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A Whole that is Greater than the Sum of its Individual Parts

Like bundled stalks of "padi" or rice plants, the founders of the Association of Southeast Asian Nations (ASEAN) envisioned its member countries being bound together in friendship and solidarity.[1] In the same way, the ASEAN Federation of Endocrine Societies was established 36 years ago "with the goal of strengthening the cooperation and understanding among member scientists of ASEAN countries, to provide better medical care in the field of endocrinology and metabolism in each of the member nations."[2]

"Togetherness," a common theme for both the ASEAN and the AFES, is not simply a geographic accident, as it means unity among member nations to the former, and common academic and scientific pursuits to the latter. Indeed, every two years since the Federation's inception, a regional endocrinology conference was held, to provide a viable venue for sharing knowledge, collaborating in research, and creating networks of endocrinology practitioners.

The theme for this year's Conference in Myanmar is "Synergy Among ASEAN," a phrase that not only captures the aspirations of both the ASEAN *and* the AFES, but also hints at efforts and outputs beyond mere togetherness.

"Synergy" originated from two Greek words: *syn* ("together") and *ergon* ("work"). Its first known use was in the 1650s, referring to "joint work, a working together, cooperation."[3-4] The word's meaning eventually included "combined activities of a group" in the 1850s; and evolved, to a "sense of advanced effectiveness as a result of cooperation" in the 1960s – this later definition a predecessor of the word's present connotation of "a whole that is greater than the sum of its individual parts."[4]

When the Philippines' Endocrine society was accorded the task of reviving the JAFES, the Federation's official publication, there was both the idealism of ASEAN "togetherness" on one hand, and the concern of country involvement on the other. Truth be told, the challenge of inviting and getting submissions from the other member states seemed unnerving. In all objectivity, that challenge still remains. From 2011 to present, the distribution of published articles, which is supposedly a reflection of the research contribution of each member state to the journal, still shows a wide disparity and irregularity (Figure 1).

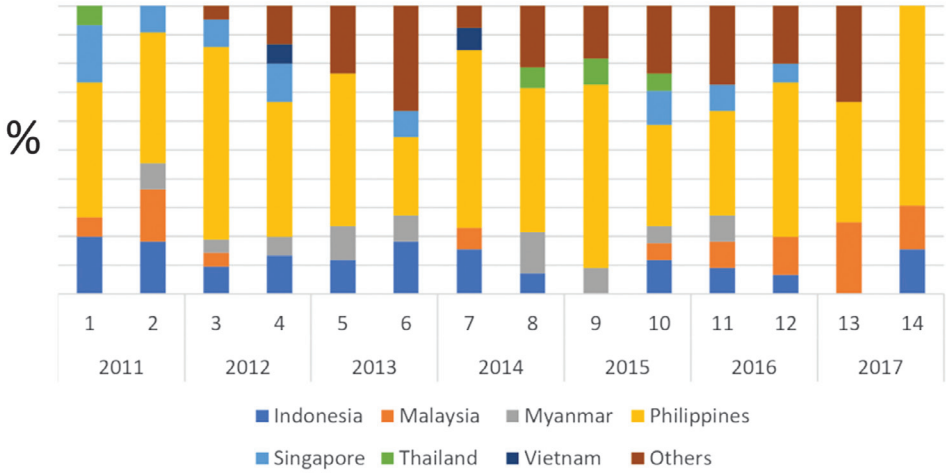

Figure 1. Percentage (%) distribution of articles published in the JAFES 2011-2017.

The region, teeming with tremendous potential, is not without its unique areas for research and publication. We echo the statement of Dr. Nguyen Thy Khue, former President of the VADE, in her message during the 2011 AFES, that although "endocrinology research in ASEAN countries is not as advanced as in western countries…prevalence of and risk factors for common diseases have not been well documented."[5] There *are* significant gaps in country and regional data on endocrinology that we, as member states, should take on.

While the journal continues to aim for providing an impetus for action through translation of country-specific research to public health programs, policies, and clinical practice, the numbers do not seem to agree, as JAFES submissions per year do not go beyond 100 articles nor tend yet to increase significantly (Figure 2).

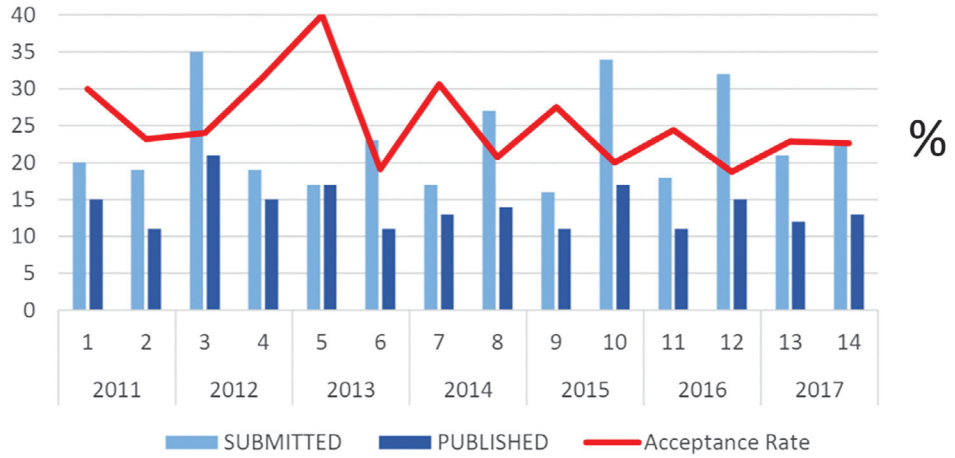

Figure 2. Summary of submitted vs published manuscripts and acceptance rates 2011-2017.

In the midst of competition with more established and more prestigious international and local journals, the editorial team has recognized that JAFES must exert greater effort to become the "journal of choice" among researchers *and* clinicians in the region. It is this particular challenge that keeps the team focused, continuously improving its operations by attending conferences for medical editors, benchmarking, improving the journal's online presence, and incorporating international best practices (Open Access, ICMJE, COPE, CrossRef, Similarity Check, ORCID, Creative Commons).[6] That JAFES was finally able to achieve Scopus indexing in 2016 meant that all of these efforts are starting to pay off.

The JAFES remains faithful to its goal of advancing endocrine research *and* practice in the region,[7] and it can accomplish this with the full support of, and participation by, the member states. We hope to renew everyone's commitment to unity and collaboration, for JAFES to be a true embodiment of synergism, of a whole that is greater than the sum of its individual parts, a strong bundle of "padi."

Elizabeth Paz-Pacheco
Editor-in-Chief

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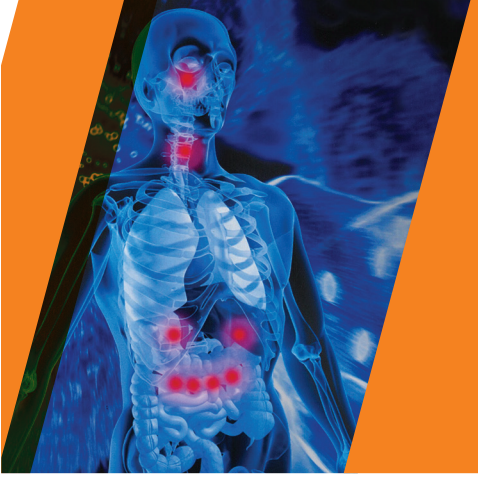
References

1. ASEAN Emblem. Retrieved from http://asean.org/asean/about-asean/asean-emblem/.
2. Synergy. Retrieved from https://www.merriam-webster.com/dictionary/synergy.
3. Synergy. Retrieved from http://www.etymonline.com/word/synergy.
4. Paz-Pacheco E, Mirasol R. ASEAN Federation of Endocrine Societies (AFES): 1981-2011 Renewing our commitment to the ASEAN region after 30 Years. J ASEAN Fed Endocr Soc. 2011; 26(1): 12-6. https://doi.org/10.15605/jafes.026.01.02.
5. Thy Khue N. Greetings from AFES. J ASEAN Fed Endocr Soc.2014;26(2):96. https://doi.org/10.15605/jafes.026.02.02.
6. Paz-Pacheco E. Full Circle. J ASEAN Fed Endocr Soc.2015;30(2):91-2. https://doi.org/10.15605/jafes.030.02.18.
7. Paz-Pacheco E. JAFES: Advancing endocrine research in the ASEAN region. J ASEAN Fed Endocr Soc. 2011;26(1):5-6. https://doi.org/10.15605/jafes.026.01.01.



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DR JAMES ANDREWS

Dr. James Andrews is a professor of Radiology with the Mayo Clinic College of Medicine. Research interests include regional management of hepatic malignancy, hepatic artery embolization/chemoembolization, TheraSphere therapy for hepatic tumors, portal vein embolization as an adjunct to hepatic resection, pharmacology of hepatic artery chemotherapy, FUDR-associated sclerosing cholangitis, venous sampling to localize endocrine neoplasms, and management of complex biliary disease. Dr. Andrews is co-investigator for "Evaluation of the Medtronic Vascular Talent Thoracic Stent Graft System for the Treatment of Thoracic Aortic Aneurysms" (funded by Medtronic Vascular).

DR BART CLARKE

Bart L. Clarke, M.D. is Consultant and Chair of the Metabolic Bone Disease Core Group in the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at the Mayo Clinic, and Associate Professor of Medicine in the Mayo Clinic College of Medicine. His research interests include metabolic bone diseases, including postmenopausal osteoporosis, primary hyperparathyroidism, and hypoparathyroidism. He is a member of the American Society for Bone and Mineral Research, The Endocrine Society, American Association of Clinical Endocrinologists, and the American College of Physicians. He is a member of the Editorial Board for the Journal of Bone and Mineral Research, and a current Chair of the Mayo Clinic Institutional Review Board.

DR WILLIAM YOUNG

Dr. Young is Professor of Medicine in the Mayo Clinic College of Medicine. He is a Past President of the American Endocrine Society and is the current Chair of the American Board of Internal Medicine Subspecialty Board in Endocrinology. Dr. Young has published over 240 articles on endocrine hypertension and adrenal and pituitary disorders—resulting in 8,500 citations and an h-index of 52. He has been the recipient of multiple education awards and has presented at over 350 national and international meetings and he has been an invited visiting professor for more than 100 medical institutions.

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REVIEW ARTICLE

Bone Metabolism and Fracture Risk in Diabetes Mellitus

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Abstract

Individuals with Type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are at increased risk for fragility fractures. Bone mineral density (BMD) is decreased in T1DM but often normal or even elevated in T2DM when compared with age-matched non-DM populations. However, bone turnover is decreased in both T1DM and T2DM. The pathophysiologic mechanisms leading to bone fragility is multifactorial, and potentially leads to reduced bone formation, altered bone microstructure and decreased bone strength. Interestingly, different antidiabetic treatments may influence fracture risk due to effects on glycemic control, triggering of hypoglycemic events or osteoblastogenesis.

Key words: bone metabolism, diabetes mellitus, bone remodeling, biomarkers

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic non-communicable disease with increasing global prevalence. By 2015, there were over 415 million adults living with DM, and this number is expected to increase to 642 million by 2040.[1] Apart from the major DM-related complications such as cardiovascular diseases, osteoporotic fracture is increasingly recognized as an important complication of type 1 DM (T1DM) and type 2 DM (T2DM) in both men and women.[2] Worldwide, over 9 million osteoporotic fractures occur annually, and the effect of reduced bone mineral density (BMD), including osteoporosis, is predicted to result in over 5 million disability adjusted life years (DALY) and 188,000 deaths each year. The incidence of hip fractures in individuals with T1DM was 383 per 100,000, six-fold higher than the overall incidence of hip fracture in the age-matched, non-diabetic population.[3] The odds ratio of vertebral fracture in T2DM was 1,86 and 4,73 in women and men,[4] respectively, with a relative risk of 1,83 (95% CI: 1,25-1,53).[5] These studies were largely done using the cross-sectional design and showed only associations rather than causality of DM and the incidence of fracture. However, taken together, these data indeed show the increased fracture risk in individuals with DM. The presence of microvascular complications in DM have also been associated with reduction of BMD in T1DM[5] and with bone micro-architectural abnormalities in T2DM.[6-9]

Increasing evidence shows the interaction between plasma glucose levels and bone metabolism, revealing mechanisms through which bone fragility may develop in DM. Whether this interaction translates into increased risk for fragility fractures and decreased BMD in all DM populations remains unclear. Studies reported conflicting findings of changes in BMD. Whereas BMD is decreased in T1DM,[10-15] it is either increased or unchanged in T2DM.[16-21] Intriguingly, a meta-analysis found that both DM types are associated with increased risk of hip fracture.[2] In this review, we discuss bone metabolism and remodeling, the pathophysiologic mechanisms by which bone fragility may occur in DM, and the effects of glucose-lowering drugs on bone health.

Bone Metabolism and Remodeling

The structural components of bone consist of a largely mineralized extracellular matrix, collagen, and cells. Bone is a living organ that is continuously being remodeled, in a process that involves a balance in the tearing down of bone structure (bone resorption) and its rebuilding (bone formation). This resorption and formation allows for the repair of micro-fractures and the modification of structure in response to stress.[22] Bone resorption is initiated by osteoclasts, which attach to bone surface and secrete acid and hydrolytic enzymes that resorb bone, releasing minerals and collagen fragments.[23] After osteoclastic

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resorption is completed, a reversal phase takes place in which mononuclear cells prepare the bone surface for new osteoblasts to begin bone formation by laying down a layer of glycoprotein-rich material to which the osteoblasts can adhere.[24] Bone formation is subsequently initiated by osteoblasts, which produced type I collagen and other proteins, such as osteocalcin, which then form osteoid, a substrate for which mineralization can occur. The newly formed osteoid then begins to accumulate matrix molecules and mineralize.[22] In healthy adults, bone resorption and formation is a tightly balanced process. Both high or low rates of remodeling with an imbalanced bone resorption and formation can be associated with decreased or increased bone mass.

The synthesis of type I collagen during the bone formation phase involves the intertwining of one alpha-2 and two alpha-1 polypeptide chains to form a helical structure known as procollagen, followed by cleavage of their amino-terminal and carboxy-terminal peptides to form tropocollagen. The N-telopeptide (NTX) is the pyridinoline crosslink in the N-telopeptide region that joins alpha-1 chains to alpha-2 chains,[25] whereas the C-telopeptide (CTX) is a fragment of the alpha-1 peptide with an isomerized bond between the aspartate and the glycine from the carboxytelopeptide region.[26] NTX and CTX, together with the bone-specific alkaline phosphatase and amino terminal propeptide of type 1 procollagen (P1NP) are the most clinically useful markers of bone turnover.[27,28] Osteoblasts produce osteocalcin, which is also used as a marker of bone formation.[29] Furthermore, bone resorption results in the release of bone mineral and the collagen-rich osteoid, whereas osteoid formation involves the production of the byproducts of collagen and other proteins. These substances may be released in the circulation, and can be measured in serum and urine to provide information on the rate of bone resorption and formation, and are collectively termed in the clinic as "bone turnover markers" (BTM)[23] (Table 1).

Fracture Risk and Diabetes Mellitus

Fracture risk is significantly higher in both T1DM and T2DM populations when compared to the general population.[2] The incidence of hip fracture in individuals with T1DM were reported to be six times higher than in the population (mean age 65 years) and 2,5-fold higher than in the T2DM population.[3]

T1DM

A meta-analysis of 5 studies reported that T1DM is associated with an overall relative risk (RR) of 8,9 (95% CI 7,1–11,2) for hip fractures when compared with an age-matched nondiabetic population.[2] Most studies in young and older, male and female individuals with T1DM reported a decrease in BMD at the radius and femur.[30-38] This decrease ranges from 22 to 37%.[5] Individuals with T1DM showed decreased trabecular and/or cortical volumetric BMD at the distal radius or tibia compared with non-diabetic controls,[30,39-43] and some studies reported the associations of these alterations with poor glycemic control.[40, 41]

T2DM

The risk of hip fracture is particularly increased in individuals with T2DM.[21,44,45] The risk is even higher in those treated with insulin[3,46] and poor glycemic control,[47] as reflected by high HbA_{1c} levels, which may indicate the more advanced disease state. Studies have also reported increased fracture risk in individuals with more hypoglycemic episodes.[48] A meta-analysis of four cohorts showed that the RR of hip fractures reached 2,7 (95% CI, 1,7-4,4).[2] The risks for other fractures appear to also increase in T2DM compared to healthy individuals, such as fractures of the wrist [49] and foot,[21,50] as well as of the vertebrae.[4]

Although earlier studies reported lower or unchanged BMD, recent large studies found that in T2DM, in contrast with T1DM, BMD is increased when compared to controls.[20,49, 51-60] Furthermore, this increase in BMD remained after adjustment for body weight and composition,[55, 60] and ranges between 5 to 10% above age-matched, non-diabetic controls.[50] Bone fragility depends not only on the reduction in bone mineral mass, as reflected by BMD, but also from changes to the bone microstructure and the components of the bone material. This is likely to account for the increased risk of fracture despite the increased BMD seen in individuals with T2DM. Indeed, MRI studies revealed greater cortical porosity in individuals with T2DM compared with non-diabetic controls,[61,62] a finding repeated by a study using quantitative CT (Xtreme-CT), especially in those with fractures and/or microvascular complications.[6-9] Recent diagnostic advances enable the measurement of *in vivo* bone material strength (BMS) by the minimally invasive, bone microindentation testing.[7,63] Postmenopausal women with T2DM demonstrated lower BMS and greater radial cortical porosity. Poor BMS was correlated with poor long-term glycemic control over the past 10 years.[7] A study in a similar population with fragility fractures suggests that severe deficits in cortical bone quality, as depicted by an increase in porosity, is a likely cause of fragility fractures.[8] Regardless of the difference in BMD alterations between T1DM and T2DM, DM alone has been shown to be predictive of increased post-fracture mortality risk during hospitalization[64] and up to one year after discharge[65,66] in individuals with hip fracture.

Mechanisms of DM-induced Bone Fragility

The mechanisms of DM-induced bone fragility in T1DM and T2DM are complex and only partially overlap.[67] Individuals with T1DM are mainly experiencing β-cell failure and low levels of IGF1which disrupt the function of osteoblasts during growth. As a result, low peak bone

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mass can occur at a young age.[68] In contrast, individuals with T2DM developed bone fragility at a later stage of the disease, and consequently, at a later age due to the lack of insulin, glucose toxicity, advanced glycation end products (AGEs), cytokines and adipokines that are affecting osteocyte, bone turnover and collagen.[69]

Table 1. Bone turnover markers

Markers	Full name	Origin	Comment	Source of Variability		
				Renal	Liver	Circadian rhythm
Resorption						
u-CTX	Urinary carboxy-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen, generated by cathepsin K	Requires adjustment to levels of urinary creatinine Specificity: collagen type I, with highest contribution probably from bone Changes in levels of u-CTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of u-CTX[110]			X
s-CTX	Serum carboxy-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen, generated by cathepsin K	Source of variability: food consumed (so must be collected after an overnight fast) Changes in levels of s-CTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of s-CTX[110]	X	X	X
u-NTX	Urinary amino-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen type I	Requires adjustment to levels of urinary creatinine Specificity: collagen type I, with highest contribution probably from bone Changes in levels of u-NTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of u-NTX[110]			X
s-NTX	Serum amino-terminal cross-linking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen type I, generated by cathepsin K	Specificity: collagen type I, with highest contribution probably from bone Changes in levels of u-NTX were reported in both T1DM and T2DM Pioglitazone is associated with increased levels of s-NTX[110]	X		X
s-ICTP or CTX-MMP	Carboxy-terminal crosslinking telopeptide of type I collagen	Osteoclastic hydrolysis of collagen generated by matrix metalloproteinases	Specificity: collagen type I, with highest contribution probably from bone Marker is not responsive to usual treatments for osteoporosis Lower s-PICP to s-ICTP ratio were reported in T2DM[12] Troglitazone use in T2DM individuals is associated with a decrease in s-ICTP[111]	X	X	X
u-DPD	Urinary deoxypyridinoline	Proteolytic hydrolysis of collagen, found in bone	Requires adjustment to levels of urinary creatinine Specificity: highest contribution from bone Sources of variability: UV radiation Changes in levels of u-DPD were reported in both T1DM and T2DM[112] Troglitazone use in T2DM individuals is associated with a decrease in u-DPD[111]			X
u-PYD	Urinary pyridinoline	Found in bone, cartilage, tendon, blood vessels	Requires adjustment to urinary creatinine Specificity: highest contribution from bone and cartilage Sources of variability: active arthritis and UV radiation		X	X
s-TRAP	Serum tartrate-resistant acid phosphatase	Includes two isoforms: type 5a (platelets, erythrocytes and other sources) and type 5b (osteoclasts)	Sources of variability: influenced by haemolysis and blood clotting Changes in levels of s-OC were reported in both T1DM and T2DM[112] Levels of s-TRAP is affected by long-term use of insulin in T1DM[36]			X
Formation						
s-OC	Serum osteocalcin	Hydroxyapatite-binding protein exclusively synthesised by osteoblasts and odontoblasts	Specificity: specific marker of osteoblast function Rapid degradation in serum may lead to heterogeneity of OC fragments measured Sources of variability: large inter-laboratory variation Changes in levels of s-OC were reported in both T1DM and T2DM	X		X
u-OC	Urinary osteocalcin	Hydroxyapatite-binding protein exclusively synthesised by osteoblasts and odontoblasts	Adjusted to levels of urinary creatinine (/Cr) Specificity: specific marker of osteoblast function Changes in levels of u-OC were reported in non-insulin dependent DM[112]	X		X
s-ALP	Serum alkaline phosphatase (total)	Ubiquitous, membrane bound tetrameric enzyme located on the outer cell surface of various tissues: liver, bone, intestine, spleen, kidney and placenta	Specificity: non-specific for bone (about 50% is liver isoform in healthy individuals) Changes in levels of s-ALP were reported in both T1DM and T2DM Troglitazone use in T2DM individuals is associated with a decrease in s-ALP[111]			X
s-BALP	Serum bone-specific alkaline phosphatase	Ubiquitous, membrane bound tetrameric enzyme located on the outer cell surface of osteoblasts	Specificity: specific for bone, but with some cross-reactivity with liver isoform (up to 20%) Changes in levels of s-BALP were reported in T2DM[112] Troglitazone use in T2DM individuals is associated with a decrease in s-BALP[111]			X
s-PICP	Procollagen type I C propeptide	Precursor molecules of collagen type I synthesised by osteoblasts	Specificity: mostly derived from bone collagen type I (around 90%). Short serum half-life. Regulated by hormones (thyroid, IGF-1) Lower s-PICP to s-ICTP ratio were reported in T2DM[12]			X
s-PINP	Procollagen type I N propeptide	Precursor molecules of collagen type I synthesised by osteoblasts	Specificity: mostly derived from bone collagen type I A ssay: may recognise trimer alone (intact) or trimer and monomer (total PINP) Changes in levels of s-P1NP were reported in both T1DM and T2DM			X

Adapted from Vasikaran et al.[109]

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Table 2. Studies reporting on bone turnover in individuals with DM

Study author	Participants	BTM measured	Comments
Reyes-Garcia et al.; 2013[110]	78 T2D (43 men, 35 women), 55 controls	OC (ns)- RIA) (DiaSorin, Stillwater, Minnesota USA; normal range 1.8–6.6 ng/ml, CTX ↓ EIA (Elecsys ß CrossLaps, Roche Diagnostics SL, Barcelona, Spain; normal range 0.01–6 ng/ml)	Vertebral fractures in 27.7% of T2D and 21.7% of controls Cross-sectional
Yamamoto et al.; 2012[111]	255 T2D (postmenopausal women and men), 240 controls	OC↓, CTX↓ (electrochemiluminescence immunoassay on an automated analyzer; Roche Diagnostics GmbH, Mannheim, Germany), PTH↓	Excluded if serum creatinine was higher than normal range
Manavalan et al.; 2012[112]	18 T2D PM, 27 controls PM	OC↓, ELISA (IDS), CTX ↓ ELISA	At least 1 year use of antiglycemic medication eGFR b 60 ml/min excluded
Bhattoa et al.; 2013[113]	68 male T2D, 68 male controls	OC↓, CTX↓ electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).	Renal disease excluded Case-control
Ardawi et al.; 2013[114]	482 T2D PM women, 482 controls PM	LIASON autoanalyzer (DiaSorin Inc., Stillwater, MN, USA)	VF in 24.5% of T2D and none in controls
Hamilton et al.; 2012[115]	26 T1D, 27 T2D	CTX ↑, OC (ns), PTH (ns)	
Akin et al.; 2003[116]	57 T2D PM, 20 controls PM	OC↓, NTX↓	BMI significantly lower in controls, fasting, chronic disease excluded
Reyes-Garcia et al.; 2013[110]	78 T2D, 55 controls	CTX↓, PTH↓, enzyme immunoassay (EIA) and ELISA	Vertebral fractures in 27.7% of T2D and 21.7% of controls
Jiajue et al.; 2014[117]	236 T2D PM, 1055 controls PM	CTX↓, P1NP↓	Renal disease excluded
Farr et al.; 2014[7]	30 T2D PM, 30 controls PM	CTX↓, P1NP↓	Stage 4 and 5 chronic kidney diseases excluded MI significantly lower in controls. Performs microindentation
Manavalan et al.; 2012[112]	18 T2D PM, 27 controls PM	Circulating OC(+) cells ↓	At least 1 year use of antiglycemic medication eGFR b 60 ml/min excluded
Bhattoa et al.; 2013[118]	68 male T2D, 68 male controls	OC↓, CTX↓	Renal disease excluded
Gaudio et al.; 2012[119]	40 T2D PM, 40 controls PM	CTX↓	Renal bone disease excluded
Ardawi et al.; 2013[114]	482 T2D PM, 482 controls PM	IGF-1↓, sclerostin ↑, OC↓, CTX↓, P1NP↓, NTX↓	VF in 24.5% of T2D and none in controls
Hernandez et al.; 2013[120]	2431 subjects of these 45 T2D	CTX and P1NP↓ in T2DM individuals who use statins	PM females and older men , Coexisting medical disorder that might affect bone metabolism was excluded.
Sarkar and Choudhury; 2013[121]	108 T2D, 50 controls	OC↓	T2D was newly diagnosed.
Movahed et. al.; 2012[122]	382 PM of these 102 T2D	OC↓, CTX↓	The diabetes group is a subgroup of the total population.
Sosa et al.; 1996[123]	47 female NIDDM, 252 female controls	OC (ns), ALP (ns)	No renal disorders
Chen et al.; 2013[124]	55 T2D, 27 controls	Plasma ALP↑, OC↓	No history of metabolic bone disease

Alkaline phosphatase (ALP), C-terminal cross-link of collagen (CTX), estimated glomerular filtration rate (eGFR), insulin-like growth factor-1 (IGF-1), myocardial infarction (MI), Non-insulin dependent diabetes mellitus (NIDDM), not significant (ns), tosteocalcin (OC), procollagen type 1 N-terminal propeptide (P1NP), postmenopausal (PM), parathyroid hormone (PTH), type 1 diabetes (T1D), type 2 diabetes (T2D), vertebral fracture (VF),

Low Bone Turnover

Most published studies in individuals with DM have reported low bone turnover (Table 2). Osteocalcin level, a marker of bone formation, is decreased in both T1DM and T2DM,[70-72] and is negatively correlated with HBA_{1c} level.[70] The negative correlation with HBA_{1c} was also reported for CTX, a marker of bone resorption.[70] When looking separately at T1DM and T2DM, osteocalcin levels have been reported to be decreased in T1DM and only borderline significantly decreased in T2DM.[73] Similarly, P1NP and NTX also tended to be lower in individuals with DM.[5] Consistently, histological study of DM found decreased number of osteoblasts and osteoid.[74] In general, the processes involved in the decreased bone formation in T2DM include a decrease in bone quality, alterations of the mesenchymal cell differentiation and bone microcirculation, as well as changes in osteoblasts and osteoclasts (Figure 1).

Adipokines

Adiponectin, a protein hormone secreted by adipose tissue, was found to be decreased in T2DM.[75] Adiponectin was reported to have an anabolic effect on osteoblasts and inhibits osteoclastic activity *in vitro*.[76] However, clinical studies reported conflicting findings on whether there were negative correlations between adiponectin levels and BMD in individuals with T2DM. Leptin, another adipokine which is secreted by white adipose, bone marrow adipocytes and osteoblastic cells, was found to be lower in individuals with DM compared with controls. A negative correlation between leptin and NTX was found in individuals with T2DM, whereas a positive correlation was found with leptin and Z-scores at the distal radius, but not at the femoral neck or lumbar spine.[77] Interestingly, in vitro and animal studies showed that high glucose level increases the expression of adipogenic markers such as the peroxisome proliferator-activated receptor (PPAR)-γ, adipocyte fatty acid binding protein (aP2), resistin and adipsin, whereas it suppresses cell growth, mineralization, and expression of osteogenic markers including Runx2, collagen I, osteocalcin, osteonectin.[78,79] Further studies are needed to precisely explain the role of adiponectins in affecting bone fragility.

Advanced Glycation End Products (AGEs)

Individuals with DM have increased levels of AGEs due to hyperglycemia and increased levels of oxidative stress.[80] The main mechanisms by which AGEs contribute to damaging the bone tissue are: 1) by forming cross-links with target protein, permanently altering cellular structure, and 2) by interacting with specific receptors to increase oxidative stress and inflammation.[81] The receptor

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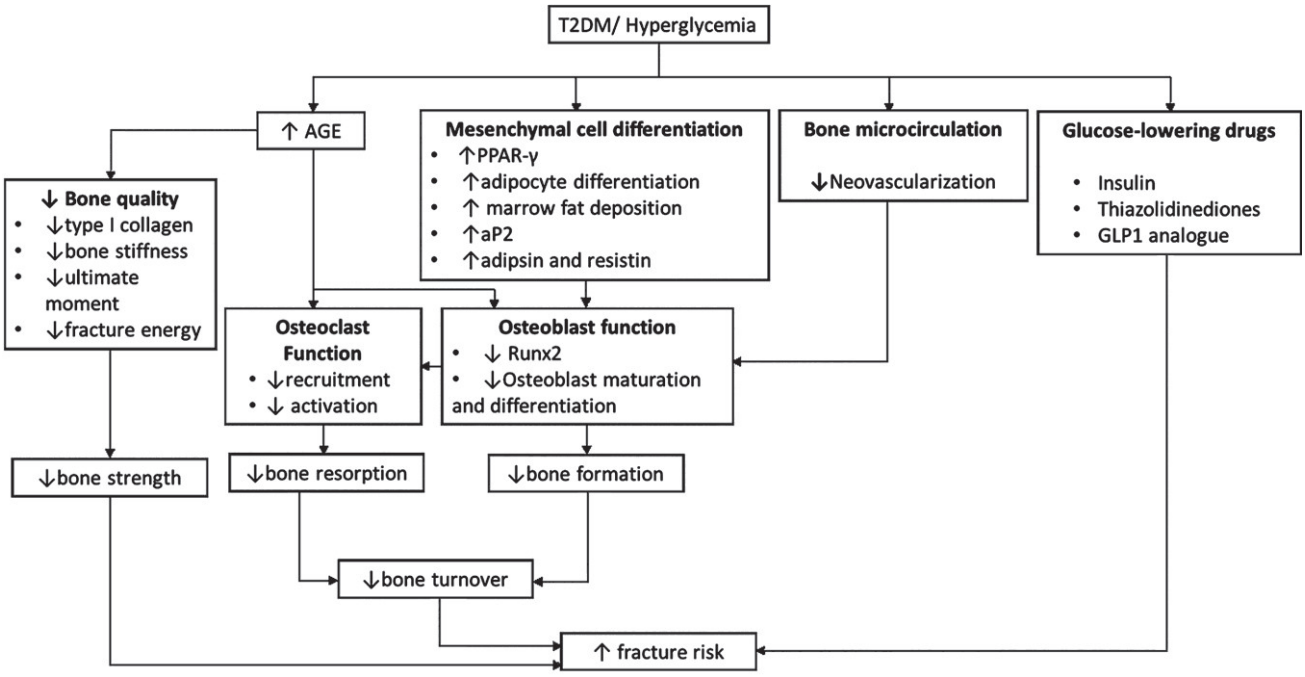

Figure 1. Process involved in the decrease of bone turnover and increase of fracture risk.

for AGEs (RAGE) initiates the intracellular signaling through the binding of AGEs.[82] The soluble isoform of RAGE (known as soluble RAGE, sRAGE) is thought to be produced by proteolytic cleavage of disintegrin and metalloproteinase domain-containing proteins (ADAMs). Activation of the RAGE signaling pathway leads to a positive feedback loop by enhancing the NF-kB expression. Subsequently, important inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, and C-reactive protein (CRP) are upregulated through both AGE- and NF-kB-mediated pathways.[82] Increased AGE concentration is negatively associated with bone density and mineralization,[83] and the cross-linking of AGE with collagen alters the mechanical properties of bone, disrupting its remodeling, increasing its stiffness and fragility.[84-86] Pentosidine, a well-known AGE, was also shown to disrupt osteoblast differentiation.[87] Studies found that poor glycemic control was associated with increased risk of fractures in individuals with DM, and suggest that HbA_{1c} level of <8% could reduce fracture risk in individuals with DM.

Insulin and IGF1

Insulin exerts an anabolic effect on bones by promoting osteoblast proliferation and differentiation.[88] Animal studies have shown that diabetic rodents have impaired bone formation following bone injury whereas insulin injection normalized it.[89] Insulin deficiency, as in T1DM, is characterized by low levels or activity of insulin-like growth factor 1 (IGF1). The stimulating activity of IGF1 on osteoblasts is inhibited by high concentration of AGEs or glucose.[90,91] In contrast with T1DM, T2DM is a disease that mainly shows insulin resistance. It remains unclear how in T2DM insulin resistance and insulin deficiency at its later stage may affect bone metabolism and fragility.

Pro-inflammatory cytokines

Pro-inflammatory cytokines have been implicated in both T1DM and T2DM and in the development of complications of both diseases. Elevated pro-inflammatory cytokine levels, such as TNF and IL-6, can activate osteoclastogenesis and inhibit osteoblast differentiation.[92,93] Indirectly, the reactive oxygen species generated due to the exposure of tissue to IL-1, IL-6 and TNF can affect the differentiation and survival of osteoclasts, osteoblasts, and osteocytes.

Glucose-lowering Drugs and Bone Metabolism

Antidiabetic treatment is aimed at achieving good glucose control to reduce the risk of complications. Data showed that 1% reduction in HBA_{1c} levels led to 37% reduction in microvascular complication endpoints.[94] As HBA_{1c}, microvascular complications and bone fragility have been shown to be interrelated, it is reasonable to consider that optimal glucose control may reduce fracture risk. Individuals with poor glycemic control have increased risk for fractures.[47,95,96] In individuals with T2DM, HBA_{1c} levels ≥7,5% were reported to have 62% higher risk for fractures compared to those with HBA_{1c} levels <7,5%. The ACCORD trial reported that there was no substantial benefit for fracture prevention or BMD changes in lowering HBA_{1c} below 7,5%.

Insulin was shown to increase the risk of falls in insulin-treated individuals if their HBA_{1c} levels were ≤6%. It appeared that more aggressive glycemic control in elderly individuals with long term disease might increase hypoglycemic events and thus the risk for falls and fractures.[97] Metformin, the first line drug for DM, was found from most clinical studies to have positive or

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neutral effect on BMD and fracture risk in large cohorts.[46,98,99] Sulfonylureas show neutral effect on BTM levels, and studies on its clinical effect has not been established.[46] However, sulfonylureas should be avoided in individuals at risk for bone fragility due to its risk for inducing hypoglycemic events.[67,100] Thiazolidinediones, which includes rosiglitazone and pioglitazone, activate peroxisome proliferator-activated receptors (PPARs), particularly PPAR-γ. *In vitro* and *in vivo* studies show increased adipogenesis and impaired osteoblastogenesis. Meta-analyses confirmed an increased risk for fractures (OR 2.23, 95% CI 1.65–3.01[101] and OR=1.94; 95%CI: 1.60-2.35[102]) in women treated with pioglitazone or rosiglitazone, but not in men. The evidence on the incretin-based treatments, GLP1 analogues and DPP4 inhibitors, are less conclusive.[67] A meta-analysis found that two different GLP1 analogues, liraglutide and exenatide, had protective and negative effects, respectively, on fracture risk. However, these studies were not designed for bone outcomes and differ in their design and power.[103] Studies on DPP4 inhibitors also did not find consistent effects on fracture outcomes.[104,105] Sodium/glucose co-transporter 2 (SGLT2) inhibitors are new generation antidiabetics which exert effects by inhibiting glucose reabsorption in the proximal tubule of the kidney.[106] Data has also not been consistent in this group of drugs. While dapagliflozin and empagliflozin seem to have a neutral effect on bone turnover and BMD parameters, canagliflozin was reported to cause bone loss at the hips[107,108] and increase the risk for hip fractures.

CONCLUSIONS

Fracture risk is known to be increased in both T1DM and T2DM. Levels of BTM were also lower in individuals with DM compared to non-DM controls. Despite increasing data on the association between BMD, BTM and fracture in individuals with DM, there are still challenges in identifying those with high fracture risk. Oxidative stress, inflammation and the production of AGEs increase the risk of complications. Additionally, disturbances in bone collagen metabolism and bone mineralization also reduce bone strength, while altered fat metabolism also affects bone health. A population of individuals are treated with insulin, but its use has been associated with increased fracture risk.[46] It remains unclear whether insulin use is merely a marker for the severity or duration of disease, or induces more hypoglycemic events that lead to falls. Furthermore, it is unknown whether in DM, changes in bone metabolism occurs earlier in the disease course. It is therefore important to consider the treatment approach and education of fall prevention in these individuals who are already at increased risk for fractures. Medications with favorable effect on bone metabolism such as metformin or incretin-based treatments may be the preferred treatment while thiazolidinediones should be used with careful evaluation and patient education. Evaluation by use of BTM may be of benefit, but needs further studies in particular populations of individuals with DM such as premenopausal women or the Indonesian population.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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References

1. International Diabetes Federation. IDF Diabetes Atlas, 7th ed, 2015.
2. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol. 2007;166(5):495-505. PMID: 17575306. https://doi.org/10.1093/aje/kwm106.
3. Janghorbani M, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: The nurses' health study. Diabetes Care. 2006;29(7):1573-8. PMID: 16801581. https://doi.org/10.2337/dc06-0440.
4. Yamamoto M, Yamaguchi T, Yamauchi M, Kaji H, Sugimoto T. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. J Bone Miner Res. 2009;24(4):702-9. PMID: 19049338. https://doi.org/10.1359/jbmr.081207.
5. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes -- a meta-analysis. Osteoporos Int. 2007;18(4):427-44. PMID: 17068657. https://doi.org/10.1007/s00198-006-0253-4.
6. Burghardt AJ, Issever AS, Schwartz AV, et al. High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010;95(11):5045-55. PMID: 20719835. PMCID: PMC2968722. https://doi.org/10.1210/jc.2010-0226.
7. Farr JN, Drake MT, Amin S, Melton LJ 3rd, McCready LK, Khosla S. In vivo assessment of bone quality in postmenopausal women with type 2 diabetes. J Bone Miner Res. 2014;29(4):787-95. PMID: 24123088. PMCID: PMC3961509. https://doi.org/10.1002/jbmr.2106.
8. Patsch JM, Burghardt AJ, Yap SP, et al. Increased cortical porosity in type 2 diabetic postmenopausal women with fragility fractures. J Bone Miner Res. 2013;28(2):313-24. PMID: 22991256. PMCID: PMC3534818. https://doi.org/10.1002/jbmr.1763.
9. Shanbhogue VV, Hansen S, Frost M, et al. Compromised cortical bone compartment in type 2 diabetes mellitus patients with microvascular disease. Eur J Endocrinol. 2016;174(2):115-24. PMID: 26537860. https://doi.org/10.1530/EJE-15-0860.
10. Muñoz-Torres M, Jódar E, Escobar-Jiménez F, López-Ibarra PJ, Luna JD. Bone mineral density measured by dual X-ray absorptiometry in Spanish patients with insulin-dependent diabetes mellitus. Calcif Tissue Int. 1996;58(5):316-9. PMID: 8661964.
11. Miazgowski T, Czekalski S. A 2-year follow-up study on bone mineral density and markers of bone turnover in patients with long-standing insulin-dependent diabetes mellitus. Osteoporos Int. 1998;8(5):399-403. PMID: 9850345. https://doi.org/10.1007/s001980050082.
12. Jehle PM, Jehle DR, Mohan S, Böhm BO. Serum levels of insulin-like growth factor system components and relationship to bone metabolism in type 1 and type 2 diabetes mellitus patients. J Endocrinol. 1998;159(2):297-306. PMID: 9795371.
13. Tuominen JT, Impivaara O, Puukka P, Rönnemaa T. Bone mineral density in patients with type 1 and type 2 diabetes. Diabetes Care. 1999;22(7):1196-200. PMID: 10388989.
14. Gallacher SJ, Fenner JA, Fisher BM, et al. An evaluation of bone density and turnover in premenopausal women with type 1 diabetes mellitus. Diabet Med. 1993;10(2):129-33. PMID: 8096168.

15. Weber G, Beccaria L, de'Angelis M, et al. Bone mass in young patients with type I diabetes. Bone Miner. 1990;8(1):23-30. PMID: 2306551.
16. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995;332(12):767-73. PMID: 7862179. https://doi.org/10.1056/NEJM199503233321202.
17. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ; Blue Mountains Eye Study. Diabetes and risk of fracture: The Blue Mountains Eye Study. Diabetes Care. 2001;24(7):1198-203. PMID: 11423502.
18. Nicodemus KK, Folsom AR; Iowa Women's Health Study. Type 1 and type 2 diabetes and incident hip fractures in postmenopausal women. Diabetes Care. 2001;24(7):1192-7. PMID: 11423501.
19. Wakasugi M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T. Bone mineral density measured by dual energy x-ray absorptiometry in patients with non-insulin-dependent diabetes mellitus. Bone. 1993;14(1):29-33. PMID: 8442999.
20. van Daele PL, Stolk RP, Burger H, et al. Bone density in non-insulin-dependent diabetes mellitus. The Rotterdam Study. Ann Intern Med. 1995;122(6):409-14. PMID: 7856988.
21. Schwartz AV, Sellmeyer DE, Ensrud KE, et al. Older women with diabetes have an increased risk of fracture: A prospective study. J Clin Endocrinol Metab. 2001;86(1):32-8. PMID: 11231974. https://doi.org/10.1210/jcem.86.1.7139.
22. Hadjidakis DJ, Androulakis II. Bone remodeling. Ann N Y Acad Sci. 2006;1092:385-96. PMID: 17308163. https://doi.org/10.1196/annals.1365.035.
23. Taylor AK, Lueken SA, Libanati C, Baylink DJ. Biochemical markers of bone turnover for the clinical assessment of bone metabolism. Rheum Dis Clin North Am. 1994;20(3):589-607. PMID: 7984780.
24. McKee MD, Nanci A. Osteopontin at mineralized tissue interfaces in bone, teeth, and osseointegrated implants: Ultrastructural distribution and implications for mineralized tissue formation, turnover, and repair. Microsc Res Tech. 1996;33(2):141-64. PMID: 8845514. https://doi.org/10.1002/(SICI)1097-0029(19960201)33:2<141::AID-JEMT5>3.0.CO;2-W.
25. Hanson DA, Weis MA, Bollen AM, Maslan SL, Singer FR, Eyre DR. A specific immunoassay for monitoring human bone resorption: Quantitation of type I collagen cross-linked N-telopeptides in urine. J Bone Miner Res. 1992;7(11):1251-8. PMID: 1466251.
26. Christgau S, Rosenquist C, Alexandersen P, et al. Clinical evaluation of the Serum CrossLaps One Step ELISA, a new assay measuring the serum concentration of bone-derived degradation products of type I collagen C-telopeptides. Clin Chem. 1998;44(11):2290-300. PMID: 9799756.
27. Fink E, Cormier C, Steinmetz P, Kindermans C, Le Bouc Y, Souberbielle JC. Differences in the capacity of several biochemical bone markers to assess high bone turnover in early menopause and response to alendronate therapy. Osteoporos Int. 2000;11(4):295-303. PMID: 10928218. https://doi.org/ 10.1007/PL00004183.
28. Hannon R, Blumsohn A, Naylor K, Eastell R. Response of biochemical markers of bone turnover to hormone replacement therapy: Impact of biological variability. J Bone Miner Res. 1998;13(7):1124-33. PMID: 9661076. https://doi.org/10.1359/jbmr.1998.13.7.1124.
29. Seibel MJ. Biochemical markers of bone turnover part I: Biochemistry and variability. Clin Biochem Rev. 2005;26(4):97-122. PMID: 16648882. PMCID: PMC1320175.
30. Forst T, Beyer J, Pfützner A, et al. Peripheral osteopenia in adult patients with insulin-dependent diabetes mellitus. Diabet Med. 1995;12(10):874-9. PMID: 8846677.
31. Kemink SA, Hermus AR, Swinkels LM, Lutterman JA, Smals AG. Osteopenia in insulin-dependent diabetes mellitus; prevalence and aspects of pathophysiology. J Endocrinol Invest. 2000;23(5):295-303. PMID: 10882147. https://doi.org/10.1007/BF03343726.
32. Hadjidakis DJ, Raptis AE, Sfakianakis M, Mylonakis A, Raptis SA. Bone mineral density of both genders in type 1 diabetes according to bone composition. J Diabetes Complications. 2006;20(5):302-7. PMID: 16949517. https://doi.org/10.1016/j.jdiacomp.2005.07.006.
33. Strotmeyer ES, Cauley JA, Orchard TJ, Steenkiste AR, Dorman JS. Middle-aged premenopausal women with type 1 diabetes have lower bone mineral density and calcaneal quantitative ultrasound than nondiabetic women. Diabetes Care. 2006;29(2):306-11. PMID: 16443878.
34. Mastrandrea LD, Wactawski-Wende J, Donahue RP, Hovey KM, Clark A, Quattrin T. Young women with type 1 diabetes have lower bone mineral density that persists over time. Diabetes Care. 2008;31(9):1729-35. PMID: 18591404. PMCID: PMC2518333. https://doi.org/10.2337/dc07-2426.
35. Campos Pastor MM, López-Ibarra PJ, Escobar-Jiménez F, Serrano Pardo M, García-Cervigón AG. Intensive insulin therapy and bone mineral density in type 1 diabetes mellitus: A prospective study. Osteoporos Int. 2000;11(5):455-9. PMID: 10912849.
36. Eller-Vainicher C, Zhukouskaya VV, Tolkachev YV, et al. Low bone mineral density and its predictors in type 1 diabetic patients evaluated by the classic statistics and artificial neural network analysis. Diabetes Care. 2011;34(10):2186-91. PMID: 21852680. PMCID: PMC3177712. https://doi.org/10.2337/dc11-0764.
37. Joshi A, Varthakavi P, Chadha M, Bhagwat N. A study of bone mineral density and its determinants in type 1 diabetes mellitus. J Osteoporos. 2013;2013:397814. PMID: 23607045. PMCID: PMC3628496. https://doi.org/10.1155/2013/397814.
38. Soto N, Pruzzo R, Eyzaguirre F, et al. Bone mass and sex steroids in postmenarcheal adolescents and adult women with type 1 diabetes mellitus. J Diabetes Complications. 2011;25(1):19-24. PMID: 19955005. https://doi.org/10.1016/j.jdiacomp.2009.10.002.
39. Bechtold S, Dirlenbach I, Raile K, Noelle V, Bonfig W, Schwarz HP. Early manifestation of type 1 diabetes in children is a risk factor for changed bone geometry: Data using peripheral quantitative computed tomography. Pediatrics. 2006;118(3):e627-34. PMID: 16908617. https://doi.org/10.1542/peds.2005-2193.
40. Danielson KK, Elliott ME, LeCaire T, Binkley N, Palta M. Poor glycemic control is associated with low BMD detected in premenopausal women with type 1 diabetes. Osteoporos Int. 2009;20(6):923-33. PMID: 18830554. PMCID: PMC2748939. https://doi.org/10.1007/s00198-008-0763-3.
41. Heap J, Murray MA, Miller SC, Jalili T, Moyer-Mileur LJ. Alterations in bone characteristics associated with glycemic control in adolescents with type 1 diabetes mellitus. J Pediatr. 2004;144(1):56-62. PMID: 14722519. https://doi.org/10.1016/j.jpeds.2003.10.066.
42. Lettgen B, Hauffa B, Möhlmann C, Jeken C, Reiners C. Bone mineral density in children and adolescents with juvenile diabetes: Selective measurement of bone mineral density of trabecular and cortical bone using peripheral quantitative computed tomography. Horm Res. 1995;43(5):173-5. PMID: 7782045.
43. Saha MT, Sievänen H, Salo MK, Tulokas S, Saha HH. Bone mass and structure in adolescents with type 1 diabetes compared to healthy peers. Osteoporos Int. 2009;20(8):1401-6. PMID: 19083073. https://doi.org/10.1007/s00198-008-0810-0.
44. Forsén L, Meyer H, Midthjell K, Edna TH. Diabetes mellitus and the incidence of hip fracture: Results from the Nord-Trøndelag Health Survey. Diabetologia. 1999;42(8):920-5. PMID: 10491750. https://doi.org/10.1007/s001250051248.
45. Ahmed LA, Joakimsen RM, Berntsen GK, Fønnebø V, Schirmer H. Diabetes mellitus and the risk of non-vertebral fractures: The Tromsø study. Osteoporos Int. 2006;17(4):495-500. PMID: 16283065. https://doi.org/10.1007/s00198-005-0013-x.
46. Napoli N, Strotmeyer ES, Ensrud KE, et al. Fracture risk in diabetic elderly men: The MrOS study. Diabetologia. 2014;57(10):2057-65. PMID: 24908567. PMCID: PMC4344350. https://doi.org/10.1007/s00125-014-3289-6.
47. Li CI, Liu CS, Lin WY, et al. Glycated hemoglobin level and risk of hip fracture in older people with type 2 diabetes: A competing risk analysis of Taiwan Diabetes Cohort Study. J Bone Miner Res. 2015;30(7):1338-46. PMID: 25598134. https://doi.org/10.1002/jbmr.2462.
48. Johnston S, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab. 2012;14(7):634-43. PMID: 22335246. https://doi.org/10.1111/j.1463-1326.2012.01583.x.
49. de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: The Rotterdam Study. Osteoporos Int. 2005;16(12):1713-20. PMID: 15940395. https://doi.org/10.1007/s00198-005-1909-1.
50. Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, et al. Risk of fracture in women with type 2 diabetes: The Women's Health Initiat.ive Observational Study. J Clin Endocrinol Metab. 2006;91(9):3404-10. PMID: 16804043. https://doi.org/10.1210/jc.2006-0614.
51. Kwon DJ, Kim JH, Chung KW, et al. Bone mineral density of the spine using dual energy x-ray absorptiometry in patients with non-insulin-dependent diabetes mellitus. J Obstet Gynaecol Res. 1996;22(2):157-62. PMID: 8697346.

ONLINE FIRST | October 15, 2017 | https://doi.org/10.15605/jafes.032.02.14

52. Pérez-Castrillón JL, De Luis D, Martín-Escudero JC, Asensio T, del Amo R, Izaola O. Non-insulin-dependent diabetes, bone mineral density, and cardiovascular risk factors. J Diabetes Complications. 2004;18(6):317-21. PMID: 15531180. https://doi.org/10.1016/S1056-8727(03)00072-2.
53. Lunt M, Masaryk P, Scheidt-Nave C, et al. The effects of lifestyle, dietary dairy intake and diabetes on bone density and vertebral deformity prevalence: The EVOS study. Osteoporos Int. 2001;12(8):688-98. PMID: 11580083.
54. Hanley D, Brown J, Tenenhouse A, et al. Associations among disease conditions, bone mineral density, and prevalent vertebral deformities in men and women 50 years of age and older: Cross-sectional results from the Canadian Multicentre Osteoporosis Study. J Bone Miner Res. 2003;18(4):784-90. PMID: 12674340. https://doi.org/10.1359/jbmr.2003.18.4.784.
55. Dennison E, Syddall H, Sayer AA, Craighead S, Phillips D, Cooper C. Type 2 diabetes mellitus is associated with increased axial bone density in men and women from the Hertfordshire Cohort Study: Evidence for an indirect effect of insulin resistance? Diabetologia. 2004;47(11):1963-8. PMID: 15565368. https://doi.org/10.1007/s00125-004-1560-y.
56. Barrett-Connor E, Holbrook TL. Sex differences in osteoporosis in older adults with non—insulin-dependent diabetes mellitus. JAMA. 1992;268(23):3333-7. PMID: 1453525.
57. Gerdhem P, Isaksson A, Akesson K, Obrant KJ. Increased bone density and decreased bone turnover, but no evident alteration of fracture susceptibility in elderly women with diabetes mellitus. Osteoporos Int. 2005;16(12):1506-12. PMID: 15824889. https://doi.org/10.1007/s00198-005-1877-5.
58. Schwartz AV, Sellmeyer DE, Strotmeyer ES, et al. Diabetes and bone loss at the hip in older black and white adults. J Bone Miner Res. 2005;20(4):596-603. PMID: 15765178. https://doi.org/10.1359/JBMR.041219.
59. Dobnig H, Piswanger-Solkner JC, Roth M, et al. Type 2 diabetes mellitus in nursing home patients: effects on bone turnover, bone mass, and fracture risk. J Clin Endocrinol Metab. 2006;91(9):3355-63. PMID: 16735485. https://doi.org/10.1210/jc.2006-0460.
60. Strotmeyer ES, Cauley JA, Schwartz AV, et al. Diabetes is associated independently of body composition with BMD and bone volume in older white and black men and women: The Health, Aging, and Body Composition Study. J Bone Miner Res. 2004;19(7):1084-91. PMID: 15176990. https://doi.org/ 10.1359/JBMR.040311.
61. Pritchard JM, Giangregorio LM, Atkinson SA, et al. Changes in trabecular bone microarchitecture in postmenopausal women with and without type 2 diabetes: A two year longitudinal study. BMC Musculoskelet Disord. 2013;14:114. PMID: 23530948. PMCID: PMC3618189. https://doi.org/10.1186/1471-2474-14-114.
62. Pritchard JM, Giangregorio LM, Atkinson SA, et al. Association of larger holes in the trabecular bone at the distal radius in postmenopausal women with type 2 diabetes mellitus compared to controls. Arthritis Care Res (Hoboken). 2012;64(1):83-91. PMID: 22213724. PMCID: PMC5096917. https://doi.org/10.1002/acr.20602.
63. Randall C, Bridges D, Guerri R, et al. Applications of a new handheld reference point indentation instrument measuring bone material strength. J Med Device. 2013;7(4):0410051-6. PMID: 24115973. PMCID: PMC3792445. https://doi.org/ 10.1115/1.4024829.
64. Dubey A, Aharonoff GB, Zuckerman JD, Koval KJ. The effects of diabetes on outcome after hip fracture. Bull Hosp Jt Dis. 2000;59(2):94-8. PMID: 10983258.
65. Huang YF, Shyu YI, Liang J, Chen MC, Cheng HS, Wu CC. Diabetes and health outcomes among older Taiwanese with hip fracture. Rejuvenation Res. 2012;15(5):476-82. PMID: 22998328. https://doi.org/10.1089/rej.2011.1308.
66. Muraki S, Yamamoto S, Ishibashi H, Nakamura K. Factors associated with mortality following hip fracture in Japan. J Bone Miner Metab. 2006;24(2):100-4. PMID: 16502115. https://doi.org/10.1007/s00774-005-0654-z.
67. Napoli N, Chandran M, Pierroz DD, et al. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol. 2017;13(4):208-19. PMID: 27658727. https://doi.org/10.1038/nrendo.2016.153.
68. Hough FS, Pierroz DD, Cooper C, Ferrari SL; IOF CSA Bone and Diabetes Working Group. Mechanisms in endocrinology: Mechanisms and evaluation of bone fragility in type 1 diabetes mellitus. Eur J Endocrinol. 2016;174(4):R127-38. PMID: 26537861. https://doi.org/10.1530/EJE-15-0820.
69. Napoli N, Strollo R, Paladini A, Briganti SI, Pozzilli P, Epstein S. The alliance of mesenchymal stem cells, bone, and diabetes. Int J Endocrinol. 2014;2014:690783. PMID: 25140176. PMCID: PMC4124651. https://doi.org/ 10.1155/2014/690783.
70. Maggio AB, Ferrari S, Kraenzlin M, et al. Decreased bone turnover in children and adolescents with well controlled type 1 diabetes. J Pediatr Endocrinol Metab. 2010;23(7):697-707. PMID: 20857842.
71. Adami S. Bone health in diabetes: Considerations for clinical management. Curr Med Res Opin. 2009;25(5):1057-72. PMID: 19292601. https://doi.org/ 10.1185/03007990902801147.
72. Díaz-López A, Bulló M, Juanola-Falgarona M, et al. Reduced serum concentrations of carboxylated and undercarboxylated osteocalcin are associated with risk of developing type 2 diabetes mellitus in a high cardiovascular risk population: A nested case-control study. J Clin Endocrinol Metab. 2013;98(11):4524-31. PMID: 24037881. https://doi.org/10.1210/jc.2013-2472.
73. Starup-Linde J, Eriksen SA, Lykkeboe S, Handberg A, Vestergaard P. Biochemical markers of bone turnover in diabetes patients—a meta-analysis, and a methodological study on the effects of glucose on bone markers. Osteoporos Int. 2014;25(6):1697-708. PMID: 24676844. https://doi.org/10.1007/s00198-014-2676-7.
74. Leite Duarte ME, da Silva RD. Histomorphometric analysis of the bone tissue in patients with non-insulin-dependent diabetes (DMNID). Rev Hosp Clin Fac Med Sao Paulo. 1995;51(1):7-11. PMID: 8762647.
75. Weyer C, Funahashi T, Tanaka S, et al. Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86(5):1930-5. PMID: 11344187. https://doi.org/ 10.1210/jcem.86.5.7463.
76. Williams GA, Wang Y, Callon KE, et al. In vitro and in vivo effects of adiponectin on bone. Endocrinology. 2009;150(8):3603-10. PMID: 19406946. https://doi.org/10.1210/en.2008-1639.
77. Tamura T, Yoneda M, Yamane K, et al. Serum leptin and adiponectin are positively associated with bone mineral density at the distal radius in patients with type 2 diabetes mellitus. Metabolism. 2007;56(5):623-8. PMID: 17445536. https://doi.org/10.1016/j.metabol.2006.12.008.
78. Wang W, Zhang X, Zheng J, Yang J. High glucose stimulates adipogenic and inhibits osteogenic differentiation in MG-63 cells through cAMP/protein kinase A/extracellular signal-regulated kinase pathway. Mol Cell Biochem. 2010;338(1-2):115-22. PMID: 19949837. https://doi.org/10.1007/s11010-009-0344-6.
79. Botolin S, Faugere MC, Malluche H, Orth M, Meyer R, McCabe LR. Increased bone adiposity and peroxisomal proliferator-activated receptor-gamma2 expression in type I diabetic mice. Endocrinology. 2005;146(8):3622-31. PMID: 15905321. PMCID: PMC1242186. 10.1210/en.2004-1677.
80. Bucala R, Vlassara H. Advanced glycosylation end products in diabetic renal and vascular disease. Am J Kidney Dis. 1995;26(6):875-88. PMID: 7503061.
81. Gefter JV, Shaufl AL, Fink MP, Delude RL. Comparison of distinct protein isoforms of the receptor for advanced glycation end-products expressed in murine tissues and cell lines. Cell Tissue Res. 2009;337(1):79-89. PMID: 19415334. https://doi.org/10.1007/s00441-009-0791-0.
82. Ramasamy R, Yan SF, Schmidt AM. Advanced glycation endproducts: From precursors to RAGE: Round and round we go. Amino Acids. 2012;42(4):1151-61. PMID: 20957395. PMCID: PMC3062728. https://doi.org/10.1007/s00726-010-0773-2.
83. Odetti P, Rossi S, Monacelli F, et al. Advanced glycation end products and bone loss during aging. Ann N Y Acad Sci. 2005;1043:710-7. PMID: 16037297. https://doi.org/10.1196/annals.1333.082.
84. Hein GE. Glycation endproducts in osteoporosis—is there a pathophysiologic importance? Clin Chim Acta. 2006;371(1-2):32-6. PMID: 16777084. https://doi.org/10.1016/j.cca.2006.03.017.
85. Dong XN, Qin A, Xu J, Wang X. In situ accumulation of advanced glycation endproducts (AGEs) in bone matrix and its correlation with osteoclastic bone resorption. Bone. 2011;49(2):174-83. PMID: 21530698. PMCID: PMC3117937. https://doi.org/10.1016/j.bone.2011.04.009.
86. Tang S, Zeenath U, Vashishth D. Effects of non-enzymatic glycation on cancellous bone fragility. Bone. 2007;40(4):1144-51. PMID: 17257914. PMCID: PMC4398019. https://doi.org/10.1016/j.bone.2006.12.056.
87. Sanguineti R, Storace D, Monacelli F, Federici A, Odetti P. Pentosidine effects on human osteoblastsin vitro. Ann N Y Acad Sci.

2008;1126:166-72. PMID: 18448811. https://doi.org/10.1196/annals.1433.044.

88. Yang J, Zhang X, Wang W, Liu J. Insulin stimulates osteoblast proliferation and differentiation through ERK and PI3K in MG-63 cells. Cell Biochem Funct. 2010;28(4):334-41. PMID: 20517899. https://doi.org/10.1002/cbf.1668.
89. Gandhi A, Beam HA, O'Connor JP, Parsons JR, Lin SS. The effects of local insulin delivery on diabetic fracture healing. Bone. 2005;37(4):482-90. PMID: 16027060. https://doi.org/10.1016/j.bone.2005.04.039.
90. McCarthy AD, Etcheverry SB, Cortizo AM. Effect of advanced glycation endproducts on the secretion of insulin-like growth factor-I and its binding proteins: Role in osteoblast development. Acta Diabetol. 2001;38(3):113-22. PMID: 11827431.
91. Terada M, Inaba M, Yano Y, et al. Growth-inhibitory effect of a high glucose concentration on osteoblast-like cells. Bone. 1998;22(1):17-23. PMID: 9437509.
92. Gilbert L, He X, Farmer P, et al. Inhibition of osteoblast differentiation by tumor necrosis factor-α 1. Endocrinology. 2000;141(11):3956-64. PMID: 11089525. https://doi.org/10.1210/endo.141.11.7739.
93. Glantschnig H, Fisher JE, Wesolowski G, Rodan GA, Reszka AA. M-CSF, TNFα and RANK ligand promote osteoclast survival by signaling through mTOR/S6 kinase. Cell Death Differ. 2003;10(10):1165-77. PMID: 14502240. https://doi.org/10.1038/sj.cdd.4401285.
94. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. BMJ. 2000;321(7258):405-12. PMID: 10938048. PMCID: PMC27454.
95. Oei L, Zillikens MC, Dehghan A, Buitendijk GH, et al. High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: The Rotterdam Study. Diabetes Care. 2013;36(6):1619-28. PMID: 23315602. PMCID: PMC3661786. https://doi.org/10.2337/dc12-1188.
96. Schneider AL, Williams EK, Brancati FL, Blecker S, Coresh J, Selvin E. Diabetes and risk of fracture-related hospitalization: The atherosclerosis risk in communities study. Diabetes Care. 2013;36(5):1153-8. PMID: 23248194. PMCID: PMC3631877. https://doi.org/10.2337/dc12-1168.
97. Schwartz AV, Vittinghoff E, Sellmeyer DE, et al. Diabetes-related complications, glycemic control, and falls in older adults. Diabetes Care. 2008;31(3):391-6. PMID: 18056893. PMCID: PMC2288549. https://doi.org/10.2337/dc07-1152.
98. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005;48(7):1292-9. PMID: 15909154. https://doi.org/10.1007/s00125-005-1786-3.
99. Solomon DH, Cadarette SM, Choudhry NK, Canning C, Levin R, Stürmer T. A cohort study of thiazolidinediones and fractures in older adults with diabetes. J Clin Endocrinol Metab. 2009;94(8):2792-8. PMID: 19470635 PMCID: PMC2730861. https://doi.org/10.1210/jc.2008-2157.
100. Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: A 2-year study. Diabetes Obes Metab. 2014;16(12):1239-46. PMID: 25132212. https://doi.org/10.1111/dom.12377.
101. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. Can Med Assoc J. 2009;180(1):32-9. PMID: 1907365. PMCID: PMC2612065. https://doi.org/10.1503/cmaj.080486.
102. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: An updated meta-analysis of randomized clinical trials. Bone. 2014;68:115-23. PMID: 25173606. https://doi.org/10.1016/j.bone.2014.08.010.
103. Su B, Sheng H, Zhang M, et al. Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: A meta-analysis of randomized controlled trials. Endocrine. 2015;48(1):107-15. PMID: 25074632. https://doi.org/10.1007/s12020-014-0361-4.
104. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: A Meta-analysis of randomized clinical trials. Diabetes Care 2011 34(11): 2474–6. PMID: 22025784. PMCID: PMC3198283. https://doi.org/10.2337/dc11-1099.
105. Mosenzon O, Wei C, Davidson J, et al. Incidence of fractures in patients with type 2 diabetes in the SAVOR-TIMI 53 trial. Diabetes Care. 2015;38(11):2142-50. PMID: 26358285. https://doi.org/10.2337/dc15-1068.
106. DeFronzo R, Davidson J, Del Prato S. The role of the kidneys in glucose homeostasis: A new path towards normalizing glycaemia. Diabetes Obes Metab. 2012;14(1):5-14. PMID: 21955459. https://doi.org/10.1111/j.1463-1326.2011.01511.x.
107. Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab. 2015;101(1):44-51. PMID: 26580234. PMCID: PMC4701848. https://doi.org/10.1210/jc.2015-1860.
108. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2015;101(1):157-66. PMID: 26580237. PMCID: PMC4701850. https://doi.org/10.1210/jc.2015-3167.
109. Vasikaran S, Eastell R, Bruyère O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: A need for international reference standards. Osteoporos Int. 2011;22(2):391-420. PMID: 21184054. https://doi.org/10.1007/s00198-010-1501-1.
110. Reyes-García R, Rozas-Moreno P, López-Gallardo G, et al. Serum levels of bone resorption markers are decreased in patients with type 2 diabetes. Acta Diabetol. 2013;50(1):47-52. PMID: 22042129. https://doi.org/10.1007/s00592-011-0347-0.
111. Yamamoto M, Yamaguchi T, Nawata K, Yamauchi M, Sugimoto T. Decreased PTH levels accompanied by low bone formation are associated with vertebral fractures in postmenopausal women with type 2 diabetes. J Clin Endocrinol Metab. 2012;97(4):1277-84. PMID: 22337915. https://doi.org/10.1210/jc.2011-2537.
112. Manavalan JS, Cremers S, Dempster DW, et al. Circulating osteogenic precursor cells in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2012;97(9):3240-50. PMID: 22740707 PMCID: PMC3431571. https://doi.org/10.1210/jc.2012-1546.
113. Bhattoa HP, Wamwaki J, Kalina E, Foldesi R, Balogh A, Antal-Szalmas P. Serum sclerostin levels in healthy men over 50 years of age. J Bone Miner Metab. 2013;31(5):579-84. PMID: 23525828. https://doi.org/10.1007/s00774-013-0451-z.
114. Ardawi MS, Akhbar DH, Alshaikh A, et al. Increased serum sclerostin and decreased serum IGF-1 are associated with vertebral fractures among postmenopausal women with type-2 diabetes. Bone. 2013;56(2):355-62. PMID: 23845326. https://doi.org/10.1016/j.bone.2013.06.029.
115. Hamilton EJ, Rakic V, Davis WA, et al. A five-year prospective study of bone mineral density in men and women with diabetes: The Fremantle Diabetes Study. Acta Diabetol. 2012;49(2):153-8. PMID: 21971710. https://doi.org/10.1007/s00592-011-0324-7.
116. Akin O, Göl K, Aktürk M, Erkaya S. Evaluation of bone turnover in postmenopausal patients with type 2 diabetes mellitus using biochemical markers and bone mineral density measurements. Gynecol Endocrinol. 2003;17(1):19-29. PMID: 12724015.
117. Jiajue R, Jiang Y, Wang O, et al. Suppressed bone turnover was associated with increased osteoporotic fracture risks in non-obese postmenopausal Chinese women with type 2 diabetes mellitus. Osteoporos Int. 2014;25(8):1999-2005. PMID: 24760246. https://doi.org/10.1007/s00198-014-2714-5.
118. Bhattoa HP, Onyeka U, Kalina E, et al. Bone metabolism and the 10-year probability of hip fracture and a major osteoporotic fracture using the country-specific FRAX algorithm in men over 50 years of age with type 2 diabetes mellitus: A case-control study. Clin Rheumatol. 2013;32(8):1161-7. PMID: 23588883.https://doi.org/10.1007/s10067-013-2254-y.
119. Gaudio A, Privitera F, Battaglia K, et al. Sclerostin levels associated with inhibition of the Wnt/β-catenin signaling and reduced bone turnover in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2012;97(10):3744-50. PMID: 22855334. https://doi.org/10.1210/jc.2012-1901.
120. Hernández JL, Olmos JM, Romaña G, et al. Bone turnover markers in statin users: A population-based analysis from the Camargo Cohort Study. Maturitas. 2013;75(1):67-73. PMID: 23489550. https://doi.org/10.1016/j.maturitas.2013.02.003.
121. Sarkar P, Choudhury A. Relationships between serum osteocalcin levels versus blood glucose, insulin resistance and markers of systemic inflammation in central Indian type 2 diabetic patients. Eur Rev Med Pharmacol Sci. 2013;17(12):1631-5. PMID: 23832730.
122. Movahed A, Larijani B, Nabipour I, et al. Reduced serum osteocalcin concentrations are associated with type 2 diabetes mellitus and the

ONLINE FIRST | October 15, 2017 | https://doi.org/10.15605/jafes.032.02.14

metabolic syndrome components in postmenopausal women: The crosstalk between bone and energy metabolism. J Bone Miner Metab. 2012;30(6):683-91. PMID: 22752126. https://doi.org/10.1007/s00774-012-0367-z.

123. Sosa M, Dominguez M, Navarro MC, et al. Bone mineral metabolism is normal in non-insulin-dependent diabetes mellitus. J Diabetes Complications. 1996;10(4):201-5. PMID: 8835919.

124. Chen H, Li X, Yue R, Ren X, Zhang X, Ni A. The effects of diabetes mellitus and diabetic nephropathy on bone and mineral metabolism in T2DM patients. Diabetes Res Clin Pract. 2013;100(2):272-6. PMID: 23522918. https://doi.org/10.1016/j.diabres.2013.03.007.

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ORIGINAL ARTICLE

Health-Related Quality of Life (HRQoL) of Adult Filipinos with Graves' Disease cured by Radioiodine Therapy compared to those controlled by Antithyroid Drugs at University of Santo Tomas Hospital: A Pilot Study*

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Abstract

Objective. The study aims to develop and validate the Filipino version of Thyroid-disease specific quality of life Patient Reported Outcome (ThyPROph) questionnaire, and to conduct a pilot study comparing the quality of life of patients with Graves' disease at University of Santo Tomas Hospital (USTH) after receiving radioactive iodine ablation (RAI) or anti-thyroid drug (ATD) using the validated ThyPROph.

Methodology. This study has 2 phases. Phase 1 is the development and validation of the ThyPROph with prior translation and pretesting to Graves' disease patients. Phase 2 is the pilot study involving 58 euthyroid patients with Graves' disease recruited to answer the validated ThyPROph. All of the participants completed the ThyPROph. A cross sectional comparative design was used to compare health-related quality of life (HRQoL) under two modes of treatment for Graves' disease: RAI and ATD. Likewise, correlation of the domains with the demographics was determined using Pearson correlation coefficient and Spearman rank signed test.

Results. For the phase 1 study, internal consistency exists across all domains of ThyPROph with Cronbach's alpha of 0.839. Overall, discriminant validity falls within range of 0.028-0.606 and convergent validity showed moderate correlations. Phase 2 study showed that there is a significant difference in the domains "goiter symptoms" (p=0.0209), "emotional susceptibility" (p=0.0067) and "impaired daily life" (p=0.0463). The HRQoL is significantly better in the RAI group based on these three domains. Statistically significant correlations exist between goiter grade and goiter symptoms domain (p=0.0001), gender and impaired daily life domain (p=0.016), cosmetic complaints domain with age (p=0.002), marital status (p=0.046), and disease duration (p=0.005).

Limitations. Results are not powered to achieve the primary objective because complications of Graves' disease were excluded. The reliability of the domains is reduced. A prospective randomized study is more ideal.

Conclusion. Quality of life of patients with Graves' disease as assessed by ThyPROph is significantly better with RAI compared to ATD. RAI therapy can be considered as the better treatment option in our setting especially for patients who have noticeable goiters with symptoms attributable to their goiters, and those with emotional instability.

Key words: Graves' disease, quality of life, radioactive iodine, antithyroid drug

INTRODUCTION

Graves' disease is an autoimmune disorder characterized by thyrotoxicosis, enlarged thyroid gland and ophthalmopathy. It affects various organs and tissues in the body.[1] Without treatment, complications such as infertility, cachexia, cardiac arrhythmias, cardiomyopathy, thyroid storm and even death can result.[2]

Aside from the complications of the disease, hyperthyroid Graves' patients often have neuropsychiatric complaints including memory problems, emotional lability, irritability, depression and anxiety that can negatively impact quality of life. Quality of life improves after treatment once euthyroid state is achieved.[3]

The goal of therapy is to correct the hypermetabolic state by keeping T4 and/or T3 levels within normal range with the fewest side effects and the lowest incidence of hypothyroidism. Three modalities are commonly used to treat Graves' hyperthyroidism: antithyroid drugs (ATD), surgery, or radioiodine (RAI) ablation.

ATD therapy inhibits thyroid hormone synthesis with preservation of the thyroid gland. Maximum remission or cure rates (i.e., permanent resolution of hyperthyroidism

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defined by normalization of T4 and/or TSH levels off ATDs) of up to 60% are achieved with 18–24 months of continued use. With ATD discontinuation, hyperthyroid relapse rate is up to 50%. There is no permanent hypothyroidism with this mode of treatment and for unclear reasons, the relapse rates appear to vary in different geographic regions. In a study made by Tütüncü et al., in Turkey (an iodine deficient country) remission rate decreased from 74.4% to 65.1% in the first year and after four years, thereafter. The long-term remission is not predicted by the remission achieved in 2 years' time in areas low in iodine.[4] Patients with severe hyperthyroidism and large goiters are likely to relapse when treatment is stopped, but outcome is difficult to predict. The common side effects of ATD are rash, urticaria, and arthralgia (1–5%). Rare but major side effects include hepatitis, an SLE-like syndrome and agranulocytosis (<1%).[5]

Rarely resorted to nowadays due to its cost and invasive nature, subtotal or near-total thyroidectomy is only considered for patients with very large, nodular goiters or those who relapse after anti-thyroid drugs, and based on patient's personal preference over RAI.

RAI ameliorates hyperthyroidism by permanent destruction of thyroid tissue. It is effective with remission or cure rates reaching up to 80%. It is gaining popularity as first line therapy since it is effective, safe, and easy to administer; except for contraindication to its use in pregnant and lactating women, and some controversies surrounding its use in individuals under 20 years old. Hyperthyroidism may persist for 2–3 months before radioiodine takes full effect. Persistent hyperthyroidism is usually treated with a second dose of radioiodine 6-12 months after the first dose.[6]

However, RAI usually leads to permanent hypothyroidism regardless of dosage thereby necessitating long-term thyroxine replacement in majority of patients. The risk is at least 10–20% in the first year and 5% per year thereafter. Up to 90% become hypothyroid in 25 years.[7] Efforts to calculate an optimal dose of radioiodine that achieves euthyroidism without a high incidence of hyperthyroid relapse or progression to hypothyroidism have not been successful. Due to this, many authorities currently favor an approach aimed at early permanent hypothyroidism as opposed to euthyroidism to avoid missing the diagnosis of hypothyroidism later on.

Moreover, in 15 percent of patients, Graves' ophthalmopathy can develop or get worse with use of radioactive iodine.

Anti-thyroid drugs are the predominant therapy in many centers in Europe and Japan, whereas radioiodine is more often the first line of treatment in North America. (Published data as to which treatment modality is preferred in our country is still unavailable.) These differences reflect the fact that no single approach is optimal, each has its own advantages and disadvantages.[8] Assessment of physical, social function, mental health and overall well being is, therefore, an important outcome when treating patients with this disease.

In a study by Watt et al., involving interviews with 80 thyroid outpatients, 21 of whom had Graves' disease, to identify how thyroid diseases impact the patients' lives and to select the most relevant quality of life issues for a thyroid-specific questionnaire, broader quality-of-life domains were chosen to be most relevant, especially fatigue, emotional susceptibility and impact on daily life.

In a prospective randomized open label trial by Torring, et al., involving 119 Swedish patients with Graves' disease age 33-55 years old randomly assigned treatment with either methimazole 10mg QID+LT4 100-300mcg/day +B-blocker 18 months then withdrawn (medical group), subtotal thyroidectomy +LT4 replacement (surgical group) or RAI using calculated dosimetry accounting for thyroid size and 24hr RAIU (RAI group). The cure rates at second year, which was their primary outcome, was 66% for the medical group, 79% for RAI and 92% for surgical group. Part of their secondary outcome included an assessment of the patients' views of the disease and treatment using a non-validated disease-specific questionnaire administered 3 years after the initiation of treatment. Ninety percent of the subjects in all groups were satisfied with the treatment they received, although around 30% from each arm still felt that they have not recovered even after a year. The number of sick leaves within 2 years from treatment was not statistically different among the three groups.[9]

Thyroid disease-specific quality-of-life patient-reported outcome (ThyPRO) measure was developed by Watt et al. The ThyPRO questionnaire initially has 85 items which encompass quality of life across benign thyroid diseases. The questionnaire was cross-culturally validated and currently exists in 7 translated languages namely: English, Dutch, Serbian, Italian, Indian, Danish and Swedish.[10] Utilizing the ThyPRO, the Serbian version showed that Graves' disease patients had significant improvement in their quality of life after surgery.

Before, the Short Form 36 (SF-36) Health Survey was used for benign thyroid disorders. It is a generic measure and may not target a specific disease.[11] For example, SF-36 does not include goiter symptoms. The only available HRQoL related to thyroid pathology is the validated questionnaire for differentiated thyroid cancer.[12]

There are no published questionnaire to assess quality of life of Graves' disease patients after receiving ATD or RAI in the Philippines, so a questionnaire should first be developed and validated. The assessment by comparison of quality life is the primary objective of this study and the assessment tool used is the ThyPRO originally made by

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Watt et al. To date, the comparison under these treatments has not yet been made to cases of Graves' disease patients. This small scale pilot study may serve as a guide for future large scale or multicenter study in the country with the use of culturally adapted benign thyroid disease questionnaire. Locally adapted tool will fit our local demographics adding acceptability of the assessment and evaluation of quality of life. This locally adapted tool is the ThyPROph.

In treatment of patients with benign thyroid disease, the decision for medical therapy with anti-thyroid drug or RAI depends on the balance between the benefits of being cured of hyperthyroidism and the risk of permanent hypothyroidism leading to lifetime thyroxine replacement. The patient's question about how much better he is likely to feel may be relevant to his decision as well. Information about the impact of the different treatment modalities on health-related quality of life (HRQoL), therefore, will aid clinicians in helping patients make a fully informed choice hence this study.

METHODOLOGY

Study Design and Population

The study has 2 phases. First phase is the translation and validation wherein cross-sectional analytical design was used. Second phase of the study is the comparison of quality of life scores with RAI treatment versus ATD wherein cross-sectional comparative study design was used.

The study was conducted after being approved by the University of Santo Tomas Hospital Institutional Review Board (USTH-IRB). The subjects participated after signing informed consent. The identity and other information about the respondents in the study were kept strictly confidential.

First Phase: Translation and Validation

Adult euthyroid Graves' disease patients consulting at the private and clinical division of the University of Santo Tomas Hospital (USTH) were recruited. Inclusion criteria included patients with Graves' disease who were already euthyroid (TSH+T4 or fT4 within normal ranges taken at least 2 months from date of study inclusion) for at least 6 months after RAI or after ATD treatment. Exclusion criteria included those with thyrotoxic cardiomyopathy, thyrotoxic hypokalemic periodic paralysis, pregnant or breastfeeding individuals and those who were unable to read Tagalog or English.

Description of the Study Procedure

The Questionnaire

The ThyPRO 39 which is a shorter version of the original ThyPRO questionnaire was utilized in this study. The original ThyPRO questionnaire was developed by Torquil Watt et al., in Denmark and published at European Journal of Endocrinology in 2010. The questionnaire was utilized with permission from the tool developer with approval and response received through e-mail.[13] The questionnaire consisted of 12 scales and 1 about Impact on overall QoL. Questions included 3 goiter symptoms, 4 hyperthyroid symptoms, 4 hypothyroid symptoms, 3 eye symptoms, 3 on tiredness, 3 on cognitive complaints, 3 on anxiety, 3 on depression, 3 on emotional susceptibility, 3 on impaired social life, 3 on impaired daily life, 3 on appearance and finally 1 about Impact on overall QoL. The item is rated on a 0-4 Likert scale with choices as follows: not at all, a little, some, quite a bit and very much. Table 1 shows the scale content of the ThyPRO questionnaire.

Table 1. Scale content of original ThyPRO questionnaire

Goiter Symptoms
1a- had the sensation of fullness in the neck?
1b- felt pressure in your throat?
1c- felt discomfort swallowing?
Hyperthyroid Symptoms
1d- had trembling hands?
1e- had a tendency to sweat a lot?
1f- experienced palpitations (rapid heart beat)?
1h- had an upset stomach?
Hypothyroid Symptoms
1g- been sensitive to cold?
1l- had swollen hands or feet?
1m- had dry skin?
1n- had itchy skin?
Eye Symptoms
1i- had the sensation of dryness or "grittiness" in the eyes?
1j- had impaired vision?
1k- been very sensitive to light?
Tiredness
2a- been tired?
2b-had difficulty getting motivated to do anything at all?
3a- felt energetic?
Cognitive
4a-had difficulty remembering?
4b-had slow or unclear thinking?
4c- had difficulty concentrating?
Anxiety
5a- felt afraid or anxious?
5b- felt tense?
5c-felt uneasy?
Depressivity
6a- felt sad?
6b- felt unhappy?
6c-had self-confidence?
Emotional Susceptibility
7a- noticed you easily felt stressed?
7b- had mood swings?
7c- felt in control of your life?
Impaired Social Life
8a- have difficulty being together with other people (for example, spouse, children, boy/girlfriend, friends, or others)?
8b- feel you were a burden to other people?
8c- have conflicts with other people?
Impaired Daily Life
9a- have difficulty managing your daily life?
9b- not be able to participate in life around you?
9c- feel as if everything takes longer to do?
Cosmetic Complaints
10a- has your thyroid disease affected your appearance (for example, swelling of the neck, eye changes, weight changes)?
10b- have you been bothered by other people looking at you?
10c- has your thyroid disease influenced which clothes you wear?
Impact on Overall Quality of Life
11a- has your thyroid disease had a negative effect on your quality of life

Source: Watt T, Hegedüs L, Groenvold M et al. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. European Journal of Endocrinology.2010; 162: 161–167

A. Translation Process

In the translation process, one Filipino teacher was asked to translate the questionnaire from English to Tagalog

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(forward translation 1) with the aid of the investigator. Another Filipino teacher was called upon for translation from English to Filipino as well (forward translation 2). The two translators compared the versions and agreed on a common Filipino version of the questionnaire. An English teacher served as third translator. The Filipino version was translated back to English (back-translated version). The study adviser identified and commented on differences between the original English questionnaire and the Filipino version. Suggestions were made on how this will be handled.

After approval of the study adviser, the translated ThyPRO questionnaire was presented to 2 endocrinology consultants, 2 endocrinology fellows, 1 nurse and 2 non-medical/lay persons for review for comprehensibility of the questionnaire to both medical and non-medical/lay persons. After which, the suggestions of the review committee were carried out by the study adviser and the second edited ThyPRO Filipino version was derived. .

B. Pretesting

The translated ThyPRO questionnaire was pre-tested to 5 actual patients who had hyperthyroidism before and had either medical treatment or radioactive iodine. They were asked if the questionnaire was clear and if changes were necessary. Final revision of ThyPRO Filipino version questionnaire was made to arrive at draft ThyPRO Filipino version.

C. Validation of the DRAFT ThyPRO Filipino version Questionnaire

Twenty subjects who fulfilled the inclusion criteria were asked to answer the pre-final ThyPRO Filipino version questionnaire for validation.

Assessment of validity of the pre-final ThyPRO Filipino version questionnaire was accomplished using following measures: content, internal consistency/reliability and construct validity.

1. Content validity was measured with the assessments made by the endocrine consultants and fellows, and the pretesting results of 5 patients.
2. Internal consistency was assessed using Cronbach's alpha. Acceptable consistency will be an alpha value of $\geq$0.7. Cronbach's alpha is a measure of relationships of the items in the questionnaire as a group.
3. Construct validity was assessed using convergent and discriminant validity. Spearman's rho was determined for convergent validity and Inter-Item correlation (IIC) was computed for the discriminant validity. IIC result less than 0.85 tell us that discriminant validity likely exists between the scales.

Second Phase of the Study: Comparison of Quality of Life Scores with RAI Treatment versus ATD

The same inclusion and exclusion criteria were used for the second phase of the study.

Sample Size Calculation

Currently, no study comparing the quality of life of those who underwent RAI or on ATD is available in the Philippines. As a preliminary data and in this pilot study, the following formula will be used for sample size calculation:

$$n = \frac{\ln(1-\Upsilon)}{\ln(1-\pi)}$$

where ln means logarithm, Υ is confidence level set at 95% and π is the probability level set at 5%. Based on the above formula the sample size in this study is 58 patients with Graves' disease.

Statistical Analysis

SPSS was used for statistical analysis. Means and range summarized the data in quantitative form. While counts and percentages were used for qualitative data. Differences between demographic profiles, such as gender, marital status, educational attainment, employment and goiter grade (categorical variable) were compared using Chi-Square Test; while numerical variable (age, disease duration, initiation of treatment) were compared using Independent T-test. Comparison of Quality of Life scores was done using independent t-test. Correlation of the domains with the demographics was determined using Pearson correlation coefficient (for numerical variable) and Spearman rank signed test (for categorical variable). P-value of 0.05 is considered in this study.

RESULTS

First Phase: Translation and Validation

Content Validation

The following are the output of the review committee together with the adviser which provided content validity:
Item 1a: The consensus on translation for the "fullness in the neck" is "*paninikip ng leeg*" instead of "*kapunuan sa leeg*."
Item 1b: The "pressure in your throat" is translated simply to "*bara sa lalamunan*" instead of "*bigat/bara sa lalamunan*."
Item 1f: Instead of using the Taglish "*palpitasyon*," "*pagkabog sa dibdib*" was used.
Item 2b: The English version was translated as "*nawalan ng gana sa kahit anong gawain*."

Reliability and Validity

The internal consistency or reliability of the scales was assessed using Cronbach's alpha where a value of >0.7 is consistent with good internal consistency or reliability. The Cronbach's alpha reliability of the 13 items ranged from -0.153 to 0.854. Scale on Impaired Social Life and Anxiety shows an acceptable degree of internal consistency, with Cronbach's alpha of 0.854 and 0.784, respectively. However, poor internal consistency for ThyPRO Filipino version are classified on the scales on Eye Symptoms (α=0.198), Emotional Susceptibility (α=-0.153), Cosmetic Complaints (α=0.286), Tiredness (α=0.312), Hypothyroid (α=0.499) and Hyperthyroid (α=0.270) Symptoms, Cognitive (α=0.515), Depressivity

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Table 2. Reliability and validity of the ThyPRO Filipino version , n=20, Manila

Scale	Number of items	Cronbach's Alpha	Average IIC[a]	Convergent Validity
Goiter Syndrome	3	0.657	0.007 - 0.377	0.046 - 0.537
Hyperthyroid Symptoms	4	0.270	0.014 - 0.178	0.012 - 0.597
Hypothyroid Symptoms	4	0.499	0.026 - 0.164	0.098 - 0.554
Eye Symptoms	3	0.198	0.001 - 0.220	0.009 - 0.523
Tiredness	3	0.312	0.097 - 0.377	0.014 - 0.769
Cognitive	3	0.515	0.066 - 0.420	0.130 - 0.631
Anxiety	3	0.784	0.006 - 0.278	0.062 - 0.630
Depressivity	3	0.369	0.001 - 0.302	0.100 - 0.339
Emotional Susceptibility	3	-0.153	0.027 - 0.350	0.325 - 0.719
Impaired Social Life	3	0.854	0.027 - 0.339	0.028 - 0.664
Impiared Daily Life	3	0.601	0.000 - 0.423	0.011 - 0.582
Cosmetic Complaints	3	0.286	0.035 - 0.333	0.093 - 0.398
Impact on Overall QoL	1	NA	NA	0.293
Overall	39	0.839	0.028 - 0.606	NA

[a]IIC = Inter-Item Correlation

(α=0.369), Impaired Daily Life (α=0.601). Despite the outcomes of the internal consistency reliability per scale, overall the ThyPRO Filipino version has an acceptable degree of internal consisteny with Cronbachs's alpha of 0.839 (Table 2). This is comparable to the original study wherein the Cronbach alpha is greater than 0.7.

Discriminant validity and convergent validity were used to assess the construct validity of the ThyPROph. Convergent validity measures the degree of confidence that the trait is well measured by its indicators; while discriminant validity is the degree to which measures of different traits are unrelated. The convergent validity calculated using Spearman correlation ranged from r_s=0.014–0.769. Majority of the scales of the questionnaire had a moderate correlation with Spearman correlation above r_s=0.40. The scale Emotional Susceptibility has convergent validity ranges from adequate (r_s=0.325) to high correlation (r_s=0.719). The scales Tiredness, Cognitive and Impaired Social Life has poor to high correlation of r_s=0.014–0.769, r_s=0.130–0.631 and r_s=0.028–0.664, respectively. Only the scale Depressivity has poor to adequate correlation (r_s=0.100–0.339).

Based on the discriminant validity of the scales, an average Inter-Item Correlation (IIC) result less than 0.85 tell us that discriminant validity likely exists between the scales. The discriminant validity of the scales in the questionnaire ranged between IIC=0.001 and IIC=0.423. Cognitive scale obtained an IIC=0.066–0.420; while Impaired Daily Life scale, ICC=0.000–0.423. Moreover, overall divergent validity of the ThyPRO is adequate to excellent with IIC=0.028–0.606. Since the computed IIC is below 0.85, discriminant validity exists between the different scales of ThyPROph. This is comparable to 0.77-0.89 intraclass correlation in the original study. The different scales theoretically measure different constructs from one another. Therefore, the different scales are unrelated from one another.

Second Phase of the Study: Comparison of Quality of Life Scores with RAI Treatment versus ATD

Demographic Profile of Respondents

Fifty-eight patients with Graves' disease completed the ThyPROph with 48.28% (n=28) under the RAI group, and 51.72% (n=30) under ATD group. The mean age of the patients under ATD group is higher than the RAI group, but statistically not significant (44.52 y.o. vs 41.82 y.o. respectively, p=0.4535). There were more females in the ATD group (83.33% vs 64.29%). Moreover, there were more singles (50%), high school graduates (46.43%) and employed subjects (57.14%) in the RAI group. Looking at the ATD group, majority were married (60%), high school graduates (46.67%) and unemployed (56.57%). Despite such differences, marital status (p=0.2320), educational attainment (p=0.8010) and employment status (p=0.2930) were not significantly different between groups. Distribution of goiter grading between groups were also not significantly different with both groups having more subjects with Grade 0 goiter (89.29% and 70%) (Table 3).

A significant difference is seen in disease duration (p=0.0027) and initiation of treatment (p=0.0120). Disease duration corresponds to the time the patient was diagnosed to have Graves' disease until the time the patient was seen by the investigator. The RAI group was diagnosed to have Graves' disease at a mean of 8.97 years with initiation of RAI at a mean of 7.76 years. In the ATD group, disease duration also parallels the initiation of treatment.

Health Related Quality of Life of Filipino Patients with Graves' Disease

In determining HRQoL of patients with Graves' disease, the scores of each domain were computed based on the ThyPRO scoring system. The lower the score, the better or more improved is the quality of life. There is a significant difference in the domains "goiter symptoms" (p=0.0209), "emotional susceptibility" (p=0.0067) and "impaired daily life" (p=0.0463). The HRQoL is significantly better in the RAI group based on these three domains since the mean scores were lower compared to the ATD group scores (goiter symptoms, 23.89 vs 32.17; emotional susceptibility, 44.82 vs 57.77; and impaired daily life, 29.46 vs 36.70). The remaining domains were found to be insignificantly different between groups despite lower mean final rescaled scores in the RAI group than the ATD group (p>0.05) (Table 4).

This means that goiter symptoms such as sensation or fullness in the neck, pressure in the throat and discomfort

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Table 3. Distribution of survey subjects taking ATD's or S/P RAI according to sociodemographic profile, n=58, Manila

Demographic Profile	RAI	ATD	P-value[b]
	n, %= 28 (48.28)	n,% = 30 (51.72)	
Age (yrs old, X+SD)	41.82 (15.22)	44.52 (11.92)	0.4535
Gender (F,%)			
Female	18 (64.29)	25 (83.33)	0.0980
Male	10 (35.71)	5 (16.67%)	
Marital Status (F,%)			
Single	14 (50.00)	10 (33.33)	0.2320
Married	11 (39.29)	18 (60.00)	
Separated	0	1 (3.33)	
Widow	3 (10.71)	1 (3.33)	
Educational Attainment (F,%)			
Elementary	5 (17.86)	3 (10.00)	0.8010
High School	13 (46.43)	14 (46.67)	
College	9 (32.14)	11 (36.67)	
Post Graduate	1 (3.57)	2 (6.67)	
Employment (F,%)			
Employed	16 (57.14)	13 (43.33)	0.2930
Unemployed	12 (42.86)	17 (56.57)	
Disease Duration (yr, X±SD) [a]	8.97±9.12	3.35±3.50	**0.0027**
Initiation of Treatment (yr, X±SD)	7.76±8.77	3.28±3.40	**0.0120**
Goiter Grade (F,%)			
Grade 0	25 (89.29)	21 (70.00)	0.1430
Grade 1	3 (10.71)	7 (23.33)	
Grade 2	0	2 (6.57)	

[a]SD = Standard Deviation ; [b]Statistically significant if p-value <0.05

Table 4. Comparison of domain mean scores between RAI and ATD group, n=58, Manila

ThyPRO Domains	No. of items	Mean Final Rescaled Score ±SD[a]		P-value[b]
		RAI Group n=28	ATD Group n=30	
Goiter Symptoms	1	23.89±8.25	32.17±16.62	**0.0209**
Hyperthyroid Symptoms	2	32.46±11.02	38.27±12.56	0.0671
Hypothyroid Symptoms	3	39.29±16.39	44.17±16.08	0.2574
Eye Symptoms	4	34.14±15.52	36.23±12.47	0.5729
Tiredness	5	49.79±20.28	52.62±20.80	0.6023
Cognitive	6	34.21±15.06	39.50±17.81	0.2287
Anxiety	7	42.14±19.81	42.60±22.45	0.9345
Depressivity	8	34.22±15.63	38.77±17.49	0.3019
Emotional Susceptibility	9	44.82±16.32	57.77±18.54	**0.0067**
Impaired Social Life	10	32.46±13.09	36.70±14.62	0.2507
Impaired Daily Life	11	29.46±12.23	36.70±14.62	**0.0463**
Cosmetic Complaints	12	40.32±23.15	51.27±18.48	0.0506
Impact on Overall QoL	13	40.18±25.77	52.50±24.87	0.0692

[a]SD = Standard Deviation; [b]Statistically significant if p-value <0.05

Table 5. Correlation of demographic profiles and ThyPROph domains, n=58, Manila

ThyPROph Domains	Demographic Profile	Correlation Coefficient	P-value[a]
Goiter Symptoms	Goiter Grade	0.430	0.001
Impaired Daily Life	Gender	0.316	0.016
Cosmetic Complaints	Age	-0.393	0.002
	Marital Status	-0.263	0.046
	Disease Duration	-0.368	0.005

[a]Statistically significant if p-value <0.05

in swallowing are more common in the ATD group than RAI. For the emotional susceptibility domain, it showed that subjects belonging to the ATD group more easily felt stressed with mood swings as compared to the RAI group. In the impaired daily life domain, those in the RAI group have less difficulty in managing their life.

Correlation of Demographic Profile of the Participants with their Quality of Life

Demographic profile is correlated with their Quality of Life, as measured in the domains of ThyPRO Filipino version. Goiter grade was found to be moderately correlated with goiter symptoms (p=0.0001). Goiter grade is higher for those who did not undergo RAI with goiter symptoms such as sensation of fullness in the neck, pressure in throat and discomfort in swallowing. This means that the larger the goiter, the more is the neck discomfort. The domain "impaired daily life" and gender were weakly correlated (p=0.016) (Table 5). Female subjects scored significantly lower on the "impaired daily life" domain. This means that female subjects have lesser difficulty in managing their life, participate more in life activities and do not feel as if everything takes longer to do.

The domain "cosmetic complaint" was inversely and weakly correlated with age (p=0.002), marital status (p=0.046), and disease duration (p=0.005). Cosmetic complaints were higher among single young individuals with shorter disease duration.

DISCUSSION

First Phase: Translation and Validation

All the 13 domains were retained in the ThyPROph based on the statistics which showed that ThyPROph is an acceptable tool with Cronbach's alpha and discriminant validity of 0.839 and 0.028-0.606, respectively and with moderate correlation for the convergent validity.

The translated and validated ThyPRO Filipino version (ThyPROph) can be used to assess the health related quality of life of adult Filipinos with Graves' disease.

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Second Phase of the Study: Comparison of quality of life scores with RAI treatment versus ATD

Demographic Profile of Respondents and Health Related Quality of Life of Filipino Patients with Graves' Disease

In this study, there are more singles in RAI group. In terms of fertility, it is a myth that RAI therapy for hyperthyroidism causes infertility. The exposure of the reproductive system to the dose of radioactive iodine for treating hyperthyroidism is just like when one is subjected for barium enema or intravenous pyelography. Uptake for the RAI in this case is concentrated in the thyroid gland.[14] The effect of RAI in male germinal epithelium is dependent on the cumulative dose. The risk of infertility contributed by hyperthyroidism per se is higher than the RAI itself.[15] A dose of up to 30 mci is harmless to the gonads.[16] In our country, the maximum fixed dose given as outpatient for Graves' disease treatment is 14.9 mci.

Quality of life seems to be better in the RAI group compared to the ATD group with significant differences shown in the following three domains: goiter symptoms, emotional susceptibility and impaired daily life.

The RAI group was evaluated 7.76 $\pm$ 8.77 years after initiation of treatment. At the time of interview for this study, patients belonging to the RAI group had reduced goiter size secondary to ablation and in their euthyroid state. RAI causes permanent destruction of thyroid tissue. The radioactive iodine after its uptake by the thyroid gland undergoes organification. Beta particles emitted damages the DNA and causes cellular necrosis destroying the thyroid follicular cells.[17] Reduction of thyroid volume is 30-40% after the first year and 50-60% after 3 to 5 years.[18] This is affirmed by the demographics in this study wherein the RAI group showed a trend of lower goiter grade. Lower goiter grade means lesser compression symptoms including fullness in the neck, pressure in the throat and discomfort in swallowing.

On the other hand, the ATD group evaluated 3.28 $\pm$ 3.40 years after ATD initiation was euthyroid at the time of interview. ATD normalizes serum thyroid hormone levels 6 weeks after initiation. Relapse rate is highest with ATD at 50% when this is withdrawn. Demographics in this study showed a higher goiter grade in the ATD group. ATD preserves the thyroid gland with no reduction in size even after years of treatment since ATD only inhibits thyroid hormone synthesis. Large goiter is associated with lower remission rate.[19] Large goiters results to more compression symptoms impairing quality of life. In addition, remission is measured by TSH receptor antibody (TRab) levels. The higher the TRab level, the higher the rate of non-remission. In this study, the TRab level was not determined. Some of the patients belonging to this group although with normal FT4/TSH may not be totally euthyroid (not in remission) hence are more emotionally susceptible with impaired daily life quality.

Correlation of Demographic Profile of the Participants with Quality of Life

Compared to males, females use coping mechanisms by altering emotional responses to any stressful events.[20] This might explain the inverse relationship of gender and impaired daily life domain. These emotional responses can be positive reactions to the daily stressful events and to their Graves' disease. In this modern world, cosmetic concern is the same in both genders and this study has shown as well that even single young men were concerned about their appearance.[21]

In conclusion, in this pilot study, despite both groups being euthyroid at the time of the survey, those who had undergone RAI had a better quality of life over-all and in the following domains: goiter symptoms, emotional susceptibility and impaired daily life. Nevertheless RAI can be considered as the better treatment option in our setting especially for patients who have noticeable goiters with symptoms attributable to their goiters, and those with emotional instability.

LIMITATIONS OF THE STUDY

At the time of writing, there is no available data on quality of life of patients with Graves' disease in our country. This pilot study intends to know if difference exists between two modalities of treatment by comparison of the quality of life. First limitation is the need for a larger scale study. A follow through large scale study will aid in making a generalization since the results of this pilot study is not powered to achieve the primary objective specifically in excluded patients with complications of Graves' disease (e.g., thyrotoxic heart disease, hypokalemic periodic paralysis). Moreover, this study provides a brief account of the modalities used to treat Graves' hyperthyroidism, specifically the use of anti-thyroid drugs and radioiodine ablation. Second, the reliability of the domains is reduced, despite the suitable overall reliability. The decision of the review committee to continue the use of the developed tool is on the assumption of the demographic readiness of the patients as a factor affecting the reliability of the tool. Demographic profiles (education, gender, age, occupation among others) of the subjects can influence response to translated tool. Thus, the committee's decision on the use of the tool is based on the overall reliability of the translated tool. Third, a prospective randomized study is more ideal. All three were not carried out due to time constraint. Again, follow through study is recommended to generate satisfactory results.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

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References

1. Melmed S, Polonsky KS, Larsen PR, Kronenberget. William's Endocrinology. 13th edition. Philadelphia: Elsevier, 2016.
2. Harper MB, Mayeaux EJ Jr. Thyroid disease, 6th ed. New York: Springer, 2003.
3. Bukvic B, Zivaljevic V, Sipetic S, et al. Improved quality of life in hyperthyroidism
patients after surgery. J Surg Res. 2015;193(2):724-30. PMID: 25167783. https://doi.org/10.1016/j.jss.2014.07.061.
4. Tütüncü NB, Tütüncü T, Ozgen A, et al. Long-term outcome of Graves' disease patients treated in a region with iodine deficiency: Relapse rate increases in years with thionamides. J Natl Med Assoc. 2006; 98(6):926-30. PMCID: PMC2569379.
5. Watt T, Hegedüs L, Rasmussen AK, et al. Which domains of thyroid-related quality of life are most relevant? Patients and clinicians provide complementary perspectives. Thyroid. 2007;17(7):647-55. https://doi.org/10.1089/thy.2007.0069.
6. Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. J Clin Endocrinol Metab. 2003;88 (3) :978-83. PMID: 12629071. https://doi.org/10.1210/jc.2002-020805.
7. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. New Engl J Med. 1998;338(2):73-8. PMID: 9420337. https://doi.org/10.1056/NEJM199801083380201.
8. Kasper DL, Hausen SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J. Harrison's Principles of Internal Medicine, 19th ed. United States: McGraw-Hill Education, 2015.
9. Torring O, Tallstedt L, Wallin G, et al. Graves' hyperthyroidism: Treatment with antithyroid drugs, surgery, or radioiodine-a prospective, randomized study. J Clin Endocrinol Metabol. 1996;81(8):2986-93. PMID: 8768863. https://doi.org/10.1210/jcem.81.8.8768863.
10. Watt T, Barbesino G, Bjorner JB, et al. Cross- cultural validity of the thyroid-specific quality-of-life patient-reported outcome measure, ThyPRO. Qual Life Res. 2015;24 (3):769-80. PMID: 25194574. https://doi.org/10.1007/s11136-014-0798-1.
11. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998;51(11):903-12. PMID: 9817107.
12. Li RJ, Jimeno C, Sandoval MA, et al. Development and validation of a thyroid cancer-specific health-related Quality of Life questionnaire for adult Filipinos with differentiated thyroid cancer. J ASEAN Fed Endocr Soc. 2016;31(2):87-93. https://doi.org/10.15605/jafes.031.02.03.
13. Watt T, Hegedüs L, Groenvold M, et al. Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO. Eur J Endocrinol. 2010;162(1):161–7. PMID: 19797502. https://doi.org/10.1530/EJE-09-0521.
14. Cuison R, Mercado-Asis. Thyroid Handbook, 1st ed. Philippines: Goodwill Trading Co., Inc., 2004.
15. Ceccarelli C, Canale D, Vitti P. Radioactive iodine (131I) effects on male fertility. Curr Opin Urol. 2008;18(6):598-601. PMID: 18832945. https://doi.org/10.1097/MOU.0b013e32831367b3.
16. Yaish I, Azem F, Serebro M, et al. High dose radioiodine therapy affects ovarian reserve in women with differentiated thyroid cancer. Oral presentation at: ENDO 2016; April 1-4, 2016; Boston, Massachusetts. Abstract OR22-6.
17. Abcede A, Kho S, Matawaran B, Mercado-Asis LB. Significant reduction in the size of cystic thyroid nodules with ^{131}Iodine Therapy. JEM. 2014;4 (3):12-8.
18. Weetman A. Radioiodine treatment for benign thyroid diseases. Clin Endocrinol. 2007;66(6):757–64. https://doi.org/10.1111/j.1365-2265.2007.02841.x.
19. Vitti P, Rago T, Chiovato L, et al. Clinical features of patients with Graves' disease undergoing remission after antithyroid drug treatment. Thyroid. 1997;7(3):369-75. PMID: 9226205. https://doi.org/10.1089/thy.1997.7.369.
20. Matud MP. Gender differences in stress and coping styles. Pers Indiv Differ. 2004; 37 (7): 1401-15.
21. Davis K. A dubious equality: Men, women and cosmetic surgery. Sage Journal. 2002;81 (1):49–65. https://doi.org/10.1177/1357034X02008001003.

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ORIGINAL ARTICLE

Thyroid Imaging Reporting and Data System (TIRADS) in Stratifying Risk of Thyroid Malignancy at The Medical City

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Abstract

Objective. To determine the accuracy of Thyroid Imaging Reporting and Data System (TIRADS) in detecting thyroid malignancy, determine risk of malignancy in each TIRADS category and determine the ultrasound characteristics associated with malignancy.

Methodology. This is a retrospective cross-sectional study involving patients who underwent ultrasound, thyroid fine needle aspiration biopsy (FNAB) and thyroidectomy at The Medical City from January 2014 to December 2015. Ultrasound reports were retrieved and reviewed by two radiologists on separate occasions who were blinded to the cytopathology and histopathology results. The histopathology reports were correlated with ultrasound features to determine features associated with malignancy. Stata SE 12 was used for data analysis. TIRADS sensitivity, specificity, positive predictive values and negative predictive values and accuracy were calculated.

Results. 149 patients with thyroid nodules were included. Solid composition is the ultrasound feature predictive of malignancy with adjusted OR 4.912 (95% CI 1.3257 to 18.2011, p=0.017). The risk of malignancy for TIRADS categories 3, 4a, 4b, 4c and 5 were 12.50%, 12.82%, 26.19%, 53.70% and 66.67%, respectively. The Crude OR (95% CI) for TIRADS 4a, 4b, 4c and 5 were 1.03 (0.10 to 10.23), 2.48 (0.27 to 22.54), 8.12 (0.93 to 70.59) and 14.0 (0.94 to 207.60), respectively. The sensitivity, specificity, PPV, NPV and accuracy of TIRADS in relation to surgical histopathology report were 98.00%, 7.07%, 34.75%, 87.50%, and 53% respectively in TIRADS categories 4 and 5.

Conclusion. This study showed that a solid nodule is the most frequent ultrasound feature predictive of thyroid malignancy. Higher TIRADS classification is associated with higher risk of thyroid malignancy. TIRADS is a sensitive classification in recognizing patients with thyroid cancer.

Key words: thyroid imaging reporting and data system, histopathology, thyroid cancer, malignancy risk

INTRODUCTION

Thyroid nodules are prevalent in the general population. The prevalence rates of thyroid nodules range from 2-35% depending on the study population.[1,2] In the Philippines, the estimated prevalence of nodular goiter is 8.9%.[3] Thyroid nodules are usually asymptomatic but due to the increased use of ultrasound imaging, detection of incidental thyroid nodules has also increased. Ultrasound allows the identification of a wide spectrum of sizes and characteristics that result in difficulty selecting nodules for fine needle aspiration biopsy (FNAB). Sonographic findings suggestive of malignancy are solid nodules, nodule hypoechogenicity or marked hypoechogenicity, irregular margins, microcalcifications and a shape taller than wide on a transverse view.[4] Fine needle aspiration biopsy is a simple procedure and is the preferred initial diagnostic method for the evaluation of thyroid nodules. The sensitivity and specificity for FNAB in published series range between 65% to 98% and 73% to 100%.[5] Histopathology is the gold standard to evaluate the effectiveness of the fine needle aspiration of thyroid nodules to reliably diagnose thyroid malignancy.[6] Most of the thyroid nodules biopsied are benign and only approximately 3-7% of thyroid FNAB are malignant.[7] With this, it is important to use an ultrasound classification that will help differentiate benign from malignant thyroid nodules to decrease unnecessary biopsy.

Several studies regarding Thyroid Imaging, Reporting and Data System (TIRADS) were done since 2009. This was patterned from the widely used and acceptable breast imaging reporting and data system (BIRADS) which showed a number of significant parameters for the quantitative analysis of ultrasound features.[8-10] In BIRADS, it is important to differentiate category 3 which is probably benign, from category 4 which is suspicious for malignancy, because management for category 3 is just follow-up imaging, while management for category 4 is biopsy.[11] In a study by Horvath et al., patients with

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TIRADS 3 should be followed up while patients with TIRADS 4 and 5 nodules must be biopsied or later operated on since malignancy rate for TIRADS 3 was less than 5% while for TIRADS 4 it was at 5-80%.[8]

TIRADS category ranges from TIRADS 1 to TIRADS 5. TIRADS 1 corresponds to normal thyroid gland, TIRADS 2: benign nodules, TIRADS 3: probably benign nodules, TIRADS 4: with ultrasound features suspicious of malignancy, TIRADS 5: nodules highly suggestive of malignancy. Although studies were made regarding TIRADS, they used complex systems which may be difficult to apply in our institution. A study by Horvath et al., was based on 10 ultrasound patterns.[8] Park et al., on the other hand proposed an equation for predicting the probability of thyroid malignancy on the basis of 12 ultrasound features. It is difficult to assign every thyroid nodule into the equation in clinical setting.[9] In a study by Kwak et al., a simpler TIRADS scoring was used based on the BIRADS category such as category 3 (no suspicious US features), 4a (one suspicious feature), 4b (two suspicious features), 4c (three or four suspicious features).[10] This study showed a good correlation of the risk of malignancy using TIRADS scoring.

Filipinos are reported to have a high incidence of thyroid cancer.[12-14] In a local study by Puno-Ramos et al., only microcalcification was associated with thyroid malignancy.[15] In a study by Cañete et al., it showed that firm to hard, microcalcification and irregular margins were significant predictors of thyroid malignancy which was similar to international data.[16] However no data regarding the use of TIRADS in a local setting has been reported. Although foreign studies have been done regarding TIRADS, it is important to validate it against local data to determine its applicability in our setting so as to avoid unnecessary biopsy.

The aim of this study is to determine the accuracy of thyroid imaging reporting and data system in detecting thyroid malignancy in comparison to histopathology report.

GENERAL OBJECTIVE

To determine the accuracy of Thyroid Imaging Reporting and Data System (TIRADS) in detecting thyroid malignancy in patients with thyroid nodules

SPECIFIC OBJECTIVES

To determine the ultrasound characteristics of patients with thyroid nodules associated with thyroid malignancy.

To determine the risk of malignancy in each Thyroid Imaging Reporting and Data System (TIRADS) category.

To determine the sensitivity, specificity, PPV and NPV of TIRADS in detecting malignancy of patients with thyroid nodules with surgical histopathology as gold standard.

METHODOLOGY

Study Design

This was a retrospective, cross sectional study approved by our institutional review board. The requirement to obtain informed consent was waived.

Study Subjects

All Filipino adults who underwent thyroid ultrasound, fine needle aspiration biopsy and thyroidectomy at The Medical City from January 2014 to December 2015 were included in the study.

Study Population

A minimum of 167 subjects are required for this study based on a level of significance of 5%, a prevalence of 76.13%, sensitivity of 99.6% (95% CI: 98.9-100). The values for the prevalence of malignant nodules and sensitivity of the TIRADS 4 were based from the study by Horvath et al., Prospective validation of the ultrasound based TIRADS classification: results in surgically resected thyroid nodules.

Description of Study Procedure

Cytopathology and histopathology records of all patients from January 2014 to December 2015 with thyroid nodules on ultrasound for which FNAB and surgical management were done at The Medical City were gathered from the Department of Clinical Pathology. Patient confidentiality was maintained hence no patient identifiers were used; instead subjects were assigned a number. Records without available digital thyroid ultrasound images and those with indeterminate or suspicious for malignancy on cytology that did not undergo surgery were excluded from the study.

Cytopathologic diagnosis was reported using the Bethesda System of classification.[7]

The ultrasound scans of the thyroid gland performed between 2014 and 2015 that were stored in Siemens Syngo Viewer were reviewed. Two radiologists, a resident with four-year training experience and one consultant with more than ten years of experience, reviewed the thyroid ultrasounds. Both were blinded to both the cytopathology and histopathology reports. The two radiologists reviewed the ultrasound imaging on separate occasions. In the event of discrepancies, the reading of the consultant was followed.

All thyroid nodules were characterized according to composition, echogenicity, margins, calcification and shape. Composition was either solid or mixed. A solid nodule was defined as a purely solid or predominantly solid with a cystic component comprising less than 10% of the total volume. Mixed nodule revealed features of both solid and cystic (anechoic on ultrasound).

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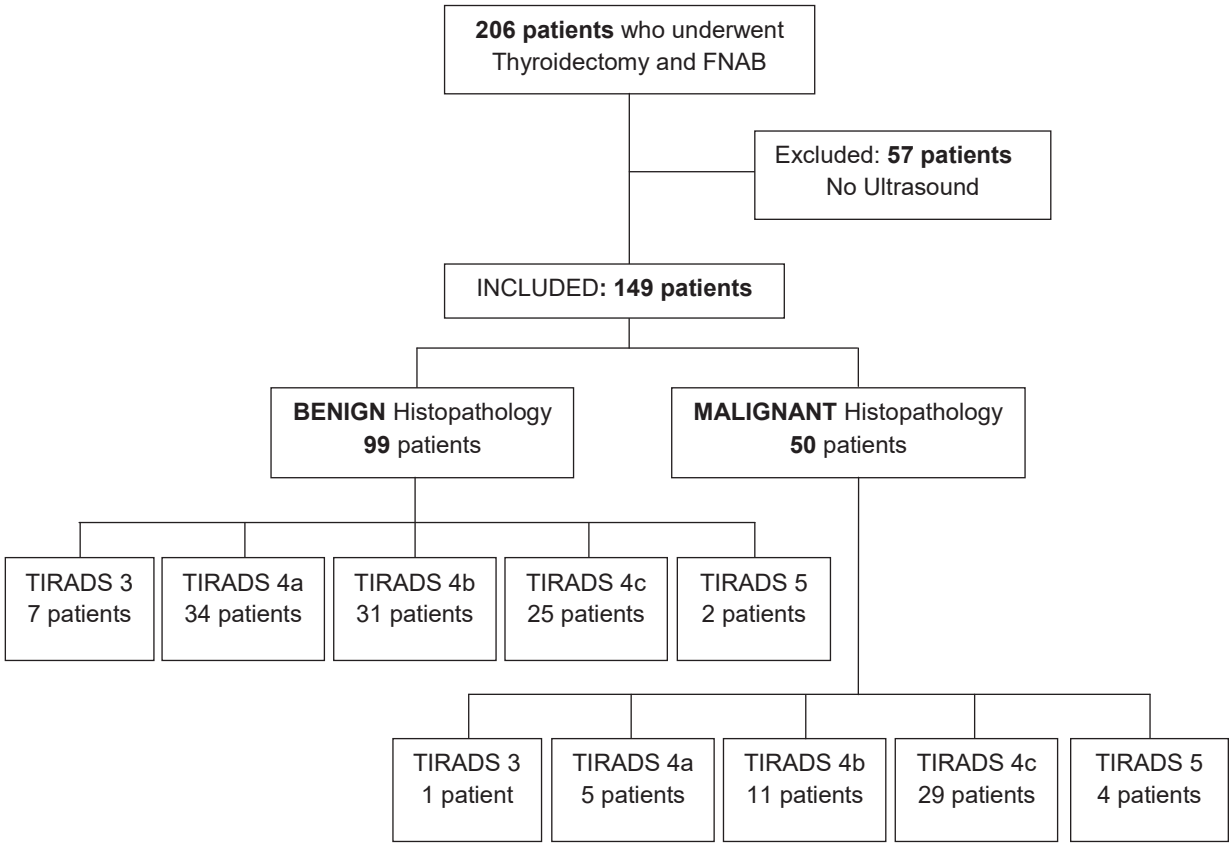

Figure 1. Summary of patient population and TIRADS classification.

Echogenicity was either classified as hyperechogenicity, isoechogenicity, hypoechogenicity or marked hypoechogenicity. Hyperechogenicity was defined as echogenicity of the nodule more than that of the adjacent thyroid parenchyma, while isoechogenicity showed similar echogenicity to the surrounding thyroid parenchyma. Hypoechogenicity was characterized as echogenicity less than that of the adjacent thyroid parenchyma but more than that of the surrounding strap muscle, while marked hypoechogenicity was described as echogenicity that was less than the strap muscle.

The margins were classified as regular, microlobulated or irregular. Regular margin was when the border was smooth, distinct, well defined and with regular outline, while microlobulated margin was defined as the presence of many small lobules on the surface of a nodule and irregular margin was when the border is ill–defined, not smooth and with indistinct interface between the nodule and adjacent thyroid parenchyma.

Calcifications when present, were categorized as either microcalcification or macrocalcification. Microcalcifications were described as tiny, hyperechoic foci less than 1.0 mm in size with no comet-tail artifacts while macrocalcifications were hyperechoic foci larger than 1.0 mm. Shape was categorized as taller than wide when anteroposterior dimension was greater than the transverse dimension, while wider than tall was defined as transverse dimension greater than anteroposterior dimension.

Kwak classification was used in this study and nodules were classified into TIRADS category (1, 2, 3, 4a, 4b, 4c, 5) based on ultrasound features.[10]

Data Analysis

Frequency and percentage, mean and standard deviation were used to summarize the clinical characteristics of patients. A two-way table was constructed to determine accuracy measures (sensitivity, specificity, predictive values, likelihood ratios) of TIRADS compared to histopathology. We used simple logistic regression to determine crude associations of surgical histopathologic malignancy with patients' demographic and clinical characteristics. The ultrasound features associated with malignancy were determined by multiple regression analysis. Crude and adjusted odds ratios and their corresponding 95% confidence intervals were determined. Null hypotheses were rejected at 0.05 alpha level of significance. STATA v12 software was used.

RESULTS

We had a total of 206 patients who underwent thyroidectomy and FNAB, of which 57 patients were excluded because these patients had no thyroid ultrasound reports. We analyzed a total of 149 patients, of whom 50 (33.56%) were confirmed to be malignant via histopathology (Figure 1).

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Majority of patients were in their 30s (23%), 40s (22%), or 50s (22%). The mean age was 46.91 ± 13.57. There were more females (87%) than males. The most frequent characteristics of nodules on ultrasound were solid in composition (62%), hypoechoic (38%) or isoechoic to hyperechoic (36%), well-circumscribed (41%), and wider than tall (83%). Microcalcifications were present in 24% of nodules, while macrocalcifications were seen in 19%. Patients with TIRADS 4a, 4b, and 4c comprised 26%, 28%, and 36% of the group, respectively. About 55% of nodules were classified as benign by Bethesda system after FNAB. On the other hand, final histopathologic diagnosis was benign in 66% of resected specimens (Table 1).

Table 1. Demographic and clinical profile of thyroidectomy patients (n=149)

Age (years)	
Below 30	17 (11.41)
30-39	34 (22.82)
40-49	33 (22.15)
50-59	33 (22.15)
60-69	29 (19.46)
70 and above	3 (2.01)
Age (years)	46.91 ± 13.57
Sex	
Female	129 (86.58)
Male	20 (13.42)
Composition	
Solid	93 (62.42)
Mixed	56 (37.58)
Echogenicity	
Hyperechoic or isoechoic	53 (35.57)
Hypoechoic	56 (37.58)
Markedly hypoechoic	40 (26.85)
Margins	
Well-circumscribed	61 (40.94)
Microlobulated	36 (24.16)
Irregular	52 (34.90)
Calcifications	
Microcalcifications	36 (24.16)
Macrocalcifications	29 (19.46)
None	84 (56.38)
Shape	
Wider than tall	123 (82.55)
Taller than wide	26 (17.45)
TIRADS category	
3	8 (5.37)
4a	39 (26.17)
4b	42 (28.19)
4c	54 (36.24)
5	6 (4.03)
Bethesda classification	
I	13 (8.72)
II	82 (55.03)
III	12 (8.05)
IV	11 (7.38)
V	27 (18.12)
VI	4 (2.68)
Surgical histopathology	
Benign	99 (66.44)
Malignant	50 (33.56)

Bethesda classification: I, non-diagnostic; II, benign; III, atypia of undetermined significance; IV, follicular neoplasm; V, suspicious for malignancy; VI, malignant.
TIRADS categories: 3, probably benign; 4a, one suspicious malignant feature on ultrasound; 4b, two suspicious malignant features on ultrasound; 4c, three or four suspicious malignant features on ultrasound; 5, five suspicious malignant features on ultrasound.
Values are expressed as frequency (%), mean ± SD

We compared select characteristics between patients with malignant versus benign thyroid nodules. Compared to mixed nodules, patients with a solid composition was 7.48 times as likely to have a malignant nodule (OR 7.48 95% CI 2.92 to 19.15, p<0.001). Those with markedly hypoechoic nodules were three times more likely to have a malignant nodule (OR 3.42 95% CI 1.40 to 8.25, p=0.007). Nodules with irregular margins were four times more likely to be malignant (OR 3.99, 95% CI 1.76 to 9.05, p=0.001). Compared to patients without calcifications, patients with macrocalcifications were less likely to be malignant (OR 0.34, 95% CI 0.15 to 0.79, p=0.012) (Table 2).

FNAB results according to Bethesda classification were: Bethesda I 8.72%, Bethesda II 55.03%, Bethesda III 8.05%, Bethesda IV 7.38%, Bethesda V 18.12%, Bethesda VI 2.68% (Table 3).

We conducted a stepwise logistic regression to determine predictors of malignant thyroid nodules. We found the following characteristics to predict malignant nodules: solid composition and higher Besthesda classes (Table 4). Our model explains 40% in the variability of the histopathology results (p<0.001).

The malignancy risk of TIRADS category 3, 4a, 4b, 4c and 5 were 12.5% (1 out of 8), 12.82% (5 out of 39), 38.10% (11 out of 42), 57.41% (29 out of 54) and 66.67% (4 out of 6), respectively. The crude odds ratio for TIRADS 4a, 4b, 4c and 5 were: 1.03 (0.10 to 10.23), 2.48 (0.27 to 22.54), 8.12 (0.93 to 70.59) and 14.0 (0.94 to 207.60), respectively. We had insufficient evidence to demonstrate a difference in TIRADS grading distribution between malignant and benign nodules (Table 5).

On comparing TIRADS results and histopathology, we found that TIRADS 4a to 5 classes had approximately 98% sensitivity, 7.07% specificity, LR+ of 1.05, LR- of 0.28, PPV of 34.75%, NPV of 87.5%, and accuracy of 53% (Table 6).

DISCUSSION

Ultrasonography of the thyroid gland even in asymptomatic patients increased the detection of thyroid nodules in the general population.[17] Current guideline for adult patients with thyroid nodules and differentiated thyroid cancer by the American Thyroid Association (ATA) 2015 recommended fine needle aspiration biopsy (FNAB) for the following: (1) thyroid nodules measuring 1 cm and above with intermediate to high sonographic pattern; (2) thyroid nodules with low suspicious pattern measuring 1.5 cm and above; and (3) thyroid nodules with very low suspicious ultrasound pattern measuring 2 cm and above.[4] Ultrasound features are important in predicting risk of malignancy. According to ATA, high suspicion ultrasonographic pattern is characterized as solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the

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Table 2. Association of patient characteristics with malignancy at surgical histopathology (n=149)

	Malignant (n=50)	Benign (n=99)	Crude Odds Ratio (95% Confidence Interval)	P-Value
Age (years)				
Below 30	9 (18)	8 (8.08)	(reference)	-
30-39	8 (16)	26 (26.26)	0.27 (0.08 to 0.94)	**0.040**
40-49	11 (22)	22 (22.22)	0.44 (0.13 to 1.47)	0.184
50-59	11 (22)	22 (22.22)	0.44 (0.13 to 1.47)	0.184
60-69	10 (20)	19 (19.19)	0.47 (0.14 to 1.59)	0.223
70 and above	1 (2)	2 (2.02)	0.44 (0.03 to 5.88)	0.538
Age (years)	46.46 ± 14.93	47.13 ± 12.91	0.996 (0.97 to 1.02)	0.775
Sex				
Female	43 (86)	86 (86.87)	(reference)	-
Male	7 (14)	13 (13.13)	1.08 (0.40 to 2.90)	0.883
Composition				
Mixed	6 (12)	50 (50.51)	(reference)	-
Solid	44 (88)	49 (49.49)	7.48 (2.92 to 19.15)	**<0.001**
Echogenicity				
Hyperechoic or isoechoic	12 (24)	41 (41.41)	(reference)	-
Hypoechoic				
Markedly hypoechoic	18 (36)	38 (38.38)	1.62 (0.69 to 3.80)	0.269
	20 (40)	20 (20.20)	3.42 (1.40 to 8.35)	**0.007**
Margins				
Well-circumscribed	13 (26)	48 (48.48)	(reference)	-
Microlobulated	10 (20)	26 (26.26)	1.42 (0.55 to 3.58)	0.471
Irregular	27 (54)	25 (25.25)	3.99 (1.76 to 9.05)	**0.001**
Calcifications				
None	18 (36)	66 (66.67)	(reference)	-
Microcalcifications	16 (32)	20 (20.20)	1.54 (0.58 to 4.11)	0.391
Macrocalcifications	16 (32)	13 (13.13)	0.34 (0.15 to 0.79)	**0.012**
Shape				
Wider than tall	37 (74)	86 (86.87)	(reference)	-
Taller than wide	13 (26)	13 (13.13)	2.32 (0.98 to 5.49)	0.055
Bethesda classification				
I or II	13 (26)	82 (82.83)	(reference)	-
III	7 (14)	5 (5.05)	8.83 (2.44 to 32.02)	**0.001**
IV	2 (4)	9 (9.09)	1.40 (0.27 to 7.23)	0.687
V	24 (48)	3 (3.03)	50.46 (13.28 to 191.80)	**<0.001**
VI	4 (8)	0	1	**-**
Dimensions				
CC	2.49 ± 1.20	3.06 ± 1.39	0.71 (0.54 to 0.94)	**0.016**
W	1.88 ± 0.98	2.34 ± 1.20	0.68 (0.49 to 0.95)	**0.023**
AP	1.66 ± 0.87	1.86 ± 0.95	0.79 (0.54 to 1.15)	0.215

Bethesda classification: I, non-diagnostic; II, benign; III, atypia of undetermined significance; IV, follicular neoplasm; V, suspicious for malignancy; VI, malignant.
CC = craniocaudal ; W = Width ; AP = Anteroposterior
Values are expressed as frequency (%), mean ± SD or median (range)

following features: irregular margins, microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component and with evidence of extrathyroidal extension.

Intermediate suspicious sonographic pattern is described as thyroid nodules with hypoechoic features with smooth margins without microcalcification, extrathyroidal extension or taller than wide shape.

Low suspicion sonographic pattern is described as isoechoic or hyperechoic solid nodule or partially cystic nodule with eccentric solid areas without microcalcification, irregular margin or extrathyroidal extension or taller than wide shape, while very low suspicion sonographic pattern is characterized as spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate or high suspicion patterns.

Table 3. Bethesda classification

Bethesda	Histopathology		
	All (n = 149)	Malignant (n=50)	Benign (n=99)
	Frequency (%)		
Bethesda I	13 (8.72)	0 (0)	13 (100)
Bethesda II	82 (55.03)	13 (15.85)	69 (84.15)
Bethesda III	12 (8.05)	7 (58.33)	5 (41.67)
Bethesda IV	11 (7.38)	2 (18.18)	9 (81.82)
Bethesda V	27 (18.12)	24 (88.99)	3 (11.11)
Bethesda VI	4 (2.68)	4 (100)	0 (0)

Bethesda classification: I, non-diagnostic; II, benign; III, atypia of undetermined significance; IV, follicular neoplasm; V, suspicious for malignancy; VI, malignant

The malignancy risks recommended by the ATA are more than 70-90% for the high suspicion pattern, 10-20% for the intermediate suspicion pattern, 5-10% for the low suspicion pattern, less than 3% for the very low suspicion pattern and less than 1% for the benign pattern.[4]

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Table 4. Clinical features associated with malignant thyroid nodules at surgical histopathology (n=149)

	Adjusted Odds Ratio	95% Confidence Interval	P-Value
Age (years)			
Below 30	(reference)	-	-
30-39	0.2823	0.0402 to 1.9818	0.203
40-49	0.4061	0.0612 to 2.6961	0.351
50-59	0.4125	0.0606 to 2.8058	0.365
60-69	0.1135	0.0146 to 0.8849	**0.038**
70 and above	0.1076	0.0009 to 12.5138	0.358
Male	0.6446	0.1113 to 3.7339	0.624
Solid composition	4.9122	1.3257 to 18.2011	**0.017**
Echogenicity			
Hyperechoic or isoechoic	(reference)	-	-
Hypoechoic	1.9757	0.6069 to 6.4319	0.258
Markedly hypoechoic	3.6708	0.8463 to 15.9214	0.082
Margins			
Well-circumscribed	(reference)	-	-
Microlobulated	2.0423	0.5823 to 7.1637	0.265
Irregular	1.6792	0.4940 to 5.7073	0.406
Bethesda classification			
I or II	(reference)	-	-
III	7.4988	1.5572 to 36.1108	**0.012**
IV	1.9548	0.3329 to 11.4788	0.458
V	36.7881	8.1908 to 165.2305	**<0.0001**
VI	-	-	-

P-value < 0.0001; R^2 = 40.82%

Table 5. TIRADS categories and risk of malignancy of patients who underwent thyroidectomy (n=149)

TIRADS	Histopathology		Risk of Malignancy (%)	Crude Odds Ratio (95% Confidence Interval)	P - Value
	Malignant (n=50)	**Benign** (n=99)			
TIRADS 3	1/8	7/8	12.50%	(reference)	-
TIRADS 4a	5/39	34/39	12.82%	1.03 (0.10 to 10.23)	0.980
TIRADS 4b	11/42	31/42	38.10%	2.48 (0.27 to 22.54)	0.419
TIRADS 4c	29/54	25/54	57.41%	8.12 (0.93 to 70.59)	0.059
TIRADS 5	4/6	2/6	66.67%	14.0 (0.94 to 207.60)	0.055

TIRADS categories: 3, probably benign; 4a, one suspicious malignant feature on ultrasound; 4b, two suspicious malignant features on ultrasound; 4c, three or four suspicious malignant features on ultrasound; 5, five suspicious malignant features on ultrasound

Table 6. Accuracy of TIRADS in predicting a malignant thyroid nodule (n=149)

TIRADS	Histopathology		Total
	Malignant (n=50)	**Benign** (n=99)	
TIRADS 4a to 5	49 (98)	92 (92.93)	141 (94.63)
TIRADS 3	1 (2)	7 (7.07)	8 (5.37)
Total	50 (100)	99 (100)	149 (100)
Sensitivity	98 (89.35 to 99.95)	Positive LR	1.05 (0.99 to 1.13)
Specificity	7.07 (2.89 to 14.03)	Negative LR	0.28 (0.04 to 2.24)
PPV	34.75 (33.24 to 36.29)	Accuracy	53%
NPV	87.5 (46.96 to 98.23)		

PPV, positive predictive value; NPV, negative predicted value; LR, likelihood ratio
Values are expressed as frequency (%) or median (range)

In our study, solid composition was 7.48 times likely to have a malignant nodule (OR 7.48 95% Cl 2.92 to 19.15, p<0.001). While those nodules with marked hypoechogenicity were three times more likely to have a malignant nodule (OR 3.42 95% Cl 1.40 to 8.25, p=0.007). Nodules with irregular margins on the other hand were four times more likely to be malignant (OR 3.99, 95% Cl 1.76 to 9.05, p=0.001). But on adjusted OR, solid nodule was the only ultrasound feature predictive of malignancy with OR 4.912 (95% Cl 1.3257 to 18.2011, p=0.017). While a local study published by Puno-Ramos et al., it showed that only the presence of microcalcification on ultrasound had a significant correlation with malignancy with odds ratio of 11.3 and it also showed that a nodule with more than two ultrasound features predictive of malignancy was more likely to be malignant on cytopathology with p-value of 0.00.[15] Smith-Bindman et al., also studied ultrasound imaging characteristics associated with malignant nodules and showed that three ultrasound nodule characteristics which were microcalcification (odd ratio (OR), 8.1; 95% CI, 3.8-17.3), size greater than 2 cm (OR 3.6; 95% CI, 1.7-7.6) and an entirely solid composition (OR, 4.0; 95% CI, 1.7-9.2) were statistically significant in predicting thyroid malignancy.[18] In a meta-analysis done by Remonti et al., on the other hand revealed that solid nodule, hypoechogenicity, irregular margins, absence of halo, microcalcifications, central vascularization, solitary

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nodule, heterogeneity, taller than wide shape and elasticity were all significantly associated with malignancy with odds ratio (OR) ranging from 1.77 to 35.7. But the sensitivity of ultrasound features predictive of malignancy only ranged from 26.7 to 63% and the author concluded that ultrasound features in isolation do not provide reliable guide as when to do FNAB.[19]

Fine needle aspiration biopsy is the preferred initial diagnostic method for the evaluation of thyroid nodules. Most of the thyroid nodules biopsied are benign and only approximately 3-7% of thyroid FNAB are malignant.[7] The sensitivity and specificity for FNAB in published series range between 65% to 98% and 73 to 100%, respectively.[5] In our study the sensitivity of fine needle aspiration biopsy was 60.00% which was slightly lower than the published series but the specificity was comparable at 87.88% with the published studies. Bethesda Classification I is not an uncommon finding. According to Cibas et al., the risk of malignancy for Bethesda I is at 1-4%.[7] But in the study by Bongiovanni et al., the malignancy rate of nondiagnostic FNAB who underwent surgical excision is approximately 17%.[20] In our study, 8.72% of the patients were classified under Bethesda I, of which all their histopathology reports were not malignant. Our patients classified under Bethesda III on the other hand were eight times likely to have malignant nodules (OR 8.0906 95% Cl 1.6951 to 38.6160, p=0.009) With this, it is important to use an ultrasound classification that will help differentiate benign from malignant thyroid nodules in order to decrease unnecessary biopsy.

Horvath et al., in 2009 first published a study with regards to the use of TIRADS classification. Its main objective was to improve the ultrasound characterization of nodules and establish risk groups for patients who will undergo FNAB.[8] They described 10 ultrasound patterns of thyroid nodules with related risk of malignancy.[8] This was followed by a study by Park et al., which proposed an equation for predicting the probability of malignancy on the basis of 12 ultrasound features.[9] Both studies correlated well with risk of malignancy, however these ultrasound patterns and equations were cumbersome and complex and are not applicable to all thyroid nodules nor in clinical practice. Hence Kwak et al., investigated a practical TIRADS classification for the management of thyroid nodules. Sonographic characteristics predictive of malignancy such as: solid echogenicity, hypoechogenicity or marked hypoechogenicity, microcalcifications, microlobulated or irregular border and taller than wide shape were used to classify TIRADS from 1 to 5. They categorized the TIRADS to 1: normal thyroid gland, 2: benign nodules, 3: probably benign nodules, 4a: one ultrasound feature suggestive of malignancy, 4b: two ultrasound features suggestive of malignancy, 4c: three or four features suggestive of malignancy and 5: five ultrasound features suggestive of malignancy.[10] The study of Kwak et al., revealed that TIRADS 3 or nodules with no ultrasound features suggestive of malignancy had a fitted probability of malignancy of 0.02-0.028 indicating that biopsy may not be necessary while for nodules with TIRADS 4-5, it had a fitted probability of malignancy of 0.036 for which FNAB is indicated and the results were comparable with the widely accepted BIRADS.[10] In a prospective study by Srinivas et al., they used the TIRADS classification as suggested by Kwak et al., and showed that the classification is a reliable modality in differentiating benign nodules from malignant nodules.[21]

Our study adapted the TIRADS classification used by Kwak et al. It showed that the malignancy risk of TIRADS category 3, 4a, 4b, 4c and 5 were 12.5% (1 out of 8), 12.82% (5 out of 39), 26.19% (11 out of 42), 53.70% (29 out of 54) and 66.67% (4 out of 6), respectively. Since majority of the population had at least one ultrasound feature suggestive of malignancy and only 8 patients had TIRADS 3, the malignancy risk of TIRADS 3 was higher compared to other studies.[8-10,21-24] The histopathology report of the patient who had a malignant result showed follicular carcinoma on top of a micropapillary carcinoma. One patient who also had TIRADS 3 had an incidental finding of micropapillary carcinoma measuring 0.5 cm within the left lobe but the FNAB was done on another nodule that measured 1.87 cm x 1.53 cm x 1.06 cm (CC x W x AP) in the right lobe. The crude odds ratio for TIRADS 4a, 4b, 4c and 5 were: 1.03 (0.10 to 10.23), 2.48 (0.27 to 22.54), 8.12 (0.93 to 70.59) and 14.0 (0.94 to 207.60), respectively. We had insufficient evidence to demonstrate a difference in TIRADS grading distribution between malignant and benign nodules.

The accuracy of TIRADS in our study was 53% which was slightly lower as compared to the studies of Ha et al., at 69.5%[22] and Russ et al., at 62%.[25] The reason for low accuracy is possibly because of a high false positive rate. The overall sensitivity of TIRADS categories 4 and 5 for malignancy was 98.00% which was higher than that reported by Ha et al., (95.5%)[22] and Yoon et al., (97.4%).[24] Although the PPV of this study was 34.75% which was lower as compared to PPVs of Horvath et al.,[8] and Ha et al.,[22] (49% and 44.5% respectively). The specificity of this study was only 7.07% which was also lower compared to other studies (29%-75%).[8,22-24]

In our study, the prevalence of malignancy was higher at 33.56% compared to an FNAB based series wherein malignancy rate was only 3 to 7%.[7] With this, PPV/NPV might be affected since an increase in prevalence leads to increase in PPV. The implication is that a screening test is more efficient in a high risk target population. If the prevalence of the disease is low, the positive predictive value will not be high even if both the sensitivity and specificity are high. When screening the general population, many people with positive test results will be false positives.[26]

Despite the relatively low accuracy, this study showed that TIRADS is a useful screening tool to defer the need for fine needle aspiration biopsy for patients with TIRADS 3 classification. The number of ultrasound features predictive of malignancy is an important guide in determining further management as to whether to observe the nodules or do appropriate intervention such as fine needle aspiration biopsy.

CONCLUSION

This study showed that presence of solid nodule in the thyroid is predictive of thyroid malignancy. Higher TIRADS classification is associated with higher risk of thyroid malignancy. TIRADS is a sensitive classification in recognizing patients with thyroid cancer and can be used as a guide in deciding the need for fine needle aspiration biopsy.

Ultrasound features such as markedly hypoechoic nodules and nodules with irregular borders were associated with increased likelihood of malignancy but did not reach statistical significance in multivariate analysis.

Limitations of the Study and Recommendations

The investigators identified a number of limitations to this study. First, the results showed a wide confidence interval which was reflective of a relatively small sample size. Second, this was a retrospective study hence there might be selection bias. All our subjects underwent surgery due to the presence of ultrasound features suggestive of malignancy. Hence, it is worth mentioning that our malignancy rate is higher at 33.56% as compared to an FNAB based series wherein malignancy rate is only 3 to 7%.[7] Third, the study did not represent equally the different TIRADS categories since majority of the population had at least 1 suspicious ultrasound feature suggestive of malignancy. Fourth, it is from a single institution which might not be reflective of the entire population. In order to validate our findings, we recommend a prospective multicenter study in evaluating the use of TIRADS. Once validated, TIRADS may be used as a reference for reporting thyroid pathology and implemented as a standardized coding for all clinicians and radiologists.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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References

1. Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med. 1994; 154(16):1838-40. PMID: 8053752.
2. Dean DS, Gharib H. Epidemiology of thyroid nodules. Best Pract Res Clnical Endocrinol Metab. 2008; 22(6):901-11. PMID: 19041821. https://doi.org/10.1016/j.beem.2008.09.019.
3. Carlos-Raboca J, Jimeno C, Kho S, et al. The Philippine Thyroid Disease Study (PhilTiDes 1): Prevalence of thyroid disorders among adults in the Philippines. J ASEAN Fed Endocr Soc. 2012;27(2):27-33. https://doi.org/10.15605/jafes.027.01.04.
4. Haugen BR, Alexander EK, Bible KC, et. al.. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1-133. PMID: 26462967. PMCID: PMC4739132. https://doi.org/10.1089/thy.2015.0020.
5. Muratli,A, Erdogan N, Sevim, S, Unal, I, Akyuz S. Diagnostic efficacy and importance of fine-needle aspiration cytology of thyroid nodules. J Cytol. 2014;31(2):73-8. PMID: 25210233. PMCID: PMC4159900. https://doi.org/10.4103/0970-9371.138666.
6. Chowdhury J, Das S, Maji D. A study on thyroid nodules: Diagnostic correlation between fine needle aspiration cytology and histopathology. J Indian Med Assoc. 2008;106(6):389-90. PMID: 18839651.
7. Cibas ES, Ali SZ, NCI Thyroid FNA State of the Science Conference. The Bethesda system for reporting thyroid cytopathology, Am J Clin Pathol. 2009;132(5):658-65. PMID: 19846805. https://doi.org/10.1309/AJCPPHLWMI3JV4LA.
8. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et. al. An ultrasound reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab. 2009;94(5):1748-51. PMID: 19276237. https://doi.org/10.1210/jc.2008-1724.
9. Park JY, Lee HJ, Jang, HW, et. al. A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid carcinoma. Thyroid. 2009;19(11):1257-67. PMID: 19754280. https://doi.org/10.1089/thy.2008.0021.
10. Kwak JY, Kim HH, Yoon, JH, Moon HJ, Son EJ, et al. Thyroid imaging reporting and data system for US features of nodules: A step in establishing better stratification of cancer risk. Radiology. 2011;260(3):892-9. https://doi.org/10.1148/radiol.11110206.
11. American College of Radiology. Breast imaging reporting and data system, breast imaging atlas . 4th ed. Roston Va: American College of Radiology, 2003.
12. Goodman MT, Yoshizawa CN, Kolonel LN. Descriptive epidemiology of thyroid cancer in Hawaii. Cancer. 1988;61(6):1272–81. PMID: 3342383.
13. Haselkorn T, Bernstein L, Preston-Martin S, Cozen W, Mack WJ. Descriptive epidemiology of thyroid cancer in Los Angeles County, 1972-1995. Cancer Causes Control. 2000;11(2):163–70. PMID: 10710201. https://doi.org/10.1023/A:1008932123830.
14. Gomez SL, Noone AM, Lichtensztajn DY, Scoppa S, Gibson JT, Liu L, et al. Cancer incidence trends among Asian American populations in the United States, 1990-2008. J Natl Cancer Inst. 2013;105(15):1096–110. PMID: 23878350. PMCID: PMC3735462. https://doi.org/10.1093/jnci/djt157.
15. Puno-Ramos MPG, Villa ML, Kasala RG, Arzadon J, Alcazaren EAS. Ultrasound features of thyroid nodules predictive of thyroid malignancy as determined by fine needle aspiration biopsy. Philipp J Intern Med. 2015;53(2):1-8.
16. Cañete EJ, Sison-Peña CM, Jimeno CA. Clinicopathological, biochemical, and sonographic features of thyroid nodule predictive of malignancy among adult Filipino patients in a tertiary hospital in the Philippines. Endocrinol Metab (Seoul). 2014;29(4):489-97. PMCID: PMC4285043. https://doi.org/10.3803/EnM.2014.29.4.489.
17. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency ultrasound examination. Eur J Clin Investig. 2009;39(8):699-706. PMID: 19601965. https://doi.org/10.1111/j.1365-2362.2009.02162.x.

ONLINE FIRST | August 2, 2017 | https://doi.org/10.15605/jafes.032.02.03

18. Smith-Bindman R, Lebda P, Feldstein V, Sellami, D, Goldstein RB, Brasic N, et al. Risk of thyroid cancer based on thyroid ultrasound imaging characteristics: Results of a population-based study. JAMA Intern Med. 2013;173(19):1788-96. PMID: 23978950. PMCID: PMC3936789. https://doi.org/10.1001/jamainternmed.2013.9245.
19. Remonti LR, Kramer CK, Leitao CB, Pinto LCF, Gross JL. Thyroid ultrasound features and risk of carcinoma: A systematic review and meta-analysis of observation studies. Thyroid. 2015;25(5):538-50. PMID: 25747526 PMCID: PMC4447137. https://doi.org/10.1089/thy.2014.0353.
20. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda system for reporting thyroid cytopathology: A meta-analysis. Acta Cytol. 2012;56(4):333-9. PMID: 22846422. https://doi.org/10.1159/000339959.
21. Srinivas MNS, Amogh VN, Gautam MS, Prathyusha IS, Vikram NR, Retnam MK, et al. A prospective study to evaluate the reliability of thyroid imaging reporting and data system in differentiation between benign and malignant thyroid lesions. J Clin Imaging Sci. 2016;6:5. PMID: 27014501. PMCID: PMC4785791. https:doi.org/10.4103/2156-7514.177551.
22. Ha EJ, Moon WJ, Na DG, Lee YH, Choi N, Kim SJ, et al. A multicenter prospective validation study for the Korean thyroid imaging reporting and data system in patients with thyroid nodules. Korean J Radiol. 2016;17(5):811-21. PMCID: PMC5007410. https://doi.org/10.3348/kjr.2016.17.5.811.
23. Horvath E, Silva CF, Majlis S, Rodriguez I, Skoknic V, Castro A, et al. Prospective validation of the ulrasound based TIRADS (Thyroid imaging and reporting data system) classification: Results in surgically resected thyroid nodules. Eur Radiol. 2017;27(6):2619-28. PMID: 27718080. https://doi.org/10.1007/s00330-016-4605-y.
24. Yoon JH, Lee HS, Kim EK, Moon HJ, Kwak JY. Malignancy risk stratification of thyroid nodules: Comparison between the thyroid imaging reporting and data system and the 2014 American Thyroid Association management guidelines. Radiology. 2016;278(3):917-24. PMID: 26348102. https://doi.org/10.1148/radiol.2015150056.
25. Russ G, Royer B, Bigorgne C, Rouxel A, Bienvenu-Perrard M, Leehardt L. Prospective evaluation of thyroid imaging and data system on 4550 nodules with or without elastography. Eur J Endocrinol. 2013;168(5):649-55. PMID: 23416955. https://doi.org/10.1530/EJE-12-0936.
26. Altman DG, Bland JM. Diagnostic tests 2: Predictive values. BMJ. 1994; 309(6947):102. PMID: 8038641. PMCID: PMC2540558.

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ORIGINAL ARTICLE

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Prevalence of Metabolic Syndrome and its Individual Features Across Different (Normal, Overweight, Pre-Obese and Obese) Body Mass Index (BMI) Categories in a Tertiary Hospital in the Philippines

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Abstract

Objective. This study aims to determine the prevalence of metabolic syndrome and its individual components across different BMI categories among patients seen at Wellness Center and Obesity and Weight Management Center, St. Luke's Medical Center Quezon City.

Methodology. This was a 3-year retrospective study of patients seen at the institution from 2013 to 2016. The patients were divided according to Asia-Pacific BMI categories and presence of metabolic syndrome was determined as defined by NCEP/ATP III-AHA/NHLBI (2005).

Results. This study included a total of 1367 adult patients with the mean age of 53 (SD=12.4). The overall prevalence of metabolic syndrome is 51.0%. Its prevalence across the different BMI categories are as follows: 29.6 % with Normal BMI (BMI 18.5-22.9 kg/m^2), 38.9% in overweight (BMI 23-24.9 kg/m^2), 56.9% in Pre-Obese (BMI 25-29.9 kg/m^2) and 62.4% in Obese (BMI ≥30 kg/m^2) subgroup. Presence of central obesity using the Asian cut-off has the highest prevalence among patients with metabolic syndrome across all categories. In the group with normal BMI, hypertension and elevated blood glucose were highest with central obesity being the least common but still with 7.3% of individuals meeting the criteria for central obesity.

Conclusion. There is high prevalence of metabolic syndrome even in patients with normal BMI. Diagnosis and screening for its individual components should not only be confined to individuals with higher BMI.

Key words: body mass index, metabolic syndrome, obesity

INTRODUCTION

Metabolic Syndrome is a common condition worldwide and has been associated with increased risk for other comorbidities notably cardiovascular events and diabetes mellitus. It is initially associated with obesity and insulin resistance and over the years, different criteria were developed for the diagnosis of this condition namely NCEP III, WHO, IDF, NCEP/ATP III-AHA/NHLBI, but this basically includes 5 main criteria: abdominal obesity, elevated triglycerides, low High Density Lipoprotein, elevated fasting blood sugar and hypertension.

Several prevalence studies have been done on obesity and numbers vary based on racial and ethnic subgroups. Its prevalence was quoted to be 23.1% to 26.7% in the United States with predominance in the female population.[1,2] In the Strong Heart Study, Metabolic Syndrome was present in 35% with 7.9% developing cardiovascular events over 7.6 ± 1.8 years of follow-up.[3] In the FINRISK study where they used the modified World Health Organization criteria for Metabolic Syndrome, it was present in 38.8% in men and 22.2% in women.[3] In a local study done by Punzalan et al., entitled Prevalence of Metabolic Syndrome among adult Filipinos, there is 14.2% prevalence of metabolic syndrome in the general population using NCEP criteria.[4] In another prevalence study of metabolic syndrome among adult Filipinos comparing 3 different criteria for diagnosis, some differences seen in the results were as follows: 11.9% using the National Cholesterol Education Program/ Adult Treatment Panel (NCEP/ATP III) criteria, 14.5% prevalence in the general population using IDF criteria and 18.6% prevalence using NCEP/ATP III criteria modified by the American Heart Association/National Heart, Lung and Blood Institute (NCEP/ATP III-AHA/NHLBI) criteria.[5] However, breakdown of prevalence of metabolic syndrome based on different BMI was not specified in this study.

There is evidence that BMI predicts metabolic syndrome differently across racial/ethnic groups. Recent studies have shown that metabolic abnormalities are not only seen in

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obese population but in normal weight subjects as well. In the CRONICAS Cohort Study which involved South American Hispanic subjects, there was 19.0% overall prevalence of individuals with normal BMI having >3 risk factors (central obesity, high triglyceride, low HDL, elevated fasting blood sugar, elevated blood pressure) of metabolic syndrome in addition to high hs-CRP and HOMA-IR and among these, 43.1 % were already classified as metabolically unhealthy.[6,7] Comparable prevalence of metabolic abnormality was observe in subjects with BMI of 25 kg/m^2 in Non-Hispanic whites as with 19.6 kg/m^2 for Asian women and 19.9 kg/m^2 for Asian men.[6]

In international studies, it has been shown that Asians and specifically Filipinas were less likely to be obese (BMI≥30 kg/m^2, 8.8%), with lower levels of HDL cholesterol as compared with their Caucasian counterpart and with higher prevalence of metabolic syndrome computed at 34% vs. 13% in Caucasians.[8] Filipinos are known to have leaner body mass index with lower incidence of obesity as compared to other race and studies have shown that typical picture of a Filipino with diabetes has lower BMI with increased visceral adiposities (by truncal fat and waist girth) after adjusting for total body fat (by DEXA) as shown in a study done by Araneta et al.[6] In a community-based cross-sectional study in the Philippines done by Pagsisihan et al., in 2016, they have shown that even at lower BMI cut-offs of 23 kg/m^2 in males and 24 kg/m^2 in females, it was already associated with the occurrence of at least 1 cardiometabolic disease (Type 2 diabetes mellitus, hypertension or dyslipidemia).[9]

Although there have been local prevalence studies of metabolic syndrome among Filipinos, there has been no study done yet to determine prevalence of metabolic syndrome among the different BMI categories and specifically those with lower and normal BMI. With the present evidences that metabolic syndrome is not only seen in obese population, the researchers would like to determine the prevalence of this group of individuals in the Filipino population. Determination of prevalence of metabolic syndrome and its individual components among the different BMI categories in Filipinos will aid us in targeting modifiable risk factors in at-risk population.

This study aims to determine the prevalence rates of metabolic syndrome and its individual components across different BMI categories (normal-weight, overweight, pre-obese, obese individuals) among patients seen at Wellness Center and Obesity and Weight Management Center, St. Luke's Medical Center Quezon City (SLMC-QC) and to describe LDL, ALT and creatinine characteristics among patients with metabolic syndrome by BMI category.

METHODOLOGY

This was a 3-year (2013-2016) retrospective study utilizing chart review of adult patients seen at the Wellness Center and Obesity and Weight Management Center at St. Luke's Medical Center Quezon City (SLMC-QC), a 650-bed capacity tertiary hospital in the Philippines. Patients seen in the Wellness Center and Weight Management Center include healthy individuals for annual executive check-up as well as individuals with previously known health concerns. Included were adult patients at least 18 years old and above seen both as outpatient and inpatient with computed BMI ≥18.5 kg/m^2 with complete anthropometric measurements (height, weight, BMI and waist circumference), blood pressure monitoring and or anti-hypertensive medications, blood chemistries (Fasting Blood Sugar (FBS), Triglycerides, High Density Lipoprotein (HDL), Alanine Amino Transferases (ALT), Creatinine). Medication history for intake of anti dyslipidemic medications, oral hypoglycemics and/or insulin were also noted and recorded. Elevated ALT was defined as >63 U/L, Elevated LDL >130 mg/dL and elevated creatinine as >1.3 mg/dL. Exclusion criteria include pregnancy, patients with missing height or weight measurement, patients with chronic kidney disease with edema and on dialysis, patients with decompensated congestive heart failure and patients with decompensated liver disease.

Lists of all patients seen at the Wellness Center and Obesity and Weight Management Center of St. Luke's Medical Center Quezon City (SLMC-QC) were retrieved. Patients with complete anthropometric measurements (height, weight, waist and hip measurement) were identified. Data were gathered through chart review and use of St Luke's Medical Center Health Care System version 1.8.1, using a data sheet. Data collected included the following: age, gender, height, weight, computed body mass index, waist and hip measurement, blood pressure, list of anti-hypertensive, anti-diabetic and lipid-lowering medications, blood chemistry results of fasting blood sugar, triglycerides and High Density Lipoprotein (HDL). Other pertinent data that were reviewed included the serum creatinine and serum alanine aminotransferase (ALT) levels. Data on their first visit were recorded and included in the analysis.

For this study, metabolic syndrome was defined as patients who meet the criteria as set by NCEP/ATP III-AHA/NHLBI (2005). Any 3 of the following 5 features: waist circumference: Southeast Asian cut-off: Male ≥ 90 cm and Female ≥80 cm; raised Triglycerides: ≥150 mg/dL or specific treatment for this lipid abnormality; reduced HDL cholesterol : <40 mg/dL in males or 50 mg/dL in females or specific treatment for this lipid abnormality; raised BP: SBP ≥130 mmHg or DBP ≥85 mmHg or treatment of previously diagnosed hypertension; raised Fasting Plasma Glucose: FPG ≥100 mg/dL or previously diagnosed Type 2 Diabetes Mellitus.

Body Mass Index was computed using weight in kilogram divided by height in meter squared and were divided into

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NORMAL: 18.5-22.9 kg/m^2; OVERWEIGHT: 23- 24.9 kg/m^2; PRE-OBESE: 25-29.9 kg/m^2 and OBESE: ≥30 kg/m^2. Classification of BMI categories was based on the Asia-Pacific cut-offs.

Sample size was calculated based on the comparison of prevalence of metabolic syndrome in the general population and in the obese individuals. Assuming that prevalence of metabolic syndrome in the general population is 14.2% (Punzalan, 2004) and in the obese population is hypothesized to be 50% higher, with an alpha error of 5%, power of 80% and 1-tailed test of hypothesis, sample size required is 356 per group or 1424 for 4 groups. Actual sample size obtained however was only 1367. Results however showed that the hypothesized 50% higher prevalence of metabolic syndrome in the obese than the non-obese turned out to be more than 100% in our results. Thus, the actual sample size obtained in the study was more than enough to get a statistically significant result.

Statistical Analysis

Data were processed and encoded in Microsoft Excel and data analysis done using SPSS version 20. Prevalence of metabolic syndrome and its individual components were tabulated and presented in percentage. Comparison of the prevalence of metabolic syndrome and its individual components across different BMI categories was computed using Chi square test. Level of significance was set at alpha level of 0.05 with 95% confidence interval. Results were considered significant if p-value was <0.05.

Ethical Consideration

The clinical protocol and all relevant documents were reviewed and approved by Institutional Ethics Review Committee of St. Luke's Medical Center, Quezon City. Patient confidentiality was respected by ensuring anonymity of patient records. All study data were recorded and investigators were responsible for the integrity of the data i.e. accuracy, completeness and legibility. The manner of disseminating and communicating the study results guaranteed the protection of the confidentiality of patient's data.

Data collection was done by the main investigator. To ensure confidentiality, each patient was assigned a reference number. Data collection forms are kept confidential and encoded in excel file. In this process, only the members of this study have access to the patients' information. Data will be kept for 10 years and stored in the research library of the section. After the study, soft copy of the data will be stored by the main proponent and any hard copy of the data collection forms will be shredded.

RESULTS

A total of 1367 subjects were included in the study. The clinical and demographic characteristics of subjects included are shown in Table 1. Mean age of patients included was 53.3 (SD=12.4 years) with youngest of 18 years old and oldest at 86 years old. In terms of gender, there is a larger percentage of females included at 52.9%. Highest percentage of the subjects was in the pre-obese subgroup at 37.2% and least are subjects in the normal subgroup at 15%. The mean BMI was 28.2 kg/m^2 with lowest of 18.5 and highest of 67.9 kg/m^2.

Table 1. Demographics and clinical characteristics of subjects (n = 1367 subjects)

Age (mean in years)	53.3 (SD = 12.4)
Sex	
Male	644 (47.1%)
Female	723 (52.9%)
Weight (kg)	74.3 (SD =19.68)
Height (cm)	161.8 (SD = 9.24)
Waist circumference (cm)	96.8(SD = 31.2)
BMI (kg/m^2)	28.2 (SD=6.22)
BMI classification	
Normal	206 (15.1%)
Overweight	257 (18.8%)
Pre-obese	508 (37.2%)
Obese	396 (29.0%)
Systolic BP (mmHg)	121±11.7
Diastolic BP (mmHg)	79±6.74
Comorbidities	
Hypertension	792 (57.9%)
Diabetes Mellitus 2/ Elevated FBS	698 (51.1%)
Fasting Blood Sugar (mg/dL)	109 (SD =39.13)
Total Cholesterol (mg/dL)	201.1 (SD = 46.75)
HDL (mg/dL)	51.4 (SD = 18.11)
LDL (mg/dL)	127.7(SD = 40.50)
Triglycerides (mg/dL)	137.6 (SD = 96.22)
Creatinine	0.88 (SD = 0.35)
Alanine aminotransferase (ALT)	46.2 (SD = 0.28)

In individuals with metabolic syndrome, there is a noted female predominance in the lower BMI at 33.3% in the normal subgroup in contrast to a male predominance of patients in the higher BMI subgroup at 64.6% in the obese subgroup as shown in Table 2.

Among the 1367 subjects, the most prevalent feature of metabolic syndrome is central obesity at 82.9%, followed by hypertension, elevated blood glucose and low HDL with high triglyceride as the least common (Table 3). Other metabolic parameters such as elevated LDL, ALT and creatinine level have 42.9%, 16.4 % and 3.4% overall prevalence rates respectively (Figure 1).

Table 2. Presence of metabolic syndrome in relation to different BMI categories and gender

BMI Category	Metabolic Syndrome		
	Male n (%)	Female n (%)	Total with Metabolic Syndrome n (%)
Normal (18.5-22.9 kg/m^2)	13 (21)	48 (33.3)	61 (29.6)
Overweight (23-24.9 kg/m^2)	41 (37.3)	59 (40.1)	100 (38.9)
Pre-obese (25-29.9 kg/m^2)	159 (60.5)	130 (53.1)	289 (56.9)
Obese (≥30 kg/m^2)	135 (64.6)	112 (69.9)	247 (62.4)
Overall			697 (51.0)

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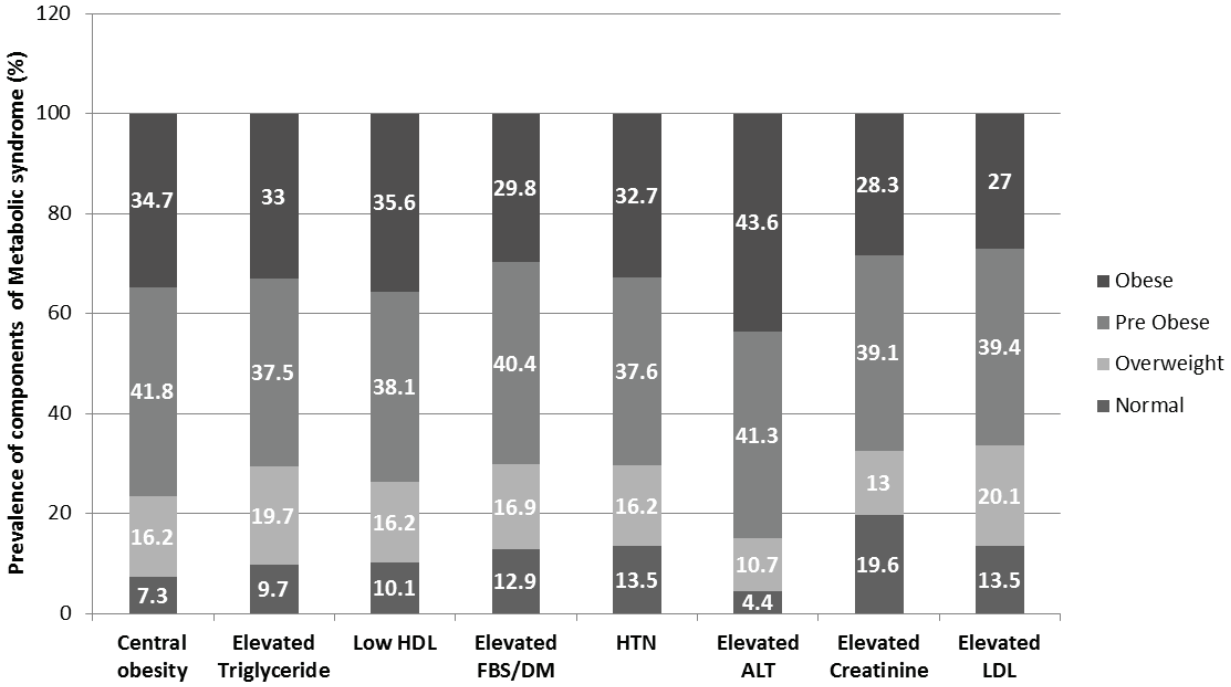

Figure 1. Prevalence of individual components of metabolic syndrome in relation to different BMI categories.

Table 3. Prevalence of individual features of metabolic syndrome, ALT, LDL and Creatinine

Individual Components of Metabolic Syndrome	n	%
Central obesity*	1133	82.9
HTN	792	57.9
Elevated FBS/DM	698	51.1
Low HDL**	464	33.9
High Triglycerides	421	30.8
High ALT	225	16.4
High LDL	586	42.9
High Creatinine	46	3.4

In the normal BMI subgroup, hypertension and elevated blood glucose have the highest prevalence rates at 12.9% and 13.5% respectively with central obesity being the least with 7.3% of individuals meeting the criterion for central obesity. In the overweight subgroup, high triglyceride level is the most common at 19.7% with almost equal prevalence of the other features of metabolic syndrome. In the pre-obese and obese subgroup, central obesity is the most common at 41.8% and 34.7% respectively. As the BMI increases, prevalence rates of the individual features of metabolic syndrome also increases and this was statistically significant.

The mean ALT level in the Normal BMI subgroup with metabolic syndrome is 32.7 U/L (SD=18.7), 42.2 (SD=11.3) in the overweight subgroup, 47.9 U/L (SD=26.2) in the pre-obese, and 59 U/L (SD=22.4) in the obese subgroup (p<0.0001). There is an increasing trend in the mean ALT levels and there is a statistically significant difference in association with the different BMI categories.

The mean creatinine level in the Normal BMI subgroup with metabolic syndrome is 1.09 mg/dL (SD=0.65), 1.0 mg/dL (SD=0.20) in the overweight subgroup, 0.98 (SD=0.19) in the pre-obese and 1.01 mg/dL (SD=0.36) in the obese subgroup (p-value = 0.003 for the effect of interaction with BMI and metabolic syndrome).

The mean LDL level in the Normal BMI subgroup with metabolic syndrome is 128.8 mg/dL (SD=40.40), 133.7 mg/dl (SD=41.58) in the overweight subgroup, 125.5 mg/dl (SD=40.63) in the pre-obese and 128.6 mg/dl (SD=42.67) in the obese subgroup (p-value of effect of Metabolic syndrome and BMI on LDL 0.148). There is a statistically significant effect or interaction between metabolic syndrome, BMI category and LDL levels (Table 4).

DISCUSSION

Metabolic syndrome in this study has been defined as having 3 out of the 5 features of the disease based on cut-offs specified by the NCEP/ATP III-AHA/NHLBI (2005). Based on these criteria, the overall incidence of metabolic syndrome in this study was reported at 51% (697/1367). This prevalence is higher than reported in the previous local study of Punzalan et al., in 2004 with the reported overall prevalence of 14.2%. This wide difference in the prevalence may be explained by the different population used in the two studies, Punzalan et al., was based on a national survey and the present study was hospital-based. This prevalence is also higher than the rates reported in previous published literature which varies widely depending on the population studied which consist mainly of whites but with a considerable percentage of Asians as well.

Prevalence of metabolic syndrome in normal BMI is higher at 29.6% as compared to the study in South American

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Table 4. Mean LDL, Creatinine and ALT across different BMI categories

Presence of Metabolic Syndrome	BMI Category	LDL*	Creatinine**	ALT ***
Yes	Obese	128.5 (SD= 42.67)	1.02 (SD=0.36)	59.0 (SD= 33.47)
	Pre obese	125.5 (SD= 40.63)	0.98(SD=0.19)	47.9 (SD= 26.22)
	Overweight	133.7 (SD= 41.57)	1.0 (SD=0.20)	42.2 (SD= 21.31)
	Normal	128.8 (SD= 40.40)	1.09 (SD=0.65)	32.8 (SD= 18.70)
	Total	128.3 (SD= 41.39)	1.01 (SD=0.35)	47.8 (SD= 28.23)
No	Obese	123.6 (SD= 40.30)	1.0 (SD=0.14)	50.4 (SD= 36.58)
	Pre obese	129.5 (SD= 38.47)	1.0 (SD=0.36)	46.0 (SD= 26.44)
	Overweight	129.6 (SD= 37.69)	0.98 (SD=0.13)	36.9 (SD= 22.36)
	Normal	117.9 (SD= 39.08)	0.90 (SD=0.30)	35.7 (SD= 25.55)
	Total	126.5 (SD= 38.89)	0.98 (SD=0.27)	43.4 (SD= 28.48)

*Effect of metabolic syndrome on LDL: p-value 0.111
*Effect of BMI on LDL : p-value 0.176
*Effect of the interaction with BMI and Metabolic syndrome on LDL: p-value 0.148
** Effect of Metabolic syndrome on Creatinine: p-value 0.011
** Effect of BMI on Creatinine : p-value 0.940
** Effect of the interaction with BMI and Metabolic syndrome on Creatinine: p-value 0.003
*** Effect of Metabolic syndrome on ALT: p-value 0.058
*** Effect of BMI on ALT: p-value <0.0001
*** Effect of the interaction with BMI and Metabolic syndrome on ALT: p-value 0.131

Table 5. Relation of BMI categories and ALT

	(I) BMI Category	(J) BMI Category	Mean Difference (I-J)	Std. Error	p-value	95% Confidence Interval	
						Lower Bound	Upper Bound
Bonferroni	Obese	Pre obese	9.36*	1.915	.000	4.30	14.42
		Overweight	16.52*	2.287	.000	10.48	22.57
		Normal	22.76*	2.425	.000	16.36	29.17
	Pre obese	Obese	-9.36*	1.915	.000	-14.42	-4.30
		Overweight	7.16*	2.130	.005	1.53	12.79
		Normal	13.40*	2.278	.000	7.38	19.42
	Overweight	Obese	-16.52*	2.287	.000	-22.57	-10.48
		Pre obese	-7.16*	2.130	.005	-12.79	-1.53
		Normal	6.24	2.598	.099	-.62	13.10
	Normal	Obese	-22.76*	2.425	.000	-29.17	-16.36
		Pre obese	-13.40*	2.278	.000	-19.42	-7.38
		Overweight	-6.24	2.598	.099	-13.10	.62

Based on observed means.
The error term is mean square (Error) = 743.772
* The mean difference is significant at the .05 level.

Hispanics which was reported at 19% in the year 2015. Overall prevalence of the syndrome is higher in males but when it broken down to different categories there is a female predominance in the normal BMI subgroup. Central obesity is the most common feature with overall 82.9% prevalence. However, it is notable that even in patients with normal BMI, 83 subjects (7.3%) met the criteria for central obesity and this reaches as high as 41.8 % in patients with BMI of 25-29.9 kg/m^2. This result is in contrast to the previous local study which showed that the most common feature in metabolic syndrome was low HDL. In terms of presence of low HDL levels based on gender specific cut-offs, 10.1% of patients in the normal BMI group met the criteria and this reaches as high as 35.6% in patients in the obese subgroup. In the normal BMI group, hypertension is the most prevalent feature of metabolic syndrome at 13.5% followed by elevated blood sugar at 12.9% and low HDL at 10.1% which is not congruent with the previous study. This may be the case since the patients in our study are mostly in the middle age and are, therefore, at higher risk to develop hypertension. Also, a significant percentage are already on medication for their dyslipidemia.

Comparing the profile of the different BMI subgroups, individuals with normal BMI presented most commonly with elevated blood pressure/presence of hypertension followed by elevated FBS/presence of DM with lesser prevalence of low HDL, elevated triglycerides and as expected, lowest prevalence of central obesity. This is in contrast to the obese population who presented with highest prevalence of low HDL and central obesity which is congruent with the result in the general population in the previous study done by Punzalan et al. In the overweight and pre-obese subgroup, there was an almost equal prevalence of the individual features.

Among the 3 other metabolic parameters, there was a significant difference in the ALT levels in relation to the different BMI categories wherein there is an increasing trend in ALT as BMI increases (Table 5). This present data support previous studies showing an increase in liver enzymes among those with metabolic syndrome. One of such study was done by Perera et al., in Thai adults[10] and one possible explanation that they offered for this association was presence of increased visceral adiposity, Non Alcoholic Fatty Liver disease (NAFLD) in association

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with hepatic insulin resistance contributing to elevation of liver markers.

In a study done by Wang et al., in 2015, they have stated that there is a positive association between higher serum creatinine levels even if within normal ranges.[11] Interaction between creatinine, presence of metabolic syndrome and BMI categories was also statistically significant in the present study however this association cannot be concluded whether it is positive or negative.

For the limitation, majority of the subjects included in this present study are at risk for metabolic abnormalities which may account for the higher prevalence rate of metabolic syndrome as compared to previous Philippine data. Subjects included and reviewed in the present study were limited only to those individuals who have access to health care facilities and only those with complete anthropometric measurements and the results of the study may not be reflective of the characteristics of the general Filipino population.

CONCLUSION

In this study, we have shown that in Filipino adults, individual components of the metabolic syndrome as defined by NCEP/ATP III-AHA/NHLBI (2005) and using the Asian cut-offs for abdominal obesity are present even in individuals with low BMI of 18.5-22.9 kg/m^2 and 23-24.9 kg/m^2. The presence of abnormal metabolic features such as central obesity, high triglycerides and low HDL levels even in patients with normal to slightly elevated BMI should prompt health care providers to consider nutrition counselling and weight management programs to these groups of individuals and not just be focus on individuals with higher BMI.

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All authors certified fulfillment of ICMJE authorship criteria.

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References

1. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey, 1999-2016. https://www.cdc.gov/nchs/data/nhanes/survey_content_99_16.pdf.
2. Ford ES. Giles WH, Mokdad AH. Increasing prevalence of metabolic syndrome among US adults. Diabetes Care. 2004;27(10):2444–9. PMID: 15451914.
3. Resnick HE, Jones K, Ruotolo G, et al. Insulin resistance, the metabolic syndrome and risk of incident cardiovascular disease in non-diabetic American Indians: The Strong Heart Study. Diabetes Care. 2003;26(3):861–7. PMID: 12610050.
4. Punzalan FER, Sy RG, Ty-Willing T. Prevalence of metabolic syndrome among adult Filipinos. Int Congress Series. 2004;1262:442-5.
5. Morales DD, Punzalan FE, Paz-Pacheco E, et al. Metabolic syndrome in the Philippine general population: Prevalence and risk for atherosclerotic cardiovascular disease and diabetes mellitus. Diabetes Vasc Dis Res. 2008;5(1):36–43. PMID: 18398811. https://doi/org/10.3132/dvdr.2008.007.
6. Araneta MR, Wingard DL, Barrett-Connor E. Type 2 diabetes and metabolic syndrome in Filipina-American women: A high risk non obese population. Diabetes Care. 2002;25(3):494–9. PMID: 11874936.
7. Benziger CP, Bernabé-Ortiz A, Gilman RH, et al. Metabolic abnormalities are common among South American Hispanics subjects with normal weight or excess body weight: The CRONICAS cohort study. PLoS ONE. 2015;10(11):e0138968. PMCID: PMC4658165. https://doi.org/10.1371/journal.pone.0138968.
8. Palaniappian LP, Wong EC, Shin JJ, Fortmann SP, Lauderdale DS. Asian Americans have greater prevalence of Metabolic syndrome despite lower body mass index. Int J Obesity. 2011;35(3):393–400. PMID: 20680014. PMCID: PMC2989340. https://doi.org/10.1038/ijo.2010.152.
9. Pagsisihan D, Sandoval MA, Paz-Pacgeco E, Jimeno C. Low indices of overweight and obesity are associated with cardiometabolic diseases among adult Filipinos in a rural community. J ASEAN Fed Endocr Soc. 2016;31(2):97-104. https://doi.org/10.15605/jafes.031.02.04.
10. Perera S, Lohsoonthorn V, Jiamjarasrangsi W, Lertmaharit S, Williams MA. Association between elevated liver enzymes and metabolic syndrome among Thai adults. Diabetes Metab Syndr. 2008;2(3):171-8. PMCID: PMC4137970. NIHMSID: NIHMS442249. https://doi.org/10.1016/j.dsx.2008.04.012.
11. Wang J, Li X, Yang K, et al. Serum creatinine levels and risk of metabolic syndrome in a middle-aged and older Chinese population. Clinica Chimica Acta. 2015; 440:177-82.

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ORIGINAL ARTICLE

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Knowledge and Practice of Diabetic Foot Care in Patients with Diabetes at Chinese General Hospital and Medical Center

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Abstract

Objective. The objective of this study is to measure the level of knowledge and practice of diabetic foot self-care and determine the factors that affect the level and knowledge and practice of diabetic foot self-care among among patients with diabetes..

Methodology. Three hundred thirty adult patients with diabetes at the outpatient clinics were given self-administered questionnaires on knowledge and practice of diabetic foot self-care. The scores were computed based on their answers. A score of >70% was gauged as good, 50 to 70% as satisfactory and <50% as poor.

Results. Of the subjects, 82.7% had good foot care knowledge, 22.4% had good foot self-care practice, and 71% had satisfactory practice score. Patients who received diabetes education were twice as likely to have a good knowledge score (OR 2.41, 95% CI, 1.09 to 5.32; *p*=0.03). Compared to patients who received diabetes care in private clinics, those who attended the charity outpatient clinic were nearly three times as likely to have a good knowledge score (OR 2.8, 95% CI, 1.32 to 5.96; *p*=0.007). Patients with known diabetes for more than ten years and those with a family history of diabetes were 50% less likely to have good practice scores (OR 0.50, 95% CI, 0.28 to 0.90; *p*=0.021 and OR 0.49, 95% CI, 0.29 to 0.83; *p*=0.008, respectively).

Conclusion. The current state of foot care knowledge in Filipino respondents with diabetes is good but the level of foot self-care practice is only satisfactory.

Key words: diabetic foot, diabetes mellitus, knowledge, self-care

INTRODUCTION

Among the complications of diabetes, those that occur in the foot are considered the most preventable. The annual incidence of new foot ulcer in patients with diabetes is 2.2%, with incidence increasing to 5.8% in three years.[1,2] The lifetime incidence of developing a foot ulcer is estimated to be as high as 25%.[3,4] Poor knowledge and poor foot care practices were identified as important risk factors for foot problems in diabetes.[5] Hence, in order to minimize, if not totally prevent, foot complications, it is important that appropriate and timely foot self-care be emphasized to patients with diabetes.[6-8]

A previous study showed that patients with diabetes often neglect foot self-care practices. The same study concluded that foot self-care practices appear underutilized as a primary complication prevention measure. Instead, patients only adopt foot care practices once complications have already occurred. Facilitators of foot self-care practices, such as patient education, appear to be reserved for individuals who have already developed foot complications.[9]

Prior to instructing proper self-care techniques to a patient, it is essential for the health care professional to understand the extent of the said patient's knowledge and practice. The authors found, during the conduct of this study, that administration of standardized written questionnaires was helpful in establishing a patient's baseline knowledge on self-care. By establishing the baseline knowledge level of the subject patients, healthcare providers may be able to determine the gaps in their knowledge and practice on foot self-care and provide feedback. Diabetes education will then be more effective in the prevention of foot complications through proper foot care.

Based on extensive literature search by the authors, there is no locally conducted study that has investigated the knowledge and foot self-care practices carried out by patients. This study aimed to determine the knowledge and practice of foot care among Filipinos with diabetes in our institution using knowledge questionnaires (Appendices 1 and 2).[10,11] We also sought to identify factors that affect the level of knowledge and practice of foot self-care. The results of this study can provide information to clinicians and healthcare providers on proper foot care.

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Health care professionals and educators may use the results of this study in the formulation of modules for diabetes-related education.

METHODOLOGY

This cross-sectional analytical study was conducted for 3 months among patients with diabetes who consulted at the Outpatient Clinics of the Chinese General Hospital and Medical Center (CGHMC), a tertiary level hospital in Manila, Philippines. The study protocol and informed consent forms were submitted to and approved by the institutional Research Ethics Review Board.

The authors used the Knowledge questionnaire developed by Hasnain and colleagues and the Nottingham Assessment of Functional Foot Care (NAFFC) (Appendices 1 and 2).[10,11] Both questionnaires were translated to the local vernacular to ensure that these would be fully understood by the patients (Appendices 3 and 4). Language experts in Filipino and English performed the forward and back translations, respectively. Ten respondents deemed eligible by the inclusion and exclusion criteria provided their opinion regarding the relevance and phrasing of the Filipino translated questions. Eight internal medicine specialists and subspecialists evaluated content validity of the final forward translated questionnaires, while 10 patients were asked to assess face validity. To determine if the Filipino version would elicit the same answers over time, it was administered twice to 10 respondents with an interval of three days in-between. Reliability of answers was analyzed using the test-retest method.[12]

Patients with type 1 or type 2 diabetes of any duration, age 18 years and older, were recruited for the actual survey. They must be able to read, comprehend and understand Filipino or English, and consent to participate in the study. The diagnosis of diabetes mellitus was based on the Unite for Diabetes Philippines Clinical Practice Guidelines: fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) after an overnight fast, two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test, or random plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or with signs and symptoms of hyperglycemic crisis.[13] Exclusion criteria were impaired fasting glucose, impaired glucose tolerance and gestational diabetes.

To ensure a high response rate, the principal investigator conducted a recruitment process and gave cover letters in English and Filipino to fully explain the purpose of the study, its significance, its risks and benefits and the personal information needed. It was emphasized that the results of this study will be used to improve how healthcare providers may improve diabetes education on proper foot self-care. Patients who qualified and gave consent were then recruited.

The respondents were encouraged to complete all the questionnaires. Pamphlets on proper foot care were given to the patients after participating in the study as a form of incentive. Patients were also advised on proper foot care after answering the questionnaire. As a matter of post-study intervention and correction of incorrect answers in the Knowledge and Practice Questionnaire, the authors taught the respondents proper foot care practice after their participation in the study.

Information collected per respondent included age, gender, address, contact number, duration of diabetes, family history of diabetes, medications, educational attainment, smoking history, family monthly income bracket (to assess economic status based on the Philippine Statistics Authority income bracket),[14] latest HbA1c when available, and where the patient received diabetes care and information on diabetes foot care. Patient history and present foot problems such as ulcers, blisters, calluses, wounds, non-healing wounds for more than two weeks, foot surgery (debridement or amputation) and paresthesia were likewise recorded.

The authors used a 15-item questionnaire answerable with "yes," "no" and "I don't know" on knowledge of diabetic foot care developed by Hasnain et al., and used by the groups of Muhammad-Lufti and Seid (Appendix 1).[10,15,16] Knowledge score was determined based on the proportion of correct answers. The level of knowledge was assessed as good if the score was more than 70% (11 to 15 correct answers out of 15). Scores of 50 to 70% (8 to 10 correct answers) were categorized as satisfactory knowledge. Scores less than 50% (7 or below correct answers) were evaluated as poor knowledge.

Responses to questions of the translated NAFFC were recorded on a categorical scale (scored 0 to 3) according to the frequency of occurrence of the behavior.[11] The NAFFC consists of 29 independent questions (Appendix 2). Pictures of examples of footwear accompanied the questionnaires. Scoring on practice was arbitrarily gauged as good for scores more than 70% (61 and above). Scores of 50 to 70% (43 to 60) were considered satisfactory practice. Scores less than 50% (42 and below) were labeled as poor practice.

A minimum of 324 subjects was required for this study based on a level of significance of 5%, with a desired width of confidence interval of 10% and a prevalence of 30.1% of good knowledge of diabetic foot care among patients with diabetes mellitus, as noted in the reference article by Desalu et al.[17,18]

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, while mean and standard deviation (SD) were applied for interval/ratio variables. Wilcoxon signed rank test was used to determine the

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content validity of the translated questionnaire using ratings from the panel of experts. Odds ratios and corresponding 95% confidence intervals from binary logistic regression were computed to determine significant predictors for good knowledge and practice of diabetic patients. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α-level of significance. STATA 12.0 was used for data analysis.[19]

RESULTS

We enrolled a total of 330 patients for this study, with a mean age (±SD) of 59.09 (±12.69) years. They were predominantly female (66%) and married (65%). Half of the patients were unemployed, and half were at least college graduates. Approximately 4 in 10 patients had a monthly family income of below PhP 15,000 (Table 1).

Table 1. Socio-demographic and diabetes-related profile of the individuals with diabetes

Characteristic	Frequency (%)
Mean age, yr	59.09 ± 12.69
Female gender	218 (66.06)
Civil status	
Single	38 (11.52)
Married/cohabiting	223 (67.57)
Widowed/annulled/separated	69 (20.91)
Occupation	
None	166 (50.30)
Employed	74 (22.42)
Self-employed	67 (20.30)
Professional	23 (6.97)
Educational attainment	
No formal training	6 (1.82)
Elementary	38 (11.52)
High school graduate	94 (28.48)
Vocational	8 (2.42)
College graduate	161 (48.79)
Postgraduate	23 (6.97)
Monthly family income, PhP[a]	
Below 15,000	143 (43.33)
15,000 to 32,000	93 (28.18)
32,000 to 80,000	45 (13.64)
80,000 to 120,000	26 (7.88)
More than 120,000	23 (6.97)
Mean duration of diabetes	
Less than a year	43 (13.03)
1 to 5 years	94 (28.48)
5 to 10 years	75 (22.73)
More than 10 years	118 (35.76)
Medication	
None	3 (0.91)
Oral	198 (60)
Insulin-requiring	129 (39.09)
Attended diabetes education	85 (25.76)
Information source of diabetic foot care	
Diabetes Center	61 (18.48)
Reading materials	73 (22.12)
Doctor	134 (40.61)
Relatives/neighbors	33 (10)
Lay forum/lectures	39 (11.82)
No information	106 (32.12)
Receives diabetic care	
Private clinic	227 (68.79)
Charity outpatient clinic	103 (31.21)
Family history of diabetes	221 (66.97)
Previous smoker/Smoker	96 (29.09)
Mean HbA1c[b]	7.57 ± 2.06

Table 1 provides the clinical profile of the patients. Of 330, there were 118 (36 %) with diabetes for more than 10 years, and 129 (39%) were insulin requiring. About a quarter (26%) of the patients had attended diabetes education. Only 18% of the subjects received proper foot self-care from the Diabetes Center.

The mean (±SD) knowledge and practice scores were 86.7% (± 16) or good and 63.2% (± 8.7) or satisfactory.

Among the 330 respondents, 82.7%, 13.3%, and 3.9% had good, satisfactory, and poor knowledge, respectively. Nearly one-third (31.5%) of respondents gave an incorrect answer or "I don't know" when asked if lukewarm water should be used for washing the feet. More than half (53%) of the patients were not aware that lotion should not be applied in between toes, and that talcum powder be used to keep the areas between the toes dry.

Regarding the level of practice on foot self-care, only 22.4% had good practice while 71.2% and 6.4% had satisfactory and poor scores, respectively. Majority of the patients examined their feet daily (76%), washed their feet daily (97%), did not use nylon stockings (71%), never used pointed shoes (77%), did not place their feet near hot objects (83 to 96%) and did not use corn paints or plasters (72%). More than half checked their shoes before putting them on (57%), dried the areas between the toes (63%), did not put lotion in between toes (54%), often checked that their feet were dry after washing (60%) and cut their toenails weekly (61%).

Although 71% of patients had satisfactory practice scores, there were foot care practices that were not observed by patients. Majority of them did not use lotion on their feet (60%), did not regularly inspect their footwear after taking them off (69%), and did not wear slippers most of the time (77%). More than 30% of the patients never practiced breaking-in new shoes, never wore seamless socks, wore shoes without socks and never checked the temperature of the water they used for washing feet. More than 60% never used dressing when they had blisters or wounds on their feet. About 45% walked barefoot indoors and about 13% walked barefoot outdoors.

We conducted simple binary logistic regression to determine factors associated with knowledge scores (Table 2). Patients who received diabetes education were twice as likely to have a knowledge score above 70% (OR 2.41, 95%CI, 1.09 to 5.32; p=0.03). Similarly, compared to patients who received diabetic care in private clinics, patients who attended the charity outpatient clinic were nearly three times as likely to have a knowledge score above 70% (OR 2.8, 95% CI, 1.32 to 5.96; p=0.007).

In the final model, however, there was insufficient evidence to establish an association between foot care/diabetes education (adjusted OR 1.63, 95% CI, 0.68 to 3.90) or receiving diabetes care in the OPD (adjusted OR 2.28, 95% CI, 1.00 to 5.22) with knowledge scores.

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Table 2. Factors associated with knowledge scores of the individuals with diabetes

Characteristic	Knowledge score >70% (n=273)	Knowledge score ≤70% (n=57)	Crude odds ratio (95% CI)	*p*-value
Socio-demographic factors				
Age 60 and above, yr	138 (50.55)	27 (47.37)	1.14 (0.64-2.01)	0.662
Gender				
Male	93 (34.07)	19 (33.33)	(reference)	-
Female	180 (65.93)	38 (66.67)	0.97 (0.53-1.77)	0.915
Civil status				
Single	33 (12.09)	5 (8.77)	(reference)	-
Married/cohabiting	178 (65.2)	45 (78.95)	0.60 (0.22-1.62)	0.314
Widowed/annulled/separated	62 (22.71)	7 (12.28)	1.34 (0.40-4.56)	0.637
Occupation				
None	142 (52.01)	24 (42.11)	(reference)	-
Employed	59 (21.61)	15 (26.32)	0.66 (0.33-1.36)	0.262
Self-employed	55 (20.15)	12 (21.05)	0.77 (0.36-1.66)	0.51
Professional	17 (6.23)	6 (10.53)	0.48 (0.17-1.34)	0.16
With college degree	25 (9.16)	6 (10.53)	0.86 (0.33-2.19)	0.748
Monthly family income 32,000 and above, PhP[a]	79 (28.94)	15 (26.32)	1.14 (0.60-2.17)	0.69
Diabetes-related factors				
Duration more than 10 yr	98 (35.90)	20 (30.59)	1.04 (0.57-1.88)	0.908
Insulin-requiring	109 (39.93)	20 (30.59)	1.23 (0.68-2.23)	0.496
Attendance to Diabetes Center	77 (28.21)	8 (14.04)	2.41 (1.09-5.32)	0.03
Diabetes Center as source of information on foot care	55 (20.15)	6 (10.53)	2.14 (0.88-5.25)	0.095
Receives diabetic care				
Private clinic	179 (65.57)	48 (84.21)	(reference)	-
Charity outpatient clinic	94 (34.43)	9 (15.79)	2.8 (1.32-5.96)	0.007
Family history of diabetes	180 (65.93)	41 (71.93)	0.76 (0.40-1.42)	0.382
HbA1c 7 or greater, %	129 (49.24)	23 (42.59)	1.31 (0.72-2.36)	0.374
No history of foot problem	86 (31.62)	19 (33.33)	0.92 (0.50-1.70)	0.801
No current foot problem	118 (43.22)	24 (42.11)	1.05 (0.59-1.86)	0.877

[a]PhP, Philippine Peso
[b]For n=316

Table 3. Factors associated with good practice scores of the individuals with diabetes

Characteristic	Practice score >70% (n=74)	Practice score ≤70% (n=256)	Crude odds ratio (95% CI)	*p*-value
Socio-demographic factors				
Age 60 and above, yr	38 (51.35)	127 (49.61)	1.07 (0.64-1.80)	0.792
Gender				
Male	32 (43.24)	80 (31.25)	(reference)	-
Female	42 (56.76)	176 (68.75)	0.60 (0.35-1.01)	0.056
Civil status				
Single	8 (10.81)	30 (11.72)	(reference)	-
Married/cohabiting	52 (70.27)	171 (66.8)	1.14 (0.49-2.64)	0.759
Widowed/annulled/separated	14 (18.92)	55 (21.48)	0.95 (0.36-2.53)	0.926
Occupation				
None	30 (40.54)	136 (53.13)	(reference)	-
Employed	16 (21.62)	58 (22.66)	1.25 (0.63-2.47)	0.519
Self-employed	22 (29.73)	45 (17.58)	2.22 (1.16-4.23)	0.016
Professional	6 (8.11)	17 (6.64)	1.6 (0.58-4.40)	0.362
With college degree	9 (12.16)	22 (8.59)	1.47 (0.65-3.35)	0.356
Monthly family income 32,000 and above, PhP[a]	21 (28.38)	73 (28.52)	0.99 (0.56-1.76)	0.982
Diabetes-related factors				
Duration more than 10 yr	18 (24.32)	100 (39.06)	0.50 (0.28-0.90)	0.021
Insulin-requiring	28 (37.84)	101 (39.45)	0.93 (0.55-1.59)	0.802
Attendance to Diabetes Center	21 (28.38)	64 (25)	1.19 (0.67-2.12)	0.559
Diabetes Center as source of information on foot care	17 (22.97)	44 (17.19)	1.44 (0.76-2.70)	0.26
Receives diabetic care				
Private clinic	49 (66.22)	178 (69.53)	(reference)	-
Charity outpatient clinic	25 (33.78)	78 (30.47)	1.16 (0.67-2.02)	0.588
Family history of diabetes	40 (54.05)	181 (70.70)	0.49 (0.29-0.83)	0.008
HbA1c 7 or greater, %	37 (52.11)	115 (46.94)	1.23 (0.72-2.09)	0.443
No history of foot problem	26 (35.62)	79 (30.86)	1.24 (0.72-2.14)	0.442
No current foot problem	40 (54.05)	102 (39.84)	1.78 (1.05-2.99)	0.031

[a]PhP, Philippine Peso

We conducted simple binary logistic regression to determine factors associated with practice scores (Table 3). Patients who were self-employed were twice as likely to have a practice score above 70% compared to unemployed patients (OR 2.22, 95% CI, 1.16 to 4.23; p=0.016). Patients who had diabetes for more than 10 years were only 50% less likely to have good practice scores (OR 0.50, 95% CI, 0.28 to 0.90; p=0.021). This was also observed in those with a family history of diabetes (OR 0.49, 95% CI, 0.29 to 0.83; p=0.008). Patients who do not have current foot problems were more likely to have good practice scores (OR 1.78, 95% CI, 1.05 to 2.99; p=0.031).

In the final model, duration and family history of diabetes were found to be significant. Those with more than 10 years of diabetes (adjusted OR 0.54, 95% CI, 0.30 to 0.98) and with family history of diabetes (adjusted OR 0.52, 95% CI, 0.30 to 0.89) were 50% less likely to have good practice scores. This model was significant, but only explains 2.78% in the variation of good and poor practice scores.

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DISCUSSION

The study results show that majority of patients (83%) had good knowledge and only a small proportion (22%) had a good score on practice on foot care.

About a third of the subjects were not knowledgeable that lukewarm water should be used for washing the feet and that the temperature of the water should be checked first before using it to wash the feet. More than half of the patients were not aware about the proper use of lotion and talcum powder on the feet. The above good practices were also not practiced by patients with diabetes in Pakistan and Malaysia.[10,15] Owing to our country's tropical climate and the general unavailability of water temperature control devices in many households, most Filipinos use water that comes out of the tap or shower without checking the temperature. Also, because the common footwear of many Filipinos are open-type sandals, the subjects may not have found it necessary to use talcum powder to keep the interdigital spaces on their feet dry. This finding indicates that healthcare providers may not have emphasized proper use of lotion and talcum powder in these patients.

Good scores on knowledge were comparable to findings in India, where 75% had good knowledge.[20] This is in clear contrast to the findings in Nigeria, where 78% had poor knowledge. Poor knowledge was significantly associated with poor educational attainment and low socioeconomic status.[17] However, our study did not show any correlation of knowledge scores with age, gender or educational attainment.

Our study showed that those who received diabetes education from the Diabetes Center were twice as likely to have good knowledge. Individuals with diabetes from the charity clinic were nearly three times as likely to have good knowledge. More patients from the charity clinic than from private practices were enrolled in diabetes education at the Diabetes Center, likely encouraged due to lower fees. Furthermore, more charity patients attended lay forums on diabetes compared to those from private clinics.

One study showed that foot care knowledge of patients who received education on complications was much better than those who did not. Patients aware of complications were willing to take action only when they learned that these were preventable.[21] Willingness to receive education to prevent diabetes-related complications should encourage healthcare providers to offer diabetes education to all patients, and healthcare institutions to improve diabetes educational programs and provide better patient access to formal diabetes education.

On the are of foot care practices, a small proportion (22%) had good practice while majority (71%) had satisfactory scores. Practices in foot self-care that most respondents did not follow included daily use of moisturizing cream or lotion, inspection of feet and footwear after use, use of adequate footwear, breaking-in shoes, use of seamless socks, checking temperature of water when washing feet, and use of dressing for blisters and wounds on feet. The most remarkable findings were that 45% of the respondents walked barefoot indoors and about 13% walked barefoot outdoors.

The scores on practice may have been affected by the choice of footwear and poor foot-care practices. Majority of patients wore slippers and flip-flops. This result is consistent with the study among Filipinos with diabetes in the preferred primary choice of footwear.[22] In India and Iran, 41% and 62% of individuals with diabetes walked barefoot indoors, respectively.[23,24] These findings in poor foot care practice may be due to the lack of perceived immediate effect of these poor practices.

Our study also found that those who were self-employed had good self-care practices. This complements a study conducted in the southeastern United States, which found that diabetes empowerment was related to better diabetes knowledge, medication adherence and improved self-care behaviors. Emphasis on empowerment and self-efficacy is relevant to improve outcomes in the management of diabetes.[25] Both studies showed that self-empowerment brought about by employment has a positive effect on the management of diabetes.

Respondents who had diabetes for more than 10 years were only 50% less likely to have good practice scores. In contrast, a study done in China found that the state of practice was influenced by duration of diabetes mellitus and education about diabetic complications.[21] Patients with longer duration of diabetes and follow-up regularly got a high score in foot self-care behavior, suggesting that these patients paid more attention to self-care. However, in our study, patients were apparently less keen in practicing proper foot care practice despite the chronic duration of their diabetes.

We found that respondents with a family history of diabetes were only 50% less likely to have good practice scores, in contrast to findings in studies in Asian populations.[26,27] A possible reason for this finding in our study is that the diabetic family members of our subjects may not have had foot complications, making our subjects less cautious about foot care practices. However, this reason was not verified in our study.

Respondents who did not have current foot problems also had higher foot self-care practice scores. This echoes the findings of Nongmaithem et al., which showed that those with diabetic foot ulcers had poor foot care practice, leading to diabetic foot ulcer.[28]

Our study found that while the respondents had a good knowledge of diabetic foot self-care, the scores for actual

practice are only satisfactory. This implies that adequate knowledge by itself does not necessarily translate to action, as shown in the study by Li et al.[21] Complications such as diabetic foot ulcers and lower extremity amputations are preventable with good knowledge and good practice of diabetic foot care. Foot care education is the most crucial tool in preventing lower leg amputations necessitated by complications.[29] Simple patient evaluation, coupled with concomitant preventive measures, significantly reduce the rates of risk among individuals with diabetes.

The advantage of this study was the use of the Filipino language in our questionnaires. These questionnaires were tested and validated. Respondents were shown accompanying illustrations to help them understand the type of footwear being asked. The questions covered the recommended good foot-care practices in the areas of feet washing techniques, inspection of foot and footwear, skin and nail care, footwear use, and self-foot care management. The questionnaire can be used as an outcome measure after attending or administering diabetes education on foot care for patients with and without diabetic foot ulcers.

We recognized certain limitations in our study. The subjects consisted of patients attending the CGHMC outpatient clinics, with a small number of patients seeking treatment for diabetic foot ulcer. Some questions in the questionnaire may not be applicable in our local setting, such as the use of lukewarm water for washing feet, placing feet near fire or use of seamless socks, which are not usually available or in fashion here in our country. Our tropical weather is markedly different from area where the Nottingham foot care questionnaire was developed. Our respondents preferred the use of flip-flops and slippers and were unaccustomed to use of socks or tights. Appropriately revised knowledge and practice questionnaires should be developed to make these applicable to Filipino patients. The revised versions of the questionnaires may be used in future studies. We also did not document foot deformities, neuropathy and peripheral arterial disease. Information on current and past history of foot problems only came from questionnaires, unverified from patient records. For future studies, knowledge and practice scores in patients at high-risk for diabetic foot ulcers may also be compared.

CONCLUSION

The current state of foot care knowledge in Filipino diabetic respondents is good, but the level of foot self-care practice is only satisfactory. Healthcare providers should focus on addressing gaps in foot care knowledge, supporting proper foot care practices and encouraging patients to participate in educational activities on diabetes.

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References

1. Abbott CA, Carrington AL, Ashe H, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabetic Med. 2002;19(5):377-84. PMID: 12027925. https://doi:10.1046/j.1464-5491.2002.00698.x
2. Ramsey SD , Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care. 1999;22(3):382-7. PMID:10097914. https://doi.org/10.2337/diacare.22.3.382
3. Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment: A report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care. 2008;31(8):1679-85. PMID: 18663232. PMCID: PMC2494620. https://doi.org/10.2337/dc08-9021
4. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with Diabetes. JAMA. 2005;293(2):217-28. PMID: 15644549. https://doi.org/10.1001/jama.293.2.217
5. Chandalia HB, Singh D, Kapoor V, Chandalia SH, Lamba PS. Footwear and foot care knowledge as risk factors for foot problems in Indian diabetics. Int J Diabetes Dev Ctries. 2008;28(4):109-13. PMID: 20165597. PMCID: PMC2822153. https://doi.org/10.4103/0973-3930.45269.
6. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Poqach LM; American Diabetes Association. Preventive foot care in diabetes. Diabetes Care. 2004;27(Suppl 1):S63-4. PMID: 14693928.
7. Pinzur MS, Slovenkai, MP, Trepman E, Shields NN; Diabetes Committee of American Orthopaedic Foot and Ankle Society. Guidelines for diabetic foot care: recommendations endorsed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society. Foot Ankle Int. 2005;26(1):113-9. PMID: 15680122. https://doi.org/10.1177/107110070502600112.
8. Bonner T, Foster M, Spears-Lanoix E. Type 2 diabetes-related foot care knowledge and foot self-care practice interventions in the United States: A systematic review of the literature. Diabet Foot Ankle. 2016;7:29758. PMID: 26899439. PMCID: PMC4761684. https://doi.org/10.3402/dfa.v7.29758. eCollection 2016.
9. Matricciani L, Jones S. Who cares about foot care? Barriers and enablers of foot self-care practices among non-institutionalized older adults diagnosed with diabetes: An integrative review. Diabetes Educ. 2015;41(1):106-17. PMID: 25480398. https://doi.org/10.1177/0145721714560441.
10. Hasnain S, Sheikh NH. Knowledge and practices regarding foot care in diabetic patients visiting diabetic clinic in Jinnah Hospital, Lahore. J Pak Med Assoc. 2009;59(10):687-90. PMID: 19813683.
11. Lincoln NB, Jeffcoate WJ, Ince P, Smith M, Radford K. Validation of a new measure of protective footcare behaviour: The Nottingham Assessment of Functional Footcare (NAFF). Pract Diab Int. 2007;24(4):207-11. https://doi.org/10.1002/pdi.1099.
12. Polit DF, Yang FM. Measurement and the measurement of change. Philadelphia: Wolters Kluwer, 2016.
13. UNITE for Diabetes Philippines: Philippine Practice Guidelines on the Diagnosis and Management of Diabetes Mellitus. http://obesity.org.ph/v4/wp-content/uploads/2014/07/Diabetes-United-for-Diabetes-Phil.pdf. Accessed August 1, 2016.
14. Philippine Statistics Authority. 2012 Family Income and Expenditure Survey Final Results: National Capital Region. Number: 2014-11. http://nso-ncr.ph/special%20release/fies/2012%20Fies.pdf. Accessed August 6, 2016.
15. Muhammad-Lutfi AR, Zaraihah MR, Anuar-Ramdhan IM. Knowledge and practice of diabetic foot care in an in-patient setting at a tertiary medical center. Malays Orthop J. 2014;8(3):22-6. PMCID: PMC4536395. https://doi.org/10.5704/MOJ.1411.005.
16. Seid A, Tsige Y. Knowledge, practice, and barriers of foot care among diabetic patients attending Felege Hiwot Referral Hospital, Bahir Dar,

Northwest Ethiopia. Advances in Nursing. 2015;2015:Article ID 934623. https://doi.org/ 10.1155/2015/934623.

17. Desalu OO, Salawu FK, Jimoh AK, Adekoya AO, Busari OA, Olokoba AB. Diabetic Foot Care: self-reported knowledge and practice among patients attending three tertiary hospital in Nigeria. Ghana Med J. 2011;45(2):60-5. PMID: 21857723. PMCID: PMC3158533.
18. Mcmillan G, Hanson TE. Sample size requirements for establishing clinical test-retest standards. Ear Hear. 2014;35(2): 283-6. PMID: 24351613. https://doi.org/10.1097/01.aud.0000438377.150036b.
19. Peacock J, Peacock PJ. Oxford handbook of medical statistics. Oxford: Oxford University Press, 2011.
20. George H, Rakesh P, Krishna M, et al. Foot care knowledge and practices and the prevalence of peripheral neuropathy among people with diabetes attending a secondary care rural hospital in southern India. J Family Med Prim Care. 2013;2(1):27-32. PMID: 24479039. PMCID: PMC3894008. https://doi.org/ 10.4103/2249-4863.109938.
21. Li R, Yuan L, Guo KH, et al. The current status of foot self-care knowledge, behaviours, and analysis of influencing factors in patients with type 2 diabetes mellitus in China. International Journal of Nursing Sciences. 2014; 1(3):266-71. https://doi.org/10.1016/j.ijnss.2014.05.023.
22. Isip J, de Guzman M, Ebison A Jr, Narvacan-Montano C. Footwear appropriateness, preferences and foot ulcer risk among adult diabetics at Makati Medical Center Outpatient Department. J ASEAN Fed Endocr Soc. 2016;31(1):37-43. https://doi.org/10.15605/jafes.031.01.07.
23. Kumhar M, Dara N, Saini T. Foot wear and footcare knowledge—an independent risk factor for diabetic foot in Indian diabetics. Indian Medical Gazette. 2014;25-8. http://imsear.hellis.org/handle/123456789/157578.
24. Khamseh ME, Vatankhah N, Baradaran HR. Knowledge and practice of foot care in Iranian people with type 2 diabetes. Int Wound J. 2007;4(4):298-302. PMID: 18154624. https://doi.org/10.1111/j.1742-481X.2007.00381.x.
25. Hernandez-Tejada MA, Campbell JA, Walker RJ, Smalls BL, Davis KS, Egede LE. Diabetes empowerment, medication adherence and self-care behaviors in adults with type 2 diabetes. Diabetes Technol Ther. 2012;14(7):630-4. PMID: 22524548. PMCID: PMC3389377. https://doi.org/10.1089/dia.2011.0287.
26. Kim SY, Hongsranagon P. Preventive behaviors regarding foot ulcers in diabetes type II patients at BMA Health Center No. 48, Bangkok, Thailand. J Health Res. 2008;22(Suppl):21-8. http://www.jhealthres.org/upload/journal/341/22(suppl)_p21-28_sonyongkim.pdf.
27. Malathy R, Narmadha M, Ramesh S, Alvin JM, Dinesh BN. Effect of a diabetes counseling programme on knowledge, attitude and practice among diabetic patients in Erode district of South India. J Young Pharm. 2011;3(1):65-72. PMID: 21607057. PMCID: PMC3094563. https://doi.org/10.4103/0975-1483.76422.
28. Nongmaithem M, Bawa AP, Pithwa AK, Bhatia SK, Singh G, Gooptu S. A study of risk factors and foot care behavior among diabetics. J Family Med Prim Care. 2016;5(2):399-403. PMID: 27843849. PMCID: PMC5084569. https://doi.org/10.4103/2249-4863.192340.
29. Nagpal J, Bhartia A. Quality of diabetes care in the middle- and high-income group populace: The Delhi Diabetes Community (DEDICOM) Survey. Diabetes Care. 2006;29(11):2341-8. PMID: 17065665. https://doi.org/10.2337/dc06-0783.

Appendix 1. Questionnaire on Knowledge of Foot Care (English version)[10]

Place a check (✓) in the appropriate column to indicate whether the statement is CORRECT or WRONG		Correct	Wrong	I do not know
1	Anti-diabetic medications should be taken regularly to prevent complications.			
2	Feet should be washed daily.			
3	Lukewarm water should be used to wash feet.			
4	The temperature of the water should be checked before washing feet.			
5	Feet should be completely dried after washing.			
6	Talcum powder should be used to keep the areas between the toes dry.			
7	Lotion or moisturizing cream should be applied on the feet to prevent dryness of skin.			
8	Lotion should not be applied between the toes.			
9	Socks should be changed daily.			
10	Toenails should be trimmed straight across.			
11	Feet should be inspected at least once a day.			
12	Diabetic patients should wear comfortable shoes.			
13	The inside of the shoes should be inspected for before wearing them.			
14	Diabetic patients should not walk barefoot.			
15	Diabetic patients should consult a doctor if their feet have redness, blisters, cuts, or wound/s.			

Appendix 2. Nottingham Assessment of Functional Foot Care (English Version)[11]

We would like to know what you do to look after your feet. Please tick (✔) the category, which best reflects what you actually do. Please answer every question. Thank you.	
1. Do you examine your feet?	☐ More than once a day (3) ☐ Once a day (2) ☐ 2-6 times a week (1) ☐ Once a week or less (0)
2. Do you check your shoes before you put them on?	☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
3. Do you check your shoes when you take them off?	☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
4. Do you wash your feet?	☐ More than once a day (3) ☐ Once a day (2) ☐ Most days a week (1) ☐ A few days a week (0)
5. Do you check your feet are dry after washing?	☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)

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6. Do you dry between your toes?	☐ Always (3) ☐ Often (2) ☐ Sometimes (1) ☐ Rarely/Never (0)
7. Do you use moisturizing cream or lotion on your feet?	☐ Daily (3) ☐ Once a week (2) ☐ About once a month (1) ☐ Never (0)
8. Do you put moisturizing cream or lotion between your toes?	☐ Daily (0) ☐ Once a week (1) ☐ About once a month (2) ☐ Never (3)
9. Are your toenails cut?	☐ About once a week (3) ☐ About once a month (2) ☐ Less than once a month (1) ☐ Never (0)
10. Do you wear sandals?	☐ Most of the time (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
	
11. Do you wear slippers?	☐ Most of the time (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
	
12. Do you wear rubber shoes or sneakers?	☐ Most of the time (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
	
13. Do you wear shoes with lace-up, Velcro or strap fastenings?	☐ Most of the time (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
	
14. Do you wear pointed-toed shoes?	☐ Most of the time (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
	
15. Do you wear flip-flops or mules (shoe that is backless)?	☐ Most of the time (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)

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16. Do you break in new shoes gradually?	☐ Always (3) ☐ Often (2) ☐ Sometimes (1) ☐ Rarely/Never (0)
17. Do you wear artificial fiber (e. g. nylon) stockings?	☐ Most of the time (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
18. Do you wear seamless socks/stockings/tights?	☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
19. Do you wear shoes without socks/stockings/tights?	☐ Never (3) ☐ Rarely (2) ☐ Sometimes (1) ☐ Often (0)
20. Do you change your socks/stockings/tights?	☐ More than once a day (3) ☐ Daily (2) ☐ 4-6 times a week (1) ☐ Less than 4 times a week (0)
21. Do you walk around the house in bare feet?	☐ Often (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
22. Do you walk outside the house in bare feet?	☐ Often (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
23. Do you use a hot water bottle in bed?	☐ Often (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
24. Do you put your feet near the fire?	☐ Often (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
25. Do you put your feet on a radiator?	☐ Often (0) ☐ Sometimes (1) ☐ Rarely (2) ☐ Never (3)
26. Do you check the temperature of the water you wash your feet in?	☐ Often (3) ☐ Sometimes (2) ☐ Rarely (1) ☐ Never (0)
27. Do you use corn (callus) remedies/corn (callus) plasters/ paints when you get a corn?	☐ Never (3) ☐ Rarely (2) ☐ Sometimes (1) ☐ Often (0)
28. Do you put a dry dressing on a blister when you get one?	☐ Never (0) ☐ Rarely (1) ☐ Sometimes (2) ☐ Often (3)
29. Do you put a dry dressing on a graze, cut or burn when you get one?	☐ Never (0) ☐ Rarely (1) ☐ Sometimes (2) ☐ Often (3)

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ORIGINAL ARTICLE

Comparison of the Clinical and Biochemical Profile of Metabolic Syndrome Between Obese Children Below and Above 10-Years Old Attending Paediatric Clinic Hospital Universiti Sains Malaysia from 2006 to 2015

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Abstract

Objectives. We aim to compare the clinical and biochemical profile of metabolic syndrome between obese children below and above 10 years attending Paediatric clinic Hospital Universiti Sains Malaysia (HUSM) from 2006 to 2015. This is to determine if age, particularly the transition to puberty, modifies the prevalence of components of metabolic syndrome in obese children.

Methodology. The medical records of 84 obese children under 18 years of age seen at Paediatric clinic HUSM from 2006 to 2015 were reviewed. Demographic (age, gender, ethnicity), anthropometric (weight and height), clinical [body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP)] and biochemical [serum total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), fasting plasma glucose (FPG)] parameters were recorded, analyzed and compared.

Results. Majority of subjects in both age groups were boys, with 68.2% <10 years old. Mean age was 9.69 years (±3.36). The clinical and biochemical parameters of metabolic syndrome were similar between those <10 years old and ≥10 years, with the exception of BMI, waist circumference, SBP and TG level. Multivariate regression analysis showed that the parameters of metabolic syndrome significantly associated with age ≥10 years were systolic hypertension (adjusted OR 7.17, 95% CI, 1.48 to 34.8) and BMI >30 kg/m^2 (adjusted OR 3.02, 95% CI, 1.16 to 7.86).

Conclusion. There were similar clinical and biochemical parameters of metabolic syndrome in both age groups. The proportions of children with metabolic syndrome were similar regardless of age group. The overall prevalence rate of metabolic syndrome was 27.3%. In view of the alarming presence of components of metabolic syndrome even in children less than 10 years of age, efforts aimed at the prevention of childhood obesity in the community should be intensified.

Key words: obesity, metabolic syndrome, children, pediatric

INTRODUCTION

The World Health Organization (WHO) estimates that 41 million children under 5 years old worldwide are obese, with 48% dwelling in Asia.[1] The numbers are rapidly increasing even in developing countries, especially in urban areas. In Malaysia, the National Health and Morbidity Survey (NHMS) showed an alarming surge in the proportion of children less than 18 years who are obese from 3.9% (0.3 million) in 2011 to 11.9% (1 million) in 2015.[2] Without prompt intervention, childhood obesity will continue into adulthood, leading to the development of complications which increase morbidity and mortality, reduce life expectancy and impair quality of life.[1-3] Metabolic syndrome is a constellation of metabolic derangements consisting of abdominal obesity, dyslipidemia, hypertension and raised plasma glucose that significantly increases the risk of developing type 2 diabetes and premature atherosclerotic cardiovascular disease.[4,5] The prevalence of pediatric metabolic syndrome is also increasing in obese adolescents, with rates as high as 28.7% in the United States National Health and Nutrition Examination Survey 1988-1994.[3] A single unified definition for pediatric metabolic syndrome was adopted only in 2007 based on the International Diabetes Federation Consensus Definition.[6] Early recognition is vital to enable prompt institution of early childhood lifestyle intervention and to prevent progression and development of complications.[6,7] When similar criteria were applied to a wider age group of children aged 4 to 20 years, the prevalence of metabolic syndrome in the study population was 38.7% in moderately obese children (BMI >95th percentile), compared to 49.7% in severely obese (BMI >98th percentile).[8] An increase in the individual components of metabolic syndrome, particularly high plasma glucose, triglycerides and systolic blood pressure, and low HDL, were found together with increasing BMI. It can be surmised that the prevalence of metabolic

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syndrome increased with increasing obesity, and was higher in obese compared to overweight subjects. A thorough history and clinical examination to locate clues for the identification of children at risk of developing metabolic complications of childhood obesity stemming from insulin resistance is essential. This includes assessment of visceral adiposity in view of its association with increased metabolic risk. Clinicians are reminded to maintain a high index of suspicion for clinically silent conditions, such as impaired glucose tolerance and non-alcoholic fatty liver disease, which may be present in this group of high risk children.[9]

Several researchers have investigated the prevalence of metabolic syndrome in the pediatric population in Malaysia. In a 2010 study on 78 schoolchildren aged 8 to 10 years old in Kuala Lumpur, 17.9% of participants were found to be obese, of which 2.9% were assessed to have the metabolic syndrome based on IDF criteria.[10] The relatively low prevalence of metabolic syndrome even in obese subjects in comparison to foreign studies was attributed to the high cut-off values used by the IDF criteria. Upon analysis of normal weight children, 9.1% had one unspecified risk factor for metabolic syndrome.[10] The study was limited by the lack of local population-specific waist circumference percentile charts at the time it was carried out, and the relatively narrow age range of participants.

In a similar study, Wee and colleagues examined 402 participants aged 9 to 12 years in Kuala Lumpur for the risk factors of metabolic syndrome. The prevalence of overweight/obesity was 5.3%, of which 5.3% had metabolic syndrome by IDF 2005 criteria.[11] At least one risk factor for metabolic syndrome was identified in 88% of obese participants, compared to 14% in those with normal weight. Comparison between overweight and obese subjects was not carried out in this study. The prevalence of metabolic syndrome was determined only in overweight/obese participants. This study was also unable to refer to age- and gender-specific local waist circumference standards. The authors attributed the lack of association between age, gender and ethnicity with metabolic syndrome to the small sample size.[11]

A recent study conducted in 2014 on 1,014 schoolchildren found that 16% were overweight and 9.4% were obese. The prevalence of metabolic syndrome by IDF criteria was 2.6% in the general study population, and 10% in the overweight/obese participants. The risk factors for metabolic syndrome were predominantly clustered in the overweight/obese group, compared to the normal weight subjects.[12] The study was limited by the inclusion of children aged 13 years old only. A comparison of risk factors between overweight and obese children was also not included.

Body mass index is a less sensitive indicator of abdominal adiposity in comparison with waist circumference, as it does not account for body fat distribution. Children with lower BMI but with greater waist circumference are at higher risk of having metabolic syndrome compared to those with higher BMI but lower waist circumference. This study aims to compare the clinical and biochemical profile of metabolic syndrome in obese children less than and more than 10 years of age attending Paediatric clinic HUSM. The cut-off point of age 10 years was chosen as it is the average age of onset of puberty in both sexes in lieu of formal pubertal assessment in the form of Tanner staging.[13,14] Puberty is associated with increased insulin resistance, which is the primary pathophysiologic mechanism for the development of metabolic syndrome. Therefore, it is hoped that this study will be able to demonstrate if there is any significant difference in the outcomes which predict predisposition to metabolic syndrome between these two groups of obese children.

METHODOLOGY

Study Procedure

Patients under 18 years old who had previously been followed up at Paediatric clinic HUSM for overweight or obesity over a 10-year period from 2006 to 2015 were identified with the assistance of the HUSM record office. Clinical records were reviewed to obtain the demographic, anthropometric, clinical and biochemical parameters. Subjects who did not fulfill the inclusion criteria and those with incomplete data were excluded.

Inclusion and Exclusion Criteria

Children less than 18 years old on Paediatric clinic HUSM follow up for obesity (BMI >95th percentile for age and sex based on CDC growth charts) between 2006 to 2015 were included. Patients with underlying history of medication use or with conditions affecting body fat composition/ distribution, such as Cushing's syndrome, hypothyroidism and Prader-Willi syndrome, were excluded. Children on medications that may alter blood glucose, lipid metabolism or blood pressure were also not included.

Statistical Analysis

Data analysis was performed using SPSS (IBM) version 22. Descriptive statistics were used to summarize the socio-demographic characteristics of subjects. Numerical data were presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (percentage). Means were compared with either independent T-test or Mann-Whitney depending on data distribution. For association between age and clinical/biochemical parameters, Chi-square test was used followed by multivariable analysis with logistic regression. Spearman rank was used to determine any relationship between two numerical variables as the data was not normally distributed.

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Operational Definitions

1. Overweight: BMI >85th percentile and <95th percentile for age and sex according to Centers for Disease Control and Prevention (CDC) growth chart
2. Obesity: BMI at or >95th percentile for age and sex according to CDC growth chart
3. Hypertension: SBP >130 mmHg and/or DBP >85 mmHg
4. Diabetes: FPG >6.9 mmol/L or random plasma glucose >11.1 mmol/L
5. Impaired glucose tolerance: plasma glucose level 2 hours after a 1.75 g/kg (maximum 75 g) oral glucose challenge 7.77 to 11.1 mmol/L
6. Impaired fasting glucose: FPG 5.6 to 6.9 mmol/L
7. Abdominal obesity: waist circumference (WC) >90th percentile
8. Metabolic syndrome: abdominal obesity with 2 or more of the following:
   Serum TG >1.7 mmol/L
   HDL <1.03 mmol/L
   SBP >130 mmHg or DBP >85 mmHg
   FPG >5.6 mmol/L

Ethical Approval

The study was approved by the Human Research Ethics Committee (HREC) USM (JEPeM code: USM/JEPeM/16040165).

RESULTS

A total of 101 subjects with follow up at Paediatric clinic HUSM for obesity from 2006 to 2015 were identified. Only 84 of the patient records retrieved were eligible for the study. The subjects were divided into 2 groups: group 1 consisted of obese children below 10 years of age, while group 2 included those 10 years and older. The demographic characteristics of both groups are illustrated in Table 1.

Majority of the 84 available subjects were boys, accounting for 68.2% and 62.8%, respectively. The overall mean age was 9.7 years. An almost equal number of children below 10 years, in comparison with those 10 years or more, had already been brought to medical attention for obesity. The proportions of children with metabolic syndrome were comparable between groups 1 and 2 (26.8% and 27.9%, respectively). There were no significant differences in terms the individual parameters of metabolic syndrome between groups 1 and 2 in terms of DBP (p=0.477), TC (p=0.082), HDL-C (p=0.475), LDL-C (p=0.163) and FPG (p=0.118). Group 2 subjects had significantly higher BMI, waist circumference, SBP and TG (Table 1).

Univariate analysis showed 3 clinical and 2 biochemical factors significantly associated with age group, with higher values in older obese patients ≥10 years old. These

Table 1. Demographic, clinical and biochemical characteristics by age group[a]

Variable	Overall	<10 years old	≥10 years old	*p*-value[b]
Gender				
Male	55 (65.5)	28 (68.2)	27 (62.8)	
Female	29 (34.5)	13 (31.7)	16 (37.2)	
Age, yr	9.7 (3.36)	6.9 (2.28)	12.4 (1.51)	
Metabolic syndrome	23 (27.4)	11 (26.8)	12 (27.9)	
Birth weight, kg	3.11 (0.75)	3.05 (0.72)	3.17 (0.8)	0.519
BMI, kg/m^2	32.44 (7.0)	30.3 (6.70)	34.48 (6.74)	<0.01
Waist circumference, cm	98.12 (18.08)	104.8 (19.24)	98.12 (18.08)	<0.01
SBP, mmHg	113.66 (19.20)	107.08 (19.79)	119.93 (16.53)	<0.01
DBP, mmHg	75.94 (11.59)	75.0 (12.44)	76.84 (10.78)	0.477
TC, mmol/L	4.91 (1.55)	4.61 (1.03)	5.21 (1.9)	0.082
TG, mmol/L	1.49 (0.74)	1.32 (0.61)	1.66 (0.82)	0.037
HDL-C, mmol/L	1.12 (0.37)	1.16 (0.46)	1.09 (0.26)	0.475
LDL, mmol/L	3.14 (1.5)	2.88 (0.89)	3.39 (1.88)	0.163
FPG, mmol/L	4.95 (1.8)	4.63 (0.69)	5.25 (2.39)	0.118

[a]Data expressed as mean (±SD) or n (%)
[b]Independent T-test

Table 2. Univariate analysis of age group and clinical characteristics[a]

Variable	Overall	<10 years old	≥10 years old	x^2 (df)	*p*-value[b]
Gender				0.67 (1)	0.412
Male	55 (65.5)	28 (68.2)	29 (52.7)		
Female	29 (34.5)	11 (37.9)	18 (62.1)		
SBP, mmHg				9.01 (1)	0.003
>130	17 (20.2)	2 (11.8)	15 (88.2)		
≤130	67 (79.7)	35 (52.2)	32 (47.8)		
DBP, mmHg				0.23 (1)	0.627
>85	25 (29.8)	10 (40.0)	15 (60.0)		
≤85	59 (70.2)	27 (45.8)	32 (54.2)		
BP				5.08 (1)	0.024
>130/85	6 (7.14)	0 (0)	6 (100.0)		
≤130/85	78 (92.9)	37 (47.4)	41 (52.6)		
BMI, kg/m^2				7.27 (1)	0.007
>30	50 (59.5)	16 (32.0)	34 (68.0)		
≤30	34 (40.5)	21 (61.8)	13 (38.2)		
Metabolic syndrome				1.36 (1)	0.244
Present	26 (30.9)	9 (34.6)	17 (65.4)		
Absent	58 (69.0)	28 (48.3)	30 (51.7)		

[a]Data expressed as n (%)
[b]Chi-square test

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Table 3. Univariate analysis age group and biochemical characteristics[a]

Variable	Overall	<10 years old	≥10 years old	x^2 (df)	*p*-value[b]
Total cholesterol, mmol/L				3.73 (1)	0.05
<5.0	54 (64.3)	28 (51.9)	26 (48.1)		
≥5.0	30 (35.7)	9 (30.0)	21 (70.0)		
Triglyceride, mmol/L				3.01 (1)	0.08
≤1.7	60 (71.4)	30 (50.0)	30 (50.0)		
>1.7	24 (28.6)	7 (29.2)	17 (70.8)		
HDL-C, mmol/L				0.645 (1)	0.422
≥1.03	33 (47.8)	16 (48.5)	17 (51.5)		
<1.03	36 (52.2)	14 (38.9)	22 (61.1)		
LDL-C, mmol/L				1.15 (1)	0.283
<3.0	30 (46.9)	11 (36.7)	19 (63.3)		
≥3.0	34 (53.1)	17 (50.0)	17 (50.0)		
FBS, mmol/L				0.001 (1)	0.977
≤5.6	76 (91.6)	33 (43.4)	43 (56.6)		
>5.6	7 (8.4)	3 (42.9)	4 (57.1)		

[a]Data expressed as n (%)
[b]Chi-square test

Table 4. Multivariate analysis of clinical and biochemical parameters of metabolic syndrome associated with age group

Variable	Crude OR (95% CI)	95% CI	Wald stat (df)	*p*-value
Waist circumference		0.67, 4.59	1.34 (1)	0.246
<95th percentile	1.0			
>95th percentile	1.76			
BMI, kg/m^2		1.37, 8.54	7.03 (1)	0.008
≤30	1.0			
>30	3.43			
Systolic hypertension		1.74, 38.7	7.07 (1)	0.008
Absent	1.0			
Present	8.2			
Diastolic hypertension		0.48, 3.27	0.23 (1)	0.627
Absent	1.0			
Present	1.27			
Total cholesterol, mmol/L		0.97, 6.47	3.64 (1)	0.05
<5.0	1.0			
≥5.0	2.51			
Triglyceride, mmol/L		0.88, 6.70	2.93 (1)	0.08
≤1.7	1.0			
>1.7	2.43			
FBS, mmol/L		(0.22, 5.03)	0.004 (1)	0.947
≤5.6	1.0			
>5.6	1.05			

Table 5. Clinical and biochemical parameters of metabolic syndrome associated with age group from the final model

Variable	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Wald stat (df)[b]	*p*-value[b]
Systolic hypertension			5.97 (1)	0.015
Absent	1.0			
Present	8.2 (1.74, 38.7)	7.17 (1.48, 34.8)		
BMI, kg/m^2			5.15 (1)	0.023
≤30	1.0			
>30	3.43 (1.37, 8.54)	3.02 (1.16. 7.86)		

[a]Simple logistic regression
[b]Multiple logistic regression

were SBP >130 mmHg (p=0.003), BP >130/85 (p=0.024), BMI >30 kg/m^2 (p=0.007), TC ≥5.0 mmol/L (p=0.05) and TG >1.7 mmol/L (p=0.08) (Tables 2 and 3). Multivariate analysis (simple logistic regression) revealed that significant clinical and biochemical parameters of metabolic syndrome associated with age ≥10 years old were BMI >30 kg/m^2 (OR 3.43, 95% CI, 1.37 to 8.54), systolic hypertension (OR 8.20, 95% CI, 1.74 to 38.7) and TC ≥5.0 mmol/L (OR 2.51, 95% CI, 0.97 to 6.47) (Table 4). However, analysis of the final model (multiple logistic regression) showed that only systolic hypertension (adjusted OR 7.17, 95% CI, 1.48 to 34.8) and BMI >30 kg/m^2 (adjusted OR 3.02, 95% CI, 1.16 to 7.86) were significant (Table 5).

To determine the correlation of factors associated with metabolic syndrome and age groups, Spearman's rank correlation was selected in view of the data's non-normal distribution (coefficient of variation >10%). The test demonstrated a significant positive correlation between age group and BMI [rho (ρ)=0.379, p<0.01], SBP (ρ=0.432, p<0.01) and waist circumference (ρ=0.416, p=0.002). There was no significant correlation between age group and DBP (ρ= 0.216, p=0.051), TG (ρ=0.161, p=0.145), HDL (ρ=-0.059, p=0.633) or FPG (ρ=0.095, p=0.392).

DISCUSSION

The proportions of obese younger children (<10 years old) compared to older subjects (≥10 years old) were almost equal (48.9% and 51.1%, respectively). Comparison of characteristics showed similar clinical and biochemical parameters of metabolic syndrome in both age groups, with the exception of BMI, waist circumference, SBP and TG. These were further supported by positive correlation

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coefficients (ρ) between age group and BMI, systolic hypertension and waist circumference. These findings may possibly be explained by the inclusion criteria specifying BMI consistent with morbid obesity (>30 kg/m^2). The higher the BMI, the more likely for comorbidities and complications associated with obesity to occur, regardless of age. Both groups had similar proportions of parameters associated with metabolic syndrome, which would explain the observed similar proportions of metabolic syndrome (Table 1).

Both chi-square and regression analyses showed that older subjects ≥10 years old had higher BMI (>30 kg/m^2), systolic hypertension and higher TC. However, only clinical parameters (BMI >30 kg/m^2 and systolic hypertension) were found to be significant in the final model of logistic regression analysis. Older subjects were 7 times more likely to have systolic hypertension than younger subjects, and 3 times more likely to have BMI >30 kg/m^2. These may be explained by the ensuing insulin resistance syndrome associated with physiologic elevations in sex hormones during puberty and visceral adiposity as observed in the older age group. Sex hormones work synergistically with growth hormone during puberty to contribute to pubertal growth spurt and to a physiologic phase of insulin resistance syndrome.[15] Visceral adiposity is a known risk for insulin resistance syndrome due to direct flux of fatty acids into the portal vein, which impairs insulin cascade signaling. Physiologic mechanisms associated with hypertension due to insulin resistance syndrome include sodium and water retention, systemic vasoconstriction and sympathetic stimulation.[16]

Similar studies by the groups of Atabek and Sangun in Turkey reported a significant difference in the proportion of obese prepubertal compared to pubertal children with metabolic syndrome (20% versus 37.6% and 33.1% versus 46.6%, p<0.001, respectively).[17,18] In contrast, we found the proportions of obese children with metabolic syndrome in both age groups were not significantly different (χ^2=0.012, p=0.091)(Table 2). On the other hand, our findings were also corroborated by the group of Rodrigues who found no statistically significant difference in the prevalence of metabolic syndrome between children (47.2 to 51.9%) and adolescents (48.1 to 52.8%).[19]

Metabolic syndrome was seen in 27.4% in the overall study population based on the IDF criteria. This is consistent with the findings of other studies that reported prevalence rates of metabolic syndrome ranging from 26.9 to 38.6% among obese children and adolescents, despite varied diagnostic criteria.[20,21] Compared to other criteria which employed percentile values, the IDF diagnostic criteria for metabolic syndrome set higher cutoff values. A comparison of 3 diagnostic criteria for metabolic syndrome done by Sangun et al reported similar proportions of metabolic syndrome (31 to 39%) among obese children and adolescents.[18] Similarly, a systematic review by Friend et al also observed a median prevalence rate of 29.2% of metabolic syndrome among obese children.[22] On the other hand, a local study by the group of Quah, which utilized the IDF classification for metabolic syndrome, reported a prevalence rate of only 2.9% among their 34 obese patients.[10] Other local authors also reported relatively low proportions of metabolic syndrome (11.9% and 5.3% respectively) among their obese participants.[11,12] On analysis, the number of obese children included by the group of Quah was relatively small, while the study by Fadzlina focused exclusively on 13-year old patients.[10,12] Additionally, the observed differences in our prevalence rates of metabolic syndrome compared to those by the groups of Quah and Fadzlina could be due to different environmental characteristics: patients referred to our hospital-based study (USM) came from diverse backgrounds, including those from rural areas, in contrast to their studies which were conducted in an urban center (Kuala Lumpur).

There was no statistically significant difference in the proportion of obese children with metabolic syndrome by gender (χ^2=0.28, p=0.596)(Table 2). However, there was a higher proportion of obese girls diagnosed with metabolic syndrome in comparison to obese boys (37.9 and 27.2%, respectively). A previous study by Ferreira et al also showed a significantly higher proportion of adolescent girls with metabolic syndrome (χ^2=3.88, p= 0.049)(Table 2), which the authors attributed to the earlier age of onset of puberty and the associated physiologic reduction in insulin sensitivity in girls.[23,24]

It is noteworthy that almost half of the obese children in our study were less than 10 years of age (n=41, 48.8%). The detection of risk factors of metabolic syndrome even in prepubertal (<10 years old) children is especially alarming, as it is anticipated that puberty, with its attendant increase in insulin resistance will increase the predisposition of these already at-risk children for the development of metabolic syndrome.[8] Early identification of these at-risk children by primary healthcare providers and prompt referral for early intervention may prevent the dire consequences of this burgeoning public health problem.[25]

The IDF criteria for the diagnosis of metabolic syndrome was utilized in our study as the diagnostic methods were readily available and fairly cost effective. While BMI is a relatively sensitive and specific measure of childhood obesity, it is less suited for the assessment of visceral adiposity.[26,27] On the other hand, waist circumference is an acceptable measurement for the inference of visceral adiposity, as well as a surrogate for insulin resistance.[15] Obese children with similar BMI for age and sex may not necessarily have the same risk of developing obesity-related metabolic comorbidities or metabolic syndrome due to differences in body fat distribution and its consequent effects on the degree of insulin resistance.[28]

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While standardized reference charts for body mass index are readily available from the WHO and the CDC, there are no similar charts for waist circumference. Comparisons of different studies may be difficult, as each employ reference charts designed for a specific population. Waist circumference reference values for this study were derived from those prepared by Wee et al.[11]

The prevalence rate of metabolic syndrome among obese children in our population may be an underestimate due to the reliance of the IDF criteria on measurement of waist circumference, which is not assessed consistently during the review of records of children referred for obesity. We found that only 54 (64.3%) of our subjects had their waist circumference recorded. The primary drawback of the retrospective nature of this study is the incomplete data from the available patient records, as only 84 of the 101 obese children identified from hospital records were available. Furthermore, complete data was not available in all the 84 identified patient records. Patient history and measurement of various clinical parameters may also not be as uniform as possible, as these were performed by different individuals over a wide range of time. Potentially relevant information, such as breastfeeding practices in infancy, duration of exercise and screen time, was not regularly documented. As the majority of sampled patients are Malay, conclusions derived from this study may not be applicable to other ethnic groups. Ideally, pubertal staging of the subjects should also be included in this study to properly stratify subjects into pre-pubertal and pubertal age groups. It was also not possible to track any progressive increase in the incidence of metabolic syndrome over the years in our study.

CONCLUSION

The clinical and biochemical parameters of metabolic syndrome were similar between those <10 years old and ≥10 years old, with the exception of BMI, waist circumference, systolic hypertension and TG level. The clinical parameters that were found to be significantly associated with age ≥10 years were BMI >30 kg/m^2 and systolic hypertension. The prevalence rate of metabolic syndrome among obese children attending Paediatric clinic in Hospital Universiti Sains Malaysia was 27.3%, which was found to be comparable to findings from other studies conducted in developed countries. The alarming presence of components of metabolic syndrome even in children less than 10 years of age should serve as an impetus for intensifying efforts aimed at prevention of childhood obesity in the community.

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

Author Disclosure
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References

1. World Health Organization. Report of the Commission on Ending Childhood Obesity. Geneva, Switzerland: World Health Organization, 2016. http://apps.who.int/iris/bitstream/10665/204176/1/9789241510066_eng.pdf?ua=1.
2. Institute for Public Health, Ministry of Health Malaysia. National Health and Morbidity Survey (NHMS) 2015 Fact Sheet. http://www.iku.gov.my/images/IKU/Document/REPORT/NHMS2015-FactSheet.pdf.
3. Cook S, Weitzman M, Auinger P, Nguyen M, Dietz WH. Prevalence of a metabolic syndrome phenotype in adolescents: findings from the third National Health and Nutrition Examination Survey, 1988-1994. Arch Pediatr Adolesc Med. 2003;157(8):821-7. PMID: 12912790. https://doi.org/10.1001/archpedi.157.8.821.
4. Guo SS, Wu W, Chumlea WC, Roche AF. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. Am J Clin Nutr. 2002;76(3):653-8. PMID: 12198014.
5. Whitaker RC, Wright JA, Pepe MS, Seidel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med. 1997;337(13):869-73. PMID: 9302300. https://doi.org/10.1056/NEJM199709253371301.
6. Zimmet P, Alberti KG, Kaufman F, et al; IDF Consensus Group. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr Diabetes. 2007;8(5):299-306. PMID: 17850473. https://doi.org/10.1111/j.1399-5448.2007.00271.x.
7. Silveira LS, Buonani C, Monteiro PA, Mello Antunes BM, Freitas Júnior IF. Metabolic syndrome: criteria for diagnosing in children and adolescents. Endocrinol Metab Synd. 2013;2:118. https://doi.org/10.4172/2161-1017.1000118.
8. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. N Engl J Med. 2004;350(23):2362-74. PMID: 15175438. https://doi.org/10.1056/NEJMoa031049.
9. Weiss R, Kaufman FR. Metabolic complications of childhood obesity: Identifying and mitigating the risk. Diabetes Care. 2008;31(Suppl 2):S310-6. PMID: 18227502. https://doi.org/10.2337/dc08-s273.
10. Quah YV, Poh BK, Ismail MN. Metabolic syndrome based on IDF criteria in a sample of normal weight and obese school children. Mal J Nutr. 2010;16(2):207-17. http://nutriweb.org.my/publications/mjn0016_2/PohBK%20207-217.pdf.
11. Wee BS, Poh BK, Bulgiba A, Ismail MN, Ruzita AT, Hills AP. Risk of metabolic syndrome among children living in metropolitan Kuala Lumpur: a case control study. BMC Public Health. 2011;11:333. PMID: 21592367. PMCID: PMC3111384. https://doi.org/10.1186/1471-2458-11-333.
12. Fadzlina AA, Harun F, Nurul Haniza MY, et al. Metabolic syndrome among 13 year old adolescents: prevalence and risk factors. BMC Public Health. 2014;14(Suppl 3):S7. PMID: 25437226. PMCID: PMC4251137. https://doi.org/10.1186/1471-2458-14-S3-S7.
13. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291-303. PMID: 5785179. PMCID: PMC2020314.
14. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45(239):13-23. PMID: 5440182. PMCID: PMC2020414.
15. Chiarelli F, Marcovecchio ML. Insulin resistance and obesity in childhood. Eur J Endocrinol. 2008;159(Suppl 1):S67-74. PMID: 18805916. https://doi.org/10.1530/EJE-08-0245.
16. Sorof J, Daniels S. Obesity hypertension in children: a problem of epidemic proportions. Hypertension. 2002;40(4):441-7. PMID: 12364344.
17. Atabek ME, Pirgon O, Kurtoglu S. Prevalence of metabolic syndrome in obese Turkish children and adolescents. Diabetes Res Clin Pract. 2006;72(3):315-21. PMID: 16325296. https://doi.org/10.1016/j.diabres.2005.10.021.
18. Sangun Ö, Dündar B, Köşker M, Pirgon Ö, Dündar N. Prevalence of metabolic syndrome in obese children and adolescents using three different criteria and evaluation of risk factors. J Clin Res Pediatr Endocrinol. 2011;3(2):70-6. PMID: 21750635. PMCID: PMC3119444. https://doi.org/ 10.4274/jcrpe.v3i2.15.
19. Rodrigues LG, Mattos AP, Koifman S. Prevalence of metabolic syndrome in overweight and obese outpatient children and adolescents: comparative analysis using different clinical definitions. Rev Paul Pediatr. 2011;29(2):178-85.
20. de Ferranti SD, Gauvreau K, Ludwig DS, Neufeld EJ, Newburger JW, Rifai N. Prevalence of the metabolic syndrome in American

ONLINE FIRST | October 14, 2017 | https://doi.org/10.15605/jafes.032.02.06

adolescents: findings from the Third National Health and Nutrition Examination Survey. Circulation. 2004;110(16):2494-7. PMID: 15477412. https://doi.org/10.1161/01.CIR.0000145117.40114.C7.

21. Rashidi H, Payami SP, Latifi SM, et al. Prevalence of metabolic syndrome and its correlated factors among children and adolescents of Ahvaz aged 10 - 19. J Diabetes Metab Disord. 2014;13:53. PMID: 24860794. PMCID: PMC4031928. https://doi.org/10.1186/2251-6581-13-53.
22. Friend A, Craig L, Turner S. The prevalence of metabolic syndrome in children: a systematic review of the literature. Metab Syndr Relat Disord. 2013;11(2):71-80. PMID: 23249214. https://doi.org/10.1089/met.2012.0122.
23. Ferreira AP, Nóbrega Ode T, França NM. Association of body mass index and insulin resistance with metabolic syndrome in Brazilian children. Arq Bras Cardiol. 2009;93(2):147-53. PMID: 19838492.
24. Goran MI. Measurement issues related to studies of childhood obesity: assessment of body composition, body fat distribution, physical activity, and food intake. Pediatrics. 1998;101(3 Pt 2):505-18. PMID: 12224657.
25. Siwik V, Kutob R, Ritenbaugh C, et al. Intervention in overweight children improves body mass index (BMI) and physical activity. J Am Board Fam Med. 2013;26(2):126-37. PMID: 23471926. PMCID: PMC4010584. https://doi.org/10.3122/jabfm.2013.02.120118.
26. Reilly JJ, Dorosty AR, Emmett PM, Avon Longitudinal Study of Pregnancy and Childhood Study Team. Identification of the obese child: adequacy of the body mass index for clinical practice and epidemiology. Int J Obes Relat Metab Disord. 2000;24(12):1623-7. PMID: 11126215.
27. Mei Z, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI, Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. Am J Clin Nutr. 2002;75(6):978-85. PMID: 12036802.
28. Bacha F, Saad R, Gungor N, Arslanian SA. Are obesity-related metabolic risk factors modulated by the degree of insulin resistance in adolescents? Diabetes Care. 2006;29(7):1599-604. PMID: 16801585. https://doi.org/10.2337/dc06-0581.

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ORIGINAL ARTICLE

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Differences in the Insulin Resistance Levels Measured by HOMA-IR between Patients with Erosive and Non-Erosive Gastroesophageal Reflux Disease

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Abstract

Background. Insulin resistance is the core of Metabolic Syndrome which carries a high risk for cardiovascular events. Insulin resistance had been reported to be higher in GERD patients than subjects without GERD, specifically in erosive esophagitis. Objective. To compare the degree of insulin resistance, using HOMA-IR index, between erosive and non-erosive reflux disease.

Methodology. A cross-sectional study of 84 adult patients with GERD symptoms was conducted. The subjects were recruited consecutively between January 2017 and April 2017 at Cipto Mangunkusumo National Hospital in Jakarta. Gastroesophageal Reflux Disease Questionnaire (GERDQ) was used for subject recruitment. Homeostatic model assessment-insulin resistance (HOMA-IR) index was used to evaluate insulin sensitivity. Esophageal erosions were diagnosed using upper gastrointestinal endoscopy. Bivariate analysis was used to determine HOMA-IR difference between esophagitis and non-esophagitis group.

Results. The median of HOMA-IR in all subjects was 1.46 (0.32-13.85). Mann-Whitney test revealed that HOMA-IR index was higher in patients with erosive esophagitis [median 1.74 (0.35-13.85)] than those without erosive esophagitis [median 1.21 (0.32-10.78)] (p=0.05).

Conclusion. Insulin resistance is significantly higher in gastroesophageal reflux disease patients with esophageal erosions than in those without esophageal erosion.

Key words: insulin resistance, erosive esophagitis, esophageal erosion, HOMA-IR

INTRODUCTION

Insulin resistance is the disturbance of insulin action that needs higher levels to reach normal physiologic effects in regulating glucose.[1] In clinical context, insulin resistance may manifest as interrelated symptoms such as obesity, dyslipidemia, and hyperglycemia, which carry a high risk of cardiovascular events, called Metabolic Syndrome.[2] The prevalence of metabolic syndrome is increasing and has become a public health issue. According to National Health Survey of 2013, the proportion of high triglyceride, low HDL, and hypertension were 13%, 22.9% and 28.6%, respectively.[3] Another survey in Jakarta revealed that the prevalence of metabolic syndrome in 2006 had reached 28.6%.[4]

Aside from cardiovascular events, insulin resistance is also associated with other conditions such as polycystic ovary syndrome, non-alcoholic fatty liver disease, and gastroesophageal reflux disease (GERD).[1] Gastroesophageal reflux disease is a common finding in daily practice. The prevalence of GERD in Jakarta in 2002 was 25.15%.[5] This condition has a wide clinical spectrum from mild to severe that can be related to a low quality of life.[6,7]

There were several studies conducted to learn the association between GERD and insulin resistance. Pointer et al., showed that insulin resistance was significantly higher in obese women with GERD than in non-GERD subjects.[8] Insulin resistance was also reported to be higher in erosive esophagitis than those without erosive

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esophagitis in obese subjects in South Korea.[9] Another study in Japan failed to show an association between insulin resistance and the severity of GERD.[10]

The high prevalence of the metabolic syndrome and its components in Indonesia has urged us to identify factors related to the pathogenesis, which is insulin resistance. Insulin resistance has been shown to be higher in GERD patients, particularly in those with erosive esophagitis. Nevertheless, data regarding insulin resistance in this population is scarce. Racial and lifestyle differences from previous studies emphasize the need to conduct the study in our country.

A cross-sectional study was conducted from January, 2017 to April, 2017 in the gastroenterology outpatient clinic of Cipto Mangunkusumo Hospital, Jakarta. This is a tertiary national referral hospital with a capacity of 900 beds. The general objective of this study was to analyze the difference of insulin resistance between erosive and non-erosive reflux disease in patients with GERD. The specific objective of this study was to compare the clinical characteristic associated with metabolic syndrome in patients with erosive esophagitis and without erosive esophagitis, to obtain the HOMA-IR index of patients with GERD, and the difference of HOMA-IR index between each group. It is hypothesized that insulin resistance, measured by HOMA-IR index, is higher in subjects with erosive esophagitis than in those without erosive esophagitis. This study was approved by the ethical board of Faculty of Medicine Universitas Indonesia (No: 982/UN2.F1/ETIK/2016).

METHODOLOGY

Subjects

A minimum number of 82 subjects is needed to obtain the HOMA-IR index using the sample size formula for numerical descriptive data, $n = \left(\frac{Z\alpha\, S}{d}\right)^2$, ($Z\alpha$=1.64, d= 0.2, S=1.1) A minimum of 36 subjects in each group is needed to determine the difference in HOMA IR index between non-erosive reflux disease and erosive reflux disease which was calculated using the unpaired categoric-numeric analysis formula, $n1 = n2 = 2\left[\frac{(Z\alpha+Z\beta)S}{X1-X2}\right]^2$, ($Z\alpha$=1.64, β=80%, Zβ=0.84, S=1.7, X1-X2=0.7)

The subjects with GERD were consecutively recruited using GERD-Q score greater than or equal to 8. The inclusion criteria were as follows: age greater than or equal to 18 years old, no intake of proton-pump inhibitor (PPI), or H2 receptor antagonist (H2RA), or had been off the drugs for at least two weeks. Subjects who were pregnant, had DM type 1, or other esophageal abnormalities such as malignancy were excluded for this study.

Methodology

Subjects identified by GERD-Q score greater than 8 were asked for written consent for every procedure taken in this study. Subjects using PPI or H2RA treatment longer than 8 weeks were excluded. For subjects on PPI (omeprazole or lansoprazole) or H2RA (ranitidine, 2 doses daily) for greater than or equal to 4 weeks, the PPI and H2RA were discontinued and replaced with antacids for 2 weeks. Data consisting of age, sex, comorbidities, smoking status and alcohol drinking status were obtained from subjects with informed consent. Physical examination measurements obtained were seated blood pressure (after a 5-min rest using a calibrated sphygmomanometer, waist circumference (using flexible measuring tape above the upper iliac crests through the umbilicus), height and weight (using a calibrated scale). A venous blood sample was drawn to assess fasting glucose and fasting insulin (for assessing HOMA-IR), and lipid profile. All samples were analyzed in the Clinical Pathology Laboratory in Cipto Mangunkusumo Hospital. All subjects underwent esophagogastroduodenoscopy procedure in the Digestive Endoscopy Center/*Pusat Endoskopi Saluran Cerna* Cipto Mangunkusumo Hospital. The procedure was performed by qualified gastroenterology staff in the center. The results of endoscopy were further categorized as erosive esophagitis or non-erosive disease.

Statistical analysis

Statistical analysis was carried out using SPSS© version 17.0 for windows. Bivariate analysis using Mann-Whitney was performed to evaluate the association between esophageal erosion and insulin resistance for non-parametric data. P value <0.05 was considered statistically significant.

RESULTS

A total of 84 subjects who fulfilled the inclusion criteria were accounted for analysis in this study. The median of HOMA-IR index in this study population is 1.46 (0.32-13.85). Characteristics of the subjects can be seen in Table 1.

The age of subjects in this population ranged from 17 to 40 years old. Majority of the subjects were female. The mean BMI was 23.3 kg/m^2, which is categorized as overweight. A total of 33.3% of the subjects were obese. Most of the subjects had normal lipid profile and fasting blood glucose.

Most of the subjects had minor esophageal erosion seen from the upper endoscopy, with 34 subjects (40.5%) having esophagitis grade A, and 10 subjects (11.9%) having esophagitis grade B. A total of 36 subjects (42.9%) had non-erosive reflux disease.

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Table 1. Characteristics of the study subjects

Variable	Value (n= 84)
Age, median in years (min-max)	53 (18-76)
<40 (%)	19 (22)
≥40 (%)	65 (77.4)
Sex (female), n (%)	58 (69)
Habit	
Smoking (%)	5 (6)
Alcohol consumption (%)	1 (1.2)
Smoking and alcohol consumption (%)	3 (3.6)
Comorbidities (T2DM, Hypertension, Dyslipidemia)	
None (%)	50 (59.5)
1 comorbidity	24 (28.6)
≥2 comorbidities (%)	10 (11.9)
Body Mass Index, (kg/m^2), mean (SD)	23.3 (4.8)
Waist circumference (cm)	
Male, mean (SD)	86.4 (14.8)
Female, median (min-max)	84.5 (62-113)
Blood pressure	
Systolic Blood Pressure ≥140 and/or Diastolic Blood Pressure ≥90	24 (28.6)
Systolic Blood Pressure <140 and/or Diastolic Blood Pressure <90	60 (71.4)
Fasting blood glucose (mg/dL), median (min-max)	85.5 (68- 246)
Triglyceride, (mg/dL), median (min-max)	92.5 (40-494)
HDL, (mg/dL) median (min-max)	48 (23-95)
LDL, (mg/dL), mean (SD)	122.4 (34.4)
Total cholesterol (mg/dL), mean (SD)	184.3 (38.1)
HOMA-IR, median (min-max)	1.46 (0.32-13.85)
Endoscopic results, n (%)	
Non-erosive	36 (42.9)
Esophagitis grade A	34 (40.5)
Esophagitis grade B	10 (11.9)
Esophagitis grade C	3 (3.6)
Esophagitis grade D	1 (1.2)

Metabolic characteristics were categorized based on esophageal erosion to determine the difference in insulin resistance in each group. Comparison of the metabolic characteristics showed that fasting blood glucose (FBG), proportion of Type 2 DM (T2DM) and body mass index (BMI) were similar in each category. Other variables such as the proportion of hypertension, dyslipidemia, high triglyceride, high waist circumference, and low HDL were higher in subjects with esophageal erosion. There were significant differences in waist circumference and HDL level between erosive and non-erosive group. The comparison can be seen in Table 2.

The difference in HOMA-IR between erosive esophagitis and non-erosive disease can be seen in Table 3. Mann-Whitney test showed a significantly higher HOMA-IR index in subjects with esophageal erosion than in those without esophageal erosion (p=0.015). This result indicated a higher insulin resistance in these subjects.

DISCUSSION

Characteristics of subjects with GERD

Most of the subjects in this study were above 40 years old which is similar to several other studies which showed a tendency for patients with GERD to be above 40 years old.[11-15] Also, the higher prevalence of women in this population was similar to studies in Indonesia, Turkey, Albania, and Japan.[11-14] A study in Japan showed that older patients and women had higher psychologic stress scores than men and women tend to be older than men.[13] Nevertheless, the association between age or sex and GERD was still controversial. Some studies showed positive correlation; others showed no significant correlation.[11-14] This finding indicates that the subjects' characteristics depend on the demographic data of the population.

Table 2. Comparison of clinical and metabolic characteristics of subjects with GERD based on presence or absence of esophageal erosion

Variable	Without esophageal erosion (n=36)	With esophageal erosion (n=48)	p
Hypertension			
No (%)	28 (78.8)	28 (58.3)	0.061a
Yes (%)	8 (22.2)	20 (41.7)	
Type 2 DM			
No (%)	31 (86.1)	42 (87.5)	1.00b
Yes (%)	5 (13.9)	6 (12.5)	
Dyslipidemia			
No (%)	20 (55.6)	22 (45.8)	0.378a
Yes (%)	16 (44.4)	26 (54.2)	
Body mass index			
<25 kg/m^2 (%)	24 (66.7)	32 (66.7)	1.00a
≥25 kg/m^2 (%)	12 (33.3)	16 (33.3)	
Fasting blood glucose			
<100 mg/dL (%)	32 (88.9)	42 (87.5)	1.00b
≥100 mg/dL (%)	4 (11.1)	6 (12.5)	
Triglyceride			
<150 mg/dL (%)	29 (80.6)	36 (75)	0.547a
≥150 mg/dL (%)	7 (19.4)	12 (25)	
HDL (mg/dL)			
Male ≥40, female ≥ 50 (%)	26 (72.2)	23 (47.9)	0.025a
Male <40, female < 50 (%)	10 (27.8)	25 (52.1)	
Waist circumference (cm)			
Male <90, female < 80 (%)	20 (55.6)	15 (31.3)	0.025a
Male ≥90, female ≥80 (%)	16 (44.4)	33 (68.7)	

a: chi square

Table 3. Difference in HOMA-IR index in erosive and non-erosive reflux disease

	HOMA-IR Median (Min-Max)	p*
Without esophageal erosion (n= 36)	1.21 (0.32-10.78)	0.015
With esophageal erosion (n= 48)	1.74 (0.35-13.85)	

*Mann-whitney test

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The mean body mass index (BMI) in this study was 23.3 (SD 4.8) kg/m^2. This is similar to a study carried out among Indonesian medical doctors which showed that the mean BMI was 23.62 (SD 4.41) kg/m^2.[15] On the other hand, the study in Albania showed a higher mean BMI of 26.2 kg/m^2.[14] This difference may be due to racial or lifestyle difference of the study population.

A total of 36 subjects (42.9%) did not have esophageal erosion and the other 48 (47.1%) patients had esophageal erosion. A study in Taiwan showed a larger proportion of subjects with GERD as having non-erosive disease (82%).[16] A study in Egypt also revealed the proportion of non-erosive reflux disease (76%) to be higher than erosive esophagitis (24%).[17] One study in China showed that there was a rise in esophagitis rates from 20.7% to 51% among subjects with GERD, which was similar to the esophagitis proportion in this study.[18] This difference might be due to the difference in the questionnaire used to diagnose GERD, the smoking and alcohol drinking habit, or lifestyle. Nevertheless, the distribution of each Los Angeles (LA) grade esophagitis was similar to a study in South Korea.[9]

Most of the study subjects had normal fasting blood glucose and lipid profiles. According to a study in Egypt on patients with GERD, the level of triglyceride, total cholesterol and fasting blood glucose were higher than in this study.[19] Hsien et al., showed that the mean HDL and LDL were in the normal range, 53.6 (SD16.1) kg/m^2 and 125.5 (SD 33.3) mg/dL respectively and most of their study subjects had similar BMI with this study.[20] The similarity of the subjects' characteristics signified that the difference of study characteristics might be due to the racial and lifestyle differences of the population.

The index of HOMA-IR is a mathematical model to represent insulin resistance in one population. The HOMA-IR index in patients with GERD in Indonesia has not been studied before. The index is affected by race, age, and metabolic disturbances. This study revealed that the median HOMA-IR was 1.46 (0.32-13.85). This index was lower than those found in other studies in Indonesia among obese and non-alcoholic fatty liver disease, and the geriatric population, which were 3.92 (SD 2.09) and 2.87 (SD 8.08), respectively.[21,22] The difference was that the BMI and lipid profiles in those other studies were in the above normal range. This study involved subjects with relatively normal metabolic conditions as seen from the normal range of lipid profile and fasting blood glucose. Therefore, it is not surprising that the HOMA-IR index in this study was lower than those in other population. This finding was similar to the finding in a study in Iran which concluded that the cut-off for metabolic syndrome in a nondiabetic population was 1.77.[23] The study in Egypt showed the mean HOMA-IR index in subjects with GERD to be 2.86 (SD 2.189).[19] The higher HOMA-IR index in that study might be due to the higher BMI in that population, which was 2.8 (SD 6.5) kg/m^2.

Insulin resistance in erosive and non-erosive reflux disease in GERD patients

Insulin resistance in this study was calculated using HOMA-IR which had been validated with a good correlation with euglycemic clamp as the gold standard. Higher HOMA-IR index indicates higher insulin resistance. There is no cut-off in HOMA-IR that can be applied globally, because of the variance in each country and race.[24,25] Therefore, it is important to understand the range of insulin resistance index in different populations. Gayoso-Diz et al., revealed that there was a tendency for the cut-off for insulin resistance to be higher in western countries than in Asian countries. In that study, the highest cut-off for insulin resistance was in France (3.8), and the lowest cut-off was in Thailand (1.55).[24]

Mann Whitney analysis was performed to analyze comparative hypothesis of unpaired numeric variables with abnormal distribution. Through this analysis, the HOMA-IR index was significantly higher in esophageal erosive subjects compared with non-esophageal erosive subjects ($p=0.015$). There were several studies which had similar results. A study by Hsu et al., in Taiwan showed higher HOMA-IR in erosive esophagitis compared with non-erosive esophagus, which were 2.1 (SD 2.7) and 1.4 (SD1.4) respectively OR 1.19, 95% CI (1.08–1.30), $p <0.00$. In addition, the subjects in this study had similar BMI and age distributions.[16] A study in an obese population in China also showed a significantly higher HOMA-IR in erosive esophagitis compared with subjects without esophageal erosion.[26] A study by Park et al., in Korea, which had similar characteristics in BMI, age, blood pressure and fasting blood glucose with this study, also revealed a significantly higher HOMA-IR in subjects with erosive esophagitis, compared with subjects with non-erosive disease, which were 2.41(SD 1.10) and 2.18 (SD 0.89) respectively ($p <0.001$). In addition, this study stated that higher grade of esophagitis was associated with higher HOMA-IR index.[9] However, a study by Kamal et al., in a population with higher BMI and lipid profile level, revealed that the degree of esophagitis was not related to HOMA-IR.[19] A study in Japan also showed no association between the severity of GERD, measured by Frequency Scale for the Symptoms of GERD (FSSG) score, and insulin resistance.[10] The reliability of FSSG score was found to be lower than GERD-Q score to detect esophageal erosion.[27]

The association between erosive esophagitis and insulin resistance may involve inflammatory mechanisms which influence each other. The exposure of the esophagus to refluxate stimulates esophageal epithelial cells to secrete chemokines which later activate immune cellular mechanism to exacerbate cell injury. Acid reflux causes the formation of platelet activating factor (PAF) by the

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esophageal mucosa. This leads to the production of IL-6, H2O2, and IL-1beta that can reduce neurogenic muscle contraction by inhibiting acetylcholine release.[28] These proinflammatory cytokines are abundantly found in the esophageal mucosa and serum. A study in Japan revealed that IL-6 levels and IL-1beta levels were higher in reflux esophagitis compared with control.[29] Conditions that produce significant level of proinflammatory cytokines such as TNF α, IL-1, and IL-6, may cause insulin resistance.[30] Porwal et al., showed that there was a positive correlation between IL-6 and HOMA-IR.[31]

The prevalence of certain clinical metabolic characteristics based on the presence or absence of esophageal erosions can be seen in Table 2. Through the comparison, the proportion of hypertension, low HDL-cholesterol, high triglyceride, and high waist circumference were higher in subjects with esophageal erosion, with a distinctive difference in HDL and waist circumference. This finding was consistent with several previous studies. According to the studies carried out by Hsu et al., in Taiwan, and Park et al., in South Korea, there were higher proportion of metabolic profile abnormalities such as low HDL-cholesterol, high triglycerides, and high waist circumference in subjects with esophageal erosion.[9,16] Those conditions were components of metabolic syndrome and are signs of insulin resistance. These findings are in concordance to the results of this study, which revealed a higher HOMA-IR index in subjects with esophageal erosion.

The proportion of obesity based on BMI in subjects with and without esophageal erosion was equal. This finding was consistent with other study in non-alcoholic fatty liver disease population, which described that the severity of GERD was positively correlated with insulin resistance, but not with BMI.[33] Although the obesity proportion based on BMI was equal, there was a prominent difference of waist circumference between groups. Waist circumference is more sensitive than BMI in predicting insulin resistance. Body mass index is an indicator of over-all obesity. However, waist circumference is a measurement of central obesity that consists of visceral and subcutaneous fat. Fox et al., described that visceral fat correlates more with metabolic abnormalities compared with subcutaneous fat.[34] Other studies have shown that visceral fat is positively correlated to HOMA-IR index in the next 10 years. Visceral fat is associated with more potent lipolysis and produces inflammatory mediators that can cause insulin resistance.[35]

This is the first study to investigate insulin resistance in GERD patients in Indonesia. This study was designed to confirm findings from previous studies in other countries. This study showed that insulin resistance is higher in patients with erosive reflux disease. Therefore, patients with erosive reflux disease should have a thorough evaluation for clinical insulin resistance syndrome and the patients' management should target both diseases.

There are several limitations that warrant mention. The cross-sectional method used in this study was not able to determine the causal relationship between erosive esophagitis and insulin resistance. This study only aimed to compare the HOMA-IR index (insulin resistance) between non-erosive and erosive gastroesophageal reflux disease patients. Therefore, further studies with longitudinal design and paired controls are required to learn possible causal relationships between insulin resistance and esophageal erosion. In addition, the pathophysiology and interactions of other factors are complicated; therefore, further studies to evaluate these related factors are required. Lastly, the diagnosis of GERD in this study only used GERD-Q questionnaire which is not as good as using pH-metry for diagnosis.

CONCLUSION

In summary, our data demonstrate that subjects with esophageal erosion have higher insulin resistance as measured by HOMA-IR index, compared with subjects without esophageal erosion. This finding suggests an early detection of insulin resistance in patients with esophageal erosion.

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

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References

1. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005;26(2):19-39. PMCID: PMC1204764.
2. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009;2(5-6):231-7. PMID: 19407331. PMCID: PMC2675814. https://doi.org/10.1242/dmm.001180.
3. Badan Penelitian dan Pengembangan Kesehatan RI. Riset Kesehatan Dasar (Riskesdas). Jakarta, 2013.
4. Soewondo P, Purnamasari D, Oemardi M, Waspadji S, Soegondo S. Prevalence of metabolic syndrome using NCEP/ATP III criteria in Jakarta, Indonesia: The Jakarta primary non-communicable disease risk factors surveillance 2006. Acta Med Indones.2010;42(4):199-203. PMID: 21063040.
5. Indonesian Society of Gastroenterology. National consensus on the management of gastroesophageal reflux disease in Indonesia. Acta Med Indones. 2014;46(3):263-71. PMID: 25348191.
6. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. World J Gastrointest Pharmacol Ther. 2014;5(3):105-112. PMCID: PMC4133436. https://doi.org/10.4292/wjgpt.v5.i3.105.
7. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–28. PMID: 23419381. https://doi/org/10.1038/ajg.2012.444.

8. Pointer SD, Rickstrew J, Slaughter JC, Vaezi MF, Silver HJ. Dietary carbohydrate intake, insulin resistance and gastro-oesophageal reflux disease: A pilot study in European-and African-American obese women. Aliment Pharmacol Ther 2016;44(9):976–88. PMID: 27582035. PMCID: PMC5048546 [Available on 2017-11-01]. http://doi.org/10.1111/apt.13784.
9. Park JH, Park DI, Kim HJ, et al. Metabolic syndrome is associated with erosive esophagitis. World J Gastroenterol. 2008;14(35):5442-7. PMCID: PMC2744163. https://doi/org/10.3748/wjg.14.5442.
10. Fujiwara M, Eguchi Y, Fukumori N, et al. The symptoms of gastroesophageal reflux disease correlate with high body mass index, the aspartate aminotransferase/alanine aminotransferase ratio and insulin resistance in Japanese patients with non-alcoholic fatty liver disease. Intern Med. 2015;54(24):3099-104. PMID: 26666594. https://doi.org/10.2169/internalmedicine.54.4297.
11. Abdullah M, Makmun D, Syam AF, et al. Prevalence, risk factors and socio-epidemiological study of gastroesophageal reflux disease: An urban population based study in Indonesia. Asian J. Epidemiol. 2016;9(1-3):18-23. Available online: http://www.scialert.net/qredirect.php?doi=aje.2016.18.23&linkid=pdf.
12. Mungan Z. Prevalence and demographic determinants of gastroesophageal reflux disease (GERD) in the Turkish general population: A population-based cross-sectional study. Turk J Gastroenterol 2012;23(4):323-32. https://doi.org/10.4318/tjg.2012.0352.
13. Fujiwara Y, Arakawa T. Epidemiology and clinical characteristics of GERD in the Japanese population. J Gastroenterol. 2009;44(6):518-34. PMID: 19365600. https://doi.org/10.1007/s00535-009-0047-5.
14. Çela L, Kraja B, Hoti K, et al. Lifestyle characteristics and gastroesophageal reflux disease: A population-based study in Albania. Gastroenterol Res Pract. 2013;2013: 93672. PMCID: PMC3595718. https://doi.org/10.1155/2013/936792.
15. Syam AF, Hapsari PFC, Makmun D. The prevalence and risk factors of GERD among Indonesian medical doctors. Makara J Health Res. 2016;20(2):35-40. https://doi.org/ 10.7454/msk.v20i2.5740.
16. Hsu CS, Wang PC, Chen JH, et al. Increasing insulin resistance is associated with increased severity and prevalence of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011;34(8):994-1004. PMID: 21848629. https://doi.org/ 10.1111/j.1365-2036.2011.04817.x.
17. Gado AS, Ebeid BA, Abdelmohsen AM, Axon A. Prevalence of reflux esophagitis among patients undergoing endoscopy in a secondary referral hospital in Giza, Egypt. AJM. 2015;51(2):89-94. https://doi.org/10.1016/j.ajme.2013.09.002.
18. Jung HK. Epidemiology of gastroesophageal reflux disease in Asia: A systematic review. J Neurogastroenterol Motil. 2011;17(1):14-27. PMID: 21369488. PMCID: PMC3042214. https://doi.org/10.5056/jnm.2011.17.1.14.
19. Kamal M, Elbahrawy A, Monem MA, et al. Study of insulin resistance in patients with variable grades of gastroesophageal reflux diseases. Nature and Science. 2016;14(9):150-6. Available online: http://www.sciencepub.net/nature/ns140916/21_31173nsj140916_150_156.pdf.
20. Li CH, Hsieh TC, Hsiao TH, et al. Different risk factors between reflux symptoms and mucosal injury in gastroesophageal reflux disease. Kaohsiung J Med Sci. 2015;31(6):320-7. PMID: 26043412. https://doi.org/10.1016/j.kjms.2015.02.007.
21. Gosal F, Waleleng BJ, Pandelaki K. Hubungan kadar TNF α, nilai HOMA-IR dan pelemakan hati sederhana nonalkoholik pada pelajar SMA dengan obesitas. J Indon Med Assoc. 2013; 63(1):27-31.
22. Nasution IR, Setiati S, Trisnohadi HB, Oemardi M. Insulin resistance and metabolic syndrome in elderly women living in nursing homes. Acta Med Indones. 2006;38(1):17-22. PMID: 16479027.
23. Esteghamati A, Ashraf H, Khalilzadeh O, et al. Optimal cut-off of homeostasis model assessment of insulin resistance (HOMA-IR) for the diagnosis of metabolic syndrome: Third national surveillance of risk factors of non-communicable diseases in Iran (SuRFNCD-2007). Nutri Metab (London). 2010;7:26. PMID: 20374655. PMCID: PMC2857836. https://doi.org/10.1186/1743-7075-7-26.
24. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut off values and the metabolic syndrome in a general adult population: Effect of gender and age: EPIRCE cross sectional study. BMC Endocr Disord. 2013;13:47. PMID: 24131857. PMCID: PMC4016563. https://doi.org/ 10.1186/1472-6823-13-47.
25. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487-95. PMID: 15161807.
26. Tai CM, Lee YC, Tu HP, et al. The relationship between visceral adiposity and the risk of erosive esophagitis in severely obese Chinese patients. Obesity. 2010;18(11): 2165–9. https://doi.org/10.1038/oby.2010.143.
27. Saragih RH, Rey I. FSSG scale system in comparison with GERD questionnaires in predicting endoscopic findings with reflux esophagitis. INA-JGHE. 2012;14(3):136-40.
28. Rieder F, Biancani P, Hatnett K, Yerian L, Falk GW. Inflammatory mediators in gastroesophageal reflux disease: Impact on esophageal motility, fibrosis, and carcinogenesis. Am J Physiol Gastrointest Liver Physiol. 2010;298(5):G571–81. PMCID: PMC2867418. https://doi.org/10.1152/ajpgi.00454.2009.
29. Nam SY, Choi IJ, Ryu KH, et al. The effect of abdominal visceral fat, circulating inflammatory cytokines and leptin levels on reflux esophagitis. J Neurogastroenterol Motil. 2015;21(2):247-52. PMCID: PMC4398239. https://doi.org/10.5056/jnm14114.
30. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006;116(7):1793-1801. PMID: 16823477. PMCID: PMC1483173. https://doi.org/10.1172/JCI29069.
31. Porwal NB, Ghildiyal A, Singh S, et al. Circulating interleukins (IL6)-An early predictor of insulin resistance. AJMS. 2016;7(6):20-5. https://doi.org/10.3126/ajms.v7i6.15250.
32. Chen J, Wildman RP, Hamm L, et al. Association between inflammation and insulin resistance in U.S. nondiabetic adults. Diabetes Care. 2004; 27(12):2960–5. PMID: 15562214.
33. Fujikawa Y, Tominaga K, Fujii H, et al. High prevalence of gastroesophageal reflux symptoms in patients with non-alcoholic fatty liver disease associated with serum levels of triglyceride and cholesterol but not simple visceral obesity. Digestion. 2012;86(3):228–37. PMID: 22964626. https://doi.org/10.1159/000341418.
34. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: Association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007:116(1):39-46. PMID: 17576866. https://doi.org/10.1161/CIRCULATIONAHA.106.675355.
35. Hayashi T, Boyko EJ, McNeely MJ, Leonetti DL, Kahn SE, Fujimoto WY. Visceral adiposity, not abdominal subcutaneous fat area, is associated with an increase in future insulin resistance in Japanese Americans. Diabetes. 2008;57(5):1269-74. PMID: 18299316. https;//doi.org/10.2337/db07-1378.

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ORIGINAL ARTICLE

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Factors Associated with Mild Cognitive Impairment among Elderly Filipinos with Type 2 Diabetes Mellitus

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Abstract

Objectives. This study aims to identify factors associated with mild cognitive impairment (MCI) among elderly Filipinos with Type 2 diabetes mellitus.

Methodology. This is an analytic cross-sectional study involving 133 elderly (≥60 years old) with Type 2 diabetes mellitus consecutively sampled from the General Medicine and Diabetes Clinics of the Philippine General Hospital. Eligible subjects were interviewed to gather demographic and clinical data. Body mass index, waist-hip ratio and mean blood pressure were computed. HBA1c, lipid profile, creatinine and urine proteinuria were tested or recorded if done recently. Dilated fundus examination via indirect ophthalmoscopy and 10-gram monofilament test were performed to detect retinopathy and neuropathy. The Montreal Cognitive Assessment-Philippines tool was administered to detect patients with probable MCI using a cutoff score of ≤21. Multivariate logistic regression analysis was performed to determine the associated factors.

Results. Using MoCA-P tool, MCI has a rate of 45% among elderly Filipino diabetics. Having more than 12 years of education is significantly associated with lower odds of MCI. (OR 0.38 CI 0.18, 0.80, p value 0.010).

Conclusion. The rate of MCI among Filipino elderly diabetics is high. Higher education is associated with lower odds of having MCI. Case-control or prospective cohort studies involving larger sample and non-diabetic population are recommended.

Key words: older persons, mild cognitive impairment, type 2 diabetes mellitus

INTRODUCTION

Cognitive impairment is a global public health concern as the number of older population is rising. In 2014, 489,000 older Filipinos were estimated to have dementia.[1] It is also in the elderly where the prevalence of Type 2 diabetes mellitus peaks, and thus in the past decade, it has been implicated in the development of cognitive impairment. A meta-analysis by Cheng et al., showed that subjects with Type 2 diabetes, had a higher risk for Alzheimer's disease, vascular dementia and mild cognitive impairment (MCI).[2] Using Montreal Cognitive Assessment (MoCA) tool, MCI was reported to have a prevalence of 31.5% and 32.7% in Polish and Korean patients with type 2 diabetes, respectively.[3,4]

A range of vascular, metabolic and socio-demographic risk factors have been linked to the development of cognitive impairment among diabetics but these factors differed from one study to another. High HBA1c, high systolic blood pressure, high triglycerides, low high-density-lipoprotein (HDL),[5,6] non-HDL cholesterol,[7] presence of diabetic retinopathy,[3,8] peripheral neuropathy[6] and nephropathy,[9] age, educational background,[3,4] increased total body fat mass and central adiposity[10] were associated with worse cognitive performance. In contrast, two studies showed that dyslipidemia, specifically total cholesterol was protective.[8,11] Yaffe et al., showed that a hypoglycemic event had a two-fold increased risk for developing dementia.[12]

The spectrum of pathologic cognitive decline ranges from pre-clinical state to dementia with MCI as the intermediate clinical state. The International Working Group on Mild Cognitive Impairment defined the criteria of MCI as 1) cognitive decline as evidenced by self and/or informant and/or clinician report and impairment on objective cognitive tasks, and/or evidence of decline over time on objective tasks; 2) preserved activities of daily living (ADL); and 3) does not meet Diagnostic and Statistical

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Manual of Mental Disorders (DSM) IV, International Classification of Diseases (ICD) 10 criteria for a dementia syndrome.[13] In contrast to dementia, MCI does not interfere with ADL. Half of patients with MCI have an increased risk of developing dementia in 5 years with an estimated annual conversion rate of 10-15%.[14] On the other hand, up to 44% of patients with MCI at their first visit are estimated to return to normal after a year.[15]

Several screening tools are available for detecting cognitive impairment. The Montreal Cognitive Assessment (MoCA) was developed as a 30-point, 10-minute test that evaluates visuospatial and executive function, orientation, language, attention and recall. It is more sensitive (90% vs 18%) than MMSE in detecting mild cognitive impairment with a specificity of 87%.[16] Locally, Dominguez et al., have adapted and validated the Montreal Cognitive Assessment-Philippines (MoCA-P) version. The Filipino version has an excellent internal consistency (Cronbachs α = 0.938).[17] A cutoff score of ≤21 was shown to have better sensitivity (83.5%) in detecting probable mild Alzheimer's disease without sacrificing specificity (72.3%). Two points are added to the total score if subjects have education less than 7 years.[18]

Cognitive performance can be affected by anxiety and depression, hence, it is important to exclude these disorders as confounders. The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-assessment questionnaire designed to identify probable cases of anxiety and depressive disorders among medically-ill patients. The Hospital Anxiety and Depression Scale – Pilipino (HADSP) version has been validated locally. An optimal cut-off score of 11 is recommended for Filipinos with a sensitivity of 75%, specificity of 70%, and positive predictive value of 75%.[19]

The critical element in differentiating MCI from dementia is determining independence in ADL. The Alzheimer's Disease Association of the Philippines Guidelines 2014 recommends the use of Adapted Functional Activities Questionnaire (A-FAQ) to assess functional impairment with a Class IIB evidence. This scale has been translated and used in local studies. The optimal cut-off score of <6 has a sensitivity of 80.3%, specificity of 87.0%, and 84.7% classification accuracy in identifying patients with impairment in instrumental activities of daily living.[1]

Although diabetes control has been a mainstay in the prevention of other diabetic complications, it is difficult to apply in the prevention or delaying the progression of dementia because it is yet unknown which of the diabetes-related factors are associated with MCI. This study aims to identify factors associated with mild cognitive impairment among elderly Filipinos with Type 2 diabetes mellitus. In the lack of therapeutic options for cognitive impairment, identification of these potentially modifiable factors can help identify high-risk population that would benefit from early screening, referral to specialists and aggressive management, thus, preventing or delaying progression to dementia.

METHODOLOGY

Participants

One hundred thirty-three participants ≥60 years old with Type 2 diabetes mellitus of any duration, literate, independent in ADL, with no known neurocognitive, neurologic or psychiatric disorder, no intracranial neoplasm, infectious disease, constant alcohol or substance abuse, significant use of possible or known cognition-impairing drugs in the past 4 weeks and severe visual, hearing, mobility or motor coordination impairment were consecutively sampled from the General Medicine and Diabetes clinics of the Philippine General Hospital (PGH), a tertiary government hospital, from August 2016-May 2017. The sample size was estimated based on the percentage of MCI in patients with and without nephropathy, 24% and 6.5% respectively, and percentage of diabetic patients with nephropathy, that is 35%,[6] with level of significance set at 5% and power of 80%. A written informed consent was obtained from each participant.

Assessment of Anxiety, Depression, Functional Independence and Mild Cognitive Impairment

Eligible participants answered the Hospital Anxiety and Depression Scale–Pilipino (HADS-P) and the interviewer-guided Adapted Functional Activities Questionnaire. A score of <11 and <6 respectively, were used to define absence of anxiety and depression and functional independence on instrumental activities of daily living. The Montreal Cognitive Assessment–Philippines (MoCA-P) test was administered to detect mild cognitive impairment using a cut-off score of ≤21.

Assessment of Variables

The participants were interviewed for their age, civil status, highest level of education, duration of diabetes, smoking status, presence of hypoglycemic symptoms or capillary blood glucose (CBG) <70 mg/dl in the past 4 weeks. Comorbidities, medications used, blood pressure (BP) in the past 2 visits, HBA1c, lipid profile, creatinine, and urinalysis done in PGH in the past 30 days were obtained from the medical chart. Anthropometrics (height, weight, waist and hip circumference) and current blood pressure were taken during the second visit. Body mass index (BMI), waist-hip ratio (WHR) and mean BP were computed. For participants without recent laboratory tests, blood samples were taken after a 12-hour fast to assess lipid profile as well as HBA1c and serum creatinine. Urine samples were collected to assess proteinuria. Diabetic nephropathy was assessed by spot urine proteinuria in the absence of urinary tract infection, hematuria and exercise within 24 hours and estimated glomerular filtration rate

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(eGFR) as computed via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and was classified as no nephropathy (no proteinuria and eGFR ≥90) and with nephropathy (with proteinuria and/or decreased eGFR). Diabetic neuropathy was defined by loss of sensation in at least 2 sites on a 10-gram monofilament test. Diabetic retinopathy was assessed by funduscopic examination carried out through dilated pupils by an ophthalmologist and was classified according to the Early Treatment for Diabetic Retinopathy Study and International Clinical Diabetic Retinopathy Disease Severity Scales.[20]

Statistical Analysis

The rate of MCI was computed as total of participants with MCI against total of participants who completed the study. Demographic and clinical data were reported through descriptive statistics using quantitative variables (mean, standard deviation, median, interquartile range) and qualitative variables (frequency, percentage). Student's T test was used to compare normally distributed continuous variables between two groups while Chi square test was used to compare categorical variables. Prior to predictive modelling, test for collinearity and confounding were done. Multi-collinearity was assumed if the variable inflation factor was >10. Collinear variables identified were total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL), hence, the first two were not included in the logistic model. Confounding was considered if the change in odds ratio in the crude and adjusted logistic model was >10%. No significant confounders were identified. Univariate logistic regression analysis was done to estimate crude odds ratios. Variables were entered into an exploratory multivariate logistic regression model for mild cognitive impairment if with p-value <0.2. After stepwise backward elimination, the remaining significant variables formed the final predictive model. Hypothesis testing was done with a 95% level of significance. All data analyses were done using Stata SE version 13.

The study protocol was approved by the Technical Review Board and the University of the Philippines Manila Research Ethics Board.

RESULTS

A total of 226 elderly diabetics were consecutively enrolled, 53 (23%) were excluded due to probable anxiety and depression, 1 due to dependence in ADL and 2 due to past history of cerebrovascular disease. Thirty seven patients did not come back for second visit, and only 133 were included in this analysis. Table 1 summarizes the demographic and clinical characteristics of the participants. They had a mean age of 67 (4.8) years and were mostly females, married, and overweight or obese. Forty percent reached college level education. The

Table 1. Demographic and clinical characteristics of patients with and without mild cognitive impairment (MCI)

Variables	Total n=133	Without MCI n= 73	With MCI n= 60
Age (years)	67 (±4.8)	66.8 (±4.8)	67.2 (±4.9)
Sex n (%)			
Females	93 (69.9)	48 (65.8)	45 (75)
Civil Status n (%)			
Married	123 (92.5)	67 (91.8)	56 (93.3)
Single	10 (7.5)	6 (8.2)	4 (6.7)
Education (years)			
>12	53 (39.9)	36 (49.3)	17 (28.3)
≤12	80 (60)	37 (50.7)	43 (71.7)
Duration of diabetes (years) median (IQR*)	12 (±12)	12 (±11)	11.5 (±12)
Treatment n (%)			
Insulin	43 (32.3)	25 (34.3)	18 (30)
1 OHA	63 (47.4)	33 (45.2)	30 (50)
≥2 OHA	59 (44.4)	33 (45.2)	26 (43.3)
Co-morbidities n (%)			
Hypertension	120 (90.2)	66 (90.4)	54 (90)
Dyslipidemia	79 (59.4)	43 (58.9)	36 (60)
Ischemic Heart Disease	19 (14.3)	10 (13.7)	9 (15)
Heart Failure	21 (15.8)	12 (16.4)	9 (15)
Chronic Kidney Disease	32 (24.1)	17 (23.3)	15 (25)
Smoking n (%)	42 (31.6)	28 (28.4)	14 (23.3)
Hypoglycemia n (%)	34 (25.6)	20 (27.4)	14 (23.3)
BMI Classification n (%)			
Normal/Underweight	37 (27.8)	25 (34.3)	12 (20)
Overweight/Obese	96 (72.2)	48 (65.8)	48 (80)
Abdominal Obesity n (%)	91 (68.4)	46 (63)	45 (75)
Systolic BP (mmHg)	132.8 (±13.4)	131.1 (±13.3)	134.8 (±13.4)
Diastolic BP (mmHg)	77.7 (±9.1)	76.8 (±9.2)	78.7 (±9)
HBA1c (%)	7.6 (±1.9)	7.7 (±1.8)	7.5 (±2.1)
Total Cholesterol (mg/dl)	176.8 (±52.9)	175.4 (±56.8)	178.5 (±48)
Triglyceride (mg/dl) median (IQR*)	122.1 (±71.9)	120 (±60.2)	125.7 (±102.8)
HDL (mg/dl)**	49.1 (±12)	50.8 (±11.4)	47 (±12.6)
LDL* (mg/dl)**	102 (±48.4)	100.7 (±52.1)	103.6 (±43.8)
Non-HDL (mg/dl)	121.7 (±51.6)	124.6 (±54.8)	131.5 (±47.6)
Microvascular complications n (%)			
Retinopathy	37 (28)	18 (24.7)	19 (32.2)
Neuropathy	22 (16.5)	12 (16.4)	10 (16.7)
Nephropathy	113 (85)	60 (82.2)	53 (88.3)

*IQR – interquartile range; **HDL – high density lipoprotein; ***LDL – low density lipoprotein

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median duration of diabetes was 12 years. The participants had relatively well-controlled diabetes, blood pressure and serum lipids.

Using MoCA-P tool, sixty of 133 participants (45%) had MCI. Patients with MCI had significantly lower educational attainment. Other variables did not vary between the groups. The mean scores of patients with MCI reached at least 50% of perfect scores in visuo-spatial/executive function, attention and orientation. They scored poorly in language and recall.

Table 2 summarizes the results of univariate logistic regression analysis. Without correcting for other factors, increasing age, obesity, and high blood pressure appear to increase the odds of having MCI, while high HDL suggests protection although these were not significant. Having more than 12 years of education (OR 0.41, CI 0.20, 0.84, *p*-value 0.015) is significantly associated with lower risk of MCI. Years of education, smoking, overweight/obesity, abdominal obesity, systolic BP and triglyceride reached statistical significance ($p<0.2$) to be included in the multivariate logistic regression modelling.

After multivariate logistic regression analysis using stepwise backward elimination and removal of non-significant confounders and collinear variables, having more than 12 years of education (OR 0.38 CI 0.18, 0.80, *p*-value 0.010) was the only factor left to be significantly associated with MCI.

DISCUSSION

The results of this study revealed a higher rate (45%) of MCI among elderly Filipinos compared to the 31.5%[3] and 32.7%[4] reported prevalence among Korean and Polish population respectively. Prevalence rates of MCI vary among studies due to different tools and cut-offs used or in the characteristics of the study participants involved. All these three studies used the same MCI assessment tool with locally validated cut-offs used to define MCI.

The population in the foreign studies were even older (mean age of ≥70 years) and have almost the same duration of diabetes (8-12 years) and HBA1c (7.5%) as the participants in this study. The Polish study reported even lower years of education (mean duration of 9.7 years). Considering the inherent characteristics of our population, it is also important to note that this study was conducted in a public hospital where most of the patients belong to the lower socioeconomic status, which would explain the lower educational attainment. This can possibly overestimate the rate of MCI. Although a baseline rate of MCI among the general population should be sought, this high rate among diabetics suggests that greater efforts on prevention, early detection and delaying progression to dementia are warranted.

It is interesting that during the screening process in this study, we found a rate of 23% of possible anxiety and depression among elderly Filipinos with type 2 diabetes. This post hoc data approximates 29.7% recorded in the Polish study.[4] As these can also affect patients' adherence to treatment of diabetes, this aspect must also be looked into by the physicians and caregivers.

The domains in which our participants with MCI scored poorly include language and recall. This is inconsistent with the report from the Shanghai Aging Study and Mayo Clinic Study of Aging that diabetes is associated with worse executive function.[21] Although this could be due to the difference in the tools used, this can be seen as an

Table 2. Univariate logistic regression analysis of factors associated with mild cognitive impairment

Variables	Unadjusted Odds Ratio	95% Confidence Interval	P-value
Age, years	1.01	(0.95, 1.09)	0.646
Sex, females	1.6	(0.73, 3.34)	0.249
Married	1.25	(0.34, 4.67)	0.736
≥12 years of education	0.41	(0.20, 0.84)	0.015
Duration of diabetes, years	1.0	(0.96, 1.04)	0.959
Treatment			
Insulin	0.82	(0.4, 1.71)	0.603
≥2 OHA	0.87	(0.42, 1.77)	0.694
Comorbidities			
Hypertension	0.95	(0.30, 3)	0.937
Dyslipidemia	1.05	(0.52, 2.1)	0.898
Ischemic Heart Disease	1.11	(0.42, 2.94)	0.831
Heart Failure	0.9	(0.35, 2.3)	0.821
Chronic Kidney Disease	1.1	(0.49, 2.44)	0.818
Smoking	0.49	(0.23, 1.05)	0.066
Hypoglycemia	0.81	(0.37, 1.78)	0.593
Overweight/Obese	2.08	(0.94, 4.6)	0.071
Abdominal Obesity	1.76	(0.83, 3.74)	0.141
Systolic BP	1.02	(0.99, 1.05)	0.116
Diastolic BP	1.02	(0.98, 1.06)	0.254
HBA1c	0.94	(0.78, 1.13)	0.502
Triglyceride	1	(1, 1.01)	0.113
HDL	0.97	(0.94, 1)	0.736
Non-HDL	1	(1, 1.01)	0.444
Microvascular complications			
Retinopathy	1.45	(0.68, 3.11)	0.338
Neuropathy	1.02	(0.41, 2.55)	0.972
Nephropathy	1.64	(0.61, 4.42)	0.327

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advantage since effective self-care in diabetes requires a complex behavioral regimen involving executive function. An intact executive function among our patients would translate to the ability to make sustained efforts in overriding habits like dietary indiscretion and sedentary lifestyle that are challenges in the management of diabetes.

The results of the univariate logistic regression analysis showed that increasing age, high blood pressure and obesity appear to increase the likelihood of having MCI although they were not significant. These findings are consistent with other studies that showed association of these factors with worse cognitive performance.[3-5,7,19] The relation of hypertension to cognitive impairment is attributed to vascular dysfunction compromising blood and glucose supply to the brain as well as reduced clearance of substances causing oxidative stress and eventually neuronal degeneration. On the other hand, high HDL showed a trend towards decreased likelihood of MCI although, again, it was not significant. Several studies have reported the association of lower HDL and cognitive impairment.[7,22-24] Proposed mechanisms of HDL as a negative risk factor to cognitive impairment include its anti-inflammatory properties and prevention of aggregation and polymerization of β-amyloid.[25]

After the multivariate logistic regression analysis, we have demonstrated that having more than 12 years of education is significantly associated with lower odds of having MCI. A study among Chinese elderly showed the same association. It is postulated in the cognitive reserve hypothesis that higher level of education increases neuronal plasticity and connectivity.[26] Increasing educational opportunities then can be regarded as a potential strategy in decreasing the odds of having cognitive impairment in later life.

The single result of this analysis suggests that factors associated with development of MCI could be non-diabetes related. There are several limitations in this study though. The participants in this study showed relatively well-controlled glucose, BP and serum lipids. This is a cross-sectional study in which only one HBA1c value was used and previous glycemic control measures were not considered. This could possibly explain the lack of association between HBA1c and several parameters to MCI. The stringent inclusion and exclusion criteria also prevented us from including patients who were too sick, with unstable comorbidities and worse complications, hence, our results can underestimate associations.

CONCLUSIONS

In conclusion, our results show that there is a high rate of MCI among elderly Filipinos with type 2 diabetes despite having relatively well-controlled disease and comorbidities. Attainment of higher years of education is significantly associated with lower odds of having MCI. Larger studies involving non-diabetic population are suggested to estimate baseline rate of MCI among Filipino elderly and investigate further association of factors.

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

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References

1. De la Vega S, Orteza G, Ledesma L. Recommendations on the diagnosis, prevention and management of Alzheimer's disease, 2nd ed. Philippines: Alzheimer's Disease Association of the Philippines, 2014.
2. Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: A meta-analysis of longitudinal studies. Intern Med J. 2012;42(5):484-91. PMID: 22372522. https://doi.org/10.1111/j.1445-5994.2012.02758.x.
3. Gorska-Ciebiada M, Saryusz-Wolska M, Ciebiada M, Loba J. Mild cognitive impairment and depressive symptoms in elderly patients with diabetes: Prevalence, risk factors and comorbidity. J Diabetes Res. 2014;2014:179648. PMCID: PMC4241577. https://doi.org/10.1155/2014/179648.
4. Lee YJ, Kang HM, Kim NK, et al. Factors associated for mild cognitive impairment in older Korean adults with type 2 diabetes mellitus. Diabetes Metab J. 2014; 38(2):150-7. PMCID: PMC4021302. https://doi.org/ 10.4093/dmj.2014.38.2.150.
5. Umegaki H, Kawamura T, Kawano N, et al. Factors associated with cognitive decline in elderly diabetics. Dement Geriatr Cogn Disord Extra. 2011; 1(1):1-9. PMID: 22163228. PMCID: PMC3199895. https://doi.org/10.1159/000323188.
6. Umegaki H, Iimuro S, Shinozaki T, et al. Risk factors associated with cognitive decline in the elderly with type 2 diabetes: Baseline data analysis of the Japanese Elderly Diabetes Intervention Trial. Geriatr Gerontol Int. 2012;12(1):103-9. PMID: 22435945. https://doi.org/10.1111/j.1447-0594.2011.00817.x.
7. Niu MJ, Yin FZ, Liu LX, Fang Y, Xuan XM, Wu GF. Non-high density lipoprotein cholesterol and other risk factors of mild cognitive impairment among Chinese type 2 diabetic patients. J Diabetes Complications. 2013;27(5):443-6. PMID: 23845902. https://doi.org/10.1016/j.jdiacomp.2013.06.001.
8. Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive impairment and dementia in older people diabetes. Diabetologia. 2008;51(2):241-8. PMID: 18060658. https://doi.org/10.1007/s00125-007-0894-7.
9. Verny C, Doucet J, Bauduceau B, et al. Prevalence of cognitive decline and associated factors in elderly type 2 diabetic patients at inclusion in the GERODIAB cohort. Eur Geriatr Med. 2015;6(1):36-40. https://doi.org/10.1016/j.eurger.2014.10.006.
10. Abbatecola AM, Lattanzio F, Spazzafumo L, et al. Adiposity predicts cognitive decline in older persons with diabetes: A 2-year follow-up. PLoS One. 2010;5(4):e10333. PMCID: PMC2859057. https://doi.org/10.1371/journal.pone.0010333.
11. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: The action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care. 2009;32(2):221-6. PMID: 19171735. PMCID: PMC2628683. https://doi.org/10.2337/dc08-1153.

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12. Yaffe K, Falvey CM, Hamilton N, et al. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. JAMA Intern Med. 2013;173(14):1300-6. PMID: 23753199. PMCID: PMC4041621. https://doi.org/10.1001/jamainternmed.2013.6176.
13. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment--beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004; 256(3):240-6. PMID: 15324367. https://doi.org/10.1111/j.1365-2796.2004.01380.x.
14. Eshkoor SA, Hamid TA, Mun CY, Ng CK. Mild cognitive impairment and its management in older people. Clin Interv Aging. 2015;10:687-93. PMID: 25914527. PMCID: PMC4401355. https://doi.org/10.2147/CIA.S73922.
15. Wada-Isoe K, Uemura Y, Nakashita S, et al. Prevalence of dementia and mild cognitive impairment in the rural island town of Ama-cho, Japan. Dement Geriatr Cogn Disord Extra. 2012;2:190–9. PMID: 22719745. PMCID: PMC3379729. https://doi.org/10.1159/000338244.
16. Nasreddine ZS, Phillips N, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005; 53(4):695-9. PMID: 15817019. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
17. Dominguez JC, Orquiza MGS, Soriano JR, et al. Adaptation of the Montreal Cognitive Assessment for elderly Filipino patients. East Asian Arch Psychiatry. 2013;23(3):80-5. PMID: 24088400.
18. Dominguez JC, Soriano JR, Magpantay CD, et al. Early detection of mild Alzheimer's disease in Filipino elderly: Validation of the Montreal Cognitive Assessment-Philippines (MoCA-P). Adv Alzheimer Dis. 2014;3(4):160-7. https://doi.org/10.4236/aad.2014.34015.
19. De Guzman MLR. A validation of the hospital anxiety and depression scale in medically ill. Acta Medica Philippina. 2013;47(3):53-61. http://actamedicaphilippina.com.ph/sites/default/files/fulltexts/vol-47-no-3-a-validation.pdf.
20. Grading diabetic retinopathy from stereoscopic color fundus photographs -- An extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):786-806. PMID: 2062513.
21. Zhao Q, Roberts RO, Ding D, et al. Diabetes is associated with worse executive function in both Eastern and Western populations: Shanghai Aging Study and Mayo Clinic Study of Aging. J Alzheimers Dis. 2015; 47(1):167–76. PMCID: PMC4617674. NIHMSID: NIHMS726844. https://doi.org/10.3233/JAD-150073.
22. Van Exel E, de Craen AJ, Gussekloo J, et al. Association between high density lipoprotein and cognitive impairment in the oldest old. Ann Neurol. 2002;51(6):716-21. PMID: 12112077. https://doi.org/10.1002/ana.10220.
23. Bonarek M, Barbeger-Gataeu P, Letenneur L, et al. Relationships between cholesterol, apolipoprotein E polymorphism and dementia: A cross-sectional analysis from the PAQUID study. Neuroepidemiology. 2000;19(3):141-8. PMID: 10705232.
24. Singh-Manoux A, Gimeno D, Kivimaki M, Brunner E, Marmot MG. Low HDL-C cholesterol is a risk factor for deficit and decline in memory in midlife: The Whitehall II study. Arterioscler Throm Vasc Biol. 2008;28(8):1556-62. PMID: 18591462. PMCID: PMC2581752. HALMS:HALMS277029.https://doi.org/10.1161/ATVBAHA.108.163998.
25. He Q, Li Q, Zhao J, et al. Relationship between plasma lipids and mild cognitive impairment in the elderly Chinese: A case-control study. Lipids Health Dis. 2016;15(1):146. PMCID: PMC5011904.
26. Su X, Shang L, Xu Q, et al. Prevalence and predictors of MCI in Xi'an: A community based study among the elders. PLoS ONE.2014; 9(1): e83217. PMID: 24421876. PMCID: PMC3885430. https://doi.org/10.1371/journal.pone.0083217.

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ORIGINAL ARTICLE

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Risk Factors Associated with the Activity and Severity of Graves' Ophthalmopathy among Patients at the University of the Philippines Manila-Philippine General Hospital

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Abstract

Background. Asians with Graves' ophthalmopathy (GO) may have earlier compressive features due to narrower orbital apex and increased orbital volume.

Objective. To determine the risk factors associated with activity and severity of GO among adults.

Methodology. This was a cross-sectional analytical study of 163 adults with Graves' disease (GD) from the outpatient clinics of the Philippine General Hospital. Demographics, clinical data, thyrotropin receptor antibody (TRAb) and urine iodine (UIE) levels were obtained. All participants were evaluated for activity and severity of GO by a single ophthalmologist.

Results. The population was predominantly composed of females (81%) and nonsmokers (69%), with a mean age of 35 ± 11 years and median GD duration of 2 years. Median TRAb was 8.9 U/L while UIE was 171 mcg/L. Eight percent exhibited active GO, with 85% having mild disease. Multivariate analysis showed male sex to be associated with severe disease (OR 3.71, p=0.041), while elevated TRAb was associated with both active (OR 1.03, p=0.002) and severe GO (OR 1.02, p=0.007).

Conclusion. Lower rates of active and severe GO were seen compared to previous reports. In this population of predominantly nonsmokers, elevated TRAb emerged as a risk factor for active and severe GO.

Key words: Graves□ophthalmopathy, Graves□disease, thyrotropin receptor antibody

INTRODUCTION

Graves' ophthalmopathy (GO) is the most common extrathyroidal manifestation of Graves' disease (GD).[1] It is the most frequent orbital disorder and is the most common cause of unilateral and bilateral proptosis in adults.[2-4] Internationally, it is detectable in approximately 10 to 60% of GD patients.[5] The prevalence of GO in Asians with hyperthyroidism was noted to be between 35% to 60%.[6-7] Locally, prevalence of GO was 48%, occurring more frequently among patients aged between 30 and 49 years. The most common signs were eyelid retraction, proptosis, and lid lag.[2] Unpublished reports show that GO comprised 24% of ophthalmology consults and was the leading cause of initial consult at the Orbit Clinic of the University of the Philippines-Philippine General Hospital (UP-PGH) in 2013 (unpublished data).

The major clinical risk factor for developing thyroid eye disease is smoking.[1,8] Smokers are estimated to represent 64% of patients with GD and GO.[9] The risk of GO is found to be related to active smoking and is proportional to the number of cigarettes smoked per day. Previous smokers were also found to have significantly lower risk than current smokers.[10]

Other risk factors previously studied included genetic polymorphisms of the thyrotropin receptor. At present, genetic testing is not yet warranted as none of the polymorphisms impart a high enough risk of GO.[10] Thyrotropin receptor antibody (TRAb) may be useful in predicting course of GD and response to therapy but it is unknown if they are predictive of GO development.[10]

Iodine-replete areas show an increased incidence of autoimmune thyroid disease but its association with the development and progression of GO in Western countries has not been shown.[11] The Philippines is now considered an iodine-sufficient area based on a median urinary iodine level of 133 μg/L.[12] Iodine status showed no relation to the occurrence or progression of GO in a Danish population,[11] however, there are still no Philippine data at the moment.

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Other risk factors related to autoimmunity are menarche at an age less than 15 years and late menopause (≥51 years of age) and is attributed to the estradiol effect. The use of oral contraceptives is said to have a protective effect against the development of GD due to yet unknown mechanisms.[13] A history of allergy is related to a slower decrease in TSH receptor antibodies, a lower chance of GD remission, and increased relapse owing to elevated levels of IgE.[13] Only an association with GD was elucidated in these studies but not with the development of GO.

The clinical presentation may vary from very mild disease such as tearing, photophobia, and conjunctival injection to severe irreversible sight-threatening complications due to compressive optic neuropathy.[3,14-15] Overall, 13% of patients without GO at baseline will develop the condition. Of these, 42% will have mild GO and 2.6% will develop moderate-severe GO over an 18-month period during treatment with anti-thyroid drugs. For those with mild GO, 58% will show spontaneous improvement over an 18-month period, while about 2.4% will have progression to moderate-severe GO.[16] Approximately 6% of patients with GO develop optic neuropathy, a potentially blinding complication.[17] After an acute inflammatory phase lasting months, the chronic phase follows, characterized by hypertrophy and fibrosis of extraocular muscles, lacrimal glands and orbital fat, with subcutaneous eyelid changes which are permanent and unresponsive to immunosuppressive treatment.[14]

Management of GO is based on three pillars: restoration and maintenance of euthyroidism, smoking cessation, and rehabilitative surgery if warranted.[18-19] It can vary from watchful waiting and symptomatic management of eye dryness in mild disease to use of corticosteroids, radiotherapy and surgery depending on the severity of the condition.[19] Glucocorticoid therapy for GO has shown favorable response in 50 to 80% of cases, depending on route of administration but is not without adverse events.[20] Trials on efficacy of orbital radiotherapy report conflicting results,[19] and the procedure is associated with transient exacerbation of eye symptoms and risk of carcinogenesis, especially in younger patients. Orbital decompression as a form of rehabilitative surgery was associated with a 53% development of diplopia post-operatively.[21]

Compared to Caucasians, Asians in particular have earlier compressive features, increased orbital volume and a narrow orbital apex.[17] This finding further strengthens the need to promote early identification of patients likely to have progression of the disease. In the Philippines, studies on associated risk factors and predictors of severity as well as on long term outcome of this group of patients are still lacking. Despite advances in treatment, there are still no effective means of preventing GO or reliably altering its course. Current therapeutic options are aimed at the consequences of the disease rather than the cause. Unfortunately, these treatments do not prevent or reverse the pathological changes in the orbital tissues.[3] Apart from the medical implications of GO, data indicate that 45% of patients suffering from GO complained of restrictions in daily activities attributed to visual complaints with 38% reporting impaired self-perception.[22]

The lack of effective means of preventing or reversing GO and the variable effectiveness of available therapeutic options has shifted the focus on early detection and identification of patients most likely to have worsening of the condition.

This study aimed to describe the clinical profile of GD patients with GO, classify them based on activity and severity, and to determine the risk factors associated with the activity and severity of GO among patients at the UP-PGH.

METHODOLOGY

This was a cross-sectional analytical study done on 163 patients recruited from the outpatient clinics of Internal Medicine, Ophthalmology, Otolaryngology, and Family Medicine at the UP-PGH, a tertiary hospital in Manila, Philippines. Patients included were adults age 19 and above who were diagnosed with GD and have consented to participate in the study. Those who have other causes of thyroid-associated orbitopathy, such as those seen in Hashimoto's thyroiditis and thyroid carcinoma, were excluded. Those who had undergone radioactive iodine therapy (RAI) or thyroidectomy as definitive treatment for hyperthyroidism were excluded, as well as those with a negative TRAb coupled with a low uptake on thyroid scan.

Using NCSS-PASS (Power Analysis and Sample Size) 2008 software, the minimum sample size requirement was at least 105 based on the percent of patients with severe GO among smokers and nonsmokers (0.33 and 0.107, respectively, with alpha level = 5% and power = 80%). Adjusting for a 20% non-response rate, the minimum sample size requirement was set at 132. Except for the alpha and power levels which were set by the researchers, all other parameters were taken from the study by Lee et al.[15]

All cases diagnosed with Graves' disease at the outpatient clinics were screened. If found to be eligible, the participant was included in the study after giving consent. Complete history and physical examination was done by the principal investigator. A diagnosis of GD was made in the presence of hyperthyroid symptoms, laboratory evidence of elevated free thyroxine (FT4) and suppressed thyroid stimulating hormone (TSH), diffuse thyromegaly on ultrasound, and presence of TRAb. In the absence of TRAb, an increased uptake on thyroid scan confirmed the diagnosis.

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The following data were collected from each patient: age in years, sex, history of thyroid storm, presence of comorbidities (such as diabetes, hypertension and other autoimmune disorders), history of atopy, current glucocorticoid use, family history of thyroid disease, duration of GD, antithyroid drug (ATD) used, duration of ATD treatment, and current FT4 level. A FT4 level greater than 24 pmol/L was considered to be elevated. For females, the following information were also obtained: age of menarche, late menopause (with late menopause being defined as cessation of menses ≥51 years of age), and current oral contraceptive (OCP) use. Socioeconomic status was measured by monthly household income. High income class were defined as those households earning greater than PhP 2,393,125 (USD 47,537) annually or PhP 199,927 (USD 3,971) per month. Low income class were those with an annual income less than PhP 294,296 (USD 5,846) or PhP 24,524 (USD 487) per month. Those with an annual income falling between these amounts were classified as middle income households based on cluster analysis of population data and Consumer Price Index by the National Statistical Coordination Board.[23] Smoking history was reported as those who never smoked, previous smoker (defined as cessation of smoking before the diagnosis of GD) and current smokers.

All participants were then assessed at the Orbit Clinic for a complete ophthalmologic evaluation to determine presence or absence of GO. A board-certified ophthalmologist who was undergoing subspecialty training in Orbit performed the examination. Using the criteria of the American Academy of Ophthalmology guidelines,[2] GO was diagnosed if eyelid retraction occurs together with objective evidence of thyroid dysfunction, or exophthalmos, or optic-nerve dysfunction, or extraocular-muscle involvement. If eyelid retraction is absent, then GO may be diagnosed only if exophthalmos, optic nerve involvement, or restrictive extraocular myopathy coexists with thyroid dysfunction and no other causes for the ophthalmologic features are apparent.

Disease activity was assessed based on the Modified Clinical Activity Score (CAS) of the European Group on Graves' Orbitopathy (EUGOGO)[19] as described by Mourits et al., using clinical features of inflammation. The CAS will be based on the presence of each clinical feature for every patient. One point will be given for every criteria present: spontaneous retrobulbar pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival swelling or edema, conjunctival redness, and inflammation of the caruncle or plica. A CAS ≥3/7 indicates active GO. Patients found to have active GO were managed accordingly.

Disease severity was based on the classification of EUGOGO[19] with modifications used at the Orbit Clinic of the Philippine General Hospital. Severity was classified as mild, moderate to severe, or sight-threatening based on one or more of the following: lid retraction, soft tissue involvement, degree of proptosis, presence of diplopia, corneal exposure, and optic nerve involvement. Lid retraction was measured based on the distance of the upper or lower lid margins to the corneal light reflex, otherwise known as margin reflex distance (MRD). Measurement was done using a single millimeter ruler. Soft tissue involvement was determined based on the presence of periorbital swelling. The degree of proptosis was measured using a Hertel exophthalmometer. The normal value for Filipinos is between 10 to 19.5 mm. Proptosis was present if the measurement exceeded 19.5 mm, or if there was a difference of 3 or more between the two eyes. The presence of relative afferent pupillary defect (RAPD) pointed to optic nerve involvement.

A patient was diagnosed to have mild GO if any of the following were present: the MRD is less than 2 mm or if the upper lid retraction measures 4 or 5 mm, mild soft tissue involvement, degree of proptosis is less than 3 mm above the normal limit for Filipinos, no or transient diplopia, if corneal exposure is responsive to lubricants, and there is absent RAPD. A patient was diagnosed to have moderate-to-severe GO if any of the following are present: MRD ≥2 mm or upper lid >5 mm, presence of festooning or overhang of tissue, degree of proptosis is ≥3 mm above the normal limit for Filipinos, inconstant or constant diplopia, and negative RAPD. A patient was diagnosed to have sight-threatening GO if there is corneal breakdown and/or optic nerve involvement.

After ophthalmic evaluation, TRAb determination was done using a commercial receptor assay utilizing I^{125}-labelled TSH (Immunotech s.r.o-Radiova 1, Prague, Czech Republic). Normal level is <1.0 U/L. Values between 1.1 to 1.5 U/L are considered equivocal. Values greater than 1.5 U/L were considered positive. Those found to have negative or equivocal TRAb titers underwent thyroid scan to determine uptake. A spot urine specimen was then collected for urinary iodine excretion (UIE) to determine iodine nutrition in this population. The urine specimens were sent to the Food and Nutrition Research Institute for processing using ammonium persulfate digestion with spectrophotometric detection of the Sandell-Koltholff reaction. A median UIE between 100 to 199 mcg/L is considered reflective of adequate iodine nutrition for the population. All specimens were stored and discarded using standard laboratory procedures.

This study underwent technical and ethical review by the hospital ethics board. Patient anonymity and confidentiality were maintained throughout the study.

Data Analysis

Data analysis was done using Stata SE version 13, and included both descriptive and inferential statistics.

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Categorical variables were reported as frequencies and percentages. Continuous variables were reported as means and standard deviation if normally distributed, or median and interquartile ranges if not normally distributed. Comparison of characteristics between patients with and without activity was analyzed using independent t-test for quantitative variables, and Fisher's exact test for qualitative variables. The association of the different factors with the activity and severity of GO was analyzed using logistic regression. The level of significance was set at 5%.

RESULTS

A total of 199 patients were recruited in this study. Five were excluded as they had undergone RAI before data gathering was completed. Thirty-one patients did not undergo ophthalmologic exam or had no TRAb or thyroid scan. A total of 163 patients were included in the analysis. The population came from low-income households and was predominantly composed of nonsmokers and females. The demographic and clinical characteristics of the study population are summarized in Table 1. The use of methimazole was comparable between those with active and inactive GO, as well as across GO severity groups. In our population, 127/163 (78%) had positive TRAb titers, with a median level of 8.9 U/L. Also, 52/163 (32%) had insufficient iodine intake with UIE levels of less than 100 mcg/L. 67/163 (41%) exhibited excess iodine intake with UIE levels greater than 199 mcg/L. Only 13/199 (8%) had active GO as the median duration of disease for this population was 2 years. The greater majority had mild disease (139/163 or 85%) while 8% had moderate to severe GO. Only 1 patient had sight-threatening GO due to the presence of corneal ulcers. None of the patients presented with optic neuropathy.

Patients with active GO tended to have had glucocorticoid use (p=0.012) and elevated TRAb titers (p=0.003). On univariate analysis (Table 2), elevated TRAb titers were found to be significantly associated with active GO. Smoking history, UIE levels, male sex, or duration of the disease were not significantly associated with active GO. Multivariate analysis of all significant factors revealed TRAb titers (OR 1.03, 95% CI 1.01-1.04, p=0.002) to be associated with active GO.

Of the male participants, 5/31 (16%) had severe GO compared to 9/132 (7%) of female patients. Those with severe GO tended to have elevated TRAb titers (Mean 43 ± 27 U/L; p=0.0097) compared to those with mild disease (Mean 22 ± 29 U/L). Females with mild disease (44/149 or 36%) were more likely to be on an OCP (p=0.029). None of

Table 1. Demographic and clinical characteristics of Filipino patients with GO

Variable	Inactive N=150	Active N=13	N=163
Age (years)	35 ± 11	38 ± 16	35 ± 11.45
Male Sex	26 (17%)	5 (38%)	31 (19%)
Menarche earlier than age 15 years (N=132)	100 (81%)	6 (75%)	106 (80%)
Menopause at age ≥51 years (N=17)	6 (38%)	0	6 (35%)
Oral contraceptive use (N=132)	42 (34%)	2 (25%)	44 (33%)
Household monthly income* (in PhP)	9418 ± 8332	6269 ± 9162	8000 (3000-12000)
Disease duration (months)*	47 ± 48	28 ± 34	24 (12-60)
ATD used			
Propylthiouracil	16 (11%)	0	16 (10%)
Methimazole	130 (87%)	13 (100%)	143 (88%)
Carbimazole	4 (3%)	0	4 (2%)
Duration of ATD treatment (months)*	30 ± 40	19 ± 16	12 (4-36)
History of thyroid storm	18 (12%)	2 (15%)	20 (12%)
Glucocorticoid use	4 (3%)	3 (23%)	7 (4%)
Current or past smoker	47 (31%)	4 (31%)	51 (31%)
History of allergy or atopy	29 (19%)	2 (15%)	31 (19%)
Presence of other comorbid illness	30 (20%)	5 (38%)	35 (21%)
Family history of thyroid disease	75 (50%)	10 (77%)	85 (52%)
FT4 (pmol/L)*	30 ± 25	25 ± 12	19.82 (13.30-38.98)
TRAb (U/L)*	21 ± 28	51 ± 32	8.9 (1.7-40)
UIE (mcg/L)*	216 ± 175	209 ± 185	171 (82-288)

Values are expressed as mean + SD, frequency (%)
** Median (interquartile range)*

Table 2. Univariate analysis of factors associated with GO activity

Variables	OR	95% CI	P
Age	1.02	0.98-1.07	0.315
Male Sex	2.98	0.90-9.84	0.073
Menarche earlier than age 15 years (N=132)	0.72	0.14-3.79	0.698
Late menopause (N=17)	†	†	†
Oral contraceptive use (N=132)	0.65	0.13-3.36	0.608
Household income (PhP)	0.99	0.99-1.00	0.195
Disease duration (months)	0.99	0.97-1.01	0.181
History of thyroid storm	1.33	0.27-6.51	0.722
Smoking history	0.97	0.29-3.32	0.966
History of atopy	0.76	0.16-3.61	0.729
Presence of comorbidities	2.5	0.76-8.19	0.130
Family history of thyroid disease	3.33	0.88-12.59	0.076
FT4	0.99	0.96-1.02	0.532
TRAb	1.03	1.01-1.04	0.001
UIE	0.99	0.99-1.00	0.896

Values are expressed as mean ± SD, frequency (%)
† Cannot be computed

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Table 3. Univariate analysis of factors associated with GO severity

Variables	OR	95% CI	P
Age (years)	1.01	0.97-1.06	0.591
Male Sex	2.63	0.81-8.48	0.106
Menarche earlier than age 15 years (N=132)	0.46	0.11-1.98	0.297
Late menopause (N=17)	†	†	†
Oral contraceptive use (N=132)	†	†	†
Household income (PhP)	0.99	0.99-1.00	0.075
Disease duration (months)	0.99	0.98-1.01	0.467
History of thyroid storm	2.12	0.54-8.36	0.284
Smoking history	1.73	0.57-5.28	0.334
History of atopy	1.81	0.53-6.20	0.346
Presence of comorbidities	2.20	0.69-7.06	0.183
Family history of thyroid disease	1.25	0.41-3.77	0.696
FT4	1.01	0.99-1.03	0.143
TRAb	1.02	1.00-1.03	0.015
UIE	0.99	0.99-1.00	0.124

Values are expressed as mean ± SD, frequency (%)
† Cannot be computed

Table 4. Multivariate analysis for GO severity

Variables	OR	95% CI	P
TRAb	1.02	1.01-1.04	0.007
Male sex	3.71	1.05-13.07	0.041

those with moderate to severe disease were on glucocorticoids. None of the females with moderate to severe disease had late menopause. The household income, disease duration, smoking history, FT4 levels, UIE levels, and treatment duration were comparable across groups. Univariate analysis (Table 3) showed elevated TRAb titers to be associated with increased GO severity. Multivariate analysis (Table 4) showed elevated TRAb levels (p=0.007) and male sex (p=0.041) to be associated with more severe GO.

DISCUSSION

In this study we described the clinical characteristics of a younger, predominantly non-smoking Filipino population with GO seen in a tertiary university hospital in Manila who had GD for a median of 2 years and had been treated with anti-thyroid drugs for a median of 1 year. Only 8% exhibited active GO, likely as a consequence of having long-standing disease. The clinical course of GO, as characterized by Rundle,[24] is biphasic. Thus, the study population is mostly in the chronic fibrotic phase of GO wherein clinical indices of inflammation have already subsided. This is lower than the reported prevalence of active GO in the literature, which range from 11 to 32%.[25-28] The differing rates of reported prevalence may be due to the use of varying criteria to define GO activity. Moreover, the duration of GD or GO was not reported for all studies. Thus it is unclear whether these were based on patients with newly diagnosed or longstanding disease.

The prevalence of moderate-to-severe or sight-threatening disease in our study was also lower than those reported in the literature,[6,15,25-26] with the exception of Tanda et al.,[16] who reported 5.8% of moderate-to-severe active GO in their newly diagnosed GD patients. As with the case of classifying GO activity, the criteria used to define GO severity were also dissimilar.

International data have shown several well-known risk factors associated with the development and deterioration of GO. These included (1) gender, with the disease being more prevalent in women but more severe in men, (2) smoking, especially smokers receiving radioactive iodine treatment, (3) radioactive iodine treatment, and (4) thyroid dysfunction including hyper- and hypothyroidism.[10]

Males have three times the risk of having more severe GO compared to females, corroborating previous reports. Surprisingly, smoking history did not show any significant association with both GO activity and severity. In contrast to other studies, our population exhibited a lower fraction of current or past smokers. The development of GO is associated more with the number of cigarettes smoked after the diagnosis of GD rather than the cumulative number smoked in a patient's lifetime.[29] Previous studies have reported age to be associated with active[25] and severe GO, specifically dysthyroid optic neuropathy.[26] However, in our study, age was not associated with either GO activity or severity, similar to the report of Lee at al.[15] The duration of GD, duration of treatment with ATD, presence of comorbidities or atopy, family history of thyroid disease, UIE levels, and FT4 levels also did not show significant association with GO activity or severity.

Elevated TRAb titers emerged as a risk factor for both active and severe GO. Previous studies have reported conflicting results with regards to the association of TRAb with GO activity and severity.[15,25-27,30-32] However, these studies and our own differ in several respects: 1) duration of GO or GD in the study population; 2) criteria used to define activity and severity; and 3) TRAb assay used. TRAb assays display wide intermethod variability,[33] thus contributing to the heterogeneity of results.

TRAb titers are expected to decrease following ATD therapy.[34] It is interesting to note that the titers for these patients are still elevated despite longstanding disease and ATD treatment. Given that majority of this population are already in the burnt out phase of GO, it seems that the autoimmune process is still ongoing despite the absence of

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clinical signs of orbital inflammation that is seen in active GO. Indeed, an observational study by Eckstein et al.,[35] reported that elevated TBII tiers at different time points after GO onset have higher risk of severe disease, independent of age and smoking.

The molecular pathogenesis of GO is still not precisely known. Orbital fibroblast have been shown to express functional thyrotropin receptors (TSHR), making them possible target cells. It is postulated that enhanced activation of the TSHR results in hyaluronic acid synthesis and adipogenesis in the orbit,[36] which are the pathologic hallmarks of GO. Whether TRAb is the one which effects this activation is not yet known with certainty. Another putative self-antigen postulated to underlie GO is insulin-like growth factor-1 receptor (IGF-1R). It is theorized that TSHR and IGF-1R are involved in the crosstalk to effect the pathologic changes in GO through any of the following mechanisms: 1) binding and activation of IGF-1R by stimulating IGF-1 like agonists; 2) enhancement/inhibition of TSHR signaling by IGF-1R; or 3) physical hybridization of a functional tyrosine kinase and G protein-coupled receptor.[37]

Given that the TSHR is postulated to participate in the pathogenesis of GO either as an autoantigen or as a molecular conduit for downstream signaling,[38] the demonstration of a clinical association of TRAb with GO activity and severity makes it a possible contributor in the pathogenesis of the disease.

However, our study is limited in several aspects. First, the population included patients in a variety of stages of GO, as evidenced by the wide range in disease duration. Second, only a small proportion exhibited active or severe GO. The sample size may not have been enough to elucidate the association of the variables with disease activity or severity given the low smoking rates and low prevalence of active or severe GO. Moreover, the cross-sectional design precluded determination of causality from the associations observed in this study. Lastly, the assay used cannot differentiate between stimulating, blocking, and neutral antibodies. There is a heterogeneity in the types and affinity of TRAb in a single patient.[36] In order to confirm the association found in this study, future investigators should look into prospective or longitudinal studies on new-onset GO with repeated determinations of TRAb over the course of the disease, utilizing assays that can differentiate the different types of TRAb. This may help determine if TRAb will be clinically useful in prognosticating the course of GO for patients.

CONCLUSION

This study reported lower rates of active GO and moderate-to-severe or sight-threatening GO compared to those reported in literature. In this cohort of predominantly nonsmoking Filipinos with GO, an elevated TRAb titer emerged as a risk factor for active GO and a severe disease course.

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

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References

1. Abboud M, Arabi A, Salti I, Geara F. Outcome of thyroid associated ophthalmopathy treated by radiation therapy. Radiat Oncol. 2011;6:46-51. PMCID: PMC3108307. https://doi.org/10.1186/1748-717X-6-46.
2. Palisoc E, Morabe E, Pagkatipunan PM. Prevalence of Graves' ophthalmopathy among patients with thyroid disease. Philipp J Ophthalmol. 2010; 35(1):32-5.
3. Maheshwari R, Weis E. Thyroid associated orbitopathy. Indian J Ophthalmol. 2010; 60: 87-92. https://doi.org/10.4103/0301-4738.94048.
4. Kalmann R, Mourits MP. Diabetes Mellitus: A risk factor in patients with Graves' orbitopathy. Br J Ophthalmol. 1999;83(4):463-5. PMCID: PMC1723016.
5. Piantanida E, Tanda ML, Lai A, Sassi L, Bartalena L. Prevalence and natural history of Graves' orbitopathy in the XXI century. J. Endocrinol. Invest. 2013;36(6): 444-9. PMID: 23587873. https://doi.org/10.3275/8937.
6. Lim SL, Lim AKE, Mumtaz M, Hussein E, Bebakar WMW, Khir AS. Prevalence, risk factors, and clinical features of thyroid-associated ophthalmopathy in multiethnic Malaysian patients with Graves' disease. Thyroid. 2008;18(12): 1297-301. PMID: 19012471. https://doi.org/10.1089/thy.2008.0044.
7. Besharati MR, Rastegar A. Clinical study of ophthalmopathy in patients with Graves' disease. Asian J of Ophthalmol. 2005;7(3): 108-12.
8. Tellez M, Cooper J, Edmonds C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. Clin Endocrinol (Oxf). 1992;36(3):291-4. PMID: 1563082.
9. Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: Reality and perspectives. Endocr Rev. 2000; 21(2):168-99. PMID: 10782363. https://doi.org/10.1210/edrv.21.2.0393.
10. Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. Thyroid. 2010; 20(7):777-83. PMID: 20578901. PMCID: PMC3357079. https://doi.org/10.1089/thy.2010.1634.
11. Laurberg P, Berman D, Pedersen I, Andersen S, Carlé A. Incidence and clinical presentation of moderate to severe Graves' orbitopathy in a Danish population before and after iodine fortification of salt. J Clin Endocrinol Metab. 2012;97(7):2325-32. PMCID: PMC3387399.
12. Food and Nutrition Research Institute-Department of Science and Technology. 7th National nutrition survey: 2008. http://www.fnri.dost.gov.ph/index.php/19-nutrition-statistic/108-7th-national-nutrition-survey. Accessed November 7, 2015.
13. Prummel M, Strieder T, Wiersinga W. The environment and autoimmune thyroid diseases. Eur J Endocrinol. 2004;150(5):605–18.PMID: 15132715. https://doi.org/ 10.1530/eje.0.1500605.
14. Campi I, Vannucchi G, Salvi M. Endocrine dilemma: Management of Graves' orbitopathy. Eur J Endocrinol. 2016; 175: R117-133. https://doi.org/ 10.1530/EJE-15-1164.
15. Lee JH, Lee SY, Yoon JS. Risk factors associated with the severity of thyroid-associated orbitopathy in Korean patients. Korean J Ophthalmol. 2010;24(5): 267-73. PMCID: PMC2955268. https://doi.org/10.3341/kjo.2010.24.5.267.

ONLINE FIRST | September 7, 2017 | https://doi.org/10.15605/jafes.032.02.09

16. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et.al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed Graves' hyperthyroidism seen at a single center. J Clin Endocrinol Metab. 2013;98(4):1443-9. PMID: 23408569. https://doi/org/10.1210/jc.2012-3873.
17. Chan LL, Tan HE, Fook-Chong S, Teo TH, Lim LH, Seah LL. Graves' ophthalmopathy: The bony orbit in optic neuropathy, its apical angular capacity, and impact on prediction of risk. AJNR Am J Neuroradiol. 2009;30(3):597-602. PMID: 19147718. https://doi.org/10.3174/ajnr.A1413.
18. Wiersinga WM. Graves' orbitopathy: Management of difficult cases. Indian J Endocr Metab. 2012;16(Suppl 2):S150-2. PMCID: PMC3603013.
19. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy guidelines for the management of Graves' orbitopathy. Eur Thyroid J. 2016;5(1):9-26. PMID: 27099835. PMCID: PMC4836120. https://doi.org/10.1159/000443828.
20. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for Graves' orbitopathy: Efficacy and morbidity. J Clin Endocrinol Metab. 2011; 96(2):320-32. PMID: 21239515. https://doi.org/10.1210/jc.2010-1962.
21. Palmero MO, Lucarelli MJ. Evolving techniques in orbital decompression of thyroid orbitopathy. Philipp J Ophthalmol. 2007;32(1):28-31.
22. Ponto KA, Pitz S, Pfeiffer N, Hommel G, Webber MM, Kahaly GJ. Quality of life and occupational disability in endocrine orbitopathy. Dtsch Arztebl Int. 2009; 106(17):283-9. PMID: 19547630. PMCID: PMC2689575. https://doi.org/10.3238/arztebl.2009.0283.
23. Virola, R. "How rich is rich?" Family income and expenditures survey and consumer Price indexes of the National Statistics Office. 2010. http://www.nscb.gov.ph/headlines/StatsSpeak/2010/061510_rav_joe.asp. Accessed November 7, 2015.
24. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. Clin Sci. 1945;5(3-4):177-94. PMID: 21011937.
25. Savku E, Gündüz K. Diagnosis, follow-up and treatment results in thyroid ophthalmopathy. Turk J Ophthalmol. 2015;45(4):156-63. PMCID: PMC5082274. https://doi.org/ 10.4274/tjo.93609.
26. Khong JJ, Finch S, De Silva C, Rylander S, Craig JE, Selva D, et al. Risk factors for Graves' orbitopathy; The Australian thyroid-associated orbitopathy research (ATOR) study. J Clin Endocrinol Metab. 2016;101(7):2711-20. PMID: 27055083. https://doi.org/10.1210/jc.2015-4294.
27. Mukasa K, Noh JY, Kouzaki A, et al. TSH receptor antibody titers measured with a third-generation assay did not reflect the activity of Graves' ophthalmopathy in untreated Japanese Graves' disease patients. Endocr J. 2016; 63(2):151-7. https://doi.org/10.1507/endocrj.EJ15-0137.
28. Lim NC, Sundar G, Amrith S, Lee KO. Thyroid eye disease: A Southeast Asian experience. Br J Ophthalmol. 2015;99(4):512-8. PMID: 25361748. https://doi.org/10.1136/bjophthalmol-2014-305649.
29. Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: Impact of smoking severity and current vs. lifetime cigarette consumption. Clin Endocrinol (Oxf). 1996; 45: 477–81. PMID: 8959089.
30. Gerding MN, van der Meer JWC, Broenink M, Bakker O, Wiersinga WM, Prummel MF. Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. Clin Endocrinol (Oxf). 2000; 52(3):267-71. PMID: 10718823.
31. Noh JY, Hamada N, Inoue Y, Abe Y, Ito K, Ito K. Thyroid-stimulating antibody is related to Graves' ophthalmopathy, but thyrotropin-binding inhibitor immunoglobulin is related to hyperthyroidism in patients with Graves' disease. Thyroid. 2000;10(9):809-13. PMID: 11041459. https://doi.org/10.1089/thy.2000.10.809.
32. Woo YJ, Jang SY, Lim THT, Yoon JS. Clinical association of thyroid stimulating hormone receptor antibody levels with disease severity in the chronic inactive stage of Graves' orbitopathy. Korean J Ophthalmol. 2015; 29(4):213-9. PMCID: PMC4520863. https://doi.org/10.3341/kjo.2015.29.4.213.
33. Massart C, Sapin R, Gibassier J, Agin A, d'Herbomez M. Intermethod variability in TSH-receptor antibody measurement: Implication for the diagnosis of Graves disease and for the follow-up of Graves ophthalmopathy. Clin Chem. 2009; 55(1):183-6. PMID: 19028818. https://doi.org/10.1373/clinchem.2008.115162.
34. Kamath C, Adlan MA, Premawardhana LD. The role of thyrotrophin receptor antibody assays in Graves' disease. J Thyroid Res. 2012;2012:525936. PMID: 22577596. PMCID: PMC3345237. https://doi.org/10.1155/2012/525936.
35. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of disease. J Clin Endocrinol Metab. 2006;91(9):3464-70.PMID: 16835285. https://doi.org/10.1210/jc.2005-2813.
36. Iyer S, Bahn R. Immunopathogenesis of Graves' ophthalmopathy: The role of the TSH receptor. Best Pract Res Clin Endocrinol Metab. 2012;26(3):281-9. PMCID: PMC3361679. NIHMSID: NIHM334372. https://doi.org/10.1016/j.beem.2011.10.003.
37. Smith TJ, Janssen JA. Building the case for insulin-like growth factor receptor-I involvement in thyroid-associated ophthalmopathy. Front Endocrinol (Lausanne). 2016;7:167. PMCID: PMC5206614. https://doi.org/ 10.3389/fendo.2016.00167.
38. Smith TJ. TSH-receptor-expressing fibrocytes and thyroid-associated ophthalmopathy. Nat Rev Endocrinol. 2015;11(3):171-81. PMID: 25560705. PMCID: PMC4687015. https://doi10.1038/nrendo.2014.226.

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ORIGINAL ARTICLE

Development and Validation of a Questionnaire Evaluating Impaired Hypoglycemia Awareness among Adult Filipino Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction. Hazards of hypoglycemia include accidents, cardiovascular events, neurologic damage, and impaired hypoglycemia awareness (IHA) which presents as inability to perceive and respond to hypoglycemic warning symptoms.

Objective. This study aimed to develop the first questionnaire evaluating IHA adapted from Clarke Hypoglycemia Index (CHI) and validated among adult Filipino patients with Type 2 Diabetes Mellitus (T2DM).

Methodology. A questionnaire development study was conducted involving CHI linguistic translation, its modification through literature review and focus group discussions, panel synthesis, and content validity. A cross-sectional analytic study followed by administration of the questionnaire to 117 adult Filipinos with T2DM, advanced age, long-standing T2DM, insulin or sulfonylurea, polypharmacy, comorbidities and/or prior hypoglycemia. There were 9 participants in pilot testing, 69 in criterion validity against continuous glucose monitoring (CGM), and 108 in construct validity.

Results. IHA domains in the concept map included Elusive Euglycemia Model, Developmental Model, and Cognitive Model. The Filipino-CHI formulated had 8 questions with content validity scores ranging from 87.5-93.75%. Owing to brevity, its internal consistency Cronbach's alpha was 0.45. Criterion validity against CGM yielded 21 patients with biochemical hypoglycemic events, of which 2 had clinical hypoglycemic events and 19 were positive monitor-identified IHA. A questionnaire IHA cutoff score of ≥4 had sensitivity of 89.47%, and area under the curve of 0.55.

Conclusion. An 8-item questionnaire evaluating IHA among adult Filipino T2DM patients was developed and validated.

Key words: diabetes mellitus, hypoglycemia, questionnaire

INTRODUCTION

Landmark trials established benefits of glycemic control but forewarned against severe hypoglycemia.[1] Associated factors include those on insulin, sulfonylurea, or polypharmacy; with antecedent hypoglycemia, increasing age, prolonged diabetes, menopause, neurologic, renal, cardiovascular, or hepatic diseases. Hazards include dementia, fall, cardiovascular events, poor quality of life, IHA, further hypoglycemia and mortality. Akin to hypoglycemia is IHA, forming a vicious cycle.[2] IHA is defined as the onset of hypoglycemia before autonomic warning symptoms, presents as inability to perceive hypoglycemic symptoms, and is linked to hypoglycemia-associated autonomic failure.[3] Clamp studies demonstrated lower magnitude of glucagon and epinephrine responses even when glucose dropped to 59 mg/dL among elderly diabetic patients.[4] At blood glucose below 50 mg/dL on a day post-hypoglycemia, epinephrine release was lowered to 200 ng/L which was half that observed when with prior hyperglycemia.[5] Brain lactate, the alternative fuel source, decreased among patients with Type 1 diabetes with IHA whereas those without showed stable lactate.[6] Thalamic blood flow increase that positively correlated with epinephrine response observed during moderate hypoglycemia.[7] IHA prevalence approaches 10% among T2DM patients on insulin, and 6% among those on oral hypoglycemic agents.[8] IHA prevention starts with detection. Current methods of symptom reporting and monitoring are either costly or irrelevant to symptoms hence the role of symptom-dependent questionnaires. Defining hypoglycemia remains challenging because thresholds for symptoms decrease with hypoglycemia, but increase with worsening diabetes. Currently recommended for IHA and recurrent hypoglycemia, CGM detects IHA with 88% specificity and 75% sensitivity.[9-10]

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Among 4 IHA questionnaires published, namely GS (Gold Score), CHI (Clarke Hypoglycemia Index), PBQ (Pederson-Bjergaard Questionnaire), Hypo-AQ (Hypoglycemia Awareness Questionaire), only the single-question Likert scale GS and the eight-item questionnaire CHI were validated.[11-14] A comparison study among GS, CHI, and PBQ demonstrated hypoglycemia at 24%, 26%, and 62% respectively, with only the first two approximating prevalence studies at 25%.[15] Whereas CHI has Spanish and Catalan versions recently validated, there is no Filipino questionnaire.[16]

This study aimed to develop a validated questionnaire on IHA adapted from CHI by: (1) formulating a culturally-adapted Filipino version of CHI; (2) evaluating content validity of the translated and modified CHI; (3) the criterion validity against CGM with activity diary and receiver operator curve; (4) appraising the internal consistency.

METHODOLOGY

The first phase: Questionnaire Construction Phase, a questionnaire development study consisted of a linguistic translation of CHI and modification by: (1) literature review, (2) focused group discussions, (3) synthesis by an expert panel. The second phase: Questionnaire Administration Phase was a cross-sectional analytic study with: (1) pre-testing, (2) construct validity, (3) internal reliability, and (4) criterion validity test. It involved adult Filipinos with physician-diagnosed T2DM, based on American Diabetes Association Standards of Medical Care 2017 (Table 1), voluntarily recruited by active recruitment, gathered by purposive sampling from the Out-Patient Department of Philippine General Hospital. Patients were: Filipino by ethnicity, nationality, and residence; with physician-diagnosed T2DM, age 19 years and above, with informed consent, and any of the following: long-standing diabetes mellitus, on insulin or sulfonylurea, co-morbidities, and antecedent hypoglycemia. Patients unable to read and write, with retinopathy, cerebrovascular disease deficits, fractures, or amputations, were still included provided they had caregivers to assist them with the questionnaire. Patients who were pregnant, or with psychiatric comorbidities, or who did not give their consent were not included in the study. For Phase I Part 2, Questionnaire Modification Phase, a focused group discussion with 6-8 study participants per group, and a total of 4 groups were conducted.[17] For Phase II Part 1 or Pre-testing, 10% of the final testing sample size or a group of 8 patients participated.[18] For Phase 2 Part 2 Criterion Validity, using the prevalence of 6%, confidence interval of 95%, maximum margin of error of 7%, and preset sensitivity of 90%, the calculated sample size of 68 T2DM patients were recruited.[19] For Phase 2 Part 4 Construct Validity, 108 patients were recruited, the sample size to account for subject-to-item exploratory factor analysis ratio of 10 respondents for every 1 item question, that is minimum 80.[18]

Table 1. Operational definition of terms

Terms	Definition
Type 2 Diabetes Mellitus adult	Patients aged 19 and above, with physician-diagnosed Type 2 Diabetes Mellitus in accordance with American Diabetes Association[9]
Biochemical Hypoglycemia	Any recorded instantaneous continuous glucose monitoring at or below 70mg/dl, the alert level in accordance with American Diabetes Association[9]
Clinical Hypoglycemia	Any recorded neuroglycopenic or autonomic symptom noted on the Activity Diary of the patient such as trembling, cold clammy sweating, hunger, nausea, incoordination, light-headedness, confusion, sudden behavioral changes, loss of consciousness, resolved by glucose administration
Monitor-identified Impaired Hypoglycemia Awareness	Onset of Biochemical hypoglycemia without Clinical Hypoglycemia
Questionaire-identified impaired awareness of hypoglycemia	Score at or above the identified cutoff value signifying impaired recognition of hypoglycemia, calculated by criterion validity test

Phase I: Questionnaire Construction

Phase I Part 1: Translation, Backward translation and Synthesis

Komisyon ng Wikang Filipino translated the Clarke Hypoglycemia Index into Filipino. *Sentro ng Wikang Filipino* independently translated the Filipino version back into English. Forward and backward translations were collated by an expert panel of: (1) adult endocrinologist, (2) public health doctor, (3) the previous forward and back translators, who formulated the Translated CHI version.

Phase I Part 2: Modification

Phase I Part 2.a: Literature Review and Focused group discussion (FGD)

Literature search from PUBMED, HERDIN, and Google Scholar was used then incorporated into concept list. There were 4 Focus Group Discussions (FGD) held, each with 6-8 patients. Translated CHI was modified using the concept list and FGD into a concept map (Figure 1), as recommended by expert panel of doctors specialized in: (1) adult endocrinology, (2) internal medicine, (3) neurosciences, and (4) public health. The output was Modified CHI.

Phase I Part 2.b: Content Validity

Modified CHI was graded by Content Validity Scores (CVS), a Likert scale of 1 to 4 with: 1- least relevant and must be removed, 2- must modify entire statement to be included, 3- must modify a word to be included, or 4- most relevant and must be included. A CVS of at least 83% qualified it for inclusion.[20] The output was Filipino-CHI draft.

Phase 2: Questionnaire Administration

Phase 2 Part 1: Pretesting

Filipino-CHI draft was pretested on 9 adult Filipino T2DM patients interviewed regarding clarity, acceptability, and tolerability of the instructions and questions. Length of time taken was recorded. The output was Pre-tested Filipino-CHI.

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Phase 2 Part 2: Criterion Validity Test against CGM

Pre-tested Filipino-CHI was compared with the hypoglycemic events noted on a CGM not recorded as symptomatic on the patient's activity diary. Patients were admitted in the wards for 24-hour observation wearing the validated iPro2 CGM. Patients recorded activities, meals, exercise, autonomic or neuroglycopenic symptoms in the Activity Dairy. CGM data, calibrated to validated capillary blood glucose, was uploaded to the iPRO2 software, and was correlated with Activity Diary. Biochemical Hypoglycemic Events (BHE) was defined as instantaneous glucose monitoring below 70 mg/dl in concordance to the consensus of ADA and Endocrine Society. Clinical Hypoglycemic Event (CHE) was defined as at least one hypoglycemic autonomic or neuroglycopenic symptom noted on Activity Diary (Table 1). Any BHE without concurrent CHE was considered as Monitor-identified IHA (mIHA). This was to differentiate it from the Questionnaire-identified IHA (qIHA) or the number of questions signifying IHA in the Pre-tested Filipino CHI. Calculations were done by: (1) arbitrarily setting cutoffs for qIHA scores compared against mIHA scores; (2) plotting 1-Specificity against Sensitivity for every set cutoff; (3) depicting a resulting Receiver Operator Curve; (4) identifying the topmost intersecting point value representing the Pre-tested Filipino CHI cutoff for IHA.

Phase 2 Part 3: Internal Consistency Test

Pre-tested Filipino CHI was answered by 108 patients to assess Cronbach's alpha coefficient of internal consistency.

Data analysis was done by an independent analyst separately for each corresponding phase. Study data was encoded in Microsoft Excel then was analyzed using Stata SE v.13 software. University of the Philippines Manila Research Ethics Board Panel approved the research. Developers of the CHI provided written approval for study.

RESULTS

Phase I: Questionnaire Construction Output

Phase I Part 1: Translation, Backward translation and Synthesis Output

Forward translation was done by *Komisyon ng Wikang Filipino*. Back translation was done by *Sentro ng Wikang Filipino*. Both translations were assessed faithful to the original version, except for minor correctable grammatical errors.

Phase I Part 2: Modification Output

Literature search in PUBMED using keywords as follows: "hypoglycemia" [MeSH Terms] OR Hypoglycemia [Text Word] AND questionnaire AND unawareness yielded 103 hits, from which questionnaires GS, CHI and its Spanish/Catalan translations, PBQ, Hypo-AQ were gathered. For local data, a search in HERDIN using keyword "hypoglycaemia," local publication type, dating 1990-2015, resulted in 4 hits, none of which showed a questionnaire on impaired hypoglycemia awareness in Filipino.

Focused group discussions noted that adult Filipino diabetic patients differed from other patients, mostly in the lack of comprehension of hypoglycemia and IHA, necessitating a two-step explanation to introduce IHA. Elaboration of symptomatology and inciting events served as cues to help patients recall IHA.

IHA literature list and IHA discussion list generated a concept map (Figure 1) from which the final modified CHI-Filipino version was formulated. Concept domains identified included: (1) Elusive Euglycemia model, (2) Developmental Model, and (3) Cognitive Models. The first model pertained to patients' issues of being anxious about inability to consistently reach the ideal glucose level which cause patient maladaptation practices risking hypoglycemia and IHA. This was represented by Question Number 4 which related to fear of hypoglycemia; and Question Number 8 which related to patient-identified change or reduction of sensitivity to his/her hypoglycemia episodes. Developmental model pertained to exposures predisposing to the occurrence of IHA. This was represented by Questions Number 2, 3, 5 evaluating severe hypoglycemia episodes and symptomatic hypoglycemia. Cognitive model pertained to presence of patient's baseline ability to sense hypoglycemia as was represented by Questions Number 1, 6 and 7. The significant domain was hypoglycemia, a cause and effect factor of IHA, and a cause of all 3 other domains, hence separately connected to impaired hypoglycemia awareness, and all three models. Subheadings of each domain were represented by the introductory paragraph elaborating on hypoglycemia preceding the IHA questions.

Questionnaire was evaluated for Content Validity Scores showing: Questions Number 1-6 with 93.75%, Questions Number 7 and 8 with 87.5% (Table 2).

Phase II: Questionnaire Administration Output

Phase II Part 1: Pilot testing Output

Pilot testing on 9 participants identified recommendations for: (1) change of "*instruksyon*" to "*panuto*"; (2) use of complete phrases in choices; (3) removal of glucose units "mg/dL"; (4) addition of choice "*hindi naitala ang asukal ko sa dugo*"; (5) inclusion of checkmark. Length of time to finish the questionnaire remained acceptable ranging from 2 to 21 minutes, with a median of 6 minutes. This could be attributed to the patients' tendencies to forget the first half of the relatively longer questions, such as Questions Number 2 and Number 3, necessitating rereading. The output was Filipino-CHI Pretested.

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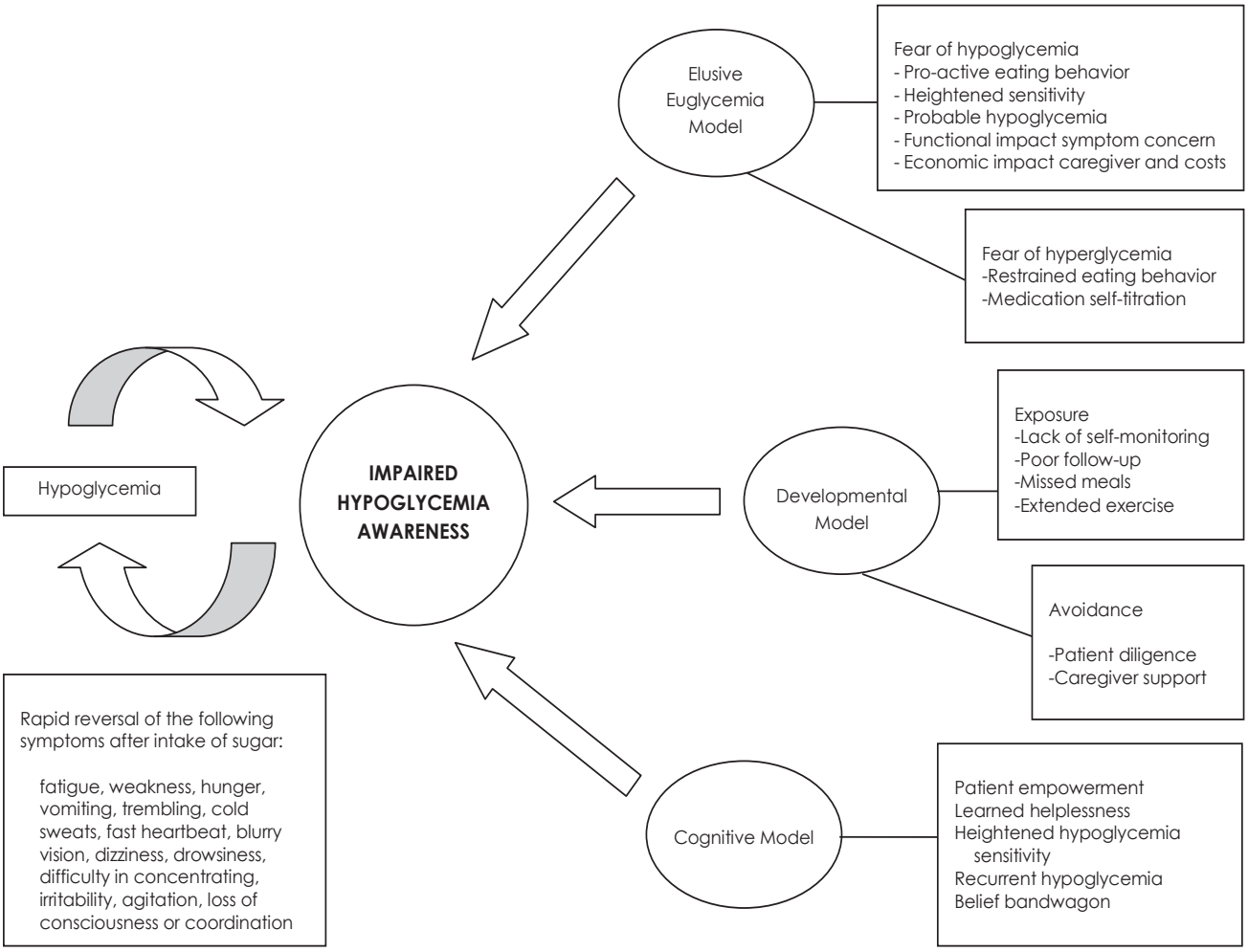

Figure 1. Concept map (English) of the Filipino version of Clarke Hypoglycemia Index.

Table 2. Content validity scores of item questions of Filipino-CHI

Expert Panelist	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Epidemiology	3	4	4	4	4	4	4	3
Neurology	4	3	3	3	4	4	3	4
Medicine	4	4	4	4	4	4	4	3
Endocrine	4	4	4	4	3	3	3	4
Average	93.75	93.75	93.75	93.75	93.75	93.75	87.5	87.5

Phase II Part 2: Criterion Validity Output

Criterion validity was assessed among 69 participants (Table 3). Congruence between CGM and Activity Diary among 69 patients yielded 21 patients or 30.4% with Biochemical Hypoglycemic Events (BHE), among which only 2 patients had Clinical Hypoglycemic Events (CHE) corresponding to intact hypoglycemia awareness or negative Monitor-identfiied IHA (mIHA). The remaining 19 patients or 90.4% had asymptomaic or positive mIHA.Questionnaire-identified IHA which corresponds to the performance of the Filipino-CHI questionnaire in detecting impaired hypoglycemia awareness was assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value of each item question and of the entire questionnaire (Table 4). Adjustments for the Filipio-CHI questionnaire cutoff score defining impaired hypoglycemia awareness were done to identify the optimal cutoff scores. Setting questionnaire-identified IHA (qIHA) scores 4 yields an acceptable sensitivity of 89.47%, but specificity could not be properly calculated, owing to only 2 patients with negative mIHA, both of which barely scored 4/8 hence incorrectly labeled qIHA+ by the Filipino-CHI questionnaire. Setting qIHA scores 5 improved the Specificity to 100%, because then these 2 patients with negative mIHA become correctly labeled qIHA- by the questionnaire in the study, but at the expense of sensitivity diminishing to 26.31%. In the setting of only 21 hypoglycemia patients and 2 negative mIHA patients, the calculated area under the curve was 0.55.

Phase II Part 3: Internal Consistency Output

Internal consistency was assessed among 108 particpants (Table 3), none previously participating on the pilot testing, by calculating Cronbach's alpha. Among them, 77.27% were females, 62.35% of whom were post-menopausal. The mean present age was 52.89 years old, mean age at diagnosis of diabetes is 45.29 years old, and the mean duration of diabetes is 10.8 ± 7.1 years. Among them, more than half completed secondary educational level, 17.59% completed elementary educational level, and the remaining 13.89% completed college or vocational degrees. Among them, 40.74% were on metformin alone, 32.4% were treated with human insulin and metformin, 7.4% with gliclazide and metformin. Among them, 30.56%

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Table 3. Demographic and clinical characteristics of study participants (Phase 2)

Characteristics	CRITERION VALIDITY (n=69) Mean±SD or n (%)	INTERNAL RELIABILITY (n=108) Mean±SD or n (%)
Age	52.8±9.7 years	52.8±9.7
Sex (female)	53 (77%)	85 (77.27%)
Duration of diabetes	10.8±7.1 years	10.8±7.1
Age at diagnosis of diabetes	45.2±9.1 years	45.2±9.1
Menopause	40 (75%)	53(62.35%)
Treatment		
Metformin alone	24 (34.6%)	44 (40.74%)
Human insulin and metformin	23 (33.2%)	35 (32.41%)
Gliclazide and metformin	6 (8.8%)	8 (7.40%)
Insulin glargine and metformin	4 (5.6%)	5 (4.6%)
Level of education		
Elementary graduate	32 (46.5%)	19 (17.59%)
High School graduate	23 (33.3%)	74 (68.51%)
College graduate with vocational course	14 (20.3%)	15 (13.89%)
Polypharmacy of 4 or more drugs	31 (44.9%)	33 (30.56%)
Co-morbidities		
Chronic kidney disease	15 (23.2%)	17 (15.74%)
Diabetes-related eye disease	14 (20.3%)	15 (13.89%)
Cardiac disease	11 (15.9%)	9 (8.33%)
Neuropathy	8 (11.6%)	7 (6.48%)
Chronic cerebrovascular disease	3 (4.2%)	3 (2.78%)
History of diabetic foot ulcer	2 (2.8%)	2 (1.85%)
Chronic Liver Disease	1 (1.4%)	1 (0.95%)
Antecedent Hypoglycemia		
Prior hypoglycemia requiring assistance from others	25(36.2%)	29 (26.85%)
Prior hypoglycemia requiring hospitalization	3 (4.2%)	5 (4.63%)
Recurrent hypoglycemia	14 (20.3%)	14 (12.96%)

Table 4. Performance of item question and of the questionnaire in predicting impaired hypoglycemia awareness

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
ITEM QUESTION				
Item #1	90.48	50	95	33
Item #2	86	50	95	25
Item #3	43	50	90	8
Item #4	10	100	100	10
Item #5	10	100	100	10
Item #6	33	0	40	0
Item #7	95	50	95	50
Item #8	48	0	83	0
QUESTIONNAIRE CUTOFF				
Score cutoff 8	0	100	0	9.52
Score cutoff 7	0	100	0	9.52
Score cutoff 6	10.52	100	100	10.52
Score cutoff 5	26.3	100	100	11.76
Score cutoff 4	89.5	0	89.47	0
Score cutoff 3	89.5	0	89.47	0
Score cutoff 2	100	0	100	0
Score cutoff 1	100	0	100	0
Score cutoff 0	100	0	100	0

were on polypharmacy of 4 or more drugs, 15.74% had nephrologist-diagnosed chronic kidney disease, 13.89% had ophthalmologist-diagnosed diabetic retinopathy or non-traumatic cataract. Among them, 26.85% had prior hypoglycemic episodes requiring assistance from others, 12.76% had recurrent hypoglycemia, and 4.63% had prior severe hypoglycemia requiring hospital management.

With only 8 questions subdivided into only 3 domains answered by this particular group of 108 participants, Cronbach's alpha of the entire questionnaire was 0.45, Elusive Euglycemia Model domain 0.17, Developmental Model domain 0.39, Cognitive Model domain 0.33.

DISCUSSION

An eight-item Filipino-CHI questionnaire was formulated tailored to adult Filipino T2DM patients by literature review, four focus group discussions with patients and their caregivers, and consultations with relevant specialists who altogether graded each finalized item question with acceptable content validity scores. Gold Score (GS), the first internationally developed, is a validated visual analogue scale with the single question "Do you know when your hypos are commencing?" to be answered in a Likert scale of 1 to 7, where scores above 4 are labeled IHA. This single question is represented as Question number 1 in CHI and, Spanish and Catalan versionsof CHI, and this Filipino-CHI questionnaire. Similar to the original, Spanish and Catalan versions of CHI, the Filipino-CHI had impaired hypoglycemia awareness cutoff score optimally set at ≥4 answers that correspond to "R or reduced awareness". Contrary to other questionnaires evaluating hypoglycemia awareness, this Filipino-CHI questionnaire was the only tool which underwent criterion validity testing against a measurable

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biochemical variable, the continuous glucose monitoring. This is crucial because hypoglycemia awareness depends on baseline knowledge and symptom recognition hence making it a highly subjective concept with considerable inter-individual differences in perception. A cutoff level of R≥4 gives an acceptable screening tool performance with a sensitivity of 89.47%. The area under the curve (AUC) of 0.55 could not be properly assessed due to the limited percentage of patients experiencing hypoglycemia that is only 21 out of 69, of which only 2 out of 21 tested negative monitor-identified IHA could be used for calculating specificity and AUC. Still this is relatively higher than reportted IHA prevalence as a result of the inclusion criterion of IHA associated factors, informed monitoring, regulated diet, activity, compliance, and sleep of participants. BHE cutoff set at hypoglycemia safety alert level 70 mg/dL instead of hypoglycemia symptom occurrence level 55 mg/dL may also have prematurely labeled some patients as mIHA.[21]

In assessing its internal consistency, Cronbach's alpha coefficient yielded unfavorable results, owing to the minimal number of item questions and domains into which the concise concept of impaired hypoglycemia awareness was categorized. Covering all the impaired hypoglycemia issues accumulated in the concept map, only 8 item questions about IHA were generated. The concept map illustrated the broadness of hypoglycemia concept and the conciseness of hypoglycemia awareness itself. This was reflected in the finalized questionnaire with a preceding comprehensive description of the concept of hypoglycemia, followed by the succinct eight-item interrogation about hypoglycemia awareness. For this reason, content validity test and criterion validity test may be more relevant than internal reliability, because the latter improves with increasing number of concept domains and item questions. Cronbach's alpha is lowered by brevity of the test, because it is improved by each related item question testing the same concept.[22] More importantly, Cronbach's alpha is a function of the scores on a test from that specific group of participants, for which it is recommended not to depend on published alpha estimates and is advised to measure alpha each time a test is utilized. Because this study was conducted in the service out-patient clinics of a government-subsidized tertiary referral center, the participants involved were mostly aged, females, with long-standing T2DM, and notably non-working attaining secondary level education only.

Prevalence studies among Filipino T2DM patients revealed characteristics similar in being mostly aged 61.56 ± 11.3 years old, females at 68%, long-standing 9 ± 6 years, but strikingly dissimilar in educational attainment that is a greater percentage reaching college level in 50% than secondary level in 32%.[23] Because this questionnaire evaluated impaired hypoglycemia awareness, sensitivity to and ability to report hypoglycaemia necessitates adequate knowledge, understanding, memory and logic which may be improved with increasing educational attainment. This questionnaire may hence perform differently among patients with diabetes mellitus in the community. Similarly, factor analysis using Kaiser criterion or scree plot was not performed because of the initial brevity of the questionnaire formulated. For this reason, the questionnaire validity tests performed might have been limited by having to tailor to this particular group of participants in this study. Further multi-center studies conducted on a bigger number of adult patients with T2DM whose characteristics better represent adult Filipinos with T2DM in a setting that better typifies their daily activities may yield a different result.

CONCLUSION

An 8-item questionnaire evaluating IHA tailored to adult Filipinos with T2DM was developed and validated with acceptable content validity and criterion validity, and may be used in screening for IHA who may then be recommended to have confirmatory CGM. Further multi-center studies conducted on a bigger number of adults with T2DM whose characteristics better represent adult Filipinos with T2DM in a setting that better typifies their daily activities may yield a different result. Validation on population with higher risk for IHA such as patients with Type 1 Diabetes Mellitus may be a focus of future studies.

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

Author Disclosure
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References

1. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet.1998;352(9131):837-53. PMID: 9742976.
2. De Galan BE, Schouwenberg BJ, Tack CJ, Smits P. Pathophysiology and management of recurrent hypoglycaemia and hypoglycaemia unawareness in diabetes. Neth J Med 2006;64(8):269-79. PMID: 16990690.
3. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2013;369(4):362-72. PMID: 23883381. https://doi.org/10.1056/NEJMra1215228
4. Ortiz-Alonso FJ, Galecki A, Herman WH, Smith MJ, Jacquez JA, Halter JB. Hypoglycemia counterregulation in elderly humans: Relationship to glucose levels. Am J Physiol 1994;267(4 Pt 1):E497–506. PMID: 7943297.
5. Dagogo-Jack SE, Craft S, Cryer PE, Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. J Clin Invest. 1993;91(3):819-28. PMCID: PMC288033. https://doi.org/10.1172/JCI116302.
6. Wiegers EC, Rooijackers HM, Tack CJ, Heerschap A, de Galan BE, van der Graaf M. Brain lactate concentration falls in response to hypoglycemia in patients with type 1 diabetes and impaired awareness of hypoglycemia, Diabetes. 2016;65(6):1601-5. PMID: 26993070. https://doi.org/10.2337/db16-0068.

ONLINE FIRST | September 30, 2017 | https://doi.org/10.15605/jafes.032.02.10

7. Mangia S, Tesfaye N, De Martino F, et al. Hypoglycemia induced increases in thalamic cerebral blood flow are blunted in subjects with type 1 diabets and hypoglycemia unawareness. J Cerebral Blood Flow Metab. 2012;32(11):2084-90. PMCID: PMC3494000. https://doi.org/10.1038/jcbfm.2012.117.
8. Seltzer HS. Drug-induced hypoglycemia. A review of 1418 cases. Endocrinol Metab Clin North Am. 1989;18(1):163-83. PMID: 2645125.
9. American Diabetes Association. Standards of Medical Care in Diabetes-2017. Diabetes Care. 2017;40(Suppl 1):S1-132. http://www.epi.uff.br/wp-content/uploads/2013/10/dc_40_s1_final.pdf.
10. Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metab Res Rev. 2003;19(3):232-40. PMID: 12789657. https://doi.org/10.1002/dmrr.377.
11. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994;17(7):697-703. PMID: 7924780.
12. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. Diabetes Care. 1995;18(4):517-22. PMID: 7497862.
13. Pedersen-Bjergaard U, Pramming S, Heller SR, et al. Severe hypoglycemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev. 2004;20(6):479-86. PMID: 15386817. https://doi.org/10.1002/dmrr.482.
14. Speight, J, Barendse SM, Singh H, et al. Characterizing problematic hypoglycemia: Iterative design and preliminary psychometric validation of Hypoglycemia Awareness Questionnaire (HypoA-Q). Diabet Med. 2016;33(3):376-85. PMID: 26042777. https://doi.org/10.1111/dme.12824.
15. Geddes J, Wright RJ, Zammit NN, Deary IJ, Frier BM. An evaluation of methods of assessing impaired awareness of hypoglycemia in type 1 diabetes. Diabetes Care. 2007;30(7):1868-70.
16. Jansà M, Quirós C, Giménez M, Vidal M, Galindo M, Conget I. Análisis psicométrico de las versiones en lengua castellana y catalana de un cuestionario de percepción de la hipoglucemia. Medicina Clínica. 2015;144(10): 440-4. https://doi.org/10.1016/j.medcli.2013.11.036.
17. How to conduct a focus group [Online], 2014. Available in https://assessment.trinity.duke.edu/documents/How_to_Conduct_a_Focus_Group.pdf. Accessed January 26, 2016.
18. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform. 2014;48:193-204. PMID: 24582925. https://doi.org/10.1016/j.jbi.2014.02.013.
19. Nunally JC. Book review: Pychometric theory: 3rd ed. In Nunally, JC, Bernstein IH. The role of factor analysis. New York: McGraw-Hill, 1994.
20. Measuring learning & performance: A primer. Chapter 3 Psychometrics: Reliability & validity [Online] 2014. Available in http:// charlesdennishale.org/Measuring-Learning-and-Performance/3-MLP-Psychometrics-Reliability-and-Validity-3.1.pdf. Accessed August 22, 2017.
21. Cryer P. Hypoglycemia. In: Melmed, S; Polonsky K, Larsen P, et al. William's Textbook of Endocrinology, 13th ed.; Elsevier, 2016.
22. Tavakol M, Dennik R. Making sense of Cronbach's alpha. Int J Med Educ. 2011;2:53-5. PMCID: PMC4205511. https://doi.org/10.5116/ijme.4dfb.8dfd.
23. Jimeno CA, Sobrepeña LM, Mirasol RC. Diab Care 2008: Survey on glycaemic control and the status of diabetes care and complications among patients with type 2 diabetes mellitus in the Philippines. Philipp J Intern Med. 2012;50(1):15-22.

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CASE REPORT

Pituitary Abscess Mimicking a Pituitary Adenoma Presenting with Secondary Amenorrhea and Blurring of Vision: A Case Report*

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Abstract

Pituitary abscess is a rare condition. It can present with hormonal deficiencies and may affect reproductive health. We present a case of a 43-year-old female presenting with bitemporal hemianopsia and amenorrhea. Imaging of the pituitary showed a sellar-suprasellar mass 2.6 x 2.4 x 1.8 cm with an enhancing nodular component. Pre-operative diagnosis was pituitary adenoma with panhypopituitarism and compression of the optic chiasm. The patient underwent transsphenoidal excision of the tumor. Intraoperative findings revealed purulent fluid consistent with pituitary abscess. There was immediate improvement of vision post operatively. She did not develop diabetes insipidus. Gram stain showed polymorphonuclear (PMN) cells 0-1 per oil immersion field (OIF) and Gram-positive cocci 0-1 per OFI, however there was no growth on culture. The abscess was also negative for acid-fast bacilli and was negative on polymerase chain reaction. Histopathologic evaluation showed benign cyst contents. The patient was treated with ceftriaxone 2 grams every 12 hours for 14 days and was eventually discharged with prednisone and levothyroxine. Pituitary abscess is an important differential diagnosis for sellar and suprasellar masses. There are no specific clinical and radiologic features that will enable a preoperative diagnosis of pituitary abscess.

Key words: pituitary abscess, amenorrhea, blurring of vision

INTRODUCTION

Since Simmonds reported the first case of pituitary abscess in 1914, only 200 cases have been reported in medical literature. There are no specific clinical presentations and imaging features that will make a preoperative diagnosis of a pituitary abscess possible. Pituitary abscess is an important differential diagnosis in patients presenting with a sellar-suprasellar mass.

CASE

We present the case of a 43-year-old female presenting with secondary amenorrhea. Ten months prior to her admission, she presented with cessation of menses. Two months prior to admission, she had bilateral temporal loss of vision. The patient had no known prior infection or surgical procedure done. The patient was fertile and was able to conceive twice before. Apart from bitemporal hemianopsia, the rest of the physical examination was normal. Preoperative diagnosis was a non-functioning pituitary adenoma with hypopituitarism and optic chiasmal compression. During transsphenoidal surgery, instead of a solid mass, there was egress of purulent fluid upon puncturing of the capsule, findings compatible with an abscess. There was immediate improvement in visual acuity and visual fields after surgery. The patient was treated with intravenous ceftriaxone 2 g every 12 hours for 14 days. She developed a cerebrospinal fluid leak, which was successfully treated with acetazolamide and drainage of CSF via lumbar tap. There was no post-operative diabetes insipidus.

Magnetic resonance imaging (MRI) of the pituitary gland showed a hetergenous sellar-supra-sellar rim-enhancing mass (Figure 1).

Prior to surgery, her pituitary function was evaluated. Hyperprolactenemia as the cause of amenorrhea was ruled out because the prolactin level was normal at 92.2 uIU/ml, (N: 92-868). The patient had hypogonadotrophic hypogonadism as shown by the low follicle stimulating hormone (FSH) 0.35 miU/ml (N: 0.6-9.5) and low estradiol 29.7 pg/ml, (N 127-476). The patient also had secondary hypothyroidism her TSH 0.5 μiU/ml (N: 0.3-5.4) and fT4 9.4 pmol/L (N: 11-24) were both low. The patient also had secondary hypocortisolism with an 8AM cortisol of 39.54 nmol/L (N: 138-690). Serum adrenocorticotrophic hormone level was not determined.

The patient did not present with diabetes insipidus. The pre-operative serum sodium was 136 mmol/L, postoperative serum sodium was 135 mmol/L (N: 136-144). Preoperative urine specific gravity was 1.024 and post operative urine specific gravity was 1.012.

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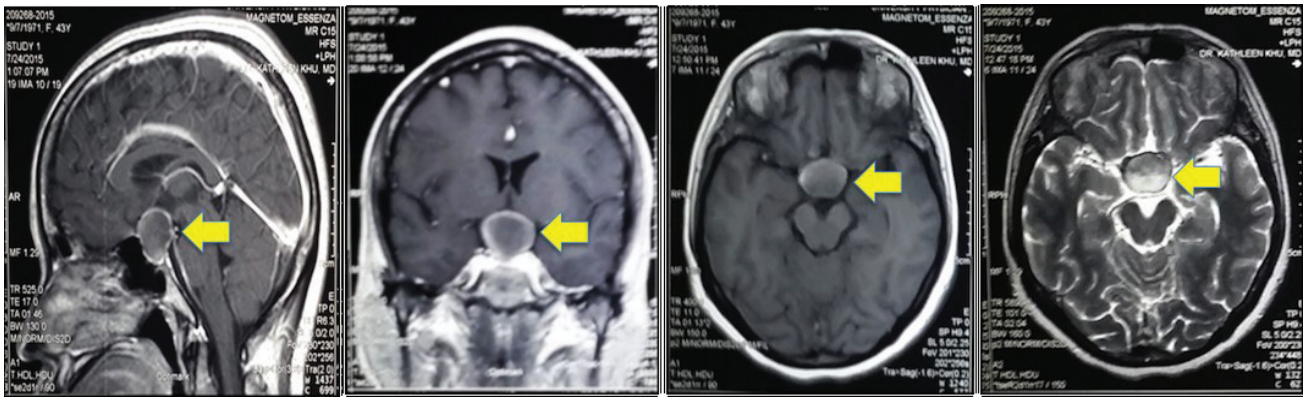

Figure 1. Post-gadolinium MRI showing (arrow) a 2.6 x 2.4 x 1.8 cm round rim-enhancing sellar-suprasellar mass with nodular component and mixed soft tissue and fluid signals compressing the optic chiasm. (a) Sagittal; (b) coronal; (c) Isointense on T1W1; and (d) hyperintenste on T2W1.

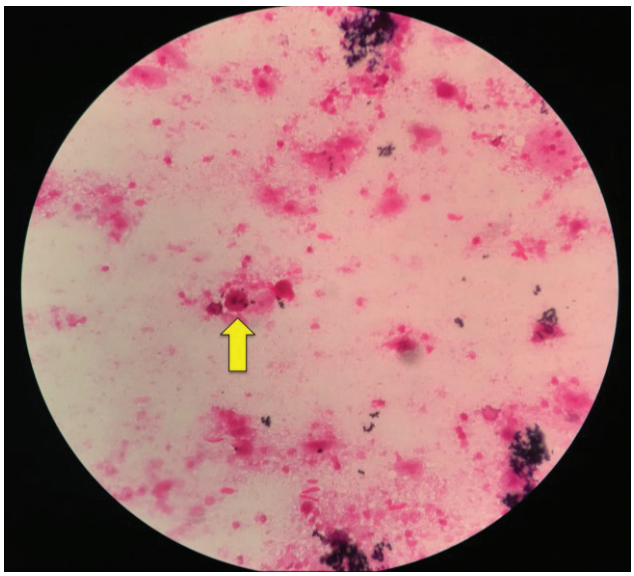

Figure 2. Histopathology specimen. Neutrophil (arrow) is seen in a background of proteinaceous or eosinophilic material with no other diagnostic cellular material (H & E, 100x).

There was no history of antecedent infection. There were no signs and symptoms such as fever. The patient had clear breath sounds and normal examination of the abdomen and genital area. Complete blood count showed a hemoglobin of 127 g/L, (N: 135-180), white blood cells 5.23 x10^9/L (N: 4.5-11.0), neutrophils 41% (N: 50-70%) and lymphocytes 46% (N: 20-50%).

Histopathology showed benign cyst contents (Figure 2). Gram stain of the abscess showed a PMN 0-1/OIF, Gram-positive cocci 0-1/OIF. However, the abscess culture had no growth after 5 days of incubations. Work up for tuberculosis was also negative. Acid-fast bacilli smear was negative, as well as the polymerase chain reaction for *M. tuberculosis*.

The primary treatment for pituitary abscess is drainage. Empiric antibiotic coverage with Ceftriaxone 2 grams was given intravenously every 12 hours for 14 days. Patient had immediate improvement of blurring of vision post-operatively. The patient was able to count fingers during visual field confrontation test. There was no post-operative diabetes insipidus. Patient had cerebrospinal leak, which was resolved by giving acetazolamide. Patient was discharged on prednisone 7.5 mg/day and levothyroxine 100 mcg/tab, once a day.

DISCUSSION

Pituitary abscess is a rare and potentially life threatening condition. Simmonds reported the first case of pituitary abscess in 1914.[1] Since then, only 210 cases have been reported worldwide.[2] It may be caused by hematogenous seeding from an infection located elsewhere in the body or via direct extension of an adjacent infection.[3] It may occur in a previously healthy patient without pre-existing infection or pituitary gland lesion such as an adenoma.[4]

In a review of 24 cases done by Vates, the most common clinical presentations were non-specific headache, pituitary dysfunction, and visual disturbances.[5] In a review of 33 cases done by Fuyi, the most common presenting symptoms of pituitary abscess are panhypopituitarism, diabetes insipidus (DI), and non-specific headache. Among the 12 females included in this review, seven presented with amenorrhea. Three of the patients had resolution of amenorrhea post operatively after 32, 44 and 57 months of follow up. Two patients had persistent amenorrhea after 57 and 188 months of follow up. There was no mention about improvement of amenorrhea in the remaining two patients.[6] In a case series done by Lemoncito et al., two cases of pituitary abscess also presented with persistent amenorrhea despite surgical drainage of the abscess after 3 and 6 months of follow up.[7] Our patient presented with panhypopituitarism, and left temporal hemianopsia. She did not present with DI or headache. She also has no prior infection. Her clinical presentation was more similar to the profile of patients described in the review of Vates. The panhypopituitarism may have been caused by the destructive process of the abscess on the pituitary leading to amenorrhea, beginning

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secondary hypothyroidism, and hypocortisolemia. The unilateral temporal hemianopsia is caused by the mass effect of the abscess, which was resolved immediately upon drainage of the abscess. However, resolution of the amenorrhea is not guaranteed as reported in the study of Fuyi and Lemoncito.[6,7] Therefore monitoring for improvement of the amenorrhea in our patient is necessary during follow up to determine the need for hormonal replacement therapy.

In the review by Vates, the most consistent finding on pituitary imaging was enlargement of the sella turcica, which demonstrated moderate to high signal levels on T2-weighted MR images, suggestive of a fluid-containing cyst and mildly intense or hypointense on T1-weighted MR images.[5] According to Fuyi, a post gadolinium rim-enhancing mass on MRI is noted in 64% of the patients with pituitary abscess.[6]

The MRI findings observed in our patient were a combination of the imaging features described in the two reviews mentioned. The MR image showed a high intensity signals on T2-weighted images and a rim enhancing mass. However, these findings are not specific for a pituitary abscess.. Differentials of rim-enhancing mass may include Rathke's cleft cysts, cystic craniopharyngiomas or cystic adenoma.[6] There seems to be no specific diagnostic features that will help in making a diagnosis of a pituitary abscess pre-operatively.

The most common isolated organisms in pituitary abscesses are Gram-positive cocci. [2,3,6] However there are two cases wherein the isolated gram-positive cocci did not grow in the culture,[5] The gram stain of the patient's abscess showed polymorphic neutrophils 0-1 /OIF and Gram-positive cocci 0-1/OIF; but there was no growth in the abscess culture. There were also no acid-fast bacilli seen and TB PCR was negative. A negative growth in the culture may have been caused by the preoperative use of antibiotics. The patient was given cefuroxime 1.5 intravenously, one hour prior to her operation.

Early diagnosis and aggressive antibiotic treatment may decrease mortality to 8.3%.[6] Together with the clinical findings, the result of the MRI can be useful to guide appropriate management. Prognosis is generally good after drainage and antibiotic therapy. However, hormonal recovery is insufficient in most case series but improvement in vision has been documented.[5] Recurrence of the abscess has been reported and monitoring should be part of follow-up care.[6]

CONCLUSION

Pituitary abscess is an important differential diagnosis for sellar and suprasellar mass even in patients without prior history of infection or surgical procedure. There are no specific clinical and radiologic features that will enable a preoperative diagnosis of pituitary abscess. Correct diagnosis is important since the management includes drainage of the abscess and appropriate antibiotic coverage. Vision may improve after drainage of abscess, however hormonal recovery is not always observed in patients with abscess even after appropriate management.

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

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

Author Disclosure
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References

1. Hanel RA, Koerbel A, Prevedello DM, Moro MS, Araújo JC. Primary pituitary abscess: Case report. Arq Neuropsiquiatr. 2002;60(3-B):861-5. PMID: 12364963. https://doi.org/10.1590/S0004-282X2002000500033.
2. Ciappetta P, Calace A, D' Urso PI, De Candia N. Endoscopic treatment of pituitary abscess: Two case reports and literature review. Neurosurg Rev. 2008;31(2):237–46. PMID: 17899232. https://doi.org/10.1007/s10143-007-0096-2.
3. Dutta P, Bhansali A, Singh P, Kotwal N, Pathak A, Kumar Y. Pituitary abscess: Report of four cases and review of literature. Pituitary. 2006;9(3): 267–73. PMID: 16845602. https://doi.org/10.1007/s11102-006-8327-z.
4. Jain KC, Varma A, Mahapatra AK. Pituitary abscess: A series of six cases. Br J Neurosurg. 1997;11(2):139-43. PMID: 9156001. https://doi.org/10.1080/02688699746492.
5. Liu F, Li G, Yao Y, Yang Y, Ma W, Li Y, et al. Diagnosis and management of pituitary abscess: Experiences from 33 cases. Clin Endocrinol (Oxf). 2011;74(1):79–88.PMID: 21039726. https://doi.org/10.1111/j.1365-2265.2010.03890.x.
6. Vates GE, Berger MS, Wilson CB. Diagnosis and management of pituitary abscess: A review of twenty-four cases. J Neurosurg. 2001;95(2):233–41. PMID: 11780892. https://doi.org/10.3171/jns.2001.95.2.0233.
7. Lemoncito MV, Lantion-Ang FL. Pituitary abscess mimicking pituitary adenoma: A review of three cases seen at the Philippine General Hospital from 2004-2007. Philipp J Intern Med. 2009;47(3): 143-50. https://www.pcp.org.ph/documents/PJIM/Volume%2047%20(2009)/Number%203%20(May-June)/8-Pituitary%20Abscess.pdf.

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CASE REPORT

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Successful Primary Medical Therapy with Somatostatin Receptor Ligand in Acromegaly with Thyroid Cancer

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Abstract

Acromegaly is a rare disease with an annual incidence of 3 to 4 cases in a million.[1] Diagnosis is often delayed due to the slow progression of the disease. Persistent elevation of growth hormone (GH) in acromegaly causes a reduction in life expectancy by 10 years. Aside from multiple cardiovascular, respiratory and metabolic co-morbidities, it has also been proven to cause an increased incidence of cancer. The main treatment of acromegaly is surgical excision of the functioning pituitary adenoma. Multiple comorbidities, including obstructive sleep apnea (OSA), left ventricular hypertrophy (LVH) and soft tissue swelling, make surgery complicated, if not impossible. Medical therapy to reduce co-morbidities may be indicated in certain situations. Somatostatin receptor ligands (SRL) are able to reduce, and possibly normalize, IGF-1 levels.[2] Reduction of insulin-like growth factor-1 (IGF-1), the main mediator of GH, is able to resolve headache, sweating, fatigue and soft tissue swelling, and also reduce ventricular hypertrophy. This case report illustrates the successful use of the SRL octreotide LAR in treating acromegaly. It also confirms the observation from several case series that thyroid cancer is the most common malignancy in acromegaly.

Key words: acromegaly, somatostatin receptor ligands, octreotide LAR, papillary thyroid cancer

INTRODUCTION

Acromegaly is characterized by somatic overgrowth, physical disfigurement, multiple co-morbidities and premature death. The main cause of this disorder is chronic hypersecretion of GH, mediating its effects directly or through IGF-1.

The control of GH secretion is the most important determinant in reducing mortality in acromegaly. Any therapy that is able to reduce GH and IGF-1 will alter the prognosis of a patient with acromegaly. Octreotide is able to normalize IGF-1 in 68% of patients and reduce GH to less than 5 μg/L in 53%.[3] A multi-center prospective study demonstrated tumor shrinkage with octreotide in all 27 newly diagnosed patients with acromegaly, with median tumor volume reduction of 49% in microadenomas and 43% in macroadenomas.[4] Thyroid cancer may also be an associated finding in long-standing undiagnosed acromegaly, as illustrated in this case report.

CASE

A 58-year-old Malay lady with underlying type 2 diabetes and hypertension for 2 years was admitted to a nearby hospital for lacunar stroke. During assessment, she was noted to have features of acromegaly. On further interview, she disclosed increased shoe (from 6 to 11) and ring (14 to 26) sizes. She also experienced hoarseness, increased sweating, weight gain and higher blood pressure on monitoring. She also observed an enlarging goiter but denied obstructive symptoms. She had severe sleep apnea symptoms based on the Epworth Sleepiness scale. There were no known endocrine disorders or malignancy in her family.

Physical examination revealed marked features of acromegaly: frontal bossing, prognathism, increased interdental separation, thick lips and coarsened facial features. Her blood pressure was 160/90 mmHg, with no clinical evidence of heart failure. She had a hard goiter with palpable cervical lymph nodes. She had moist palms and skin tags. Visual field was intact on confrontation test.

Initial tests showed elevated IGF-1 (703 μg/L, reference range 35-210) and fasting GH (10.3 ng/mL, reference range up to 8). GH was not suppressed by oral glucose loading, with a nadir of 12.9 μg/L. Follicle stimulating hormone (26.5 IU/L) and luteinizing hormone (8.6 IU/L) were low for age. Other parameters were within reference ranges (prolactin 150 IU/mL, thyroid stimulating hormone 1.15 μIU/mL, free thyroxine 13.8 pmol/L, corrected Ca 2.36 mmol/L, serum Na 138 mmol/L, serum K 4.0 mmol/L and serum creatinine 44.9 μmol/L). HbA1c was 6.9%. Sleep study yielded an Apnea-Hypopnea Index (AHI) of 36.5, indicative of severe OSA. Echocardiogram performed in

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preparation for eventual surgery showed concentric LVH and diastolic dysfunction with an ejection fraction of 65%. Magnetic resonance imaging (MRI) of the pituitary revealed a 1.5 cm x 1.8 cm x 1.1 cm macroadenoma located at the anterior pituitary invading the right cavernous sinus and encasing the right internal carotid artery. There was a clear plane separating the pituitary from the optic chiasm (Figure 1A).

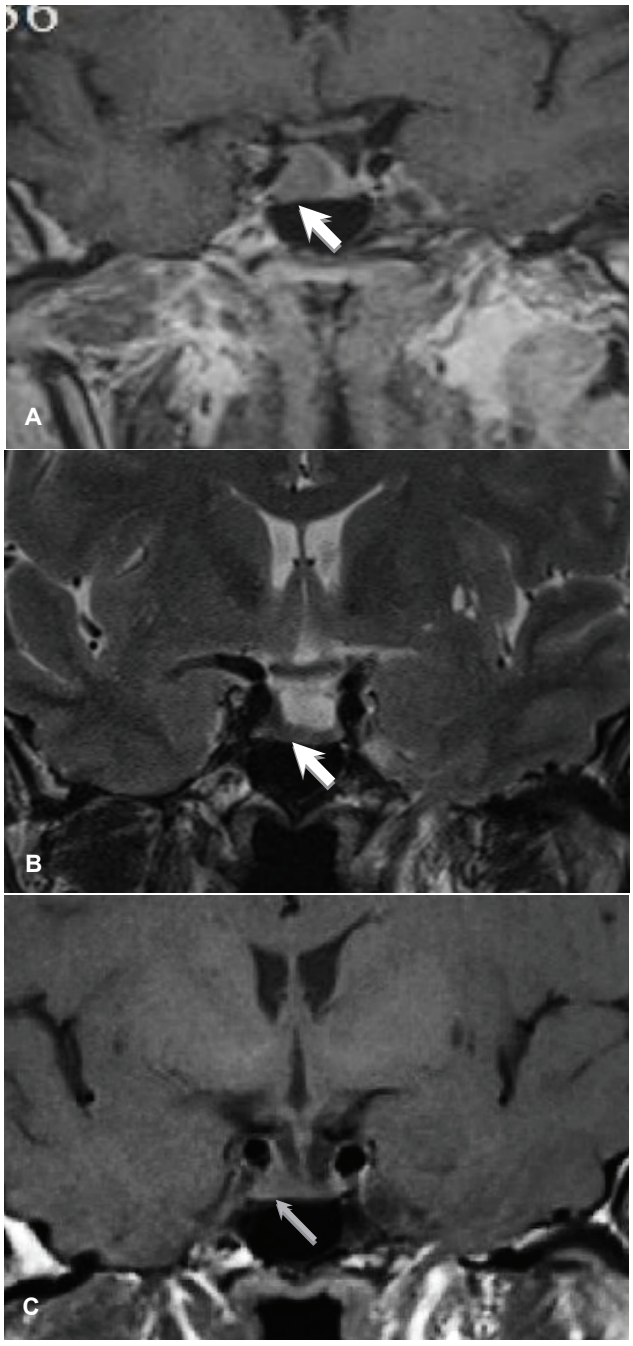

Figure 1. MRI of the pituitary gland, coronal view. **(A)** T1-weighted initial study showed a 1.5 cm x 1.6 cm x 1.1 cm adenoma *(white arrow)* on the right side of the pituitary invading the right cavernous sinus and encasing the right internal carotid artery. **(B)** on T2-weighted imaging, the tumor appeared hypointense, suggestive of dense granulation. **(C)** follow-up study showed reduction in size of the pituitary adenoma to 0.5 cm x 0.6 cm x 0.3 cm *(thin gray arrow)* after 6 months of octreotide LAR.

Neck ultrasonography showed multiple mixed solid and cystic nodules in both thyroid lobes. The thyroid nodule on the right lobe appeared solid and cystic, with wall calcification and no vascularity (Figure 2A). There were multiple predominantly solid thyroid nodules with internal microcalcifications on the left lobe, with the largest nodule measuring 3.2 cm x 3.2 cm x 4.6 cm located at the lower pole (Figure 2B). Subcentimeter cervical lymph nodes were also seen. Fine needle aspiration cytology of the thyroid nodule reported neoplastic thyroid epithelial cells displaying enlarged nuclei, nuclear grooves and intranuclei inclusions suggestive of papillary thyroid cancer.

Medical therapy with subcutaneous octreotide LAR 20 mg monthly for 6 months prior to surgery was initiated to alleviate cardiovascular, metabolic and respiratory co-morbidities. Recent lacunar strokes were also a contraindication to immediate surgery. After 3 months of medical therapy, clinical features of acromegaly and OSA improved, and IGF-1 became normal.

She underwent total thyroidectomy with therapeutic anterior and left lateral neck dissection. Histopathologic evaluation revealed papillary thyroid cancer measuring 5 cm x 5 cm, with involvement of 5 of the 8 resected lymph nodes. Subsequent remnant ablation with radioactive iodine 120 mCi was done. Post-treatment whole body scan (WBS) showed uptake at the area of the thyroid bed.

Follow-up MRI after 6 months of octreotide LAR revealed a residual 0.5 cm x 0.6 cm x 0.3 cm pituitary microadenoma (Figure 1B). Transphenoidal adenomectomy was uneventful, with no post-operative pituitary hormonal deficit and diabetes insipidus. IGF-1 remained within normal range for age and gender.

DISCUSSION

The insidiousness of acromegaly often results in a late diagnosis, as seen in our patient. High GH and IGF-1 levels affect many tissues, causing cardio-metabolic consequences and respiratory complications mainly due to central and obstructive sleep apnea. Our patient presented with difficult to control blood pressure, stroke and severe OSA.

Treatment choices in acromegaly are dependent on several factors. In our patient, the macroadenoma was confined to the sella, with apparent invasion of the right cavernous sinus and encasement of the right internal carotid artery. As it was not near the optic chiasm, there were no visual and neurologic disturbances. Urgent surgical removal was not deemed necessary at that point.

SRL pre-treatment is not routinely recommended for acromegaly with macroadenoma.[5] However, a somatostatin receptor ligand (SRL) or GH receptor antagonist such as pegvisomant may be used as initial adjuvant medical therapy in a patient with significant disease (moderate to severe signs and

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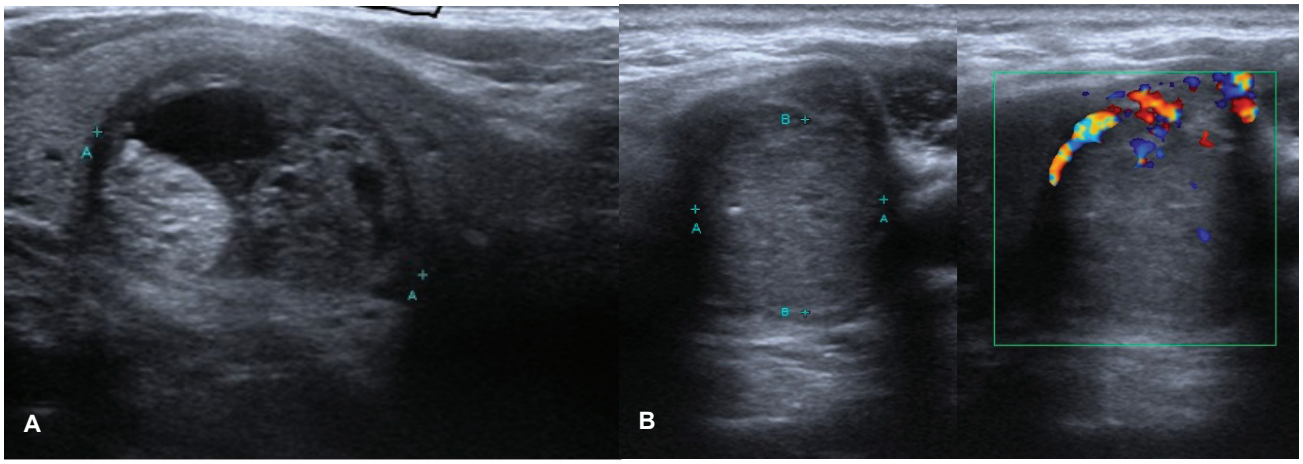

Figure 2. Thyroid ultrasonography. **(A)** mixed cystic and solid nodule with regular margin on the right lobe. **(B)** predominantly solid nodule with internal microcalcifications measuring 3.2 cm x 3.2 cm x 4.6 cm at the lower pole of the left lobe.

symptoms of GH excess without local mass effects) to improve cure rate. Pre-operative long-acting octreotide treatment in patients with invasive pituitary macroadenomas for 6 months improved metabolic, hemodynamic parameters and reduced duration of hospital stay.[6] By reducing GH hypersecretion, SRLs are efficacious in decreasing tissue overgrowth in the heart and airways, thereby alleviating respiratory and cardiovascular co-morbidities. These were evident in our patient, as seen in the reduction of her IGF-1 and blood sugar levels, improvement in blood pressure and cardiac function, and reduction of severity of OSA leading to eventual discontinuation of continuous positive airway pressure. Tumor size was reduced by 67%, compared to approximately 50% reported in literature (Figure 1C). This reduction in size was accompanied by regression of cavernous sinus invasion, which improved surgical success.

Response to SRL is said to be dependent on tumor consistency and the amount of somatostatin receptor subtype 2 (sst2) expression. Tumors that are densely granulated respond better compared to fibrous ones. Hypointense tumor signal on T2-weighted MRI, which correlate with dense tumor granularity, portend a favorable SRL response, as observed in the patient (Figure 1B). These factors can be used to guide the choice of pharmacotherapy in treating acromegaly.

The control of IGF-1 levels may mitigate the signs, symptoms and complications of acromegaly. Nadir GH is the most important determinant of mortality, followed by blood pressure and heart disease.[7-9] Symptom duration and diabetes seem to be less important determinants. Life expectancy becomes similar to the general population when GH levels are under control.[7,8] Normalization of IGF-1 is also one of the goals of treatment in acromegaly. In a study of 466 acromegaly patients due to pituitary macroadenoma, SRL was able to normalize IGF-1 in 39.9%.[9] This is mainly due to the downregulation of GH release through the sst2 receptor.

One of the main setbacks of pituitary surgery is the occurrence of post-operative pituitary hormonal failure. In an analysis of complications of transsphenoidal surgery, anterior pituitary insufficiency occurred in 19.4% of patients.[1] This risk, along with limited access to highly competent surgeons, have created a strong interest in medical therapy in acromegaly, with the goal of removing the risk of pituitary failure brought about by surgery.

Fifteen percent of mortality in acromegalic patients are attributed to malignancy. High levels of IGF-1 and IGF-binding protein 3 (IGFBP3) are seen in acromegaly. Activation of IGF-1 receptors causes cell proliferation and growth, whereas IGFBP3 promotes apoptosis. By inducing increased IGF-1 and IGFBP3 levels, excess GH promotes dysregulated cell growth characterized by dynamic signals for cell apoptosis as against cell growth. High GH leads to tissue growth, including the thyroid gland. Thyroid nodules are seen more frequently in acromegaly. Multinodularity and size correlates with duration of high IGF-1.[10] Increased tissue growth suggests malignant transformation of the thyroid nodules, as seen in our patient. Thyroid cancer was found to be the most common type of malignancy in acromegaly.[11] Our case report underscores the importance of routine screening by ultrasonography of the thyroid in these patients.

With a tumor size of more than 5 cm, capsular invasion and involvement of central and ipsilateral lymph nodes, our patient had stage IV papillary thyroid cancer (T4aN1bM0) based on the American Joint Committee on Cancer (AJCC) classification. Treatment involved total thyroidectomy with central and left lateral lymph node resection plus remnant ablation with 100 to 200 mCi radioiodine (with post-treatment WBS).[12] Follow-up of papillary thyroid cancer includes monitoring for tumor recurrence in lymph nodes, measurement of thyroglobulin and regular neck ultrasound. Monitoring of differentiated thyroid cancer has moved away from regular WBS following the availability of very sensitive assays for detection of thyroglobulin and high quality neck ultrasonography.

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CONCLUSION

Our case demonstrated the successful pre-operative use of octreotide LAR for 6 months, which resulted to remission of acromegaly without any pituitary hormonal failure. While pre-treatment with SRL is not generally recommended at this time, it was able to reduce tumor volume more than what has been commonly reported, and also improved our patient's outcome.[13] Our case also emphasized the need for close evaluation for thyroid malignancy, aside from surveillance of colonic polyps and cancer. While surgery is the current main treatment of acromegaly, the use of medical therapy, particularly SRL, may achieve remission and improve survival rate. The role of medical therapy in acromegaly for IGF-1 normalization to control concomitant malignancy warrants further research and insight.

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

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

Author Disclosure
The author declared no conflict of interest.

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References

1. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic complications of acromegaly: Epidemiology, pathogenesis, and management. Endocr Rev. 2004;25(1):102-52. PMID: 14769829. https://doi.org/10.1210/er.2002-0022.
2. Ben-Shlomo A, Melmed S. Clinical review 154: The role of pharmacotherapy in perioperative management of patients with acromegaly. J Clin Endocrinol Metab. 2003;88(3):963-8. https://doi.org/10.1210/jc.2002-020072.
3. Ezzat S, Snyder PJ, Young WF, et al. Octreotide treatment of acromegaly: A randomized, multicenter study. Ann Intern Med. 1992;117(9):711-8. PMID: 1416572. https://doi.org/10.7326/0003-4819-117-9-711.
4. Bevan JS, Atkin SL, Atkinson AB, et al. Primary medical therapy for acromegaly: An open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. J Clin Endocrinol Metab. 2002;87(10):4554-63. PMID: 12364434. https://doi.org/10.1210/jc.2001-012012.
5. Melmed S, Casanueva F, Cavagnini F, et al. Consensus statement: Medical management of acromegaly. Eur J Endocrinol. 2005;153(6):737-40. PMID: 16322377. https://doi.org/10.1530/eje.1.02036.
6. Shen M, Shou X, Wang Y, et al. Effect of presurgical long-acting octreotide treatment in acromegaly patients with invasive pituitary macroadenomas: A prospective randomized study. Endocr J. 2010;57(12):1035-44. PMID: 21099129.
7. Freda PU, Wardlaw SL, Post KD. Long-term endocrinological follow-up evaluation in 115 patients who underwent transsphenoidal surgery for acromegaly. J Neurosurg. 1998;89(3):353-8. PMID: 9724106. https://doi.org/10.3171/jns.1998.89.3.0353.
8. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: A retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab. 1998;83(8):2730-4. PMID: 9709939. https://doi.org/10.1210/jcem.83.8.5007.
9. Colao A, Lombardi G. Growth hormone and prolactin excess. Lancet. 1998;352(9138):1455-61. PMID: 9808008. https://doi.org/10.1016/S0140-6736(98)03356-X.
10. Katznelson L, Laws ER Jr, Melmed S, et al. Acromegaly: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933-51. PMID: 25356808. https://doi.org/10.1210/jc.2014-2700.
11. Dagdelen S, Cinar N, Erbas T. Increased thyroid cancer risk in acromegaly. Pituitary. 2014;17(4):299-306. PMID: 23836362. https://doi.org/10.1007/s11102-013-0501-5.
12. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016;26(1):1-133. PMID: 26462967. PMCID: PMC4739132. https://doi.org/10.1089/thy.2015.0020.
13. Carlsen SM, Lund-Johansen M, Schreiner T, et al. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenomas increases cure short-term postoperative rates: a prospective, randomized trial. J Clin Endocrinol Metab. 2008;93(8):2984-90. PMID: 18492760. https://doi.org/10.1210/jc.2008-0315.

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CASE REPORT

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"Overgrowth: Missing a Tumor" Acromegaly without Imaging Evidence of Pituitary Adenoma and No Ectopic Source: A Case Report

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Abstract

Growth hormone - secreting pituitary adenomas are the cause of acromegaly in 95% of patients. In rare circumstances, a pituitary adenoma on magnetic resonance imaging cannot be found; hence, a search for an ectopic source of GH production is done. Even rarer is an acromegalic patient without an ectopic source and without imaging evidence of pituitary adenoma. We report a case of acromegaly with no evidence of a pituitary adenoma and no evidence of an ectopic source after imaging studies; who underwent medical therapy with improving biochemical and clinical parameters.

Key words: acromegaly, pituitary neoplasms, adenoma, magnetic resonance imaging, sandostatin, cabergoline, case report

INTRODUCTION

Acromegaly is a rare, chronic disorder of excessive growth hormone (GH) and consequent overproduction of insulin growth factor-1 (IGF-1) from the liver. IGF-1 in large part mediates the effects of GH. Acromegaly is characterized phenotypically by progressive acral and facial disfigurement and is associated with cardiovascular, respiratory, metabolic, and gastrointestinal complications. Growth hormone secreting pituitary adenomas are the cause of acromegaly in 95% of patients, other rare causes are ectopic GH-secreting tumor, and ectopic or hypothalamic growth hormone releasing hormone-secreting tumor. Diagnosis of acromegaly is suggested by clinical features and confirmed by an elevated age- and sex-matched serum IGF-1 level and GH levels that fail to suppress to <1 ug/L after an oral glucose load. Confirmation of the source is done using Cranial MRI - pituitary protocol. Typically, after the MRI imaging, a GH-secreting pituitary adenoma will be identified and surgical resection of the tumor performed. Surgery is the treatment of choice and frequently results in biochemical remission after complete removal of the adenoma.

In rare circumstances, a pituitary adenoma on magnetic resonance imaging cannot be found; a search for an ectopic source of GH production is done. Even rarer is an acromegalic patient without an ectopic source and without an imaging evidence of pituitary adenoma. The treatment for this subset of patients is not well defined. We present our experience in dealing with such a case.

CASE

Our patient is a 76-year-old female of Chinese descent who came in for initial consult in year 2000 at age 61 at another institution, due to symptoms of upper airway obstruction, i.e., choking, snoring and difficulty of breathing on lying supine. On examination, she was noted to have enlarged hands, feet, tongue, lip, and nose; and a prominent mandible. She is a diabetic, maintained on oral hypoglycemic medications. An initial impression of acromegaly was given. Workup revealed an elevated IGF-1; and confirmed with an unsuppressed growth hormone levels on oral glucose challenge (Table 1). An MRI of the sella with contrast (pituitary protocol) revealed a normal pituitary. A CT scan of the neck, chest and abdomen done were also unremarkable.

After explaining treatment options and the risks associated with each intervention, our patient opted for medical management. Patient was started on octreotide [Sandostatin-LAR] 20 mg monthly for 8 months, but repeat IGF-1 level was persistently elevated. Hence, cabergoline, 0.5 mg/tab, 2 tablets twice a week was added

Table 1. Laboratory workup of the patient on diagnosis (year 2000)

GH Suppression Test (After 100g oral glucose)	Reference range < 0-2 ng/mL or undetectable
Baseline	3.8 ng/ml (Reference range: 0-10)
60 minutes	4.4 ng/ml
90 minutes	8.5 ng/ml
IGF-1	692 mcg/mL (Reference range: 114-492)

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Table 2. IGF-1 Levels from diagnosis until present

	7/18/2015	4/12/2013	2/15/2011	4/16/2010	7/11/2006	3/10/2005	12/2/2004	2000
IGF-1 (ng/ml)	52 (90-220)	243 (64-188)	249 (64-188)	301 (64-188)	438 (91-443)	253 (91-443)	411 (91-443)	692 (114-492)

reference values enclosed in parenthesis

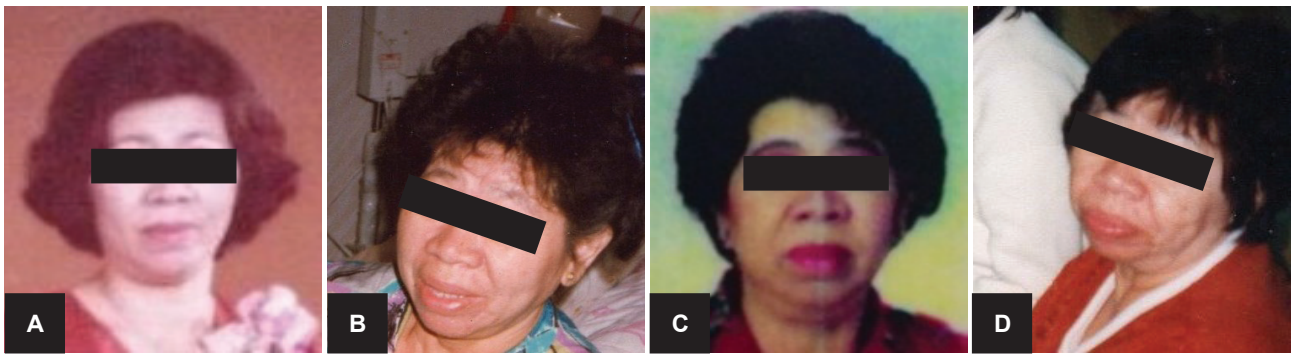

Figure 1. Pictures of the patient throughout the years (A) 1980s (B) 1989 (C) 2000 (D) 2001.

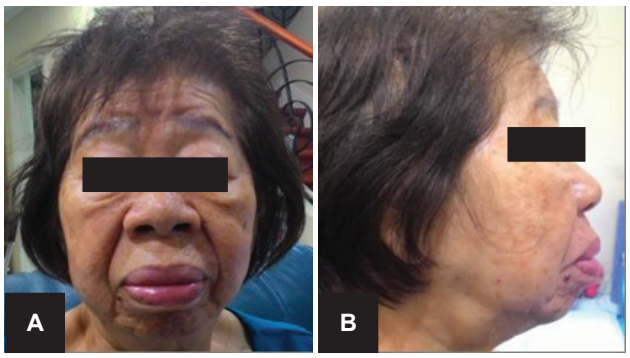

Figure 2. Latest front (A) and lateral (B) pictures of the patient taken July 2015.

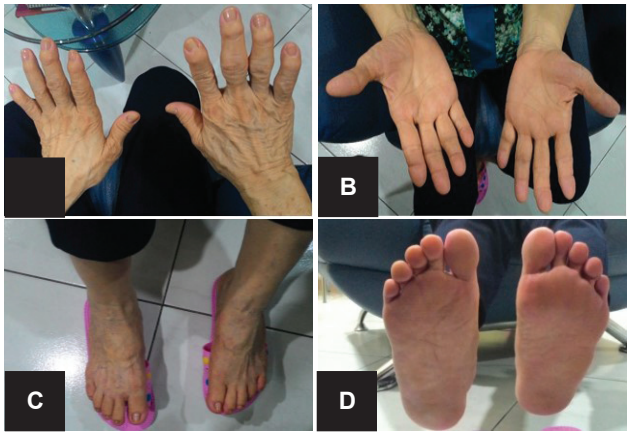

Figure 3. Picture of the patient's hands – dorsal (A) and palms (B); patient's feet – dorsal (C) and soles (D). Incidentally note that both her right hand and foot is larger than the left.

to her Sandostatin regimen. But unfortunately, due to cost, difficulty in procuring the medication, and the bothersome nature of administration (subcutaneous), patient stopped Sandostatin-LAR and continued with cabergoline, 0.5 mg, 2 tablets twice a week. A repeat pituitary MRI 2 years later (2002) showed an "empty sella." Another MRI scan of the pituitary was done in 2004, where no pituitary adenoma was again identified (Appendix A).

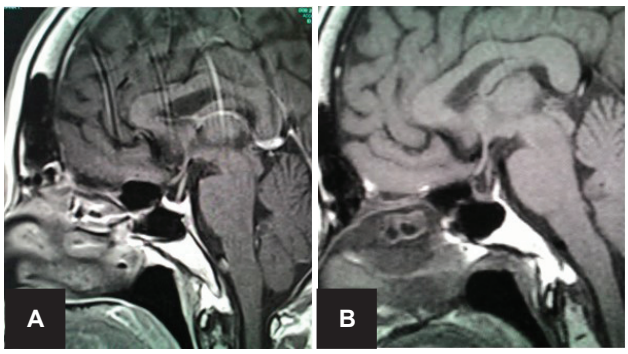

Figure 4. T1 weighted sagittal MRI image of the pituitary post contrast (A) 2015 and (B) 2004. Both showing a small pituitary gland which is pressed against the sellar floor with no internal hypoenhancement post-contrast.

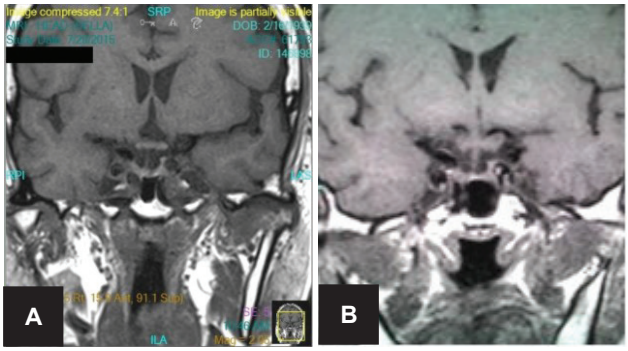

Figure 5. T1 weighted coronal MRI image of the pituitary post contrast (A) 2015 and (B) 2004. Both showing a small pituitary gland which is pressed against the sellar floor with no internal hypoenhancement post-contrast.

In June 2015, patient consulted in our institution for diabetes management follow up. The attending endocrinologist still noted coarse facial features, enlarged hands and feet (Figure 1-3). She was noted to be hypertensive on blood pressure lowering medications and diabetic on oral hypoglycemic agents. Repeat IGF-1 and levels of IGF-1 through the years are shown on Table 2. A repeat MRI imaging of the sella revealed normal pituitary, with no evidence of pituitary adenoma (Figure 4-5).

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Table 3. Latest laboratory results

	2015	2016	2017
IGF-1	52 (90-220)	180 (59-177)	181 (59-177)
Prolactin	0.65 (5.18-26.53)	-	-
Growth Hormone	1.44 (0.01-3.61)	0.37 (0.01-3.61)	0.18 (0.01-3.61)

reference values enclosed in parenthesis

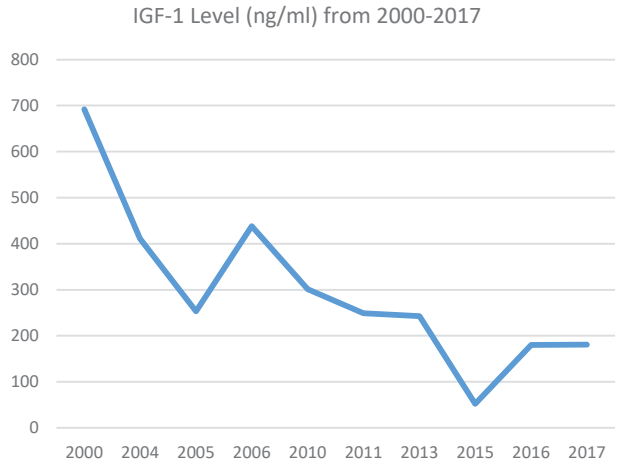

Figure 6. Line graph of IGF-1 level in ng/ml from 2000-2017.

DISCUSSION

A hyperfunctioning growth hormone-secreting pituitary adenoma is the most common cause of acromegaly. Rarer causes are ectopic or hypothalamic growth hormone releasing hormone-secreting tumor. Since the signs and symptoms of acromegaly are indolent, the time from onset of signs and symptoms to diagnosis of acromegaly is long, usually taking years. The pituitary adenomas that cause growth hormone excess are usually large and are easily identified on routine MRI imaging of the sella. Treatment would then involve resection of the pituitary adenoma via transsphenoidal surgery.

In rare cases, a pituitary MRI may show negative results. A contrast enhanced CT scan of the chest and abdomen is the next step to detect ectopic sources of GH or GH releasing hormone (GHRH) production. Acromegaly without imaging evidence of a pituitary macroadenoma or an ectopic source is very rare. Lonser et al., reported 6 patients (mean age 56 years) with signs, symptoms and biochemical evidence of acromegaly without pituitary adenoma on imaging and an ectopic source.[1] All underwent surgical exploration of the pituitary gland and GH-secreting pituitary adenoma ranging from 5 to 6.7 mm were identified and resected. Khandelwal et al., reported one patient with acromegaly who also underwent surgical exploration of the pituitary, were a GH-secreting pituitary adenoma was identified and resected.[2]

We present our 76-year-old patient with acromegaly without pituitary evidence of a pituitary adenoma and without evidence of an ectopic source who underwent medical therapy using cabergoline 0.5 mg, 2 tablets twice a week for 14 years. Patient reports less choking and snoring symptoms and slight decrease in size of her tongue and improved sleep. Due to her age, she is not a good candidate for surgical exploration of the pituitary nor did she consent to the procedure. Other treatment options include somatostatin analogues (octreotide and lanreotide), dopamine agonists (bromocriptine and cabergoline), pegvisomant, and radiotherapy; these treatment modalities are reserved for persistent disease after surgery, for unresectable tumors or poor surgical candidates. Target goal of therapy is to reach an age-normalized serum IGF-1 value, and a random growth hormone (GH) <1.0 µg/L. A target GH <1 µg/L and normalized IGF-1 values have each been shown to correlate with mortality risk reduction.[3]

Octreotide long acting release (LAR), and deep subcutaneous lantreotide depot/autogel are administered monthly. Octreotide LAR dose is 20 mg monthly with dose titration every 3-6 months down to 10 mg or up to 40 mg monthly. Lanreotide autogel/depot starting dose is 90 mg monthly, with dose titrations down to 60 mg or up to 120 mg monthly. Serum IGF-1 and GH is measured 12 weeks just prior to the next dose. Octreotide LAR produces normalization of IGF-1 levels in only 34% of patients, but with clinical relevant reduction of GH in 72% of patients, and a significant tumor reduction in 75% of patients.[4] Lantreotide autogel, also achieves biochemical control in 34% of patients,[5] with tumor shrinkage achieved in 62.9% of patients.[6] A recently concluded phase 3 controlled trial of pasireotide, a new multireceptor targeted somatostatin analogue, reported better biochemical control and tumor size reduction in patients initially poorly responsive to first generation somatostatin analogue.[7]

Pegvisomant, a human GH receptor antagonist, competes with GH for binding at its receptor and block production of IGF-1. Pegvisomant is administered as 10, 15, or 20 mg daily injections. Serum GH levels should not be measured because GH hypersecretion persists in patients given Pegvisomant; instead, IGF-1 level is recommended as the only useful biomarker to monitor treatment efficacy. Pegvisomant reduces IGF-1 levels in 81-97% of patients,[8-10] with 5 year efficacy of 63.2% with a mean dose of 18 mg daily.[11]

Dopamine agonists (bromocriptine and cabergoline) are of limited efficacy in the treatment of acromegaly, with high doses required to achieve control. Discontinuation of treatment may result in rebound growth hormone hypersecretion. Bromocriptine is usually required at a

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dose of 20-30 mg per day; while cabergoline may require high doses of up to 1 mg per day to achieve control.[12] A metaanalysis showed cabergoline to be approximately 34% effective in attaining biochemical control,[13] with response appearing to decrease with time. In the study by Freda et al., in 2004, only 21% of subjects were controlled after 18 months of cabergoline administration.[14]

Sandostatin LAR administration via subcutaneous route was initially given, however, no improvement in IGF-1 levels were seen; hence, cabergoline was added to her regimen. Octreotide was eventually withdrawn due to the bothersome nature of administration and costs. She was then switched to cabergoline regimen only. Although we found no studies on the efficacy of carbergoline in the long run, the latest results of IGF-1 of our patient may indicate efficacy of cabergoline in patients with continued intake (Table 3), although further monitoring is still needed. A repeat whole abdominal CT scan done in March 2017 was still negative for an ectopic GH-producing tumor. A repeat chest and neck CT scan is still pending.

CONCLUSION

A trial of dopamine agonist, cabergoline, may be given to patients with acromegaly and no imaging evidence of a pituitary adenoma or an ectopic source, who are poor surgical candidates and unresponsive to octreotide or other somatostatin analogues, with consideration of cost, may be given a trial of dopamine agonist, specifically cabergoline. Carbegoline therapy may have sustained response in supressing GH and IGF-1 with time, as seen in our patient who has taken cabergoline for 17 years.

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

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

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

References

1. Lonser R, Kindzelski BA, Mehta GU, Jane JA Jr., Oldfield EH. Acromegaly without imaging evidence of pituitary adenoma. J Clin Endocrinol Metab. 2010;95(9):4192-6. PMCID: PMC2936064. https://doi.org/10.1210/jc.2010-0570.
2. Khandelwal D, Khadgawat R, Mukund A, Suri A. Acromegaly with no pituitary adenoma and no evidence of ectopic source. Indian J Endocrinol Metab. 2011;15(Suppl 3):S250-2. PMCID: PMC3183531. https://doi.org/10.4103/2230-8210.84878.
3. Katznelson L, Laws E, Melmed S, et al. Acromegaly: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014; 99(11):3933-51. PMID: 25356808. https://doi.org/10.1210/jc.2014-2700.
4. Mercado M, Borges F, Bouterfa H, et al. A prospective, multicenter study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. Clin Endocrinol (Oxf). 2007;66(6):859-68. PMID: 17465997. PMCID: PMC1974838. https://doi.org/10.1111/j.1365-2265.2007.02825.x.
5. Caron PJ, Bevan JS, Petersenn, et al. Tumor shrinkage with lanreotide Autogel 120 mg as primary therapy in acromegaly: Results of a prospective multicenter clinical trial. J Clin Endocrinol Metab. 2014;99(4):1282-90. PMID: 24423301. PMCID: PMC4009579. https://doi.org/10.1210/jc.2013-3318.
6. Caron P, Bevan J, Petersen S, et al. Effects of lanreotide Autogel primary therapy on symptoms and quality-of-life in acromegaly: Data from the PRIMARYS study. Pituitary. 2016;19(2):149-57. PMID: 26603536. PMCID: PMC4799252. https://doi.org/10.1007/s11102-015-0693-y.
7. Bronstein M, Fleseriu M, Neggers S, et al. Switching patients with acromegaly from octreotide to pasireotide improves biochemical control: Crossover extension to a randomized, double-blind, Phase III study. BMC Endocr Disord. 2016;16:16. PMID: 27039081. PMCID: PMC4818908. https://doi.org/10.1186/s12902-016-0096-8.
8. Trainer PJ, Drake WM, Katznelson L, et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med. 2000;342(16):1171–7. PMID: 10770982. https://doi.org/10.1056/NEJM200004203421604.
9. van der Lely AJ, Hutson RK, Trainer PJ, et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet. 2001;358(9295):1754-9. PMID: 11734231.
10. Shimatsu A, Nagashima M, Hashigaki S, Ohki N, Chihara K. Efficacy and safety of monotherapy by pegvisomant, a growth hormone receptor antagonist, in Japanese patients with acromegaly. Endocr J.2016;63(4):337-47. PMID: 26796763. https://doi.org/10.1507/endocrj.EJ15-0619.
11. van der Lely AJ, Biller BM, Brue T, et al. Long-term safety of pegvisomant in patients with acromegaly: Comprehensive review of 1288 subjects in ACROSTUDY. J Clin Endocrinol Metab. 2012;97(5): 1589–97. PMID: 22362824. https://doi.org/10.1210/jc.2011-2508.
12. Carroll P, Jenkins P. Acromegaly. In: De Groot L Chrousos, Dungan K, et al, ed, 2016. Retrieved from http://www.endotext.org/chapter/acromegaly/. Bookshelf ID: NBK278943. PMID: 25905160.
13. Sandret L, Maison P, Chanson P. Place of cabergoline in acromegaly: A meta-analysis. J Clin Endocrinol Metab. 2011;96(5):1327-35. PMID: 21325455. https://doi.org/10.1210/jc.2010-2443.
14. Freda PU, Reyes CM, Nuruzzaman AT, Sundeen RE, Khandji AG, Post KD. Cabergoline therapy of growth hormone and growth hormone/prolactin secreting pituitary tumors. Pituitary. 2004;7(1):21-30. PMID: 15638294.

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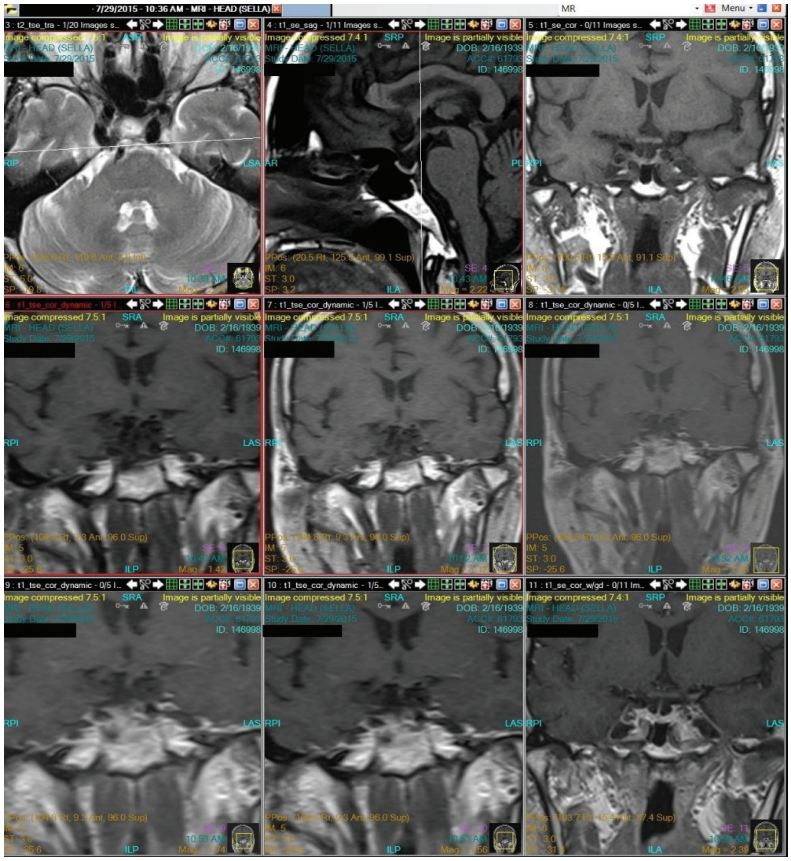
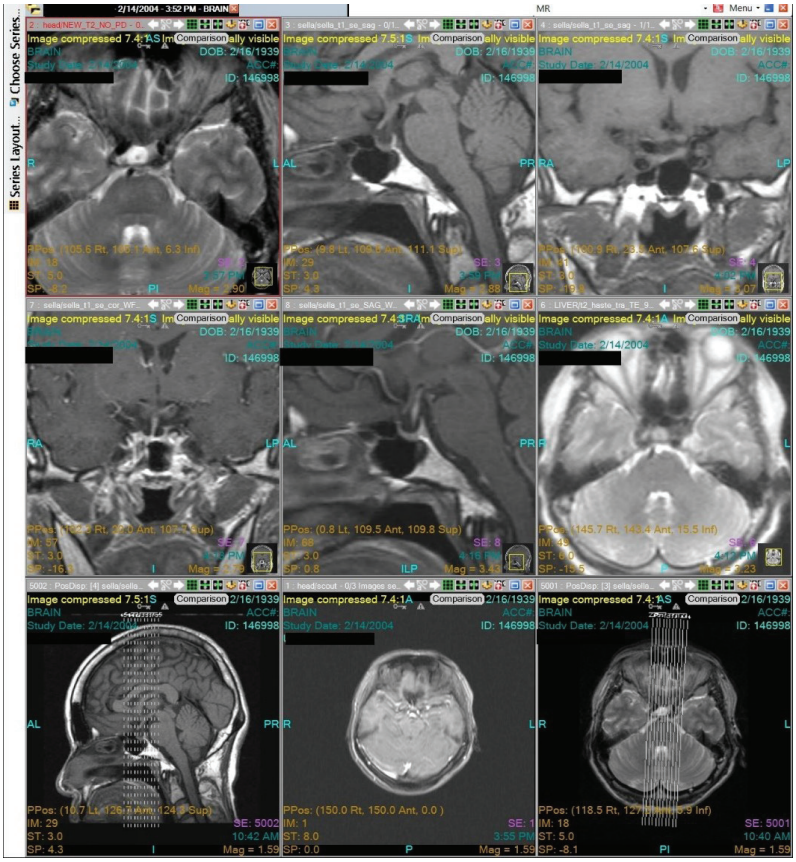
APPENDIX A

MRI scan of the pituitary showing pre- and post-contrast phase (top, 2015 scan; bottom, 2004 scan).





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and

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wish to announce the dates for the

Written and Oral Examination for Diplomate in Endocrinology, Diabetes and Metabolism

JANUARY 19, 2018 (Friday)
WRITTEN EXAMINATION

JANUARY 21, 2018 (Sunday)
ORAL EXAMINATION

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