usage among researchers without substantial funding support. In response to such limitations, the MyMAAT was specifically developed by Hatah et al., to provide a more accessible alternative.[57] The MMAS-8 reportedly has

33 language versions. Since it is widely used in various countries, it has the unique advantage of allowing cross-national comparison.[77-79]

Medication adherence rate varied depending on how adherence was defined (since they used different rating scales), and the type of population studied. It was opportune in our scoping review that we managed to identify a subset of Malaysian studies suitable for systematic review. Our meta-analysis of 10 studies using either MMAS-8 or MALMAS revealed a pooled low medication adherence rate of 34.4%. This finding confirms that at least a third of Malaysian patients with diabetes took less than the prescribed amount of medication, an observation that is similar to the pooled data from other low- and middle-income countries (43.4%, 95% CI: 17.5-69.4).[80] The high prevalence of low medication adherence among Malaysian patients with diabetes emphasizes the need for health practitioners dealing with diabetes care to recognize and act on this issue. We anticipate that this substantial problem of poor adherence has substantial clinical and financial implications, as shown in the systematic review by Kennedy et al.[79] However, our scoping review identified fewer studies investigating the factors associated with low medication adherence. The risk factors identified appeared to be heterogenous, possibly due to methodological differences such as lack of uniformity in the questionnaire investigating this issue. The variable quality of evidence investigating this aspect is also noted by other systematic reviews.[7,80] Considering the importance of medication adherence, further exploration of the reasons for this in the local context is essential to crafting subsequent tailored interventions.

Our scoping review identified 18 studies involving DMTAC, with many of them intended to assess the impact of DMTAC on glycemic control. These DMTACs are pharmacist-run diabetes service units focusing on patients with poor glycaemic control. The interventions provided beyond drug management include dietary and lifestyle modification. Although most were observational studies, it is noteworthy that 8 were randomized controlled trials.[37,66-69,71,72,74] However, it is possible that 5 of these trials were duplicated publications from one single project.[67-69,71,72]

Observational studies also potentially have the bias of including patients who were compliant with DMTAC service, especially those using cross-sectional design or are retrospective in nature. In fact, we failed to find any prospective cohort studies or randomized controlled studies that extended the study period beyond 1 year, suggesting that the long-term impact of DMTAC in Malaysia is still an unexplored area. The Malaysian DMTAC trials showed an HbA1c reduction of approximately 1% after multiple visits in one year, but the drop-out rates were not negligible. The impact of DMTAC in Malaysia is consistent with the findings demonstrated in the systematic review of international literature.[81]

This scoping review relied only on published peer reviewed scientific studies originating from Malaysia. The findings may change when more publications on this topic are published.

## CONCLUSION

This scoping review documented extensive research on medication adherence among persons with diabetes in Malaysia. The information generated from this study can help design future investigations on this topic.

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

**Author Disclosure**
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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

# Rare Case of Large Catecholamine Secreting Ganglioneuroma in an Asymptomatic Elderly Male

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**Abstract**

Ganglioneuromas (GNs) are benign tumors that originate from neural crest cells, composed mainly of mature ganglion cells. These tumors, which are usually hormonally silent, tend to be discovered incidentally on imaging tests and occur along the paravertebral sympathetic chain, from the neck to the pelvis and occasionally in the adrenal medulla. Rarely, GNs secrete catecholamines.[1] Adrenal GNs occur most frequently in the fourth and fifth decades of life, whereas GNs of the retroperitoneum and posterior mediastinum are usually encountered in younger adults.[2] Adrenal GNs are commonly hormonally silent and asymptomatic; even when the lesion is of substantial size.[3]

We report an incidentally detected asymptomatic case of an adrenal ganglioneuroma with mildly elevated urinary catecholamine levels in an elderly male. After preoperative alpha blockade, the patient underwent open right adrenalectomy. Upon microscopic examination, the right adrenal mass proved to be a ganglioneuroma, maturing type and the immunohistochemistry examination showed immunoreactivity to synaptophysin, chromogranin, and CD 56, while S100 was strongly positive at the Schwannian stroma. Following resection, catecholamine levels normalized, confirming the resected right adrenal ganglioneuroma as the source of the catecholamine excess. This case represents a rare presentation of catecholamine-secreting adrenal ganglioneuroma in the elderly.

*Key words: adrenal glands, catecholamine, ganglioneuroma*

## INTRODUCTION

Ganglioneuromas (GNs) are benign tumors that originate from neural crest cells, composed mainly of mature ganglion cells. These tumors, which are usually hormonally silent, tend to be discovered incidentally on imaging tests and occur along the paravertebral sympathetic chain, from the neck to the pelvis, and occasionally in the adrenal medulla. Adrenal GNs occur most frequently in the fourth and fifth decades of life, whereas GNs of the retroperitoneum and posterior mediastinum are usually encountered in younger adults. GNs rarely secrete catecholamines, in contrast to pheochromocytomas and neuroblastomas. They also have different origins.

## CASE

A 72-year-old man was referred to our endocrine outpatient clinic for an incidentally detected right-sided adrenal mass following a computed tomography angiography of bilateral lower limbs done for workup of critical limb ischemia measuring 121 mm x 146 mm x 141 mm with an absolute washout of -150% and relative washout of -34%. There was no evidence of metastatic disease and no obvious invasion into adjacent structures. The patient denied any paroxysmal symptoms and showed no clinical signs, except for hypertension for 20 years, well-controlled with a single agent. His urinary epinephrine (37.1 μg/day, normal range: 1.7-22.4 μg/day), norepinephrine (105.1 μg/day, normal range: 12.1-85.5 μg/day), and dopamine (587 mg/day, normal range: 64-400 mg/day) were all mildly elevated. Urinary HVA and VMA were not available. From the laboratory and imaging findings, the tumor was presumed to be a pheochromocytoma with suspected malignant potential.

The patient underwent preoperative alpha-adrenergic blockade with phenoxybenzamine two weeks prior to surgery followed by beta-blockade. The patient underwent open right adrenalectomy under general anesthesia. He had profound hemodynamic fluctuations during the operation and required vasopressor support for less than 24 hours postoperatively. He was discharged well on postoperative day 12.

On microscopic examination, the right adrenal mass proved to be a ganglioneuroma (maturing type) as there were areas containing mature ganglion cells which displayed eccentric nuclei, prominent single nucleoli with abundant eosinophilic cytoplasm with surrounding Schwannian

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**Table 1.** Differences in characteristics between pheochromocytoma, neuroblastoma, and ganglioneuroma

| Characteristics | Pheochromocytoma | Neuroblastoma | Ganglioneuroma |
|---|---|---|---|
| Location | Adrenal | Adrenal, Paraspinal | Adrenal, Paravertebral sympathetic chain |
| Origin | Chromaffin cells | Neuroblasts | Neural crest cells |
| Urinary HVA, VMA, Metanephrines | Metanephrines more specific | Predominantly HVA and VMA[4] | Metanephrines, HVA, and VMA[3,4] (Rare) |

HVA – Homovanillic acid; VMA – Vanillylmandelic acid

stroma and spindle cells. No mitosis was seen. Gold to brownish pigments were also seen in some neoplastic cells. No atypia, necrosis, or capsular breach was observed. No ganglioneuroblastic component or evidence of malignancy was seen. The immunohistochemistry examination showed immunoreactivity to synaptophysin, chromogranin, and CD 56 while S100 is strongly positive at the Schwannian stroma. They are negative for Pan Ck and GFAP.

## DISCUSSION

Ganglioneuromas are rare, benign, well-differentiated neural crest tumors arising in the paravertebral sympathetic chain, and are classically non-secretory and clinically asymptomatic.[5] Most ganglioneuromas are diagnosed incidentally on imaging. Patients may also present with non-specific symptoms such as back or abdominal pain due to tumor mass effect. As with all incidental adrenal masses, a hormonal workup should be performed to determine the etiology of the tumor. Assessment should include evaluation of catecholamine or metanephrine levels, screening for cortisol excess, and measurement of plasma renin activity and aldosterone concentration.[6]

Ganglioneuromas are histologically benign lesions and can be classified into two main categories. The "mature type" GNs comprise of mature Schwann cells, ganglion cells, and perineural cells within a fibrous stroma whilst completely lacking neuroblasts and mitotic figures. The "maturing type" GNs consist of similar cellular populations with miscellaneous maturation degrees, ranging from fully mature cells to neuroblasts.[7]

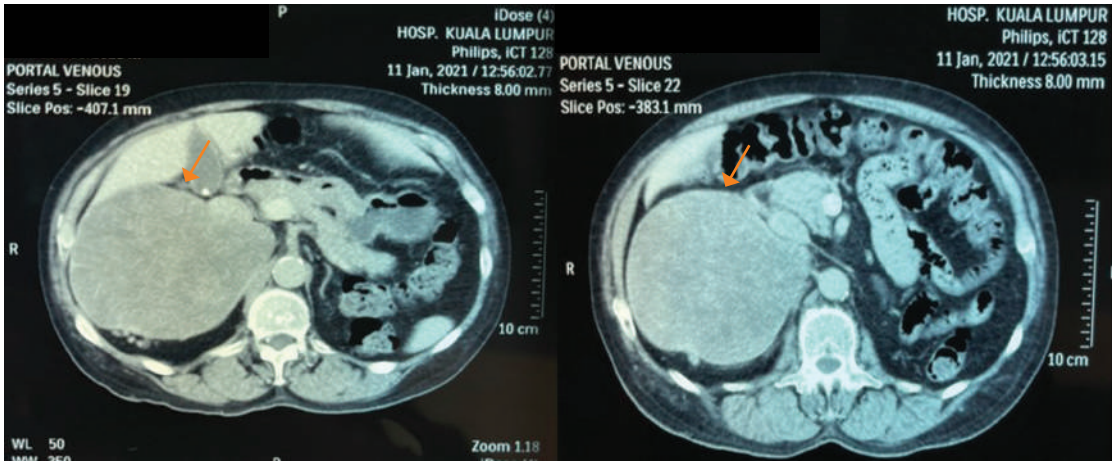


**Figure 1.** Coronal Section Contrast-Enhanced CT Adrenal images in portovenous phase showing a large heterogeneous enhancing right adrenal mass with no calcification or fat component within (arrow). The density of the mass on the plain study is 41 HU, in portovenous phase 53 HU, and delayed study 71 HU.

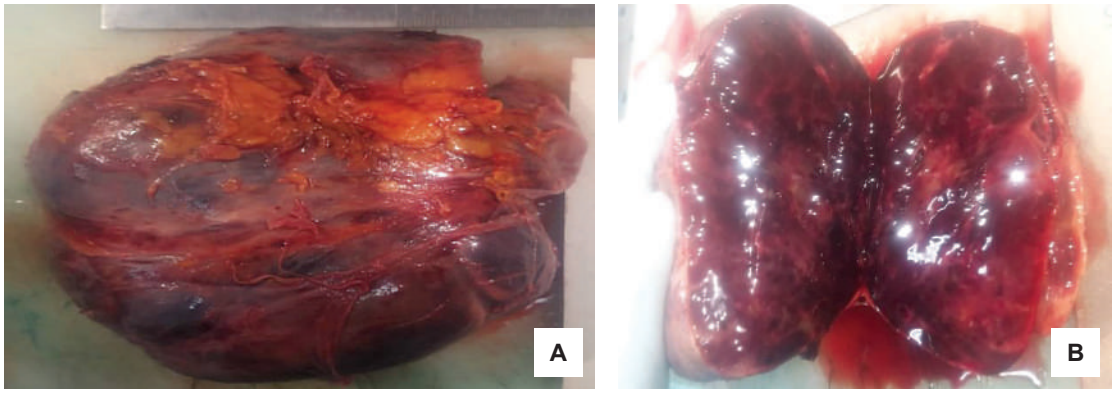


**Figure 2.** Macroscopic findings. **(A)** Right adrenalectomy specimen: Large, well-circumscribed lobular mass weighing 1167 g and measuring 155 × 140 × 85 mm. The mass is smooth and shiny on the outer surface with some attached fatty tissues. Fine vessels are seen on its brownish-grey surface; **(B)** Right adrenalectomy specimen. Cut surface showing soft dark brownish multicystic areas with extensive hemorrhage. The cystic spaces range from 5-20 mm in diameter.

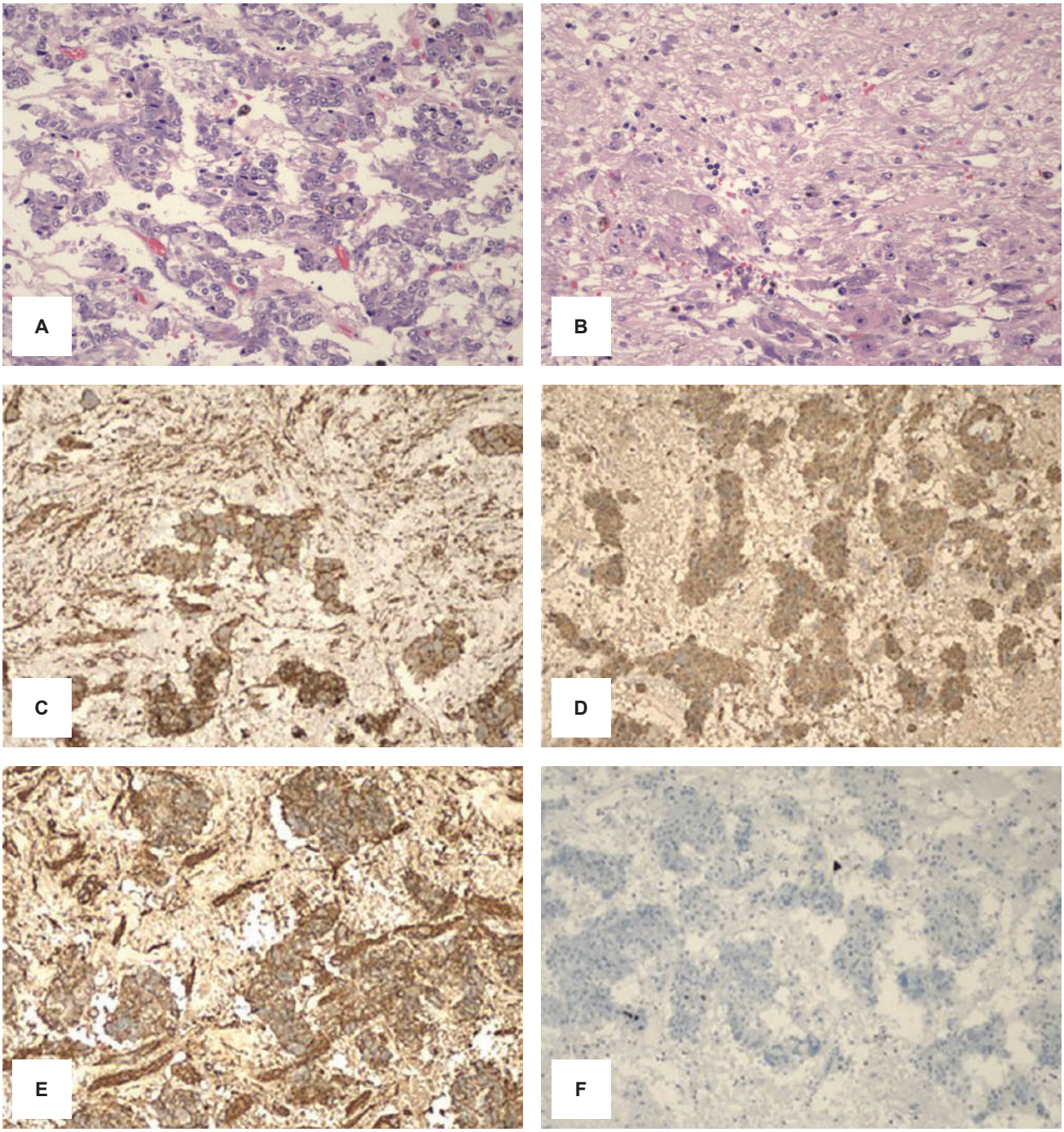


**Figure 3.** Histopathology of the mass. **(A)** Ganglioneuroma. The neoplastic cells are arranged in clusters set in loose fibrocollagenous stroma (H&E, 4x); **(B)** Ganglioneuroma. Neoplastic cells exhibiting mature ganglion cells with eccentric nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm with surrounding Schwannian stroma and spindle cells (H&E, 20x). Ganglioneuroma. Immunohistochemical stains show that the neoplastic cells are positive for **(C)** Synaptophysin, **(D)** Chromogranin, **(E)** CD56, and **(F)** negative for GFAP.

Although ganglioneuromas are thought to have no to low metabolic activity, several previous studies have reported high concentrations of catecholamines or MIBG uptake in intra- and extra-adrenal ganglioneuromas.[8,9]

It has been reported that up to 30% of patients with GNs may have elevated plasma and urinary catecholamine levels without exhibiting any symptoms of catecholamine excess.[10] Our patient was asymptomatic and definitely required surgical intervention for the large adrenal mass, however, without adequate preoperative preparation, he would have been at risk for potentially fatal complications of the surgery. Thus, it is prudent to thoroughly investigate suspicious adrenal masses biochemically to avoid missing excess catecholamine secretion from the adrenal mass as significant morbidity and mortality can ensue intraoperatively if the patient is not adequately prepared for surgery. This patient made a remarkable recovery despite the stormy intraoperative and postoperative complications that ensued.

Composite pheochromocytoma–ganglioneuroma tumors are different, rare entities, consisting of both endocrine and neural components. Embryologically, both chromaffin and ganglion cells are derived from neural crest cells and migrate to somatic areas.[11] Immunohistochemically, the individual components of these tumors resemble their normal counterparts or pure tumors of the same type. Synaptophysin and chromogranin are strongly and diffusely positive in pheochromocytoma, while weak or focal in ganglioneuroma or neuroblasts. Staining for S-100 protein identifies spindle-shaped Schwannian cells and sustentacular cells while neurofilament only stains the neural part of the composite tumor.

Histologically, the endocrine component is that of a typical pheochromocytoma, whereas the neuronal component is characterized by mixed areas of ganglioneuroma, neuroblastoma, or ganglioneuroblastoma.[12] Our patient's histopathological examination did not reveal any chromaffin cells, excluding a pheochromocytoma–ganglioneuroma.

## CONCLUSION

This case illustrates that ganglioneuromas can grow to a significant size and present incidentally. They can be asymptomatic, as in our patient, who had a catecholamine secreting, histologically and immunohistochemistry confirmed maturing type of adrenal ganglioneuroma.

Following resection, catecholamine levels normalized, confirming the resected right adrenal ganglioneuroma as the source of the catecholamine excess. The patient made a remarkable recovery subsequently.

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

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

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

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

# Gastric Outlet Obstruction Following Recurrent Pancreatitis Uncovers a Giant Parathyroid Adenoma: A Case Report

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**Abstract**

A 35-year-old female presented with abdominal pain, fever, projectile vomiting, and a diffuse tender epigastric mass. She was diagnosed to have acute persistent pancreatitis with a pancreatic pseudocyst. Elevated serum calcium levels provided an etiologic link between hypercalcemia and pancreatitis. On examination, a nodule was found in the left side of her neck which was later diagnosed as a giant left inferior parathyroid adenoma. This report highlights the critical analysis of history, examination, and investigations to reach an ultimate diagnosis. Pseudocyst drainage and parathyroidectomy resolved her symptoms.

*Key words: giant parathyroid adenoma, pancreatitis, gastric outlet obstruction, primary hyperparathyroidism*

## INTRODUCTION

Acute pancreatitis, an inflammation of the pancreas, can result in life-long morbidity and even mortality if not treated appropriately. Pancreatitis most commonly results from gallstone disease, alcohol intake, and following procedures like endoscopic retrograde cholangiopancreatography.[1] Primary hyperparathyroidism (PHPT) mediated hypercalcemia is comparatively a less common cause of pancreatitis (1.5-13%).[2]

Although PHPT is a common endocrine disorder, in Western literature, approximately 75-80% of patients are asymptomatic and are detected incidentally by routine calcium screening.[3] However, in our setup, due to lack of awareness and routine screening, patients are diagnosed in the symptomatic stage with the most common presenting features being bone pain and metabolic myopathy.[4] Seven percent of PHPT cases develop pancreatitis.[3]

However, PHPT manifesting as gastric outlet obstruction is rarely described in literature with no reports from India. Parathyroid adenomas are usually small (< 2 cm) and weigh less than 1 gram. However, in rare instances, adenomas may grow large and weigh more than 95$^{th}$ percentile or 3.5 grams. Such adenomas are labelled as "giant" adenomas.[5-7]

In this case report, we describe a young woman presenting with abdominal pain and non-bilious projectile vomiting. The features were suggestive of gastric outlet obstruction due to recurrent pancreatitis and pancreatic pseudocyst. An incidental finding of hypercalcemia was the only clue to an underlying PHPT leading to a whole gamut of signs and symptoms.

## CASE

A 35-year-old female presented to the emergency department complaining of intermittent abdominal pain over 3 months which became severe over the past two days. It was associated with fever and persistent postprandial non-bilious vomiting for seven days. She had a history of intermittent generalized body ache and epigastric pain which subsided after pain relievers. She also sustained blunt trauma to the abdomen after a fall, following which she had severe pain in the epigastric region.

She consulted in the Gastroenterology department where she was diagnosed to have acute pancreatitis based on blood investigations showing raised serum amylase (112 U/L; normal range: 28 - 100 U/L) and lipase levels (138 U/L; normal range: 13 - 60 U/L). A contrast-enhanced computed tomography (CT) of the abdomen showed a bulky pancreas

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with peripancreatic fluid collection in the head, body and tail.

During this episode, her vital signs were stable. There was no pallor, icterus, cyanosis, or edema. Examination of her abdomen revealed a diffuse, firm, and tender epigastric mass which did not move with respiration. Given the present findings and clinical background, recurrent pancreatitis with pancreatic pseudocyst was considered.

### Investigations

Ultrasound (USG) of her abdomen showed necrotic areas in the head of the pancreas with intra- and peripancreatic fluid collection. Contrast-enhanced CT (CECT) abdomen showed peripherally enhancing collection in the pancreatic bed replacing the entire pancreas with extension into the lesser sac and gastro-hepatic region with few air foci within suggestive of walled-off necrosis, likely a pseudocyst (Figure 1). These features were consistent with residual pancreatitis with a pseudocyst compressing the stomach leading to gastric outlet obstruction.

Hematologic parameters were normal except for leukocytosis (total count – 18000/mm$^3$). Blood chemistry showed normal serum amylase (38 U/L), lipase (25 U/L), and renal parameters. However, a remarkable finding was hypercalcemia (blood ionized calcium, $iCa^{2+}$- 1.9 mmol/L; normal range: 1.1 – 1.4 mmoL/L). Further evaluation of the cause of this hypercalcemia revealed raised total serum calcium (12.3 mg/dL; normal range: 8.6 – 10 mg/dL), and markedly raised parathormone (PTH) levels (PTH - 759 pg/mL; normal range: 15 – 65 pg/mL) with mild hypophosphatemia (serum phosphorus - 2.1 mg/dL; normal range: 2.5 – 4.5 mg/dL).

After noting the hypercalcemia, her neck was re-examined and a firm palpable nodule was discovered in the lower left side. Neck USG revealed a 2.3 x 1.1 x 1.8 cm hypoechoic lesion inferior to the left lobe of the thyroid. Further 4-dimensional CECT revealed a 1.5 x 1.5 cm lesion, posterolateral to the left lobe of the thyroid, with arterial enhancement and washout, suggesting a left inferior parathyroid adenoma. These findings were concordant with the results of the $^{18}$F-Fluorocholine PET/CT scan of the patient (Figure 2).

### Differential diagnosis

The possible causes of PHPT were parathyroid adenoma, parathyroid cyst, cystic adenoma and parathyroid carcinoma. USG, 4-dimensional CT, and $^{18}$F-Fluorocholine PET/CT imaging studies ruled out the possibility of a thyroid nodule or ectopic parathyroid.

### Treatment

The patient was finally diagnosed to have a left inferior parathyroid adenoma and hypercalcemia-induced recurrent

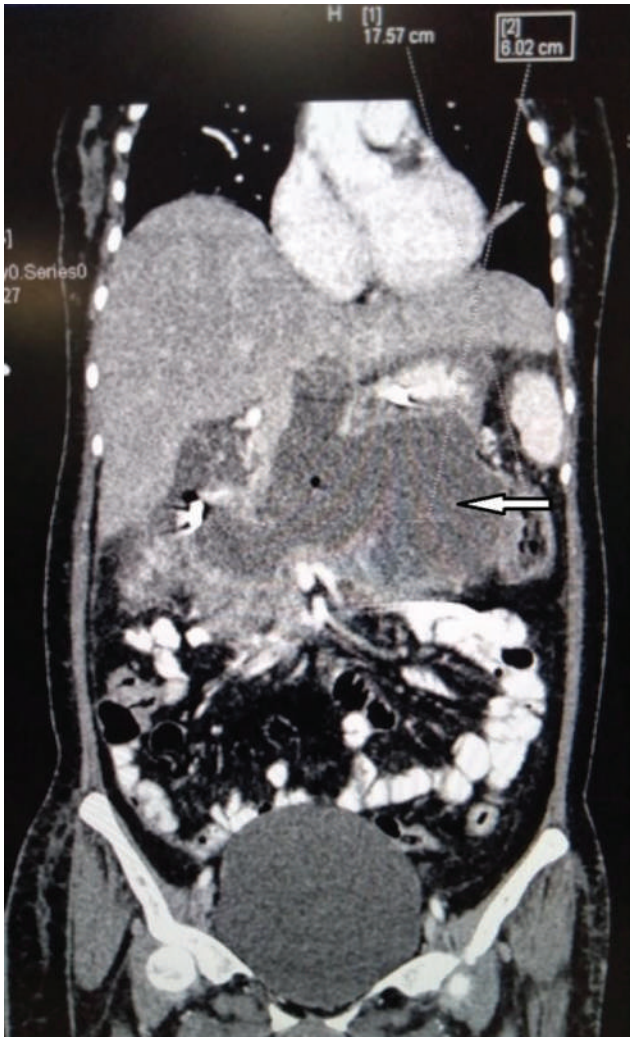


**Figure 1.** Contrast-enhanced CT scan of the abdomen showing pseudocyst of the pancreas (arrow) compressing the stomach.

pancreatitis with a pancreatic pseudocyst manifesting as gastric outlet obstruction. She was stabilized, a Freka's nasojejunal tube was inserted for feeding and a CT-guided abdominal external drain was placed to decompress the pseudocyst. The patient was prepared for focused parathyroidectomy in an elective setting with preoperative endocrine and anesthesia consults.

Intraoperatively, a parathyroid nodule was identified at the inferior pole of the left lobe of the thyroid gland and was excised (Figure 3). Gross examination of the surgically excised parathyroid specimen revealed a 2.8 cm x 3 cm globular and well-circumscribed tumor weighing 4.8 grams (Figure 4). Histological examination of the specimen was compatible with a benign adenoma (Figure 5).

Intact parathormone (iPTH) levels declined drastically in the immediate postoperative period (from 759 pg/mL to 67.25 pg/mL). Serial monitoring of serum calcium revealed hypocalcemia on the second postoperative day (serum total calcium - 8.0 mg/dL) and third postoperative day (serum total calcium - 7.8 mg/dL) accompanied by tingling and

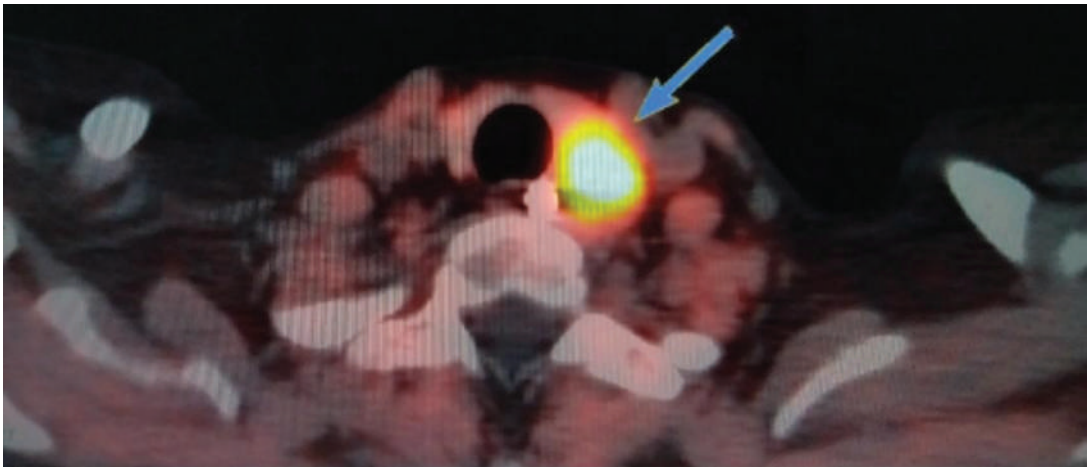

**Figure 2.** $^{18}$F-Fluorocholine PET/CT scan showing transaxial image of intense tracer uptake behind left lobe of thyroid suggesting parathyroid hyperactivity (arrow).

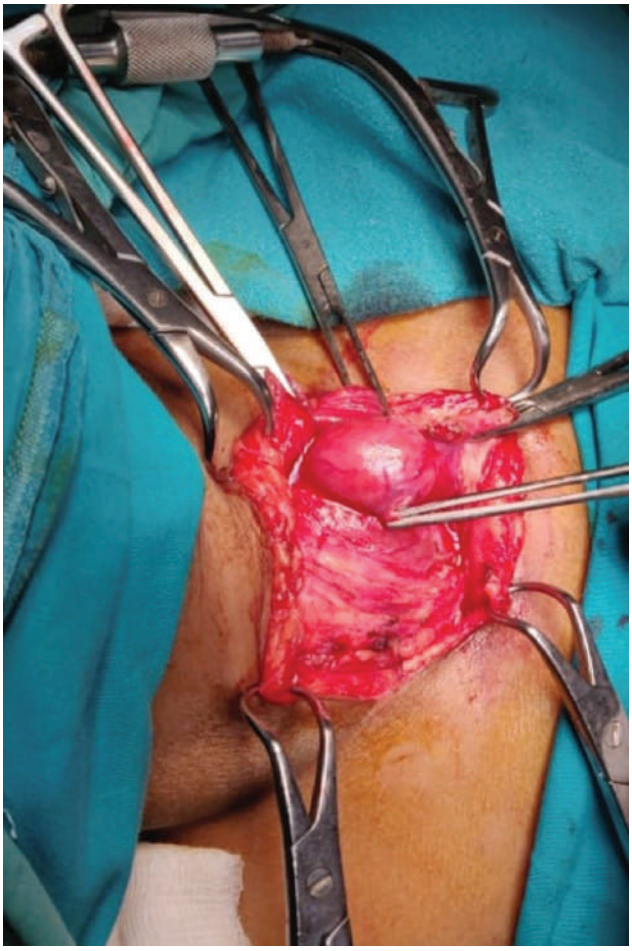

**Figure 3.** Intraoperative findings of focused parathyroidectomy showing enlarged left parathyroid.

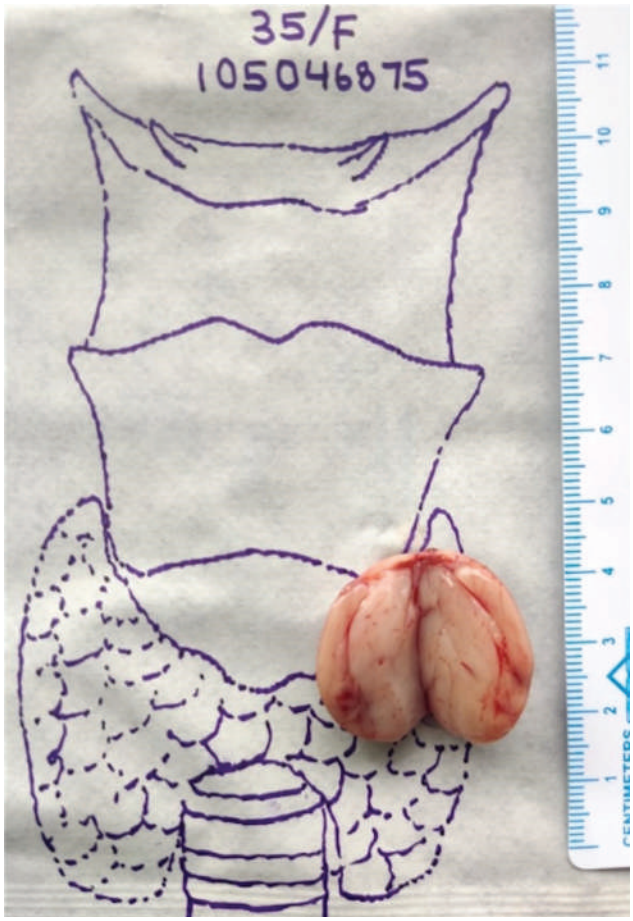


**Figure 4.** Schematic diagram showing the size and location of the parathyroid specimen with a cut section depicting gross features of adenoma.

numbness of the perioral region and extremities. These features were suggestive of hungry bone syndrome and managed with intravenous and oral calcium with vitamin D supplements.

The patient improved over 2 weeks with the resolution of abdominal pain. Postoperative abdominal USG revealed resolving pancreatitis. The nasojejunal tube was removed on the eighth postoperative day. The abdominal drain was removed on the tenth postoperative day. Oral feeding was gradually increased and was tolerated. She was discharged on the twelfth postoperative day. At 8 months follow-up, she was doing well and her serum calcium and parathormone levels were normal.

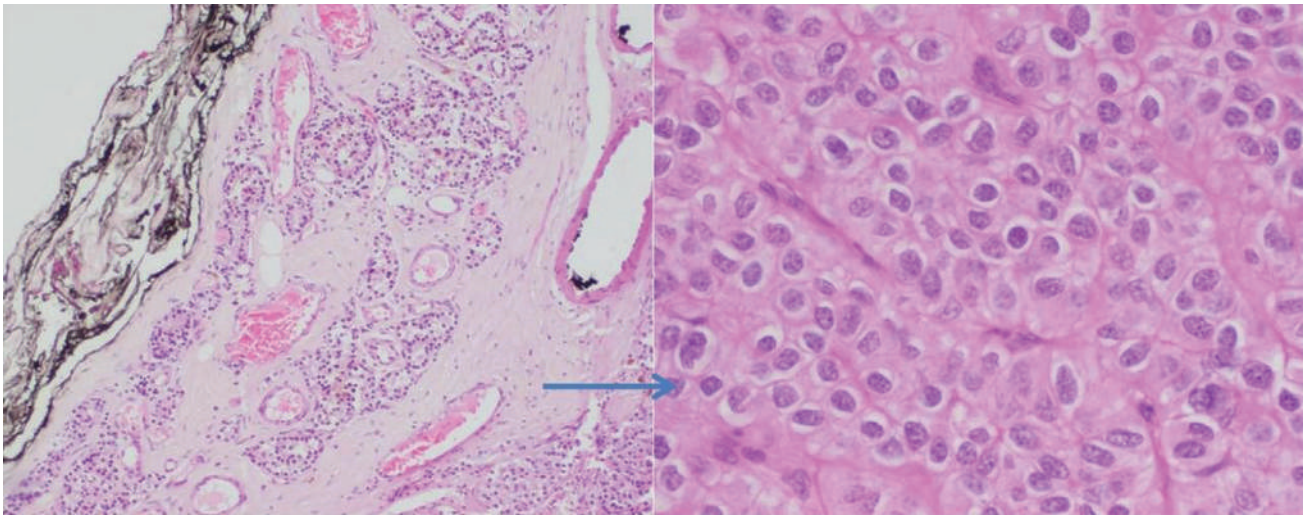

**Figure 5.** Histological examination revealed normal parathyroid tissue at the periphery of the cellular parathyroid tumor (arrow) (H&E, 100x). The inked resected surface can be seen on the upper left margin (H&E, 400x). A cellular parathyroid tumor composed of monomorphic population of chief cells. The tumor cells are arranged as nests separated by thin fibrovascular septae, showing minimal nuclear atypia and lacking mitotic activity (right).

## DISCUSSION

Primary hyperparathyroidism (PHPT) is one of the common endocrine disorders characterized by increased secretion of parathormone (PTH). It predominately affects women from the fifth to seventh decades of life.[8] Most frequent causes of PHPT include solitary parathyroid adenoma (85–90%), followed by parathyroid hyperplasia (10-15%), multiple adenomas (5%), and, rarely, parathyroid cancer (<1-5%).[9] PHPT is most commonly diagnosed in the asymptomatic stage by routine biochemical screening.[3] The classical features associated with symptomatic disease include fatigue, myalgias, bone pain, constipation, nephrolithiasis and bone demineralization.[10]

The size of parathyroid adenoma in cases of PHPT is variable and a significant correlation has been described between gland weight, calcium and PTH levels.[7] Patients with giant adenomas are more likely to have asymptomatic disease and solitary gland involvement despite higher mean preoperative calcium and PTH levels. However, symptoms of postoperative hypocalcemia are more frequent compared to non-giant adenomas.[7] Although our patient had a giant adenoma, the symptoms related to hypercalcemia were remarkable with the rare manifestation of gastric outlet obstruction.

The association of pancreatitis with PHPT is between 1.5 – 15.0% in various studies.[9,11-13] with acute, recurrent, and chronic forms of pancreatitis reported.[2] Factors precipitating pancreatitis in cases with PHPT include hypercalcemia-mediated pancreatic duct stone formation and activation of intrapancreatic trypsinogen to trypsin, both of which lead to parenchymal injury.[2] Genetic predisposition may explain the development of pancreatitis only in a subset of patients with PHPT.[11,14] The prevalence of pancreatitis in PHPT ranges from 6.8 to 15 percent in the Indian population compared to 3.2 to 8.1 percent in the Western population.[11] The incidences of PHPT-associated acute and chronic pancreatitis are almost similar in the Indian population, but acute pancreatitis predominates in the Western population.[12]

Among patients with acute pancreatitis, 7% develop pancreatic pseudocysts[15], while among those with chronic pancreatitis, 30-40% develop pancreatic pseudocysts.[16] Approximately 50% of these may remain asymptomatic or regress spontaneously; the rest may develop acute or chronic complications in the form of infection, bleeding, rupture, bile duct dilatation, gastric outlet obstruction or thrombosis of the portal or splenic vein.[17]

Gastric outlet obstruction due to pressure effect has been reported in 8%[18] of acute pancreatitis (due to any cause) related pseudocysts and 15%[17] of chronic pancreatitis (due to any cause) related pseudocysts. There is no consensus on whether surgical drainage is required for acute pancreatitis-induced pseudocyst without infection.[18] However, persistent vomiting from gastric outlet obstruction due to pseudocyst predisposes to malnutrition.[19] The risk of pseudocyst infection increases in the malnourished patient ultimately worsening the prognosis.[18] Therefore, most clinicians agree that surgical drainage is an effective treatment for pancreatic pseudocyst with features of gastric outlet obstruction.[18,20]

Symptoms of bone pain, recurrent nephrolithiasis, neuromuscular weakness and psychiatric disorders must raise the suspicion of parathyroid disease and prompt further evaluation. Elevated levels of serum calcium and PTH confirm the diagnosis.[7]

Localization of parathyroid adenoma is done by imaging studies like cervical USG, sestamibi scintigraphy, and

magnetic resonance imaging (MRI).[6,8] A Tc99m Sestamibi scan of the parathyroid glands has a sensitivity of 92% while neck USG has a sensitivity of 80% for the preoperative localization of parathyroid adenomas.[21]

Newer modalities like PET-CT imaging with $^{18}$F-fluorocholine ($^{18}$F-FCH) tracer carry advantages in terms of detection of smaller adenomas and reduced scanning time with a high sensitivity of 92% and specificity of 100%.[22] Moreover, PET-CT $^{18}$F-FCH has an advantage in identifying smaller lesions very close to the thyroid, low gland mass, and multiple gland involvement.[23]

In this case, the diagnosis was made based on the elevated serum calcium and PTH levels. Initial screening of the neck was conducted using USG, while localization of the lesion was done by 4D-CT. We also performed a PET-CT $^{18}$F-FCH to rule out ectopic parathyroid tissue.

Surgical excision of the parathyroid adenoma is the preferred treatment. Documenting intraoperative or immediate postoperative decline in iPTH levels is important to confirm successful removal of the adenoma. Close monitoring of serum calcium levels in the postoperative period is crucial for the diagnosis and management of life-threatening hypocalcemia.[24] Long-term follow-up is equally important as the postoperative course can be complicated by episodes of acute or chronic pancreatitis. However, various studies have shown significant improvement in abdominal symptoms and a low recurrence of pancreatitis when normocalcemia is achieved following removal of the parathyroid adenoma.[25,26] Our patient's symptoms also improved without any recurrence of pancreatitis over 8 months of follow-up.

## CONCLUSION

The present case report emphasizes the importance of thorough history taking and clinical examination to reach a final diagnosis. It is equally important to analyze laboratory investigations and their correlation with clinical signs and symptoms because PHPT may have myriad manifestations, and pancreatitis in a young, non-alcoholic patient warrants evaluation of endocrinologic causes.

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

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

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

**Funding Source**
None.

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CASE REPORT

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# Treatment Outcome of a β-hCG Secreting Intracranial Germ Cell Tumor in an Adult Filipino Using Definitive Chemotherapy Followed by Radiotherapy: A Case Report

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**Abstract**

We report a case of a 24-year-old Filipino male who complained of general weakness, polydipsia, weight loss, bitemporal headaches, loss of libido and behavioral changes. Endocrine work-up revealed neurogenic diabetes insipidus and panhypopituitarism. Brain MRI showed multiple intracranial tumors in the left frontal lobe, pineal and suprasellar region with moderate non-communicating hydrocephalus. Intracranial mass biopsy with ventriculo-peritoneal shunting was done. Histopathology of the mass and CSF revealed a germinoma. He underwent chemoradiotherapy while on maintenance hormone replacement.

*Key words: Germ cell tumors (GCTs), germinoma, β-hCG, hypopituitarism, diabetes insipidus*

## INTRODUCTION

Primary intracranial germ cells tumors (GCT) are rare accounting for 3-5% of pediatric intracranial tumors, but only 0.4-1% of intracranial tumors in adults.[1] The comparative incidences are 14.3% in Japan,[2] 14.0% in Taiwan,[3] 11.2% in Korea,[4] 2.3% in USA,[5] and 2.5% in Germany,[6] in various reported series. Data on pineal gland tumors from a single center in the Philippines reported close to 40% (17 of 42 patients) with pineal GCT.[7]

The World Health Organization classified intracranial GCT into three groups: germinomas, non-germinomatous germ cell tumors (NGGCTs) and mixed germ cell tumors.[8] Intracranial GCTs can also be subdivided into secreting and non-secreting tumors. Classically, secreting GCTs are defined as GCTs with cerebrospinal fluid (CSF) alpha feto protein (AFP) >10 μg/L (or above the institutional normal range) and/or a CSF beta human chorionic gonadotropin (β-hCG) level >50 IU/L. Secreting GCTs are considered more aggressive and carry a poorer prognosis than non-secreting GCTs. These typically occur in children or young adults with the majority (60-70%) under 20 years of age. GCT occurs primarily in males, with a male to female ratio of 2:1 in germinoma and 3:1 ratio in NGGCT.[1] Local data also reflects a similar epidemiology among the pediatric male population.[7]

Intracranial GCTs are heterogeneous with respect to histology, biological profile, response to treatment and secretion of AFP and β-hCG into the serum and/or CSF.[9] Clinical presentation depends upon the size and the localization of the tumor. The majority of GCTs are located at the pineal region, followed by the suprasellar region.[10] Pineal gland tumors often manifest with symptoms of obstructive hydrocephalus.[11] Suprasellar tumors are often characterized as endocrinopathies due to the disruption of the hypothalamic pituitary axis.[12] However, visual disturbances may also arise if the suprasellar tumor expands dorsally and compresses the optic chiasm.[11] In some instances, the large suprasellar mass can displace the optic chiasm and expand to the third ventricle, resulting in hydrocephalus.[13] For patients with bifocal tumors at the suprasellar area and pineal gland, hypothalamic and pituitary disorders as well as compression symptoms may be seen.[13]

Hypothalamic pituitary dysfunction may include diabetes insipidus (DI), delayed pubertal development, isolated growth hormone deficiency, hypogonadotropic hypogonadism and hypopituitarism, including central hypothyroidism and adrenal insufficiency. DI is the most common and is often the first presentation. Ophthalmic abnormalities, including bilateral hemianopsia, may also develop due to chiasmic or optic nerve compression.[1,11-13]

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Delays in diagnosis, defined as an interval of more than or equal to 6 months from the onset of symptoms to the date of cranial MRI imaging[11], are common and may exceed 12 months. The symptoms are unfortunately not recognized as an endocrinopathy, hence the delay in diagnosis. As a result of the delay, these patients have a higher incidence of disseminated disease.[11-12]

Germinomas are the most common subtype of intracranial GCTs occurring in 70–80%. They are histologically identical to testicular seminoma and dysgerminoma of the ovary.[14] Patients with pure germinoma may have elevated β-hCG but AFP is never elevated. The β-hCG secreted by GCTs causes gonadotropin-independent hypergonadism with low LH/FSH and high testosterone due to the stimulating effect of β-hCG on the LH receptor in the testes. When this happens in pediatric male patients, precocious puberty will occur. On the other hand, among pediatric female patients, development of precocious puberty requires a rise in LH and FSH on top of the increase in β-hCG. Because of this, precocious puberty is more common in pediatric males than females.[15]

Local data reports endocrine dysfunction such as diabetes insipidus, hypothyroidism, and hypocortisolism in 10 patients presenting with pineal gland tumors. Among them, 6 had bifocal (pineal and suprasellar) tumors while 4 had purely pineal gland tumors.[7]

We report this rare case of an adult with an unusual initial clinical manifestation of central DI, followed by visual abnormalities and symptoms of obstructive hydrocephalus. Referral to endocrinology was made for management of DI. Other manifestations of panhypopituitarism were recognized early and appropriate hormonal treatment was started.

## CASE

A 24-year-old male presented with behavioral changes. Seven months prior to consult, he had polyuria and excessive thirst for ice cold drinks taken every 2 hours. This persisted until 4 months prior to consult, together with poor work performance, lack of energy, insomnia and weight loss of 5 kg in 3 months.. He also experienced rotatory dizziness and unprovoked intermittent bitemporal headaches graded 5/10 relieved by rest. He sought consult and was assessed to have benign paroxysmal positional vertigo and prescribed with betahistine 24 mg taken twice daily which afforded no relief of dizziness or headache. Subsequently, he had unstable gait necessitating assistance on ambulation.

Three months prior to consult, he was noted to have hourly oral fluid intake of at least 500 mL with daily urine output of more than 5 liters which did not decrease after fluid restriction. A month later, he developed emotional instability with behavioral changes such as irritability, forgetfulness, incoherent answers with lucid intervals. He was seen by a psychiatrist who initially gave a diagnosis of schizophrenia. However, with the acuteness of symptoms and presence of diplopia, he was referred to a neurologist and an endocrinologist. On further inquiry, he had decreased libido and lack of spontaneous erection since 7 months ago. He shaved his facial hair only once a week compared to daily a year ago. He also had cold intolerance, constipation and easy fatigability. His family history was unremarkable. Physical examination revealed an adult male, chronically ill with slow speech. He had diplopia on leftward lateral gaze. He had sparse pubic and axillary hair without gynecomastia. His testes were normal in size, without any masses or tenderness.

Cranial MRI revealed a 3.3 x 2.4 cm tumor in the pineal gland, a 1.7 x 0.9 cm mass localized in the suprasellar region and 4.5 x 2.4 cm mass located in the frontal lobe with evidence of hydrocephalus (Figure 1A).

During his hospitalization, his daily urine output was 5-6 liters. Urine osmolality was low at 164 mOsm (NV: 500-800 mOsm) with serum sodium of 155 mEq/L. This suggested neurogenic diabetes insipidus (DI). He was started on desmopressin 100 mcg/tablet, ½ tablet 3x a day. This resulted in symptomatic improvement. Further hormonal work-up revealed low cortisol, low luteinizing hormone but with normal testosterone, low free thyroxine but with normal thyroid stimulating hormone. See Table 1 for complete endocrinologic workup. A diagnosis of panhypopituitarism was made based on the cranial MRI findings, and the presence of hypogonadism, central hypoadrenalism and central hypothyroidism. He was started on hormone replacement therapy of prednisone 5 mg per day and levothyroxine 50 mcg per day.

He underwent septum pellucidotomy with ventriculoperitoneal shunting and biopsy of the cranial mass. Histopathology revealed a germinoma. The tumor cells stained positive for placental-like alkaline phosphatase (PLAP) and c-Kit (CD117). The CSF AFP and CSF β-hCG are markedly elevated (Table 1). These clinched the diagnosis of Primary Intracranial NGGCT, stage M1.

He had his first cycle of chemotherapy (100 mg/m$^2$ Etoposide per day for days 1-5 as a 4-h infusion in 0.9 sodium chloride in a total of 500 mL; 20 mg/m$^2$ Cisplatin per day for days 1-5 as a 4-h infusion with 0.9 sodium chloride in a total of 500 mL, Ifosfamide with MESNA) at the Benavides Cancer Institute of the University of Santo Tomas Hospital, Manila, Philippines. A daily dose of dexamethasone 10 mg/IV was given as pre-chemotherapy medication.

After 4-6 weeks, his hormone levels were all within normal limits. He had marked improvement in mood. There was resolution of easy fatigability. He was also able to perform activities of daily living without assistance.

After three cycles of chemotherapy, repeat cranial MRI (Figure 1B) showed interval regression of the frontal

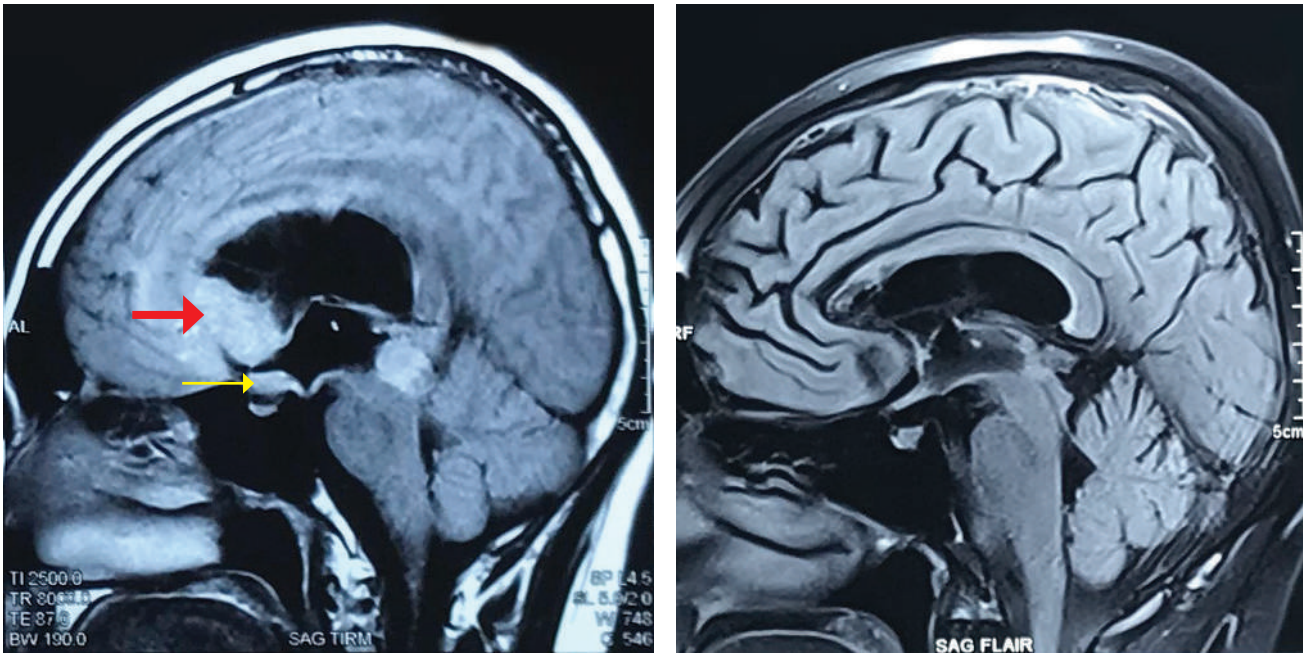


**Figure 1. (A)** Pretreatment cranial MRI in sagittal section. There was a 4.5 x 2.4 x 2.2 cm mixed signal predominantly isointense lobulated mass in the left frontal lobe parasagittal region extending across the midline with involvement of the anterior corpus callosum to the right frontal lobe *(thick arrow)*. The mass encroached into the left frontal horn and anterior third ventricle. Mixed signal lesions were also seen in the pineal gland about 3.3 x 2.4 x 2.2 cm and in the suprasellar region measuring about 1.7 x 0.9 cm *(thin arrow)*. There was also moderate non-communicating hydrocephalus. **(B)** Postreatment cranial MRI in sagittal section showing tumor size reduction (1.6 x 0.8 cm) in the frontal lobe and resolution of suprasellar and pineal masses.

**Table 1.** Summary of hormonal investigation and oncologic workup of the patient pretreatment and after treatment

| Laboratory test | Normal value | Patient's result pretreatment | Patient's result after 3rd cycle of chemotherapy | Patient's result after completing chemoradiotherapy |
|---|---|---|---|---|
| ***Endocrine workup*** | | | | |
| Urine osmolality (mOsm) | 500-800 | 164 | | |
| Serum sodium (mEq/L) | 135-145 | 155 | 139 | 139.3 |
| Luteinizing hormone (mIU/mL) | 1.7-8.6 | <0.01 | | |
| Testosterone (ng/mL) | 2.8-8.0 | 5.5 | | |
| Thyroid stimulating hormone (uIU/mL) | 0.35-4.94 | 0.83 | 0.35 | |
| Free thyroxine (ng/dL*) or (pmol/L**) | Variable | 0.54 (NV 0.70 - 1.48*) | 9.6 (NV 9 - 23.2**) | 1.18 (NV 0.93 - 1.71*) |
| Serum 8am cortisol (mcg/dL) | >15 | 1.79 | | |
| ***Oncologic Workup*** | | | | |
| Serum AFP (ng/mL) | ≤7 | 6.6 | 3.17 | |
| Serum β-hCG (mIU/mL) | 0 – 0.6 | 19.97 | <0.100 | |
| CSF AFP (ng/mL) | ≤1.5 | 2.5 | <0.61 | |
| CSF β-hCG (mIU/mL) | <1.0 | 516.81 | 1.26 | |
| Cytology | Negative | Positive | Negative | |

mass which measured 1.6 x 0.8 cm from 4.5 x 2.4 cm. The masses on the pineal gland and suprasellar region were no longer present. Repeat oncologic workup revealed marked improvement in the levels of β-hCG and AFP both in the serum and CSF (Table 1). His levothyroxine was periodically adjusted to maintain an FT4 goal at mid- to upper-limit of normal value. His desmopressin dose was adjusted based on monitoring of thirst, urine output and sodium level. Overall, he gained a total of 4 kilograms since his treatment started. He underwent another cycle of chemotherapy (total of four cycles of chemotherapy) and completed 17 fractions of craniospinal 30.6 Gy and 13 fractions of 23.4 Gy brain boost gross tumor.

## DISCUSSION

We present the case of a 24-year-old male with visual abnormality, obstructive hydrocephalus, diabetes insipidus and pituitary dysfunction. Given the multifocal tumor location, patient's hormonal dysfunction and mass compression symptoms were evident. Figure 2 explains the pathophysiology for the clinical manifestation of the patient.

Our patient had low LH but with normal testosterone. Among adults, there was one reported case of a 38-year-old man with panhypopituitarism and hyperandrogenemia

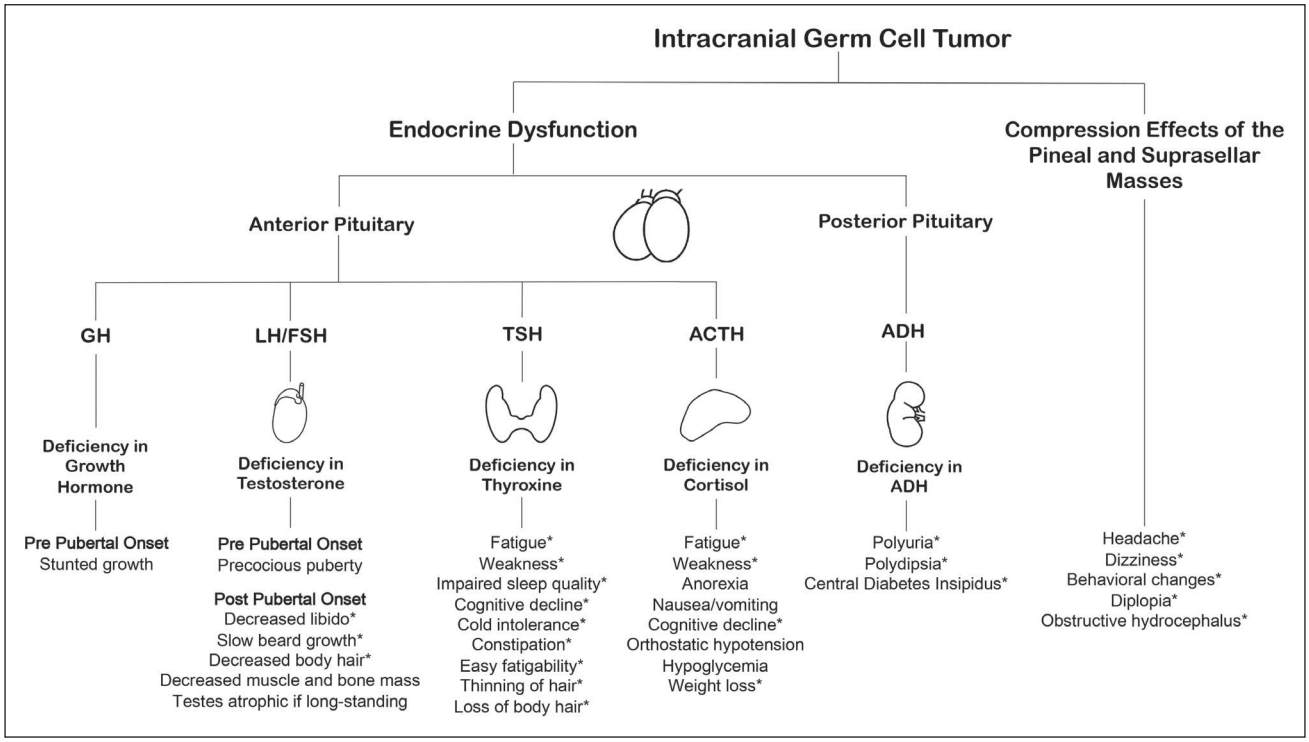


**Figure 2.** Pathophysiology of clinical presentation of intracranial germ cell tumor.
(*) represents signs and symptoms present in the patient.

associated with β-hCG secreting intracranial GCT. In spite of hyperandrogenemia, this patient experienced low libido, motivation and vitality.[16] A 32-year-old male was reported with testicular seminoma and increased β-hCG secretion, and hyperandrogenism that manifested as worsening acne and increasing muscle bulk.[17] Other case reports of testosterone excess by seminoma in testes or mediastinum presented with gynecomastia or male infertility in adult male patients.[18-19]

The behavioral change and visual abnormalities exhibited by the patient were attributed to structural compression secondary to the brain tumors. His symptoms, including fatigue and weakness, improved following hormone replacement with levothyroxine and prednisone.

Fortunately, the definitive diagnosis of GCT was obtained through histopathology and immunostaining. The majority of GCTs demonstrate immunohistochemical staining for placenta-like alkaline phophatase and c-Kit, otherwise known as CD117, which is an important mitogen for normal germ cells.[20] CSF β-hCG assays reflect the intensity of intracranial β-hCG secretion and are more sensitive than serum β-hCG levels.[20] The levels of β-hCG and AFP can be measured in the CSF and high levels could indicate malignancy. CSF cytology helps establish tumor extension to the ventricular system and spinal subarachnoid region.

The treatment options involve radiotherapy, chemotherapy and radiosurgery. Intracranial GCTs are sensitive to chemotherapy and radiotherapy. Craniospinal irradiation (CSR) or whole ventricular radiotherapy to a dose of 25–35 Gy followed by a primary tumor boost for a total dose of 45–50 Gy is associated with a superior outcome, with a 5-year survival rate of 80–99.5% in retrospective and prospective studies.[21]

When planning the initial treatment strategy against intracranial GCT, pathological subtype and disease extent (especially spinal metastasis) are the most important factors. Traditionally, CSR is considered the gold standard of treatment against intracranial germinoma. However, concerns about late neurologic detrimental effects of CSR, especially in young patients, have led physicians to omit spinal irradiation and reduce the radiation field as much as possible in limited disease.

In this regard, the German Cooperative Prospective Trials MAKEI 83/86/89 examined the outcome after radiotherapy alone at a reduced dose. After a median follow-up of 61 months, results showed that 5-year relapse-free survival rate was 91.0% and the overall survival rate was 93.7%; thus, justifying the effectiveness of reduced radiotherapy doses.[22] However, among patients with NGGCT, only 20-40% of the patients respond to radiotherapy alone; hence the need for chemotherapy as well.[23]

Based on previous reports about chemotherapy against intracranial GCT, methotrexate, ACNU, vinblastine, vincristine, bleomycin, ifosfamide, etoposide and carboplatin/cisplatin had been used as main chemotherapeutic agents. Chemotherapy with cyclophosphamide, ifosfamide, etoposide, cisplatin, and carboplatin were highly effective in CNS GCTs.[24] However, chemotherapy alone was proven

to be inferior compared to radiotherapy-based treatment protocols. The Second International CNS Germ Cell Study Group showed that intensive chemotherapy was effective only in one-third of patients with 5-year event free survival and overall survival rates were 36% and 75%, respectively, and patients were salvaged through radiotherapy.[25] Likewise, the Third International CNS Germ Cell Tumor Study also confirmed that a chemotherapy only approach led to inferior survival. The 6-year event free and overall survival was 45.6% and 75.3%, respectively.[26]

In our case of metastatic intracranial NGGCT, the standard of therapy is a multimodal treatment approach with chemotherapy and craniospinal irradiation.[27] Radiation therapy remains the backbone of the treatment regimen. Administration of chemotherapy with radiotherapy led to shrinkage of tumor size and reduction of radiotherapy dose; thus, minimizing radiation-related toxicity and improving long-term survival rates.[1,27]

The decision was to treat this patient's pituitary germinoma with 4 sessions of chemotherapy followed by radiotherapy in accordance to the SIOP CNS GCT 96 trial.[28] The chemotherapeutic agents were selected primarily based on the experience in gonadal GCT treatment. Recently, many institutions have preferentially used a combination chemotherapy consisting of ifosfamide, cisplatin and etoposide as one of the mainstays of treatment.[29] The 5-year progression-free survival and overall survival were 68% and 75%, respectively.

Significant prognostic factors included serum and/or CSF AFP >1000 ng/mL and residual disease after treatment. An AFP > 1000 ng/mL led to a progression-free survival rate of 32% as compared to 76% in those with AFP <1000 ng/mL. Moreover, residual disease after completion of chemoradiotherapy resulted in a progression-free survival rate of 48% as compared to 85% in those without residual tumors.[27]

In our patient, the post-treatment cranial MRI revealed that the tumors markedly decreased in size. Both the β-hCG and AFP levels in the serum and CSF were brought down to the normal range. The patient has maintained a stable disease status. He was followed up monthly during his chemotherapy and radiotherapy sessions for a total of 6 months. Thereafter, patient should ideally follow-up every 3 months, but he only came to clinic every 6 months, for a total of 18 months.

A retrospective review of long-term toxicity effects of radiotherapy and/or chemotherapy among adolescents and young adults showed that a significant proportion of patients developed late effects after 10 years. The most common was physician-reported neurocognitive impairment. Fifteen percent of patients developed new treatment-induced hormone deficiency, more commonly, hypothyroidism followed by hypogonadism and diabetes insipidus.[30]

In a reported case, pituitary dysfunction in the form of hypogonadotropic hypogonadism occurred secondary to germ cell tumor specific therapy; hence, hormone replacement therapy was recommended.[31] Conversely, patients who developed endocrine dysfunction secondary to suprasellar involvement do not usually recover completely and are dependent on hormone replacement therapy.[13,30] Surgery or radiation therapy may increase the severity of these endocrine and hypothalamic deficiencies. Late effects from chemotherapy are drug dependent. Cisplatin use was associated with increased risk of ototoxicity.[30]

## CONCLUSION

Pineal and suprasellar germinomas are rare tumors that can occur in adulthood and are characterized by the presence of endocrine dysfunctions such as central diabetes insipidus, hypogonadotropic hypogonadism and panhypopituitarism as initial clinical manifestations. Hormonal deficiency can manifest prior to mass compression symptoms, delaying neurologic evaluation and imaging; hence, early recognition and implementation of treatment are important to improve outcomes. Adult intracranial GCTs are sensitive to chemoradiotherapy, resulting to good overall prognosis. Late treatment effects of chemoradiotherapy can occur; thus, requiring long-term monitoring with hormonal replacement and follow-up.

**Ethical Consideration**
Upon acknowledgment from JAFES the need to seek an updated patient consent, the author reviewed his outpatient and inpatient charts for his contact information.

The first listed contact is a cellphone number that belonged to his common law partner, who accompanied the patient during his check-ups, but she did not reply when asked if she still has any contact information of the patient. She also did not answer calls.

The second contact number is a landline number but this number is “not in service.”

The third contact number did not answer to multiple attempts of text messages or calls.

The authors tried their best to reach the patient but all attempts were unsuccessful.

**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

# Ectopic Papillary Thyroid Carcinoma Presenting as Right Lateral Neck Mass: A Case Report

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**Abstract**

A lateral neck mass can be the initial presentation of a papillary thyroid carcinoma. A 24-year-old female presented with a 2.0 x 2.0 cm, non-erythematous, non-tender, right lateral neck mass. A neck ultrasound showed an enlarged right jugulodigastric (Level II) lymph node and a normal-sized thyroid gland exhibiting mild parenchymal disease with no nodules. Positron emission tomography-computed tomography scan (PET-CT) showed an enlarged intensely fluorodeoxyglucose (FDG)-avid right level III lymph node, which may be primary versus metastatic. Fine-needle aspiration biopsy (FNAB) of the lymph node showed the presence of atypical cells that are highly suspicious for metastatic carcinoma. A cervical lymph node excision biopsy was performed and histopathology showed metastatic papillary thyroid carcinoma. The patient underwent total thyroidectomy with neck dissection. The final histopathologic examination of the thyroid gland revealed chronic lymphocytic thyroiditis with the lymph nodes negative for metastasis. She eventually underwent radioactive iodine ablation (RAI) with a dose of 30mCi. Post-RAI whole-body scan showed functioning thyroid tissue remnants with no distant metastasis. This case adds to the limited data that ectopic thyroid carcinoma can be present in patients who initially present with neck masses.

*Key words: thyroid, papillary carcinoma*

## INTRODUCTION

Lateral neck mass as a manifestation of occult thyroid carcinoma is rare, comprising less than 1% of all thyroid carcinoma cases.[1] Diagnosis rests on the failure to detect a primary tumor within the thyroid gland after a thorough histopathologic examination.[2] Among the different types of thyroid cancers, papillary carcinoma has the highest rate of occurrence, similar to those found in native thyroid carcinoma. We report a female with a papillary thyroid carcinoma presenting as a lateral neck mass.

## CASE

A 24-year-old, asymptomatic Filipino female, consulted due to an incidental finding of a right lateral neck mass. She does not smoke nor does she have previous neck irradiation, thyroid disease or family history of thyroid cancer. On physical examination, there was a non-erythematous, non-tender, firm, movable, 2.0 x 2.0 cm nodule at level II of the right cervical region. Thyroid function tests were normal: TSH was 1.995 uIU/ml (reference range 0.35 – 4.94), FT4 was 0.93 ng/dl (reference range 0.7-1.48), and FT3 was 2.77 pg/ml (reference range 1.71-3.71). A neck ultrasound showed an enlarged right jugulodigastric level II lymph node and a normal-sized thyroid gland exhibiting mild parenchymal disease with no nodules (Figures 1 to 3).

PET-CT scan revealed an enlarged intensely FDG-avid right level III lymph node measuring 1.7 cm which may be a primary or metastatic lesion. FNAB of the lymph node showed atypical cells highly suspicious for a metastatic carcinoma (Figure 4). Subsequent excision biopsy showed that the lymph node architecture was predominantly effaced with the tumor. The impression was a metastatic papillary thyroid carcinoma (Figures 5 and 6).

The patient underwent total thyroidectomy with selective right neck lymph node dissection (levels III, IV, VI). The postoperative diagnosis was papillary thyroid carcinoma stage I (T0N1MX). Histopathology of the thyroid gland showed chronic lymphocytic thyroiditis with all eight lymph nodes negative for tumor (0/1 level III and 0/7 level VI) (Figure 7). The thyroid gland was submitted in its entirety and blocked for histologic evaluation. The right lobe measured 3.3 x 2.0 x 1.0 cm, the isthmus measured 1.45 x 1.1 x 0.6 cm, and the left lobe measured 4.2 x 2.4 x 2.1 cm. Thyroid tissue sections 0.2 to 0.3 cm thick were prepared with no grossly visible mass noted on inspection. Serial sections 4 microns thick for each block

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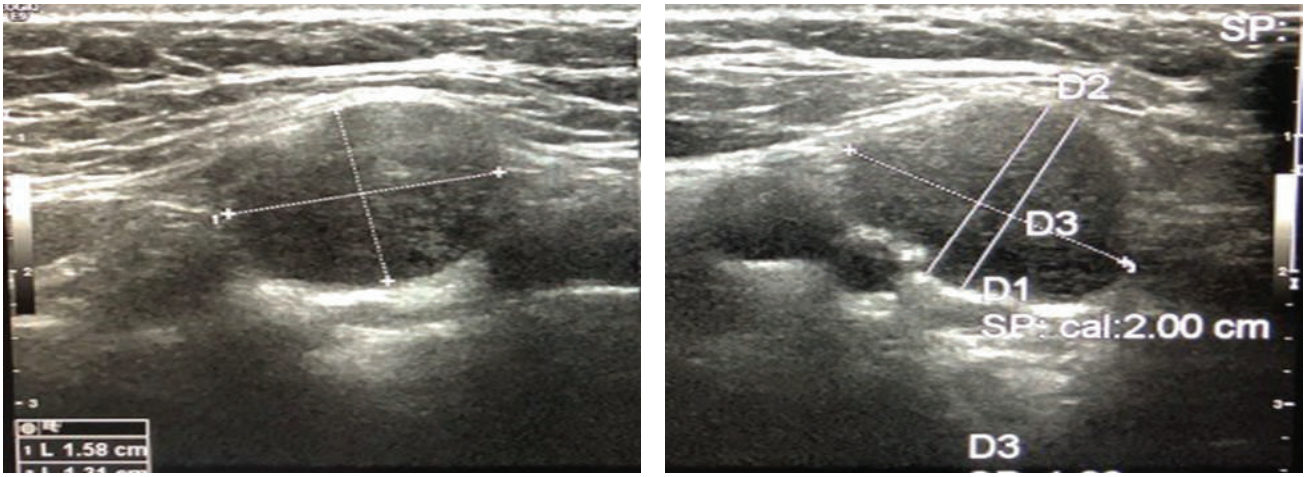


**Figure 1.** Ultrasound of the neck: 1.8 x 1.3 x 1.6 cm enlarged lymph node in the right superior jugular chain (level II), with x 10 magnification.

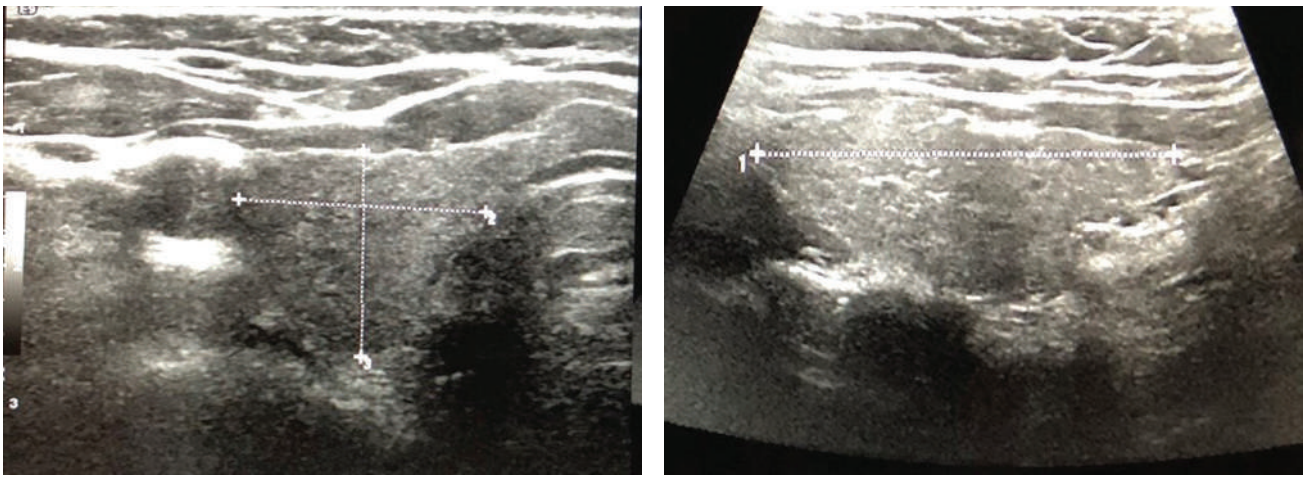

**Figure 2.** Ultrasound of the right thyroid lobe: The right lobe measured 3.3 x 2.0 x 1.0 cm, with x 10 magnification.

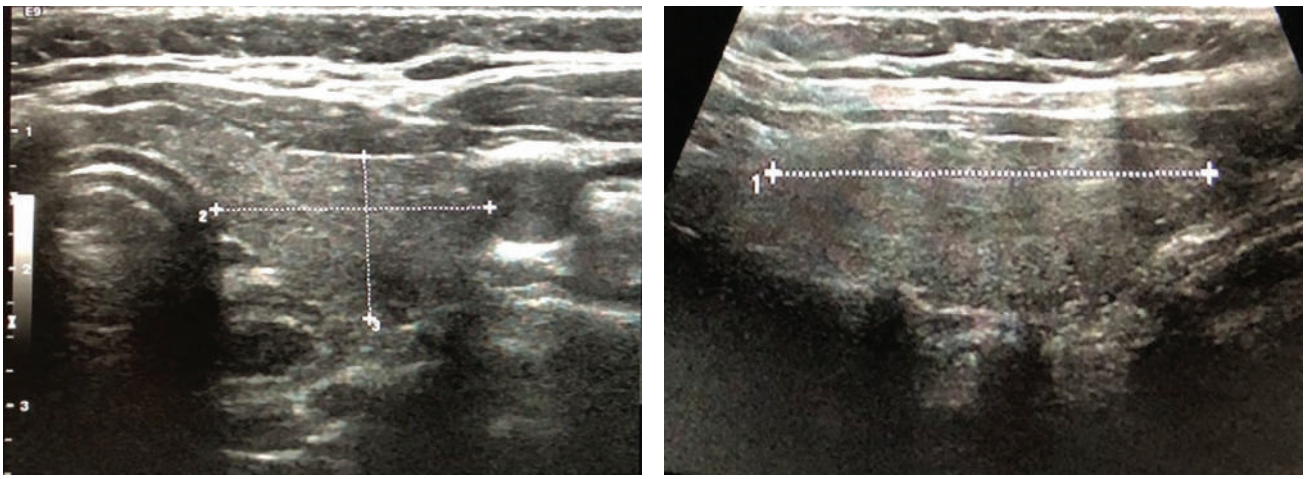

**Figure 3.** Ultrasound of the left thyroid lobe: The left lobe measured 4.2 x 2.4 x 2.1 cm, with x 10 magnification.

were analyzed; each slide was examined by at least seven different pathologists. Histopathology of the thyroid gland was negative for malignancy. The patient was managed as having papillary thyroid carcinoma from an ectopic thyroid tissue located at the right lateral cervical region.

Postoperatively, the patient underwent radioactive iodine ablation with a dose of 30mCi. Post-ablation whole-body scan showed functioning thyroid remnants with no distant metastasis. She is currently asymptomatic. She is on calcium supplementation and levothyroxine suppression.

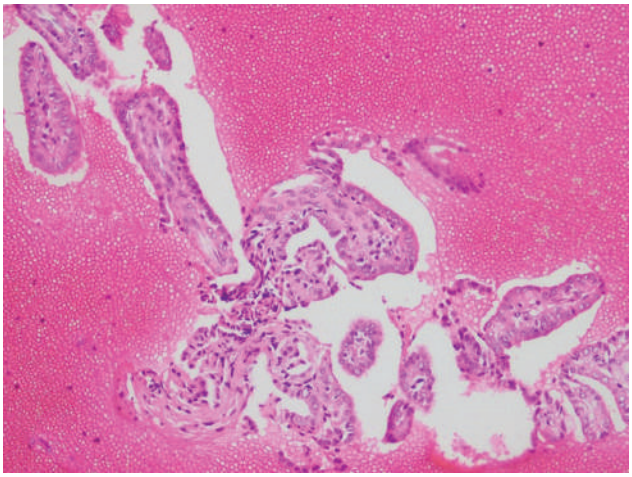

**Figure 4.** Right cervical lymph node FNAB: Atypical cells present were highly suspicious for a metastatic carcinoma (Papanicolaou Stain, 40x).

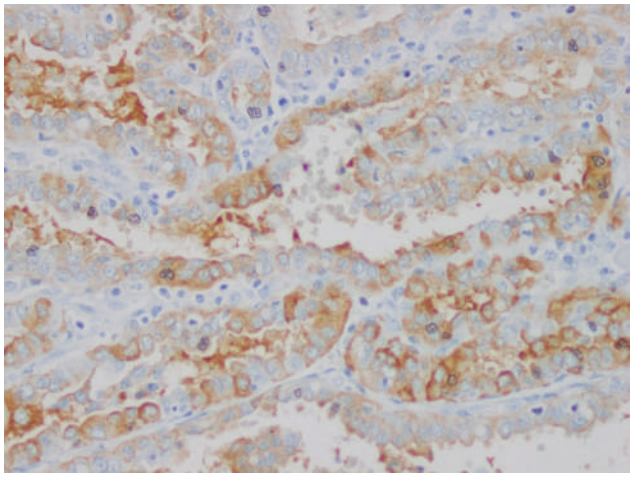

**Figure 5.** Right cervical lymph node: Immunohistochemistry (Thyroglobulin Immunoperoxidase, 100x).

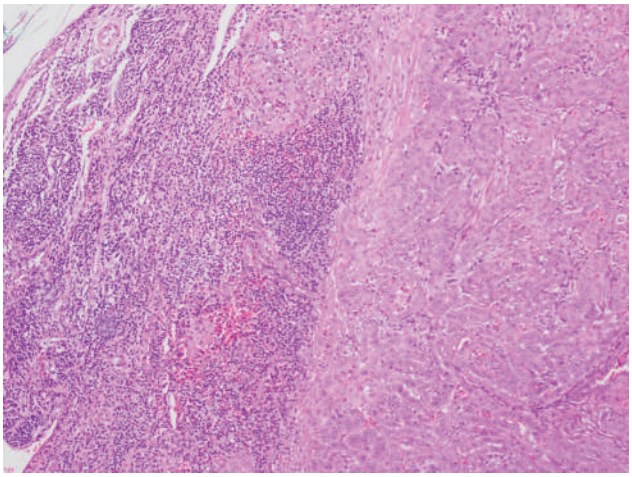

**Figure 6.** Right cervical lymph node: Papillary Thyroid Carcinoma, Metastatic (H&E, 20x).

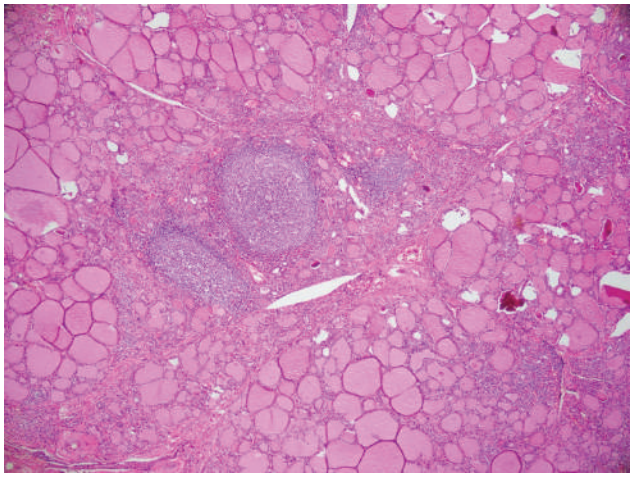

**Figure 7.** Thyroid gland: Total thyroidectomy showed Chronic Lymphocytic Thyroiditis (H&E, 10x).

Twelve months post-thyroidectomy, serum thyroglobulin level was low at <0.04 ng/ml (reference range 3.5 - 77) while anti-thyroglobulin was elevated at 22.65 IU/ml (reference range <4.11). The plan is for serial monitoring of serum anti-thyroglobulin.

## DISCUSSION

The International Agency for Research on Cancer World Health Organization Global Cancer Observatory names thyroid carcinoma as the 7th most common malignancy in the Philippines with an incidence rate of 4.1% in 2020.[3] It is more common in those aged 20 to 40 years.[4] However, the prevalence of ectopic thyroid carcinoma with no histopathologic evidence of malignancy within the orthotopic thyroid has not been determined.

Initial assessment of a patient with a lateral neck mass begins with a complete medical history with an emphasis on any history of malignancy or prior irradiation, followed by a complete physical examination of the head and neck. Appropriate diagnostic procedures include thyroid function tests and neck ultrasonography. When considering malignancy, FNAB of identified neck masses is the first step in establishing a diagnosis along with appropriate imaging modalities.[5] In our patient, a PET-CT scan was already done before the referral, and is a useful tool in the imaging of head and neck tumors. Indications for its use include the staging of a primary tumor, treatment planning, monitoring of treatment response and identification of an unknown primary.[6]

Histopathologic examination of the cervical lymph node biopsy revealed a metastatic papillary thyroid carcinoma; however, thyroid gland histopathology was negative for malignancy. This finding is unusual as the majority of ectopic thyroid malignancies also present with corresponding malignancy in the native tissue.

Standard evidence-based guidelines on the optimal treatment of primary ectopic lateral neck thyroid carcinoma have not yet been established. In published

case reports, treatment strategies employed were similar to the one presented above. In the first case reviewed, total thyroidectomy was performed on a 55-year-old male diagnosed with papillary carcinoma in the lateral ectopic thyroid gland masquerading as a submandibular gland tumor.[7] In another case report, a 63-year-old male presented with a midline neck mass anterior to the thyroid cartilage. FNAB revealed papillary thyroid carcinoma. The patient underwent total thyroidectomy with neck dissection. Histopathology revealed a normal thyroid gland with papillary thyroid carcinoma in the cervical mass. There was no identifiable metastatic involvement.[8]

Physicians should still consider the possibility of thyroid carcinoma arising from ectopic tissue in patients presenting with a lateral neck mass as prompt diagnosis and treatment increase survival.

## CONCLUSION

Thyroid carcinoma is not exclusively found in the thyroid gland. Ectopic thyroid carcinoma should be part of the differential diagnoses in patients presenting with neck masses. This case demonstrates that thyroid carcinoma in an ectopic tissue cannot be excluded, even in the presence of a normal thyroid gland. Treatment of these cases must be individualized.

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

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

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

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None.

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

**Figures and Graphs**

1. Figures or graphs should be identified by Arabic Numeral/s with titles and explanations underneath.
2. The numbers should correspond to the order in which the figures/graphs occur in the text. It is recommended that figures/graphs also be submitted as image files (preferably as .tif, .jpeg, or .png files) of high resolution (at least 300 dpi).
3. Editable figures or graphs can also be created using Microsoft Word.
4. Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
5. All identifying data of the subject/s or patient/s under study such as name or case numbers should be removed.
6. Up to a maximum of five (5) figures and graphs are allowed.

**Illustrations and Photographs**

1. Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as .tif, .jpeg, or .png files).
   1.1 There should be minimal processing of digital images submitted with a manuscript for review to the JAFES. A certain degree of image processing (lighting, color, contrast, size, orientation, cropping, placement of identifying markers and labels) is deemed acceptable only if the final image correctly and accurately represents the original information or data. Thus, JAFES requires all unprocessed, unaltered, and raw image files to be submitted with the manuscript to facilitate evaluation and review. These shall serve also as JAFES' records for issues that may arise after publication of the manuscript.
   1.2 Adjustments in brightness, color balance, or contrast should be applied equally to the whole image and should not result in the exclusion, hiding, obscuring, or deletion of any information that is present in the original image, enhancement of any particular portion of the image. Manipulations such as grouping of images for comparison should be indicated with image margins or clear demarcations, and must be described in the caption. Other types of manipulation such as copying and pasting of images and passing them off as multiple figures is not acceptable. Appropriate re-orientation of the whole image, as well as, superimposition of arrows, markers, or other figures and labels is acceptable.
2. For photomicrographs, the stain used and the resolution at which the image was acquired (e.g., H&E, 100X) should be included in the description.
   2.1 All image adjustment and processing tools/software used should be disclosed in the methodology section of original articles or described in the caption or description if in article types without a separate section on methods.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn and digitized (preferably as .tif, .jpeg, or.png files) at least 800 x 600 dpi. All letterings for illustrations should be done professionally and be of adequate size to remain readable ever after size reduction during layout.
4. All letterings for illustration should be done professionally and should be of adequate size to retain even after size reduction.
5. Figure legends should be numbered sequentially, typed double-spaced on a separate sheet of paper. Give the meaning of all symbols and abbreviations used in the figure.
6. Up to a maximum of five (5) illustrations/photographs are allowed.

**N.B.:** For tables, figures, graphs, illustrations, and photographs that have been previously published in another journal or book, a note must be placed on the specific item stating that such has been adapted or lifted from the original publication and referenced in the **References** portion. Appropriate copyrights and permissions should be secured from the original author/publisher.

**PROCESS** UPDATE

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. Each manuscript is referred to two (2) peer reviewers who are deemed as subject experts. A third reviewer may be needed in case there is discordance in the peer reviewer recommendation. The manuscript is routinely referred to the JAFES in-house statistician to check appropriateness and validity of data analysis and conclusions. In addition, the manuscript is also referred to the JAFES in-house radiologist or pathologist for review if there are diagnostic imaging studies or microscopic images, respectively. The JAFES Editor-in-Chief makes the final decision.
4. 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, (c) major manuscript revision and resubmission, or (d) not accepted for publication.
5. Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal.

**EDITORIAL OFFICE CONTACT INFORMATION:**

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## ARTICLE TYPES

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

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

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

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

**Endocrine Perspectives**
JAFES may invite topic experts to publish viewpoints, opinions, and commentaries on relevant topics. A manuscript for endocrine perspectives should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words. *Not peer reviewed.

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

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

**Images in Endocrinology**
Images may include photographs of clinical cases encountered and documented during practice. They may also include diagnostic images (e.g., photomicrographs of histopathologic diagnosis, radiographs) or special studies performed (e.g., spectral karyotype imaging, fluorescent microscope images, immunostains) that aided in diagnosis. A 250-word text should accompany the images. Submissions to this category should comply with the journal's image integrity guidelines.

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

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

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

| Checklist Guide for Submission of Manuscripts to JAFES | |
|---|---|
| **Instructions to Authors** | ☐ Review manuscript submission guidelines |
| **Cover Letter** | ☐ Include cover letter as an attachment<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 e-mail address)<br>☐ Indicate in the letter the Corresponding author: and provide complete contact information (post address, telephone, fax number, e-mail address) |
| **EQUATOR Network Guidelines** | ☐ Review manuscript if compliant with appropriate EQUATOR Network Guidelines and submit checklist (e.g., CONSORT for clinical trials, CARE for case reports) |
| **Author Form** | ☐ Ensure all authors have read and agreed to the following: (1) the Authorship Certification, (2) the Author Declarations, (3) the Author Contribution Disclosure, and (4) the Author Publishing Agreement, and (5) the Conversion to Visual Abstract (*optional for original articles)<br>☐ Submit a scanned copy of the fully accomplished form |
| **ICMJE Form for Disclosure of Potential Conflicts of Interest** | ☐ Ensure all authors have read and agreed to disclose potential Conflicts of Interest<br>☐ Submit the PDF copy of the fully accomplished form<br>*The form is also downloadable at: http://www.icmje.org/conflicts-of-interest/ |
| **Ethics Review Approval** | ☐ For Original articles, submit a scanned copy of the Ethics Review Approval of research<br>☐ For manuscripts reporting data from studies involving animals, submit a scanned copy of the Institutional Animal Care and Use Committee approval |
| **Patient Consent Form (if applicable)** | ☐ For Case Reports, Images in Endocrinology and Clinical Case Seminars, submit a scanned copy of the fully accomplished form; otherwise, obtain appropriate ethical clearance from the institutional review board. |
| **Title Page** | ☐ Full names of the authors directly affiliated with the work (First name and Last name), highest educational attainment<br>☐ Name and location of 1 institutional affiliation per author<br>☐ If presented in a scientific forum or conference, provide a footnote should be provided indicating the name, location and date of presentation |
| **Abstract** | ☐ Provide an abstract conforming with the format<br>☐ Structured for Original Articles: Objective/s, Methodology, Results, Conclusion<br>☐ Unstructured for Case Reports and Feature Articles |
| **Keywords** | ☐ Provide 3-5 keywords (listed in MeSH) |
| **Content** | ☐ Provide text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion)<br>☐ Make sure all abbreviations are spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses; the same abbreviation may then be used subsequently<br>☐ Make sure all measurements and weights are in SI units<br>☐ If appropriate, provide information on institutional review board/ethics review committee approval<br>☐ Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references; grants and subsidies from government or private institutions should also be acknowledged |
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| **Tables, Figures, Illustrations and Photographs** | ☐ All tables, figures, illustrations and photographs should be cited in the text, in numerical order per type<br>☐ Provide separate files for tables, figures and illustrations<br>☐ Provide a title and legend (if appropriate) for each table<br>☐ Provide a title, legend (if appropriate), and caption for each figure and illustration (caption should be no longer than 15-20 words)<br>☐ If table, figure, or illustration is adapted, state so and include the reference. |

Journal of the
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# Cover Letter

(Date)

To: **The Editor-in-Chief**
Journal of the ASEAN Federation of Endocrine Societies (JAFES)

Subject: **SUBMISSION OF MANUSCRIPT FOR PUBLICATION**

We intend to publish the manuscript/, entitled "_____," under the Section *[Original Article, Review Article, Feature Article, Case Report, Case Series, Interhospital Grand Rounds, Brief Communications, Letter-to-the-Editor, Special Announcements]* in the Journal of the ASEAN Federation of Endocrine Societies.

**LIST OF AUTHORS**

| Complete Name | Position/ Designation | Institutional Affiliation | Role in writing the manuscript | Email address | ORCID iD |
|---|---|---|---|---|---|
| | | | | | |
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| | | | | | |

On behalf of all the authors, I shall act as the corresponding author with the journal from this point onward.

Attached herewith are the following: the completely accomplished **Author Form with author contribution disclosure** and **author publishing agreement**, in which all the authors certified authorship criteria was satisfactorily met and the specific contributions of the authors are listed and the author copyright is retained granting publishing and distribution rights to the JAFES; the **Author Declaration** that the work is original and is not under simultaneous consideration in other journals and the **ICMJE Disclosure forms** of ALL the authors (*where all conflicts of interest have been declared/there are no conflicts of interest*).

For original articles, we submit a scanned copy of our Ethics Review Approval/registration in trial registries (as appropriate) and the appropriate EQUATOR Network checklist used in writing the manuscript.

For case reports/series, patient consent forms have been secured for the publication of information.

For animal studies, a scanned copy of the Institutional Animal Care and Use Committee approval was obtained.

Furthermore, we respectfully suggest the following **reviewer**(s) for our manuscript.

| Name and Salutation (e.g., Prof., Dr., etc) | Position/Designation | Institutional Affiliation and specialization | Email address |
|---|---|---|---|
| | | | |
| | | | |

Sincerely,
**Corresponding Author**
Name: (Salutation, First Name, Middle Initial, Last Name, Title)
Position/Designation
Name of Institution:
Complete Address of Institution **with zip code**
Tel. No. of Institution:
Fax No. of Institution:
Email address:
ORCID iD:

**Mailing Address:**
Full Name:
Complete address **with zip code**
Tel. No./ Mobile No.:

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# Author Form

**COMPLETE TITLE OF MANUSCRIPT**

**AUTHOR LISTING** (in the order agreed upon by all authors; use an additional sheet if necessary)

| **Author Name**<br>[Last name/First name] | **Institutional Affiliation** |
|---|---|
| 1. | |
| 2. | |
| 3. | |
| 4. | |
| 5. | |

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

## 1. AUTHORSHIP CERTIFICATION

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

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

☐ (1) the conception or design of the work, the acquisition, analysis and interpretation of data for the work; AND
☐ (2) drafting the work, revising it critically for important intellectual content; AND
☐ (3) that we are all responsible for the final approval of the version to be published; AND
☐ (4) we all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## 2. AUTHOR DECLARATIONS

☐ The undersigned author(s) of the manuscript hereby certify, that the submitted manuscript represents original, exclusive and unpublished material. It is not under simultaneous consideration for publication elsewhere. Furthermore, it will not be submitted for publication in another journal, until a decision is conveyed regarding its acceptability for publication in the JAFES.
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☐ The undersigned author(s) hereby certify, that the study on which the manuscript is based had conformed to ethical standards and/or had been reviewed by the appropriate ethics committee, and that no references or citations have been made to predatory/suspected predatory journals.
☐ The undersigned author(s) likewise hereby certify, that the article had written/informed consent for publication from involved subjects (for Case Report/series, Images in Endocrinology, Clinical Case Seminars).*

***NOTE: In case the involved subject/s can no longer be contacted (i.e., retrospective studies, no contact information, et cetera) to obtain consent, the author must seek ethical clearance from the institutional board to publish the information about the subject/s.**

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

**3. AUTHOR CONTRIBUTION DISCLOSURE** (Place an "x" mark where an author made the contribution)
*Adapted from Contributor Roles Taxonomy [CRediT] developed by the Consortia for Advancing Standards in Research Administration Information (CASRAI).*

| Specific Contributor role | Author 1 | Author 2 | Author 3 | Author 4 | Author 5 |
|---|---|---|---|---|---|
| **Conceptualization**<br>Ideas; formulation or evolution of overarching research goals and aims. | | | | | |
| **Methodology**<br>Development or design of methodology; creation of models | | | | | |
| **Software**<br>Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components | | | | | |
| **Validation**<br>Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs | | | | | |
| **Formal analysis**<br>Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data | | | | | |
| **Investigation**<br>Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection | | | | | |
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| **Supervision**<br>Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team | | | | | |
| **Project administration**<br>Management and coordination responsibility for the research activity planning and execution | | | | | |
| **Funding acquisition**<br>Acquisition of the financial support for the project leading to this publication | | | | | |

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**5. CONVERSION TO VISUAL ABSTRACT (for Original Articles only) **OPTIONAL****

☐ **The undersigned author(s) agree to have the published work converted as visual abstract** to improve dissemination to practitioners and lay readers.

**SIGNED:***

| **Author Name**<br>[Last name/First name] | **Signature** | **Date**<br>[MM/DD/YY] |
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| 2. | | |
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| 4. | | |
| 5. | | |

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Date: _____

Your Name: _____

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In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the **current manuscript only.**

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In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

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| | | | |
| 5 | Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events | ____None | |
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| 6 | Payment for expert testimony | ____None | |
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| 7 | Support for attending meetings and/or travel | ____None | |
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| 8 | Patents planned, issued or pending | ____None | |
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| 10 | Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid | ____None | |
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| 11 | Stock or stock options | ____None | |
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| | | | |
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Please place an “X” next to the following statement to indicate your agreement:

____ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal of the
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**For a patient's consent to publication of information about them in the Journal of the ASEAN Federation of Endocrine Societies (JAFES).**

Name of person described in article or shown in photograph: _____

Subject matter of photograph or article: _____

_____

_____

*(The Subject matter of the photograph or article is hereafter termed as the "INFORMATION.")*

JAFES manuscript number: _____

Title of article: _____

_____

_____

Corresponding author: _____

I, _____, give my consent for this information
*[please insert your full name]*
about MYSELF / MY CHILD OR WARD / MY RELATIVE relating to the subject matter above
*[please encircle correct description]*
to appear in the Journal of the ASEAN Federation of Endocrine Societies (JAFES)

subject to its publication policies and ethical standards.

***I have seen and read the material to be submitted to the JAFES and thoroughly understand the following:***

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- I can withdraw my consent at any time before publication, but once the Information has already been sent to press, it is my understanding that it will not be possible to revoke the consent.

Signed: _____ Date: _____
*[signature over complete name]*

***Witness:***
Signed: _____ Date: _____
*[signature over complete name]*

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