Journal of the
ASEAN Federation of
Endocrine Societies

Vol. 31 No. 2 November 2016 | ISSN 0857-1074 | eISSN 2308-118x

ORIGINAL ARTICLES

CASE REPORTS

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JAFES

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Journal of the
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Vol. 31 No. 2 November 2016 | ISSN 0857-1074 | eISSN 2308-118x

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We are happy to announce our journal website's recent shift to online hosting under the Public Knowledge Project (PKP), a reinforcement of our commitment to open access and to integrity in scientific publication.

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For non-profit, open-access scholarly journals in general, the situation is not without difficulty. Processing high quality, original, peer-reviewed content, improving visibility and search ability in the internet, and ensuring security of intellectual property, do entail significant resources.

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Our website recently shifted to online hosting under the **Public Knowledge Project (PKP)**, the original creator of the Open Journal Systems software. Beginning October 2016, the JAFES is no longer connected with Openjournalsystems.com.

In the website http://asean-endocrinejournal.org you will see quite a bit of change complementing the new brand and look of JAFES. Its article visualization is much improved according to the suggestion of the reviewers of the National Library of Medicine when they first reviewed JAFES for PubMed indexing. The website is also more responsive to a wider variety of devices that readers use to view content. We are excited to further develop the website with additional features to enhance readership not only for our member societies but the rest of the scientific community.

Indeed in the academic publishing world, independent open-access journals walk a challenging tightrope of maintaining integrity on top of sustaining operations. At the last Asia-Pacific Association of Medical Journal Editors (APAME) conference in Bangkok, Thailand, we bore witness to shared experiences of scholarly journals, regionally and globally, on issues of intellectual property and ethical publication, amid the unique risks posed by a world that is becoming more and more online.

JAFES continues to encourage research initiatives, to foster high quality publication standards, and to facilitate the sharing of scientific outputs from Southeast Asia to the world. Above all, we hold integrity as one of our core values, without which, JAFES will not survive and thrive. We deem safeguarding the intellectual property of the authors, reviewers and editors, who all contributed and continue to contribute to our issues, as critical to the mission. We count on the continuing support of all our readers.

Elizabeth Paz-Pacheco
Editor-in-Chief

https://doi.org/10.15605/jafes.031.02.01

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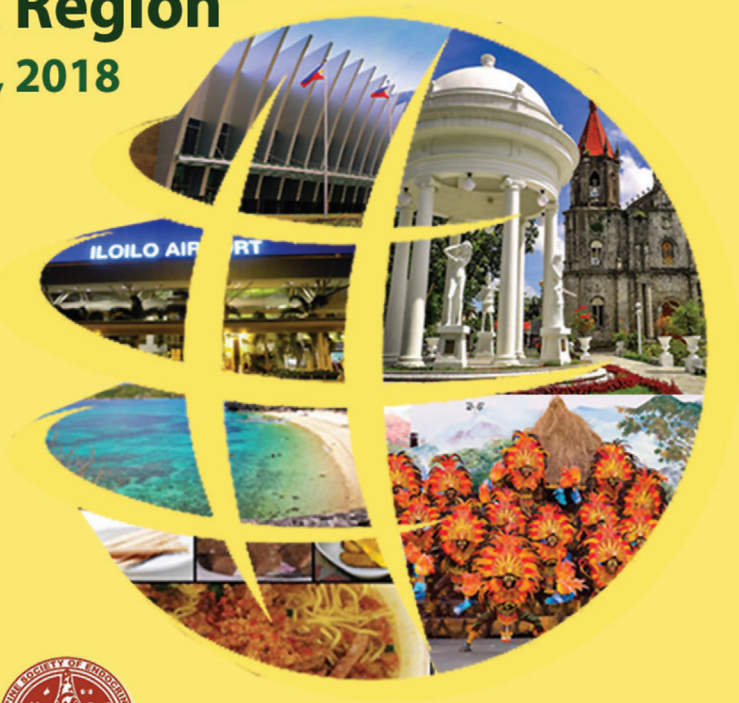

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ONLINE FIRST | October 19, 2016 | https://doi.org/10.15605/jafes.031.02.02

ORIGINAL ARTICLE

JAFES

Ethnic Disparity in Inter-Arm Systolic Blood Pressure Difference and its Determinants among Asians with Type 2 Diabetes: A Cross-Sectional Study

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Abstract

Objectives. An inter-arm difference in systolic blood pressure (IADSBP) of 10 mmHg or more has been associated with cardiovascular disease (CVD) and increased mortality in T2DM patients. We aim to study ethnic disparity in IADSBP and its determinants in a multi-ethnic T2DM Asian cohort.

Methodology. Bilateral blood pressures were collected sequentially in Chinese (n=654), Malays (n=266) and Indians (n=313). IADSBP was analyzed as categories (<10 and ≥10 mmHg). Logistic regression model was used to evaluate the determinants of IADSBP ≥10 mmHg.

Results. Malays (27.4%) and Indians (22.4%) had higher prevalence of IADSBP ≥10 mmHg than Chinese (17.4%) (p=0.002). After adjustment for age, gender, duration of diabetes, hemoglobin A1c, body mass index (BMI), heart rate, pulse wave velocity (PWV), estimated glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR), smoking, hypertension, soluble receptor for advanced glycation end products (sRAGE), and usage of hypertension medications, ethnicity remained associated with IADSBP. While Malays were more likely to have IADSBP ≥10 mmHg than Chinese (OR=1.648, 95%CI: 1.138-2.400, p=0.009), Indians had comparable odds with the Chinese. BMI (OR=1.054, 95%CI: 1.022-1.087, p=0.001) and hypertension (OR=2.529, 95%CI: 1.811-3.533, p<0.001) were also associated with IADSBP ≥10 mmHg.

Conclusion. IADSBP in Malays were more likely to be ≥10 mmHg than the Chinese which may explain their higher risk for CVD and mortality. Measuring bilateral blood pressures may identify high-risk T2DM individuals for intensive risk factor-management.

Key words: type 2 diabetes, cardiovascular disease, inter-arm difference in systolic blood pressure

INTRODUCTION

Type 2 diabetes (T2DM) is a rapidly evolving global health issue[1] and Asia is the epicenter of this worldwide epidemic.[2] The prevalence of T2DM has been predicted to double from 7.3% in 1990 to 15% in 2050 in Singapore, a multi-ethnic city-state composed of three major ethnic groups (Chinese, Malays and Indians).[3] The ethnic diversity in Singapore provided us a unique opportunity to study the ethnic disparity on T2DM-related adverse outcomes.

Ethnic disparity in the development of diabetic complications, such as cardiovascular disease (CVD) and mortality from CVD, has been reported in many Western countries.[4,5] Such ethnic disparity has also been found among Asians with T2DM in Singapore, showing higher risk for ischemic heart disease and cardiovascular mortality in Indians and Malays compared to Chinese.[6-9] In our recent studies in Singapore, we also revealed higher risk for diabetic complications in Indians and Malays compared to Chinese, such as acute myocardial infarction and cardiovascular mortality.[10,11] Several reasons have been suggested to explain their excess adverse outcomes, including less favorable metabolic and lipid profiles e.g., body mass index (BMI); lifestyle, e.g., less physical activity, less fruit and vegetable consumption; and poorer diabetes control, e.g., higher hemoglobin A1c (HbA1c). Furthermore, we observed higher central arterial stiffness, a well-established biomarker for vasculopathy, and lower level of soluble receptor for advanced glycation end-

eISSN 2308-118x
Printed in the Philippines

Received: April 22, 2016. Accepted: July 13, 2016.
https://doi.org/10.15605/jafes.031.02.02

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ONLINE FIRST | October 19, 2016 | https://doi.org/10.15605/jafes.031.02.02

products (sRAGE), a molecule with protective function on the vasculature in Malays and Indians than Chinese.[12] However, the mechanisms underlying the ethnic disparity in multifactorial diseases, such as CVD still remain largely unknown.

An inter-arm difference in blood pressure of less than 10 mmHg is classified as normal based on the new clinical guideline for hypertension.[13] Evolving evidence suggested that an inter-arm difference in systolic blood pressure (IADSBP) of 10 mmHg or more is associated with CVD and cardiovascular mortality.[14,15] It is interesting that the prevalence of IADSBP ≥10 mmHg is higher among T2DM patients (~9-10%) when compared to the general population (4.4%).[16,17] Recently, IADSBP ≥10 mmHg has been associated with CVD and cardiovascular mortality in T2DM patients, suggesting that the detection of IADSBP may identify a subpopulation at high risk of vascular events among T2DM patients.[18]

The prevalence of IADSBP ≥10 mmHg varies widely across different studies, depending on ethnicity and background of enrolled individuals.[14,15] For example, the prevalence of IADSBP ≥10 mmHg or the mean of IADSBP in Asians[19-21] is generally lower than that in Caucasians.[18,22,23] In a multi-ethnic study of atherosclerosis in USA, different prevalence rates of IADSBP ≥15 mmHg were observed in African-Americans, Caucasians and Chinese.[24] However, disaggregated information on IADSBP is limited among Asian sub-ethnicities with T2DM, notwithstanding the existence of clear ethnic disparity in diabetes-related adverse outcomes. Therefore, we aim to investigate ethnic differences in IADSBP in a multi-ethnic T2DM Asian cohort.

METHODOLOGY

Study population and design

The Singapore Study of Macro-angiopathy and Micro-vascular Reactivity in Type 2 Diabetes (SMART2D) is a cross-sectional study conducted between August 2011 and February 2014 which included a total of 2,057 adults aged 21–90 years with T2DM. Inclusion and exclusion criteria of SMART2D have been previously described.[25] We included 1,233 individuals with bilateral BP measurements in this study. These selected individuals have similar profile compared to the rest of the subjects (detailed data not shown). This study has been approved by our institution's domain-specific ethics review committee. Individual written informed consent was obtained prior to enrollment in the study.

Clinical and biochemical measurements

BMI was calculated as body weight (kg)/height $(m)^2$. Urinary albumin-to-creatinine ratio (ACR) was determined by urinary creatinine measured by enzymatic method on Roche/Hitachi cobas c system (Roche Diagnostic GmbH, Mannheim, Germany) and albumin measured by a solid-phase competitive chemiluminescent enzymatic immunoassay with a lower detection limit of 2.5 μg/ml (Immulite; DPC, Gwynedd, UK). Estimated glomerular filtration rate (eGFR) was calculated based on a widely used Modified Diet in Renal Disease (MDRD) equation in patients with diabetes.[26] HbA1c was measured based on monoclonal antibody agglutination reaction using a point-of-care immunoassay analyzer (DCA Vantage Analyzer; Siemens, Erlangen, Germany) certified by National Glycohemoglobin Standardization Program. High-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein-cholesterol (LDL-C) were quantified by enzymatic method using Kodak Ektachem chemistry slides. Total triglyceride was quantified by enzymatic colorimetric method on Roches/Hitachi cobas c system. Carotid-femoral pulse wave velocity (PWV) was measured by the foot-to-foot method using a well-validated device, SphygmoCor® (AtCor Medical, Sydney, Australia) as described previously.[27] PWV was expressed as the distance between the two recording sites (meters) divided by transit time (seconds). Total sRAGE was quantified by ELISA (R&D Systems, Minneapolis, MN) according to manufacturer's protocol. The intra- and inter-assay coefficients of variation were 5.7% and 7.7%, respectively. The sensitivity reported by the manufacturer was 4.12 pg/ml.

Blood pressure measurement

Sequentially repeated measurements of bilateral blood pressures were performed using mercury sphygmomanometers, the "gold standard" device for blood pressure measurement.[28] An appropriately sized cuff is attached to the upper arm, and a series of calibration readings are taken with the mercury sphygmomanometer to ensure that the device is giving accurate readings. After five minutes of seated rest, sphygmomanometer was placed on the arm, alternating right then left, and allowing one minute between each measurement on the same arm. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from the average of three most consistent readings. At the end of the five-minute rest, heart rate was assessed by an OMRON® digital blood pressure monitor.

Statistical analysis

Standard descriptive statistics were used to summarize the characteristics of individuals with T2DM. Normally distributed continuous data were expressed as means and standard deviations (SDs), and skewed variables were expressed as median and inter-quartile range and nature log (ln)-transformed before data analysis. Differences among ethnicity were compared by one-way ANOVA or Kruskal–Wallis test where appropriate.

ONLINE FIRST | October 19, 2016 | https://doi.org/10.15605/jafes.031.02.02

IADSBP was analyzed as categories (<10 and ≥10 mmHg). Univariate logistic regression model was used to evaluate the determinants of IADSBP ≥10 mmHg. Variables that are statistically significant in univariate analysis (p<0.25)[29] (Table S1) or known to potentially affect IADSBP and PWV[15,30-32] were added into the model. Age, gender, ethnicity, duration of diabetes, HbA1c, BMI, heart rate, PWV, smoking, hypertension (defined as any SBP ≥140 mmHg or DBP ≥90 mmHg[33]), eGFR, ACR, sRAGE, and commonly used medications in diabetes e.g., angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), were added into multivariable logistic regression model. All statistical analyses were performed using IBM SPSS (Version 22). A two-tailed p value of less than 0.05 was considered as statistically significant.

In collinearity test for each variable, the tolerance value was >0.2 and variance inflation factor was <3 for all variables, indicating that there was no serious problem with multicollinearity.

RESULTS

Table 1 shows the characteristics of T2DM patients stratified by ethnicity, including 654 Chinese (53.0%), 266 Malays (21.6%) and 313 Indians (25.4%). Compared to Chinese, Malays and Indians were younger and had higher BMI. Malays a had higher heart rate, HbA1c and ACR, and lower eGFR than Chinese and Indians. The percentages of ischemic heart disease, coronary balloon angioplasty, and history of myocardial infarction in Indians are higher than Chinese and Malays. There were no significant differences in percentages of current smoker, coronary bypass operation, stroke and proliferative retinopathy in Malays compared with Indians and Chinese.

Compared to Chinese (5.4±4.8 mmHg), IADSBP is significantly higher in Malays (7.1±6.4 mmHg, p<0.001) and non-significantly higher in Indians (6.1±6.0 mmHg, p=0.132). There is significant higher percentage of IADSBP ≥10 mmHg in Malays (27.4%) and Indians (22.4%) than Chinese (17.4%, P=0.002).

Univariate analysis shows a higher odds for IADSBP ≥10 mmHg in Malays (OR=1.791, 95% CI: 1.279-2.508, p=0.001) than the Chinese and comparable odds of Indians with the Chinese (OR=1.364, 95% CI: 0.997-1.905, p=0.068). Table 2 shows the associations of IADSBP ≥10 mmHg with ethnicity, and clinical and biochemical determinants by multivariable logistic regression models. After adjustment for age, gender, duration of diabetes, hemoglobin A1c, BMI, heart rate, PWV, eGFR, ACR, smoking, hypertension, sRAGE, and usage of hypertension medications, ethnicity remains significantly associated with IADSBP. While odds for Indians are comparable to Chinese (p=0.089), Malays are more likely to have elevated IADSBP of at least 10 mmHg (OR=1.648, 95% CI: 1.138-2.400, p=0.009). BMI (OR=1.054, 95%CI: 1.002-1.087, p=0.001) and hypertension (OR=2.529, 95%CI: 1.811-3.533), p<0.001) are also significant determinants of IADSBP ≥10 mmHg.

Table 1. Clinical and biochemical characteristics of individuals with T2DM stratified by ethnicity (n=1,233)

Variables	Total (1,233)	Malay (266)	Indian (313)	Chinese (654)	P-value
Entry age (yrs)	57.7±10.4	55.9±9.9	56.2±9.7	59.2±10.8	<0.001
Male gender (%)	51.8	45.8	50.2	55.0	0.034
Current smokers (%)	18.0	18.7	17.2	18.1	0.885
T2DM duration (yrs)*	10 (4-17)	9 (3-15)	10 (5-19)	10 (5-19)	0.007
Hba1c (%)	7.7±1.3	7.9±1.6	7.8±1.3	7.6±1.2	<0.001
BMI (kg/m^2)	27.6±5.3	29.6±5.8	28.5±5.3	26.3±4.7	<0.001
Waist circumference (cm)	96.4±15.6	100.5±20.7	100.7±14.8	92.9±12.5	<0.001
SBP (mmHg)	139.4±18.3	141.0±18.3	136.0±17.7	140.3±18.3	0.001
DBP (mmHg)	78.6±8.9	79.4±9.2	79.2±9.0	78.0±8.7	0.06
IADSBP (mmHg)*	4 (2-8)	6 (3-10)	4 (2-8)	4 (2-7)	0.001
IADSBP ≥10 mmHg (%)	20.8	27.4	22.4	17.4	0.002
Heart rate (bpm)	70.9±10.9	72.2±11.6	71.0±10.3	70.3±10.8	0.049
HDL-C (mM)	1.3±0.4	1.3±0.3	1.2±0.4	1.3±0.4	<0.001
LDL-C (mM)	2.7±0.8	2.9±0.9	2.7±0.8	2.7±0.8	0.001
TG (mM)*	1.38 (1.02-1.91)	1.58 (1.11-2.07)	1.26 (1.02-1.78)	1.36 (0.99-1.89)	0.017
eGFR (ml/min/1.73 m^2)*	85.6 (65.3-104.3)	82.7 (57.8-101.9)	89.3 (72.0-105.8)	84.9 (64.6-140.3)	0.007
ACR (mg/g)*	21 (6-89)	31.5 (9.9-129.3)	15.0 (4-43)	22 (5-96)	0.007
PWV (m/s)	9.7±2.9	10.1±3.1	9.5±3.2	9.6±2.8	0.122
sRAGE(pg/ml)*	693.8 (508.9-949.2)	733.6 (535.8-974.2)	651.5 (478.1-904.8)	714.1 (524.4-950.9)	0.021
Proliferative retinopathy (%)	10.7	10.1	9.3	11.6	0.201
Anti-hypertension Medications					
Usage of ACE inhibitors (%)	36.2	45.4	35.7	32.8	0.002
Usage of ARBs (%)	26.4	21.1	20.1	31.7	<0.001
CVD					
Ischemic heart disease (%)	10	8.3	14.8	8.4	0.014
History of myocardial infarction (%)	4.2	3.7	7.9	2.6	0.002
Coronary balloon angioplasty (%)	5.5	3.7	11.0	3.6	<0.001
Coronary bypass (%)	5.1	4.6	5.1	5.2	0.935
Stroke (%)	3.5	2.8	3.1	3.9	0.695

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG, total triglycerides; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio ACR; PWV, pulse wave velocity; sRAGE, soluble receptor for advanced glycation end products; IADSBP, inter-arm difference in SBP; ACE, angiotensin-converting-enzyme; ARBs, angiotensin receptor blockers
*expressed as median (inter-quartile range)

ONLINE FIRST | October 19, 2016 | https://doi.org/10.15605/jafes.031.02.02

Table 2. Variables associated with IADSBP ≥10 mmHg in multivariable logistic regression models in individuals with T2DM (n=1,233)

Variables	OR	(95% CI)	p value
Entry age (yrs)	1.009	(0.991-1.028)	0.318
Sex			
Male	Ref.		
Female	1.260	(0.904-1.753)	0.173
Ethnicity			
Chinese	Ref.		
Malay	1.648	(1.138-2.400)	0.009
Indian	1.380	(0.960-1.983)	0.082
Duration of diabetes (yrs)	1.006	(-0.988-1.025)	0.493
HbA1c (%)	0.985	(0.874-1.110)	0.806
BMI (kg/m^2)	1.054	(1.022-1.087)	0.001
Heart rate (bpm)	1.013	(0.999-1.027)	0.077
PWV (m/s)[1]	0.994	(0.940-1.051)	0.834
LneGFR (ml/min)	1.028	(0.689-1.529)	0.893
LnACR (μg/mg)[2]	0.978	(0.900-1.063)	0.603
LnsRAGE per SD (pg/ml)	0.867	(0.744-1.009)	0.066
Current smoker	1.076	(0.705-1.641)	0.734
Hypertension	2.529	(1.811-3.533)	<0.001
Usage of ACE inhibitors[3]	1.004	(0.714-1.413)	0.980
Usage of ARBs[4]	1.015	(0.694-1.484)	0.939

T2DM, type 2 diabetes; HbA1c, hemoglobin A1c; BMI, body mass index; PWV, pulse wave velocity; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; sRAGE, soluble receptor for advanced glycation end products; ACE, angiotensin-converting-enzyme; ARBs, angiotensin receptor blockers

[1]Results are estimated on 1,220 subjects because of 13 (1.05%) missing values

[2]Results are estimated on 1,222 subjects because of 11 (0.89%) missing values

[3]Results are estimated on 1,228 subjects because of 5 (0.40%) missing values

[4]Results are estimated on 1,227 subjects because of 6 (0.49%) missing values

DISCUSSION

In the multi-ethnic T2DM Asian cohort, we have, for the first time, demonstrated that while Malays were likely to have IADSBP ≥10 mmHg than the Chinese, the Indians have comparable odds with the Chinese. BMI and hypertension were strongly associated with IADSBP ≥10 mmHg.

The pattern of higher IADSBP in Malays and Indians compared to Chinese in this study is concordant with our previous observation of ethnic-associated greater arterial stiffness[12] and poor T2DM-related outcome.[10,11] Our finding corroborates well with prevailing literature suggesting the existence of a relationship between ethnicity and IADSBP. The IADSBP ≥10 mmHg in Chinese (6.4%, <4 mmHg),[19] Japanese (6.3%, 3.7 mmHg)[20] and Taiwanese (7.1%)[21] are lower than that in Caucasians in UK (8.6%, mean=4.6 mmHg,[18] 20%, 6.3 mmHg[22]) and USA (9.8%)[23]. In one multi-ethnic study in USA, different prevalence rates of IADSBP ≥15 mmHg were found in African-Americans (7.4%), Caucasians (5.1%), and Chinese (1.0%).[24] The generally lower IADSBP in Asians than Caucasians might be related to their lower BMI.[20] Consistently, in our study, Chinese had lower BMI, waist circumference and better lipid profile than Malays and Indians. The mechanisms underlying ethnic-disparity in vascular health is complex and may be a composite outcome of non-biological (e.g, social and economic status) and biological factors (e.g., central hemodynamics and arterial stiffness).[34,35]

We observed that BMI is an independent predictor of IADSBP ≥10 mmHg, which is consistent with previous studies, suggesting a potential causal relationship between obesity and significant IADSBP.[21,30,32] The association between hypertension and IADSBP ≥10 mmHg is in agreement with some reports,[21,30] but not others.[32] The differences in age, SBP, DBP and BP measurement methods may all contribute to the disparate findings. Taken together, weight and BP management may ameliorate IADSBP and hence, CVD in T2DM. The odds for IADSBP ≥10 mmHg were decreased by 13.3% with 1-SD increase in LnsRAGE. Advanced glycation end products (AGEs) play an important role in diabetic complications through interaction with the AGE receptor (RAGE). sRAGE is a multi-ligand receptor on vascular cells that acts as decoy, thus decreasing AGE-cellular binding. Experimental studies have demonstrated the role of AGE-RAGE axis in hypertension.[31] Decreased sRAGE level was found in non-diabetic hypertensive patients.[31] Therefore, further study on sRAGE and IADSBP is desirable.

The usual relative concordance of BP in both arms has been speculated to reflect on-going delicate and finely-tuned homeostatic processes. Reasons contributing to the perturbation of this homeostasis include anatomical (e.g., mechanical obstruction secondary to subclavian stenosis) and hemodynamic factors (e.g., endothelial function and atherosclerosis), which could in-part lead to an increase in IADSBP.[32]

CVD is known as a complex disease and can take many forms, such as stroke, myocardial infarction (MI) and ischemic heart disease (IHD).[36] The underlying mechanisms vary depending on the form of the disease. In our study, we found comparable occurrence of IHD, coronary balloon angioplasty and stroke in Malay and Chinese. MI in Malays is higher than Chinese, which agrees with our recent report.[11] It is possible IADSBP is one contributing risk factor for certain forms of CVD, such as MI. In addition to IADSBP, the development of CVD involves many different risk factors, such as genetic factors, hypertension, physical inactivity and unhealthy lifestyle. The measured and unmeasured factors may collectively explain the higher prevalence of IADSBP >10 mmHg in Malays but comparable CVD occurrence compared with Chinese.

The strength of our study is the relatively large sample size of multi-ethnic patients with T2DM living in Singapore. To the best of our knowledge, this is the first study on the association of ethnicity with IADSBP in Asians with T2DM. We are also cognizant of several limitations. We used BP measured sequentially to define IADSBP ≥10 mmHg. This might account for the prevalence of IADSBP ≥10 mmHg (20.8%) higher than most studies in T2DM.[16-18] The overestimation of IADSBP could also be attributable to white-coat effects and short-term large BP variability that escaped detection when using sequential measurement method.[14,15] Therefore, such simple sequential measurement method is recommended for screening in

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routine practice, while simultaneous measurements should be reserved for confirmation.[17] The cross-sectional design of our study precludes any causal-inference between vascular risk factors and IADSBP. Although controlling for potential confounders, we cannot rule out residual confounding from unmeasured factors that could affect blood pressure or IADSBP across three ethnic groups, such as other classes of hypertension medications (i.e., calcium channel blockers) and other renal vascular risk factors (i.e., physical activity, carotid artery intima-media thickness and coronary artery calcium score).[24,37]

CONCLUSIONS

In conclusion, our study provides the first evidence that IADSBP ≥10 mmHg in Malays with T2DM may explain their excess adverse diabetes-related vascular outcomes compared to Chinese. Therefore, measuring bilateral BP may be a simple yet clinically useful procedure to identify T2DM patients at high risk for CVD, thereby informing the need to intensify risk factor management.

Acknowledgements
We thank Dr. Darren E. J. Seah for his assistance in subject recruitment. We also thank staff from the Singapore Clinical Research Institute (SCRI) for their contribution to study protocol and database design. Study data were collected and managed using REDCap electronic data capture tools hosted at SCRI.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
The authors declare that they have no competing interests.

Funding Source
This work was supported by Singapore National Medical Research Council Grant PPG/AH(KTPH)/2011. The funder has no role in study design, data collection, analysis, interpretation and manuscript writing.

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ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.03

ORIGINAL ARTICLE

JAFES

Development and Validation of a Thyroid Cancer-Specific Health-Related Quality of Life Questionnaire for Adult Filipinos with Differentiated Thyroid Cancer

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Abstract

Objectives. The study aims to develop and validate a health-related quality of life (HRQoL) questionnaire for adult Filipinos with differentiated thyroid cancer (DTC) that can be used in combination with the European Organization for Research and Treatment of Cancer QLQ-C30 Questionnaire.

Methodology. The study had 4 phases. Phase I involved generation of HRQoL issues from literature review, focus group discussions with 6 DTC patients and 5 health care professionals (HCP). Subsequent assessment for relevance and importance of the HRQoL issues by 20 patients and HCP panel was done. Phase II was formulation of the HRQoL issues into questionnaire and subsequent translation into Filipino. Phase III was pilot testing of the questionnaire in 15 patients. Phase IV was validation of the pre-final questionnaire in 231 patients.

Results. In Phase I, 28 HRQoL issues were generated. In Phase II, a 28-item Filipino questionnaire was created. In Phase III, 22 items that were not upsetting or confusing to patients and with good range of responses were retained. After Phase IV, a 22-item questionnaire with 5 conceptual scales (perceived fears, psychological distress/anxiety, functionality, voice complaints, neck complaints) was created.

Conclusion. The developed and validated 22-item questionnaire can be used to assess HRQoL issues in adult Filipinos with DTC.

Key words: thyroid cancer, quality of life, questionnaire, Philippines, validation studies

INTRODUCTION

The incidence of thyroid cancer has continuously increased in the last three decades all over the world.[1] In the Philippines, the incidence has been stable, with an annual average increase of 0.4% and 1.6% in males and females, respectively, as of 2002.[2] High survival rates (five-year survival rates around 98.1% from 2006-2012 in the US) account for the growing number of thyroid cancer survivors.[3]

The treatment of thyroid cancer is particularly effective in early stage disease and involves surgery (total thyroidectomy or lobectomy with or without lymphadenectomy), which is usually followed by radioiodine ablation therapy and suppressive doses of levothyroxine. These treatment modalities, however can be associated with physical or psychological complaints as shown in studies by Almeida et al.,[4] Rubic et al.,[5] and Gomez et al.,[6] which revealed radioactive iodine-related complaints like problems in swallowing, hypothyroid symptoms such as fatigue and negative effects on psychological well-being in patients with thyroid cancer. Moreover, the disease can recur even after several decades or persist for years requiring treatment. Therefore, long term follow-up is needed which can also lead to psychological distress. All of these factors could significantly alter the health-related quality of life (HRQoL) of thyroid cancer patients.

HRQoL is defined by the World Health Organization as a subjective perception of health in terms of physical, mental, and social well-being of a patient.[7] Assessment of HRQoL in thyroid cancer patients can reveal the significant concerns of the patients relating to the disease. There are several studies assessing the HRQoL of thyroid

eISSN 2308-118x
Printed in the Philippines

Received: May 27, 2016. Accepted: July 11, 2016.
https://doi.org/10.15605/jafes.031.02.03

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ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.03

cancer patients. Husson et al., systematically reviewed the literature on HRQoL of thyroid cancer survivors yielding 27 studies. The review showed that thyroid cancer survivors generally have a similar or slightly worse HRQoL compared with the normative population. Some of the identified causes in decrease in HRQoL include mental problems like anxiety and depression, physical problems like hoarseness, fatigue, chills and tingling sensation and decrease in social functioning in thyroid cancer patients in comparison to normal people in some of the included studies.[8] The studies, however, used general HRQoL questionnaires, which might not reveal specific thyroid cancer-related complaints or a non-validated thyroid cancer HRQoL questionnaire.

The European Organization for Research and Treatment of Cancer (EORTC) created a quality of life questionnaire (EORTC QLQ-C30) which is one of the most widely used questionnaires for assessing quality of life in patients with cancer. This was meant to be used with supplementary modules that evaluate HRQoL in specific diseases.[9] No module currently exists specifically for thyroid cancer. The only validated thyroid cancer-specific HRQoL (THYCA-QoL) questionnaire was developed in a Dutch population of thyroid cancer patients by Husson et al., according to the methods of the EORTC Quality of Life group.[10] Currently, there is no validated thyroid cancer-specific HRQoL questionnaire in the Philippines.

A HRQoL questionnaire specific for thyroid cancer patients that can be used together with the EORTC QLQ-C30 in the Philippines will be very helpful in assessing the areas in these patients' lives that need to be addressed by physicians to maintain and/or improve quality of life. Differences between populations in terms of culture, socioeconomic status and probably treatment practices in thyroid cancer are some of the reasons for developing a new questionnaire instead of just adapting a validated questionnaire from another country.

The aim of the study was to develop a thyroid cancer-specific quality of life questionnaire in combination with the core cancer quality of life questionnaire EORTC QLQ-C30 and validate its use for adult Filipinos with differentiated thyroid cancer.

METHODOLOGY

Study Designs

The first part of the research (Phases I-III) involved questionnaire development. The second part (Phase IV) was a cross sectional analytic study to validate the questionnaire developed in the previous phases.

Study Subjects

The study subjects were adult patients aged 19 years and above with well differentiated thyroid cancer (DTC) who were recruited from the Philippine General Hospital, a tertiary hospital in Manila. The diagnosis of DTC was based on histopathology results after thyroidectomy with or without maintenance levothyroxine therapy. Subjects were only included after giving their informed consent to participate in this study.

Subjects were excluded if they satisfied any of the following criteria: presence of cognitive impairment; presence of severe/uncontrolled comorbid diseases (uncontrolled hypertension, uncontrolled diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, myocardial infarction, chronic kidney disease); presence of another coexistent cancer; and being illiterate or unable to read and write.

The study protocol was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) Panel for ethics review and approval. Implementation of the study began after approval from UPMREB. All patient information was kept anonymous and confidential. There was no conflict of interest in this study.

Description of Study Procedure

The development of a thyroid cancer-specific HRQoL questionnaire was partially based on the EORTC Quality of Life Group Guidelines for Developing Questionnaire Modules.[11]

Phase I: Preliminary Steps - Generation of Health-Related Quality of Life Components (Review of Literature, Focus Group Discussions with patients and expert panel)

Phase I was intended to generate a comprehensive list of relevant HRQoL issues for thyroid cancer patients. Literature searches were done in PUBMED and Google Scholar to identify all relevant HRQoL issues. Existing, relevant questionnaires were also reviewed. A list of all questionnaires identified and finally a list of all potentially relevant HRQoL issues were then created.

A focus group of subjects with differentiated thyroid cancer [with representatives from the different types of differentiated thyroid cancer (i.e., papillary and follicular thyroid cancer), from the different stages of the cancer, from age groups <45 and 45 or greater, and from patients <10 years and 10 or more years from diagnosis] was formed in order to discuss relevant HRQoL issues related to their disease. The researcher asked the patients to describe their experiences and showed them existing HRQoL issues from the literature review during the discussion to determine their opinions regarding them. The interviews continued until no new issue was raised. Issues raised during the discussion that were not found in the initial list were added.

The provisional list of issues was then evaluated by an expert panel of health care professionals to assess aptness

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of content and broadness of coverage. Five health professionals (2 endocrinologists, 1 otorhinolaryngologist-head and neck surgeon, 1 nuclear medicine specialist, 1 general surgeon with specialty in head and neck surgery) were included in the panel. The specialists were asked to identify the issues that, in their opinion, affect patients' HRQoL most profoundly and check if there were any missing HRQoL complaints. Additional issues based on the discussion were added to the list.

The health care providers and a sample of thyroid cancer patients [with representatives from the different types of differentiated thyroid cancer (i.e., papillary and follicular thyroid cancer), from the different stages of the cancer, from age groups <45 and 45 or greater, and from patients <10 years and 10 or more years from diagnosis] not involved in the focus group discussion were then asked to rate the issues from 1 (not relevant for thyroid cancer patients) to 4 (very relevant for thyroid cancer patients) on a Likert scale (relevance rating) and to select at the most 25 issues which they thought must be included in the questionnaire (priority rating).

Issues with high relevance ratings (mean score ≥1.5) and high priority ratings for inclusion in the module (ratings ≥25%), based on the recommendations by EORTC[11] and the study by Husson et al.,[10] for both health care providers and thyroid cancer patients were included in the final list of issues. Issues that were already present in the EORTC QLQ-C30 questionnaire, and those that were upsetting to patients were excluded.

Phase II: Construction of the Draft Questionnaire

The final list of HRQoL issues from Phase I was then structured into questions similar in format with the EORTC QLQ-C30 (response categories: 'not at all,' 'a little,' 'quite a bit' and 'very much'). Issues which had been formed into question items in previous EORTC modules were used for uniformity of the questionnaire using the EORTC QoL Item Bank with permission from the authors. For the items that are unavailable in the EORTC Item Bank, new questions were constructed. The questions were created as clear, brief and unambiguous as possible.

The resulting provisional list of items were reviewed for clarity and overlap by the panel of health care professionals and a social scientist, after which the pre-final questionnaire was translated into Filipino for use in the pre-testing phase.

The translation was conducted by two translators who were native speakers of Filipino who have high level of fluency in English. They independently translated the questionnaire into Filipino. The first and the second translators' versions were merged into one single forward translation by the primary investigator. Then two translators translated the questionnaire from the provisional forward translation back into English. The two English back-translation versions were checked by the primary investigator for consistency.

Phase III: Pilot Testing of the Draft Questionnaire

The final list of questions after Phase II was then pretested in a small number of patients with differentiated thyroid cancer [with representatives from the different types of differentiated thyroid cancer (i.e., papillary and follicular thyroid cancer), from the different stages of the cancer, from age groups <45 and 45 or greater, and from patients <10 years and 10 or more years from diagnosis] who were not involved in Phase I, after completing the EORTC QLQ-C30, to determine problems relating to the construction and comprehensibility of items. Interviews were conducted with the patients after completion of the questionnaire to ensure completeness and acceptability of the items in the list. The time it took study subjects to answer the questionnaire was recorded.

At this stage in Phase 3, a selection process which was determined beforehand was applied to remove unnecessary items. The following cut-off points were used for selection of items for retention in the final module: mean Likert scale score >1.5, prevalence ratio >30%, range >2 points, no floor or ceiling effect: responses in categories 3 and 4 or 1 and 2 >10%, no significant concerns expressed by patients (e.g., item is upsetting, ambiguous), compliance of at least 95% response to the item. Items that met five of the six criteria mentioned above were retained in the list while those that did not were excluded.

The final list of items based on the above criteria comprised the pre-final questionnaire.

Phase IV: Validation of the Pre-final Questionnaire

The resultant pre-final questionnaire was validated in a sample of well differentiated thyroid cancer patients (at least 10 patients per question item based on the recommendation by Nunnally[12]). These subjects included a diverse group of DTC patients [with representatives from the different types of differentiated thyroid cancer (i.e., papillary and follicular thyroid cancer), from the different stages of the cancer, from age groups <45 and 45 or greater, and from patients <10 years and 10 or more years from diagnosis], not involved in the previous phases of the study, from both charity and pay patients who consulted at the outpatient clinic or were admitted at the Philippine General Hospital. The subjects first completed the EORTC QLQ-C30 before answering the pre-final version of the questionnaire.

Data analyses included assessment of the response distributions for each item to examine central tendency and variability, and determine presence or absence of ceiling and floor effects; evaluation of construct validity using factor analysis; determination of scale structure using multi-trait scaling analysis; assessment of reliability using Cronbach's alpha coefficient; and ascertainment of correlation of the developed questionnaire with the EORTC QLQ-C30 utilizing Spearman correlation. Floor or

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ceiling effect (when 80% of the responses fall in one response category) impairs the ability of investigators to determine the central tendency of the data, thus question items containing either of these were removed from the questionnaire.

RESULTS

Phase I

The literature search using the keywords: "quality of life," "health-related quality of life," and "complaints" in addition to "thyroid cancer" or "thyroid carcinoma" yielded 47 studies and two thyroid cancer specific questionnaires (1 validated in a Dutch population and another non-validated questionnaire). A total of 81 HRQoL issues were identified from the studies and questionnaires.

The focus group discussion involving 6 diverse thyroid cancer patients yielded 3 more HRQoL issues. Another 9 issues were added and 7 were removed based on discussion with the expert panel. Twenty-four issues were removed because they were already covered by the EORTC QLQ-C30. A total of 62 HRQoL issues remained. These were presented to the 5 health care professionals and 20 diverse thyroid cancer patients for relevance and priority ratings using an English and Filipino Likert scale rating and priority rating tables, respectively. Thirty-four issues were removed because of low relevance and low priority ratings. A total of 28 HRQoL issues relevant to thyroid cancer patients were retained (Appendix A).

Phase II

Four HRQoL issues were constructed into items using questions from the EORTC QoL Item Bank and the remaining 24 issues which were not found in the item bank, were constructed into new questions. These questions were then reviewed by the expert panel and a social scientist resulting in a pre-final list of questions (Appendix B). The time period for the health related complaints assessed by the EORTC QLQ-C30 questionnaire is one week. However, after discussion with the panel and thyroid cancer patients, it was decided to use one month for this study because it was felt that one week is too short for the HRQoL issues in patients with thyroid cancer.

Translation of the constructed questions from English to Filipino and then back to English was done. The Filipino forward translated version had good correlation with the initially formed English questionnaire.

Phase III

Pretesting was done on 15 thyroid cancer patients. Patients did not find any annoying, confusing, upsetting, intrusive or irrelevant questions. They also did not think there were missing items from the list. There were no identified problems with the phrasing of the questions. Patients finished the questionnaire with an average time of 6 minutes, with a range of 3 to 9 minutes.

Table 1. Demographic data of subjects with differentiated thyroid cancer, N=231, Manila

Characteristic	Value
Age in years (Mean, SD)	47.67 (13.32)
Gender	
Male – n (%)	33 (14.3%)
Female – n (%)	198 (85.7%)
Educational attainment	
None – n (%)	1 (0.4%)
Elementary undergraduate – n (%)	12 (5.2%)
Elementary graduate – n (%)	42 (18.2%)
High school graduate - n (%)	119 (51.5%)
College graduate – n (%)	57 (24.7%)
Civil Status	
Single – n (%)	50 (21.6%)
Married – n (%)	155 (67.1%)
Widowed – n (%)	26 (11.3%)
Employment status	
Employed – n (%)	43 (18.6%)
Unemployed – n (%)	188 (81.4%)
Years since diagnosis (mean, SD)	5.05 (6.07)
Type of thyroid cancer	
Papillary – n (%)	204 (88.3%)
Follicular – n (%)	27 (11.7%)
Stage of cancer	
I – n (%)	131 (56.7%)
II – n (%)	46 (19.9%)
III – n (%)	29 (12.6%)
IV – n (%)	25 (10.8%)
Comorbidities	
None – n (%)	142 (61.5%)
Only 1 – n (%)	58 (25.1%)
2 or more – n (%)	31 (13.4%)
Treatment received	
Surgery only – n (%)	72 (31.2%)
Surgery & iodine-131 ablation – n (%)	157 (67.9%)
Surgery and radiotherapy – n (%)	2 (0.9%)

After Phase III of the study, 6 items were removed because of failure to meet 5 of 6 criteria for retention. The recommended number of items at the end of this phase is about 20. In this study there were 22.

Phase IV

Validation was done in 231 patients with DTC. Table 1 shows the demographic data of the subjects. Of the 231 participants, 33 (14%) were men and 198 (86%) were women. The mean age of participants was 47.67±13.32 years (range 19-79 years). Fifty (22%) were single, 155 (67%) were married, and 26 (11%) were widowed. They possessed varying degrees of formal education, with one having no formal education at all, 12 (5%) were elementary undergraduates, 42 (18%) were elementary graduates, 119 (52%) were high school graduates, and 57 (25%) were college graduates. Eighty-one percent was unemployed. Time since diagnosis of thyroid cancer ranged from 29 days to 42 years, with a mean time of 5.05±6.07 years. Two hundred four (88%) had papillary type of thyroid cancer and 27 (12%) had follicular type. The participants had different stages of cancer: 131 (57%) were stage 1, 46 (20%) were stage 2, 29 (13%) were stage 3, and 25 (11%) were stage 4. While 61% had no comorbidity, 25% had one and 13% had two comorbidities. All participants underwent surgery. Of these, two (0.87%) also had radiotherapy and 157 (68%) had iodine-131 ablation.

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Table 2. Item descriptive statistics for the question items

Item	Description	% Respondents	Mean Score (SD)	Distribution of responses (%)			
				1	2	3	4
1	Neck pain	100	1.8 (0.9)	44	35	14	7
2	Lifetime meds	100	2.3 (1.0)	29	23	40	8
3	Limit Physical activity	100	2.2 (0.9)	29	33	30	8
4	Slowed down	99.6	2.0 (0.9)	35	35	24	6
5	Repeat RAI	98.7	2.3 (1.0)	26	28	31	15
6	Regular lab tests	100	2.0 (1.0)	38	34	19	9
7	Recurrence	99.1	2.8 (1.0)	13	17	43	27
8	Cold Intolerance	99.6	1.9 (0.9)	40	32	21	7
9	Treated differently	99.1	1.4 (0.7)	72	16	10	2
10	Relatives get cancer	99.6	2.6 (1.0)	18	26	39	17
11	Neck numbness	100	1.6 (0.9)	59	24	11	6
12	Reduced motivation	100	2.0 (1.0)	44	23	27	6
13	Repeat surgery	100	2.4 (1.0)	26	24	34	16
14	Weak voice	100	2.0 (1.0)	47	22	21	10
15	Another cancer	100	2.4 (1.0)	26	24	34	16
16	Hoarseness	97.0	1.8 (1.0)	53	25	14	8
17	Sudden tiredness	100	1.8 (0.9)	50	26	21	3
18	Muscle/joint pain	99.6	2.0 (1.0)	41	32	18	9
19	Weight gain	99.6	2.1 (1.0)	37	24	35	4
20	Future uncertainty	99.6	2.0 (0.9)	40	29	25	6
21	Isolation	99.6	1.5 (0.8)	71	14	11	4
22	Take LT4 before meals	100	1.6 (0.9)	68	12	14	6

Table 3. Factor loadings of the items after oblique rotation factor analysis

Item	Pattern Matrix				
	1	2	3	4	5
Factor 1: Perceived Fears					
Fear of repeat radioiodine ablation	0.7277				
Fear of recurrence	0.8170				
Fear of relatives getting cancer	0.6173				
Fear of repeat surgery	0.7526				
Fear of another cancer from radiation	0.6728				
Feeling of uncertainty of future	0.4139				
Factor 2: Psychological Distress/Anxiety					
Bothered by lifetime intake of levothyroxine		0.6106			
Bothered by belief in limitation of activity		0.6174			
Bothered by regular laboratory tests		0.5858			
Feeling of being treated differently		0.4292			
Feeling of isolation		0.5632			
Bothered by need to take levothyroxine 30 minutes to 1 hour before breakfast		0.6871			
Factor 3: Functionality					
Feeling slowed down			0.3931		
Reduced motivation			0.4295		
Sudden attacks of tiredness			0.6786		
Muscle/joint pain			0.7293		
Weight gain			0.6272		
Factor 4: Voice Complaints					
Weak Voice				0.8999	
Hoarseness				0.9043	
Factor 5: Neck Complaints					
Neck pain					0.8360
Neck numbness					0.7958

Data analyses were done after completion of Phase IV to determine which items to retain and which to exclude. Item descriptive statistics (Table 2) showed high valid responses and absence of floor or ceiling effects for all items. Thus, no item was excluded at this point in the study.

To assess construct validity, factor analysis was done. The suitability of the data for factor analysis was tested via the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy. For a satisfactory analysis to proceed, the KMO value should be higher than 0.5. The KMO measure in the study was 0.89, thus factor analysis was done. Five factors were identified based on Cattell's scree plot which states that an eigenvalue (the amount of the total variance explained by that factor) must be greater than one for a factor to be retained. Figure 1 shows that five factors have eigenvalues of at least 1 and were thus retained.

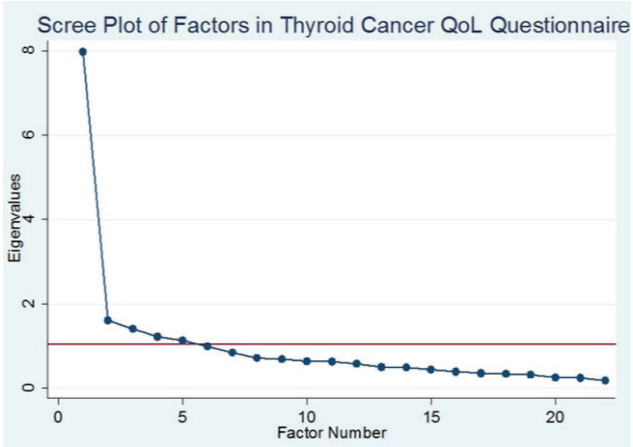

Figure 1. Scree Plot shows that five factors have eigenvalues of at least 1 which means that these five factors explain most of the variability in the data.

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Table 4. Reliability, convergent validity, divergent validity of the 5 scales

Scale/Factor	Number of Items	Cronbach's alpha	Item-Scale Convergent Validity	Item-Scale Divergent Validity
Perceived Fears	6	0.85	0.503-0.748	0.154-0.540
Psychological Distress/Anxiety	6	0.80	0.390-0.646	0.023-0.540
Functionality	5	0.74	0.257-0.592	0.050-0.527
Voice Complaints	2	0.87	0.741	0.116-0.442
Neck Complaints	2	0.73	0.542	0.078-0.278

Table 5. Spearman correlations between EORTC QLQ-C30 and thyroid cancer HRQoL Questionnaire

EORTC	Factor 1 Perceived Fears	Factor 2 Psychological Distress / Anxiety	Factor 3 Functionality	Factor 4 Voice Complaints	Factor 5 Neck Complaints	Cold Intolerance
Global Health Function	-0.3488*	-0.3305*	-0.3861*	-0.2510*	-0.0820	-0.1654
Physical Function	0.4060*	0.4149*	0.5394*	0.3350*	0.1968*	0.3779*
Role Function	0.3138*	0.3752*	0.2775*	0.3324*	0.2116*	0.3616*
Emotional Function	0.4527*	0.4971*	0.3796*	0.2480*	0.1910*	0.2857*
Cognitive Function	0.3461*	0.3360*	0.4087*	0.2580*	0.2011*	0.2197*
Social Function	0.3991*	0.5444*	0.4027*	0.2441*	0.2545*	0.3194*
Fatigue	0.2966*	0.3576*	0.5825*	0.1935*	0.1632	0.3179*
Nausea/ Vomiting	0.1817*	0.1292	0.2004*	0.0992	0.2720*	0.1292
Pain	0.3500*	0.4653*	0.4411*	0.3061*	0.2199*	0.3597*
Dyspnea	0.2808*	0.3348*	0.3777*	0.155	0.3179*	0.2224*
Insomnia	0.1878*	0.1708*	0.2086*	0.0974	0.0429	0.0733
Appetite Loss	0.1379	0.2623*	0.2033*	0.041	0.1648*	0.2235*
Constipation	0.2687*	0.2693*	0.3794*	0.1783*	0.0657	0.2775*
Diarrhea	-0.0325	-0.0205	-0.0265	-0.0327	-0.0903	-0.0202
Financial Difficulty	0.3657*	0.4944*	0.3712*	0.2709*	0.1703*	0.143

*p<0.05

Oblique rotation to determine factor loadings of each item was done (Table 3). The items that had high factor loadings (>0.35) in the same factor were grouped together indicating that these items may reflect a related groups of symptoms or complaints. Factor 1 is defined by items relating to perceived fears of the patients. Factor 2 is composed of items relating to psychological distress or anxiety. Factor 3 includes items relating to functionality of patients. Factors 4 and 5 are items dealing with voice complaints and neck complaints, respectively. Some items had high item loadings in more than 1 factor but were assigned to the factor with the items they are more compatible with. The item for cold intolerance did not have high loading in any of the factors and thus was considered as a single item.

The reliability of the five identified factors or scales was assessed using Cronbach's alpha. Acceptable Cronbach's alpha is 0.7. The convergent and divergent validity were assessed using Spearman correlation. A value of >0.4 indicate moderate to high correlation while <0.4 indicate weak correlation. Items of the same scale should have moderate to high correlation or good convergent validity while items from different scales should have weak correlation or good divergent validity.

Cronbach's alpha reliability coefficients for the five factors range from 0.73-0.87. All are greater than the preferred cut-off of 0.7 which indicates good reliability. The overall Cronbach's alpha for the entire measure is 0.91. All the scales in general have good convergent and divergent validity with some exceptions (Table 4).

Furthermore, Spearman correlations between the various scales of the EORTC QLQ-C30 and the scales and items of the created thyroid cancer specific questionnaire were done. Most scales of the thyroid cancer HRQoL questionnaire correlated poorly with the EORTC QLQ-C30 (Table 5).

DISCUSSION

This questionnaire was developed using the guidelines of EORTC, which is one of the largest questionnaire-making body for quality of life of cancer patients. Extensive literature search, and thorough interviews and consult with relevant health care professionals and thyroid cancer survivors were done to create a questionnaire that covers the multidimensional HRQoL issues in patients with DTC.

There were 5 factors or scales identified in this study. The scales all have good reliability and mostly good convergent validity (correlation of >0.4) with some exceptions in Factors 2 and 3 and good divergent validity (correlation of <0.4) with some exceptions in the 5 factors which may be explained by loading of some items in more than 1 factor. Thus, all the items were retained. Spearman correlation between the EORTC QLQ-C30 and the developed thyroid cancer questionnaire was weak which indicates that there is no redundancy between the two questionnaires. Thus, the developed and validated thyroid cancer HRQoL questionnaire can be used in combination with the EORTC QLQ-C30 for patients with DTC.

There are a few existing questionnaires specifically used in the assessment of HRQoL of thyroid cancer patients. The THYCA-QoL is a thyroid cancer HRQoL questionnaire developed and validated for the Dutch population.[10] Jeong et al., also validated a Korean version of this questionnaire which was shown to be a reliable and valid assessment tool that can be used in combination with the EORTC QLQ-C30 to assess the HRQoL of Korean thyroid cancer patients.[13] Most of the items in that questionnaire are related to physical complaints. In contrast, the results of this study

ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.03

showed several psychological as well as functional HRQoL complaints in addition to physical complaints in Filipino patients. This study shows that differences in complaints or perception of a decrease in quality of life occur in different cultures of subjects with DTC.

Another thyroid cancer HRQoL questionnaire known as City of Hope Quality of Life – Thyroid version was developed in California, USA.[14] However, it was not validated. It includes physical, psychological, social and spiritual components. EORTC is also currently developing a thyroid cancer specific HRQoL questionnaire which will be validated in the European population.[15]

Because of the usually good prognosis and prolonged life of thyroid cancer patients compared to other cancer patients, using the final questionnaire (see Appendix C for the Filipino and English versions of the final questionnaire) to assess their quality of life is of value for physicians to guide therapy. Care of these patients can be improved based on their perceived HRQoL.

CONCLUSIONS

A 22-item questionnaire to assess HRQoL specific for Filipinos with DTC that can be used in combination with the EORTC QLQ-C30 was developed and validated. Five scales (perceived fear, psychological distress/anxiety, functionality, neck complaints, voice complaints) with good reliability, and acceptable convergent and divergent validity were identified.

Acknowledgements
The authors are grateful to Professor Laurie Ramiro, a social scientist from the College of Arts and Sciences of the University of the Philippines Manila, who provided advice and suggestions critical for Phase II of the study. The invaluable comments of the consultants of the Section of Endocrinology, Diabetes and Metabolism of the Philippine General Hospital also helped improve and refine this study.

Statement of Authorship
All authors have approved the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
The Philippine Society of Endocrinology, Diabetes and Metabolism provided a monetary grant instrumental to the completion of the study.

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ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.03

Appendix A. Final list of HRQoL issues from Phase I of study

1. Weak voice
2. Neck numbness
3. Hoarseness
4. Neck pain
5. Feeling slowed down
6. Difficulty tolerating cold
7. Weight gain
8. Sudden attacks of tiredness
9. Skin problems like itchiness, dryness
10. Pain in muscles and/or joints
11. Difficulty coping with disease
12. Feeling of distress over regular laboratory tests
13. Bothered by need to take tablets for the rest of life
14. Fear of need of another radioactive iodine treatment
15. Feeling of not being in control of life
16. Feeling of uncertainty about future
17. Fear of recurrence of cancer/worsening of disease
18. Reduced motivation in daily activities
19. Feeling of dissatisfaction with life
20. Concern over limitation in activity – belief of "bawal magbuhat"
21. Fear of sterility from radioactive iodine treatment
22. Fear of another cancer from radiation
23. Fear that loved ones will also get thyroid cancer
24. Bothered by need to go to doctor regularly
25. Bothered by need to take tablets 30 minutes to 1 hour before breakfast
26. Fear of need of another surgery
27. Feeling of being treated differently due to disease
28. Feeling of isolation due to disease

Appendix B. List of constructed questions

Have you noticed that you talked with a weak voice?
Have you experienced numbness in your neck?
Have you been hoarse?
Have you experienced pain in your neck?
Have you felt slowed down?
Have you had difficulty tolerating cold weather?
Have you gained weight?
Have you had sudden attacks of tiredness?
Have you had dry, itchy, flaky or puffy skin?
Have you experienced aches or pains in your muscles or joints?
Have you had difficulty coping with your disease?
Have you felt distress over the need to undergo regular laboratory tests?
Have you been bothered by the need to take medications for the rest of your life?
Have you felt fear of needing another radiation?
Have you felt that you had no control over your life?
Have you felt uncertain about your future?
Have you felt fear of recurrence of your cancer or worsening of your disease?
Have you had reduced motivation in daily activities?
Have you felt dissatisfaction with your life?
Have you had concerns of limiting your physical activity because of your disease?
Have you felt fear of sterility from radiation?
Have you felt fear of developing another cancer from exposure to radiation?
Have you felt fear that your loved ones will also get thyroid cancer?
Have you been bothered by the need to go to the doctor regularly?
Have you been bothered by the need to take levothyroxine tablets 30 minutes to 1 hour before breakfast?
Have you felt fear of needing of another surgery because of your disease?
Have you felt that you were being treated differently because of your disease?
Have you felt isolated due to your disease?

ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.03

Appendix C. Final Questionnaire after Phase IV

Filipino Version

Talatanungan Tungkol sa Kalidad ng Buhay ng Pasyenteng May Thyroid Kanser

Kami ay interesado sa iilang bagay tungkol sa iyo at iyong kalusugan. Pakisagot lamang po ang mga tanong sa pamamagitan na pagbilog sa bilang na tumutukoy sa iyo. Walang "tama" o "maling" sagot sa tanong. Ang impormasyon na iyong ibibigay ay mananatiling lihim.

Code Number: _____ Oras Nagsimula:_____
Iyong Kapanganakan (araw, buwan, taon): _____ Oras Natapos:_____
Kasalukuyang petsa: _____
Hindi – 1; Kaunti – 2; Medyo – 3; Madalas – 4

Sa nakaraang 30 araw:	**Pakibilog ang iyong kasagutan**			
	Hindi	Kaunti	Medyo	Madalas
Nakaramdam ka ba ng kirot sa iyong leeg?	1	2	3	4
Nabahala ka ba dahil kailangan mong uminom ng gamot habang-buhay?	1	2	3	4
May mga pag-aalala ka ba na dapat maglimita ka sa mga pisikal mong gawain dahil sa iyong sakit?	1	2	3	4
Nakaramdam ka ba ng pagbagal ng pagkilos?	1	2	3	4
Nakaramdam ka ba ng takot sa posibilidad na kailangang sumailalim ka sa isa pang radiation?	1	2	3	4
Nakaramdam ka ba ng balisa dahil kailangan mong sumailalim sa regular na laboratory tests?	1	2	3	4
Nakaramdam ka ba ng takot na umulit ang iyong kanser o lumala ang iyong sakit?	1	2	3	4
Nahirapan ka bang tiisin ang malamig na panahon?	1	2	3	4
Nakaramdam ka ba na naiba ang naging pagtrato sa iyo dahil sa iyong sakit?	1	2	3	4
Nakaramdam ka ba ng takot na ang iba mong mahal sa buhay ay magkaroon din ng kanser sa thyroid?	1	2	3	4
Nakaramdam ka ba ng pamamanhid sa iyong leeg?	1	2	3	4
Nabawasan ba ang iyong sigla para sa mga gawaing pang-araw-araw?	1	2	3	4
Nakaramdam ka ba ng takot na maaari kang operahan ulit dahil sa iyong sakit?	1	2	3	4
Napansin mo bang mahina ang iyong boses kapag ikaw ay nagsasalita?	1	2	3	4
Nakaramdam ka ba ng takot na magkaroon ng iba pang uri ng kanser mula sa radiation?	1	2	3	4
Namaos ka ba?	1	2	3	4
Nakaramdam ka ba ng pag-atake ng biglaang pagkapagod?	1	2	3	4
Nakaramdam ka ba ng pagkirot ng iyong mga kalamnan at kasu-kasuan?	1	2	3	4
Nadagdagan ba ang iyong timbang?	1	2	3	4
Nakaramdam ka ba ng kawalan ng kasiguruhan sa hinaharap mo?	1	2	3	4
Nakaramdam ka ba na ikaw ay nag-iisa dahil sa iyong sakit?	1	2	3	4
Nabahala ka ba dahil kailangan mong uminom ng levothyroxine tablets 30 minuto hanggang isang oras bago ka mag-almusal?	1	2	3	4

ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.03

English Version

Thyroid Cancer-Specific Quality of Life Questionnaire

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Code Number: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): _____
Not at all – 1; A little – 2; Quite a bit – 3; Very much – 4

During the past 30 days:	**Please encircle you answer**			
	Not at all	A little	Quite a bit	Very much
Have you experienced pain in your neck?	1	2	3	4
Have you been bothered by the need to take medications for the rest of your life?	1	2	3	4
Have you had concerns of limiting your physical activity because of your disease?	1	2	3	4
Have you felt slowed down?	1	2	3	4
Have you felt fear of needing another radiation?	1	2	3	4
Have you felt distress over the need to undergo regular laboratory tests?	1	2	3	4
Have you felt fear of recurrence of your cancer or worsening of your disease?	1	2	3	4
Have you had difficulty tolerating cold weather?	1	2	3	4
Have you felt that you were being treated differently because of your disease?	1	2	3	4
Have you felt fear that your loved ones will also get thyroid cancer?	1	2	3	4
Have you experienced numbness in your neck?	1	2	3	4
Have you had reduced motivation in daily activities?	1	2	3	4
Have you felt fear of needing of another surgery because of your disease?	1	2	3	4
Have you noticed that you talked with a weak voice?	1	2	3	4
Have you felt fear of developing another cancer from exposure to radiation?	1	2	3	4
Have you been hoarse?	1	2	3	4
Have you had sudden attacks of tiredness?	1	2	3	4
Have you experienced aches or pains in your muscles or joints?	1	2	3	4
Have you gained weight?	1	2	3	4
Have you felt uncertain about your future?	1	2	3	4
Have you felt isolated due to your disease?	1	2	3	4
Have you been bothered by the need to take levothyroxine tablets 30 minutes to 1 hour before breakfast?	1	2	3	4

ONLINE FIRST | September 7, 2016 | https://doi.org/10.15605/jafes.031.02.04

ORIGINAL ARTICLE

JAFES

Low Indices of Overweight and Obesity are Associated with Cardiometabolic Diseases among Adult Filipinos in a Rural Community*

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Abstract

Objective. To determine cut-off levels of body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) for overweight/obesity associated with cardiometabolic diseases (CMDs) among adult Filipinos in a rural community.

Methodology. This community-based cross-sectional observational study utilized data from our Phase II of Diabetes Self-Management Education Program in San Juan, Batangas, Philippines. It included 332 Filipino adults with no known illnesses and residing for at least 6 months in the rural communities. Optimal cut-offs were determined by the intersection of sensitivity and specificity curves of having at least 1 or 2 CMDs.

Results. The study population included 332 participants (72.3% females). Mean BMI, WC and WHR were 23.5 kg/m^2, 79.5 cm and 0.87 respectively. Twenty eight percent, 11.1%, 78.3% and 85.8% of the participants have hypertension, diabetes, dyslipidemia, and at least 1 CMD respectively. The optimal cut-off for overweight/obesity and central obesity in males and females are BMI of 24 and 23 kg/m^2, WC of 84 and 77 cm, and WHR 0.91 and 0.85 respectively.

Conclusion. Similar to other Asian countries, cut-off levels for overweight, obesity, and central obesity associated with CMDs are lower than the currently recommended cut-offs among Filipino adults in rural communities, particularly for WC in both sexes.

Key words: overweight, obesity, metabolic diseases, Filipinos

INTRODUCTION

Overweight and obesity are considered to be major risk factors for the development of cardiometabolic diseases (CMDs) including hypertension, type 2 diabetes mellitus, and dyslipidemia.[1] Worldwide, the prevalence of overweight and obesity have been increasing across all ethnic origins[2] and current figures are expected to increase as modernization of low and middle income countries occurs.[3] In the Philippines, the prevalence of CMDs is increasing concomitantly with the escalating rate of overweight and obesity as reported by the National Nutrition and Health Survey (NNHeS) in 2003[4] and 2008.[5] The first NNHeS prevalence rate of overweight (11.8%) and obesity (1.7%) in the Philippines was reported in 1987, defined as body mass index (BMI) of 25.0 – 29.9 kg/m^2 for overweight and ≥30 kg/m^2 for obesity.[6] Twenty years later, the 2008 NNHES showed these figures have risen two- to three-folds to 21.4% and 5.3% respectively, using the same criteria.[5]

A growing body of literature, however, suggests that the global World Health Organization (WHO) BMI and waist circumference (WC) recommended cut-offs established in 1995[7] should be lowered for Asian populations,[8] since they are described as "small" or "lean" compared to Caucasians of similar age and sex.[9] The prevalence of overweight and obesity in Asia appears to be lower compared to other continents, but this is discordant with the growing incidence of obesity-related diseases in the region.[9,10] In 2000, the WHO, the International Obesity Task Force, and the International Association for the study of Obesity collaboration recommended lower BMI and WC cut-offs for Asia-Pacific populations [WHO Asia – Pacific Perspective (WHO-APP)].[11] However, even within Asian populations, a certain degree of heterogeneity exists particularly in ethnic-specific variations in body fat percentages likely due to genetic and cultural diversity which may translate to varying BMI, WC and waist-to-hip ratio (WHR) cut-off values for a given Asian population.[12]

eISSN 2308-118x
Printed in the Philippines

Received: June 1, 2016. Accepted: July 13, 2016.
https://doi.org/10.15605/jafes.031.02.04

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**Oral presentation, Asia Oceania Congress of Endocrinology, Cebu City, Cebu, Philippines, 2014.*

ONLINE FIRST | September 7, 2016 | https://doi.org/10.15605/jafes.031.02.04

Among the Southeast Asian and neighboring countries, optimal cut-offs were found to be varied relative to the occurrence of CMDs.[13-20] Given these differences in optimal cut-off points for overweight, obesity and central obesity in Asia, setting a single and common cut-off values for the region cannot be adapted universally at present. Therefore, country-specific anthropometric indices cut-offs are appropriate and clinically relevant.[9]

This study is one of the first attempts to test whether the current anthropometric indices cut-offs were appropriate for Filipinos. The objective was to determine the optimal cut-off levels of BMI, WC and WHR for overweight/obesity and central obesity associated with the occurrence of selected cardiometabolic diseases, namely hypertension, diabetes and dyslipidemia among adult Filipinos aged ≥18 years old in a rural community. Specifically, the study determined the rate of overweight, obesity and central obesity using the two cut-off points of WHO, and the accuracy of BMI, WC and WHR in predicting the presence of CMDs.

METHODOLOGY

This is a community-based cross-sectional observational study that utilized data from Phase II of Diabetes Self-Management Education (DSME) Program. Briefly, the DSME program is a 4-phase community-based study conducted by the Diabetes Study Group of the Section of Endocrinology, Diabetes and Metabolism of the University of the Philippines - Manila in San Juan, Batangas. Phase I determined the knowledge, attitudes and practices of persons with type 2 diabetes in the community.[21] Phase II determined the prevalence of pre-diabetes, type 2 diabetes, hypertension, dyslipidemia and metabolic syndrome. Phase III was the actual implementation of the program to demonstrate its effectiveness. Lastly, Phase IV aimed to determine the effectiveness of a lifestyle intervention program in preventing diabetes among those who have prediabetes. The program is currently on its Phase IV of implementation. The municipality of San Juan, Batangas, Philippines is an agricultural coastal town, subdivided into 42 *barangays*. It is approximately 115 kilometers away from Manila, and 43 kilometers away from Batangas City. The main sources of livelihood include farming and fishing, while the usual means of transportation within their *barangay* is by walking. San Juan, Batangas was chosen since it is the site of Community Health and Development Program (CHDP) of the University of the Philippines - Manila.

Phase II of the DSME program included 365 adults (>18 years old) with no known CMDs and residing for at least 6 months in the rural communities of San Juan, Batangas. Pregnant women, those taking anti-hypertensive and cholesterol lowering drugs, and those taking drugs which affect glucose metabolism such as glucocorticoids were excluded. Participants with diabetes were not excluded. In this analysis, the 33 participants who were known to have diabetes already were excluded since they were already taking oral hypoglycemic agents and practicing some form of lifestyle changes that could alter their anthropometric measurements. This reduced the study population to 332.

Participants were selected through a 3-stage stratified random sampling method. The 3 strata of sampling units were *barangays*, household and household members. For the first stratum, 12 were selected of 42 *barangays*. A list of household and household members from these *barangays* was obtained. For the second stratum, random sampling of households proportionate to population size of each *barangay* was performed. For the third stratum, random sampling of members of selected households was conducted. Three hundred sixty-five (365) were initially invited to participate. However, only 118 (32%) from the original list participated. The remaining 247 participants were co-dwellers of the same household. The reduction in the number of participants is due to limitations of performing research in a rural community including unavailability due to school or work, seeing the activity as an opportunity to be seen by a doctor and have laboratory tests done for free, and the perception of being inconsiderate should they have been turned down. The non-randomly selected household members were allowed to participate as a replacement for their randomly selected relative since these individuals made an effort to walk to the study site early in the morning after undergoing an 8-hour fast and satisfied the first and second stratification criteria.

All participants were evaluated after signing an informed consent. Demographic and socio-economic data were documented through a standardized questionnaire. Physical examination was carried out by trained research assistants. Weight in kg and height in cm (to one decimal point) were measured using a standard weighing scale (with sandals/shoes and heavy clothing removed) and measuring stick built in to the weighing scale (without shoes) respectively. The BMI (to one decimal point) was calculated as the weight (kg) divided by the square of height (m). Their WC and HC in cm (to one decimal point) were measured through a non-elastic tape measure at the midpoint between the iliac crest and the lower rib margin, and the maximum circumference around the buttocks posteriorly and pubic symphysis anteriorly respectively. Their WHR was then calculated (to two decimal points). Blood pressure (BP) was measured using a mercury sphygmomanometer. Two blood pressure determinations were taken from the right arm in a sitting position, 5 minutes apart, after a 30-minute rest. The average of the two measures was recorded for analysis. To limit inter-observer variability only one person took the anthropometric measurement and blood pressure levels of all participants.

Blood specimens were drawn after a minimum 8-hour fast for serum lipids [total cholesterol (TC), triglycerides (TG),

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high density lipoprotein (HDL), and low density lipoprotein (LDL)] and glucose. A second blood extraction was performed 2 hours post-glucose load for a 75-gram oral glucose tolerance test (OGTT). Fasting blood sugar (FBS) was determined by glucose oxidase method. Serum TC was measured enzymatically after hydrolyzation of glycerol. HDL cholesterol was measured after the precipitation of other lipoproteins with heparin manganese chloride mixture. Laboratory assays were performed at the Medical Research Laboratory of the Philippine General Hospital. Glucose and lipid levels were measured using the Biochem Tem machine.

The study has been approved by the University of the Philippines Manila Research Ethics Board (Registration No: MED 2014-336-01).

Operational Definition

Overweight and obesity were defined based on two BMI criteria, the global WHO, and WHO-APP recommendations. Central obesity was likewise defined based on global WHO and WHO-APP WC criteria, and global WHO WHR criteria.[2,11]

The diagnosis of diabetes was based on the American Diabetes Association criteria for fasting plasma glucose and/or plasma glucose 2 hours after a 75 grams oral glucose load.[22] The diagnosis of dyslipidemia was based on the 3rd report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report.[23] In this study, only abnormal levels TG and/or HDL were considered dyslipidemia as they were the only lipid parameters included for the diagnosis of metabolic syndrome (clustering of CMDs). Lastly, the diagnosis of hypertension was based on the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[24]

Statistical Analysis

Sample size was total enumeration of the population of Phase II of DSME program. Demographic data was reported using descriptive statistics, mean and standard deviation for continuous variables and frequency and percentage for nominal variables. Means of continuous and nominal variables were compared between 2 genders using independent t-test and Fisher's exact test respectively. The statistical significance level was established at alpha of 5% ($p<0.05$). Percentage of participants who were overweight, obese and centrally obese based on the global WHO and WHO-APP criteria were determined. Area under the receiver operating characteristic (ROC) curve (AUC) was used to determine the diagnostic power of BMI, WC and WHR for each, and having at least 1 and 2 CMDs. Optimal cut-offs for each of the 3 anthropometric indices associated with the occurrence of each, and at least 1 and 2 CMDs were defined by the intersection of their sensitivity and specificity curves representing the optimal balance between the two measures of diagnostic accuracy.[13,15-17] All statistical analyses were stratified by sex and were performed using Stata SE version 13.

RESULTS

A total of 332 participants with a mean age of 48.4 years (range: 18 to 88 years) were included in the study (Table 1). Seventy-two percent (72%) were female. Mean BMI, WC and WHR were 23.5 kg/m^2, 79.5 cm and 0.87 respectively. On average, males had higher weight, height, WC and WHR. There was no significant difference in terms of BMI and HC between sexes. Eighty-five percent of the participants were diagnosed with at least 1 CMD at the clinic visit, and the most prevalent was dyslipidemia (78.3%), followed by hypertension and diabetes, with no prevalence difference by sex.

Table 1. Demographic characteristics, anthropometric indices and cardiometabolic diseases in both sexes

Variable	Males (n=92)	Females (n=240)	Total (N=332)	p-value
Age, years	49.8 ± 16.2	47.9 ± 13.9	48.4 ± 14.5	0.282
Weight, kg	60.0 ± 9.5	54.5 ± 10.7	56.0 ± 10.6	*<0.001*
Height, cm	161.0 ± 5.4	151.5 ± 5.7	154.2 ± 7.0	*<0.001*
BMI, kg/m^2	23.1 ± 3.3	23.7 ± 4.1	23.5 ± 3.9	0.245
WC, cm	81.5 ± 9.5	78.8 ± 10.8	79.5 ± 10.5	*0.033*
HC, cm	89.8 ± 6.3	91.4 ± 8.2	90.9 ± 7.8	0.092
WHR	0.91 ± 0.06	0.86 ± 0.08	0.87 ± 0.08	*<0.001*
Systolic BP, mmHg	130.6 ± 20.6	125.6 ± 22.2	127.0 ± 21.9	0.064
Diastolic BP, mmHg	79.1 ± 11.8	76.8 ± 12.1	77.4 ± 12.0	0.113
FBS, mg/Dl	97 ± 24	93 ± 28.8	94 ± 28	0.234
75-g OGTT, mg/Dl	133 ± 72	133 ± 72	133 ± 72	0.984
TC, mmol/L	5.24 ± 1.46	6.0 ± 1.68	5.64 ± 1.63	*0.006*
TG, mmol/L	2.20 ± 1.69	2.0 ± 1.27	2.08 ± 1.40	0.359
HDL, mmol/L	1.13 ± 0.59	1.0 ± 0.46	1.16 ± 0.50	0.572
LDL, mmol/L	3.67 ± 1.37	4.0 ± 1.57	4.06 ± 1.54	*0.004*
Hypertension, n(%)	32 (34.8)	63 (26.3)	95 (28.6)	0.136
Diabetes, n(%)	12 (13.0)	25 (10.4)	37 (11.1)	0.559
Dyslipidemia, n(%)	69 (75.0)	190 (79.6)	259 (78.3)	0.375
At least 1 CMD, n(%)	80 (87.0)	205 (85.4)	285 (85.8)	0.861

Data are mean ± SD unless otherwise indicated.

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Table 2. Rate of overweight, obesity and central obesity by sex and WHO anthropometric cut-offs

Variable	WHO			WHO-APP		
	Male (n=92)	Females (n=240)	Total (N=332)	Male (n=92)	Females (n=240)	Total (N=332)
Overweight, %	25.0	27.5	26.8	22.8	15.4	17.5
Obesity, %	0.03	8.3	6.3	26.1	35.8	33.1
Central Obesity, %						
WC only (A)	1.1	17.4	12.9	0.8	8.3	6.2
WHR only (B)	2.2	1.1	1.9	32.9	12.1	17.9
WC and WHR (C)	1.1	2.2	1.9	20.0	40.8	35.0
Total (A+B+C)	4.3	20.7	16.7	53.8	61.3	59.2

Table 3. Areas under the ROC curve (AUC) of anthropometric indices and cardiometabolic diseases (CMD) in both sexes

CVDs	Sex	BMI AUC (95% CI)	WC AUC (95% CI)	WHR AUC (95% CI)
Hypertension	M	0.74 (0.63, 0.84)	0.75 (0.65, 0.85)	0.72 (0.62, 0.83)
	F	0.56 (0.48, 0.65)	0.59 (0.51, 0.67)	0.58 (0.50, 0.67)
Diabetes	M	0.53 (0.33, 0.73)	0.57 (0.38, 0.76)	0.67 (0.51, 0.83)
	F	0.55 (0.43, 0.67)	0.63 (0.51, 0.75)	0.70 (0.59, 0.82)
Dyslipidemia	M	0.59 (0.43, 0.73)	0.51 (0.37, 0.66)	0.46 (0.33, 0.60)
	F	0.50 (0.41, 0.59)	0.45 (0.36, 0.54)	0.46 (0.37, 0.54)
At least 1 CMD	M	0.69 (0.51, 0.87)	0.67 (0.51, 0.83)	0.61 (0.46, 0.77)
	F	0.59 (0.50, 0.68)	0.56 (0.47, 0.66)	0.53 (0.43, 0.63)
At least 2 CMDs	M	0.73 (0.62, 0.85)	0.70 (0.58, 0.82)	0.67 (0.56, 0.79)
	F	0.52 (0.43, 0.60)	0.54 (0.45, 0.62)	0.58 (0.49, 0.66)

Table 4. Optimal cut-off values, sensitivities and specificities for occurrence of cardiometabolic diseases in males

Cardiometabolic disease	BMI (kg/m^2)			WC (cm)			WHR		
	CO	Sen, %	Spe, %	CO	Sen, %	Spe, %	CO	Sen, %	Spe, %
Hypertension	23*	68.8	61.7	84*	68.8	70.0	0.91*	68.8	63.3
	23†	68.8	61.7	90†	28.1	85.0	-	-	-
	25‡	50.0	86.7	102‡	3.1	98.3	1.0‡	9.4	95.0
Diabetes mellitus	23*	58.3	52.5	83*	58.3	55.0	0.92*	66.7	63.8
	23†	58.3	52.5	90†	25.0	81.3	-	-	-
	25‡	33.3	75.0	102‡	8.3	98.8	1.0‡	16.7	95.0
Dyslipidemia	23*	52.2	60.9	81*	52.2	52.2	0.91*	47.8	52.2
	23†	52.2	60.9	90†	18.8	78.3	-	-	-
	25‡	27.5	78.3	102‡	1.5	95.7	1.0‡	5.8	91.3
At least 1 CMD	22*	66.3	66.7	79*	57.5	58.3	0.90*	57.5	66.7
	23†	51.3	66.6	90†	21.3	91.7	-	-	-
	25‡	28.8	91.7	102‡	2.5	100	1.0‡	7.5	100
At least 2 CMDs	24	66.7	70.8	84	66.7	66.1	0.91	66.7	60
	23†	74.1	61.5	90†	29.6	84.6	-	-	-
	25‡	55.6	86.1	102‡	3.7	98.5	1.0‡	7.4	93.9

CO – cut-off level; * - Optimal cut-off levels for the population; † - WHO-APP cut-off levels; ‡ - Global WHO cut-off levels

Table 5. Optimal cut-off values, sensitivities and specificities for occurrence of cardiometabolic diseases in females

Cardiometabolic disease	BMI (kg/m^2)			WC (cm)			WHR		
	CO	Sen, %	Spe, %	CO	Sen, %	Spe, %	CO	Sen, %	Spe, %
Hypertension	24*	49.2	53.7	79*	58.7	54.2	0.86*	60.3	59.3
	23†	54.0	49.8	80†	58.7	54.2	-	-	-
	25‡	44.4	67.2	88‡	27.0	81.4	0.85‡	68.3	45.8
Diabetes mellitus	24*	52.0	53.5	81*	64.0	62.3	0.88*	64.0	67.0
	23†	56.0	49.3	80†	68.0	53.0	-	-	-
	25‡	48.0	65.6	88‡	32.0	80.5	0.85‡	84.0	45.1
Dyslipidemia	24*	47.1	53.1	79*	47.7	44.9	0.86*	44.5	49.0
	23†	51.3	49.0	80†	47.7	44.9	-	-	-
	25‡	36.7	67.4	88‡	19.9	75.5	0.85‡	56.0	34.7
At least 1 CMD	23*	53.2	60.0	77*	59.0	57.1	0.85*	58.5	45.7
	23†	53.2	60.0	80†	50.7	60.0	-	-	-
	25‡	39.0	82.9	88‡	22.0	85.7	0.85‡	58.5	45.7
At least 2 CMDs	24	45.3	52.3	79	51.6	51.7	0.86	54.7	57.4
	23†	48.4	47.7	80†	51.6	51.7	-	-	-
	25‡	39.1	65.3	88‡	21.9	79.6	0.85‡	67.2	45.5

CO – cut-off level; * - Optimal cut-off levels for the population; † - WHO-APP cut-off levels; ‡ - Global WHO cut-off levels

Based on the global WHO criteria, the rate of overweight, obesity and central obesity were 26.8%, 6.3% and 16.7% respectively (Table 2). More female participants have overweight, obesity and central obesity. More participants have central obesity due to increased WC. Based on the WHO-APP criteria, the rate of overweight decreased to 17.5%, while that of obesity and central obesity increased to 33.1% and 59.2% respectively. More male participants have overweight while more female participants have obesity and central obesity. More participants have central obesity due to combination of increased WC and WHR.

The AUCs of the three anthropometric indices for the occurrence of each, and at least 1 and 2 CMDs are shown in Table 3. The AUCs were always higher for males except for diabetes mellitus. For both sexes, the highest AUC for the occurrence of hypertension, diabetes mellitus and dyslipidemia were with WC, WHR and BMI respectively.

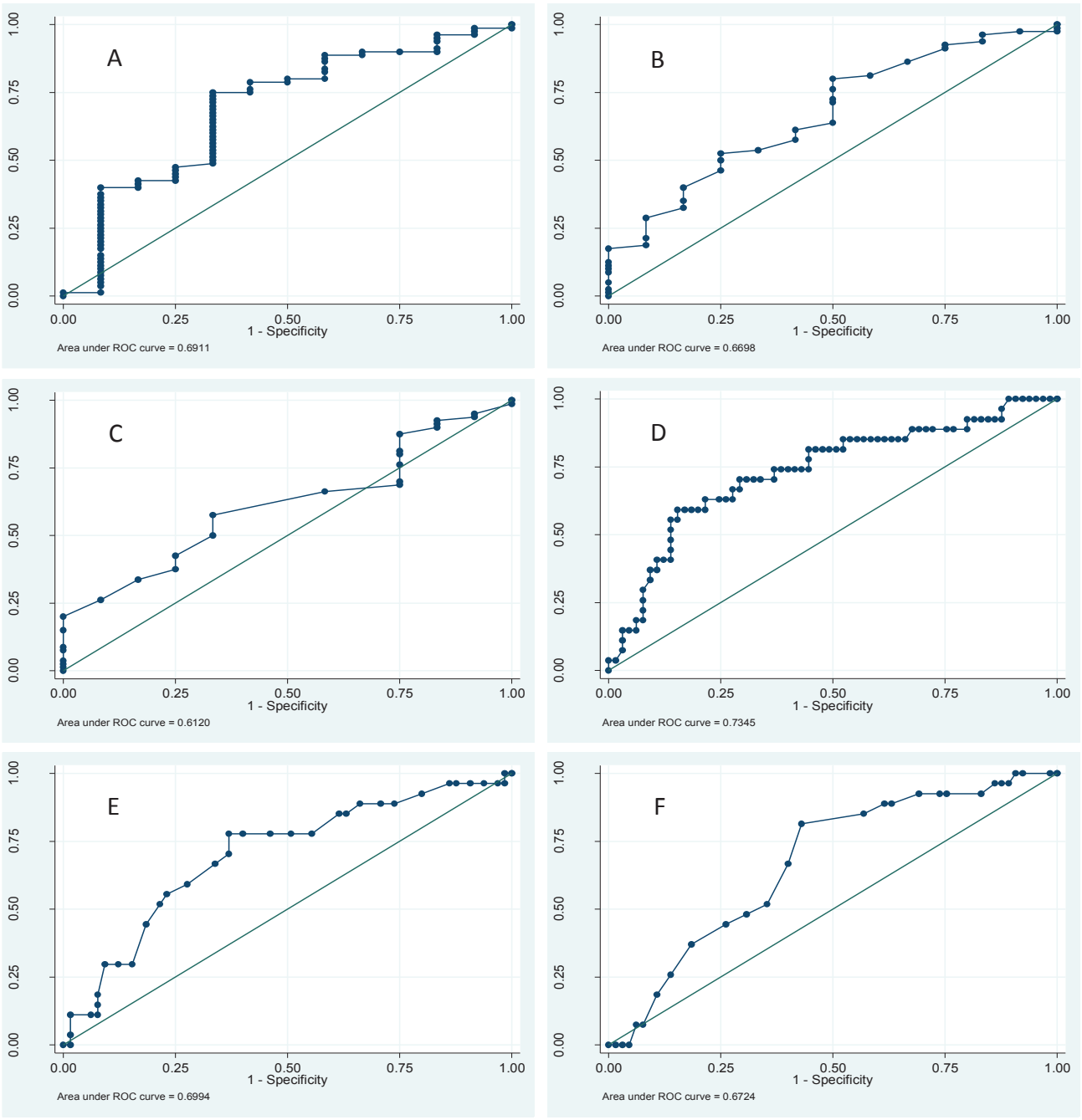

Figure 1. Area Under the Receiver Operating Curve (AUC) of the BMI, WC and WHR for predicting the presence of at least 1 and 2 CMDs in males. The AUCs were larger for all anthropometric indices for predicting the presence of at least 2 CMDs compared to at least 1 CMD. A, BMI and at least 1 CMD; B, WC and at least 1 CMD; C, WHR and at least 1 CMD; D, BMI and at least 2 CMDs; E, WC and at least 2 CMDs; and F, WHR and at least 2 CMDs.

For predicting at least 1 CMD, BMI has the highest AUC for both sexes. For predicting at least 2 CMDs, BMI and WHR have the highest AUCs for males and females respectively. The AUCs of the 3 anthropometric indices were always higher in predicting the presence of at least 2 CMDs in males. For females, the AUCs of BMI and WC were higher in predicting the presence of at least 1 CMD.

Among males, the optimal BMI cut-off associated with the occurrence of each of the CMDs was 23 kg/m^2 with highest sensitivity and specificity for hypertension (Table 4). In terms of the occurrence of at least 1 and 2 CMDs, the optimal cut-offs were 22 and 23 kg/m^2 respectively. For the WC, the optimal cut-off associated with each of the CMDs ranged from 81–84 cm with highest sensitivity and specificity for occurrence of hypertension. The optimal cut-offs associated with the occurrence of at least 1 and 2 CMDs were 79 and 84 cm respectively. The optimal WHR cut-off associated with each of the CMDs was approximately 0.91 with highest sensitivity for hypertension and specificity for diabetes. The optimal cut-offs associated with the occurrence of at least 1 and 2 CMDs were 0.90 and 0.91 respectively.

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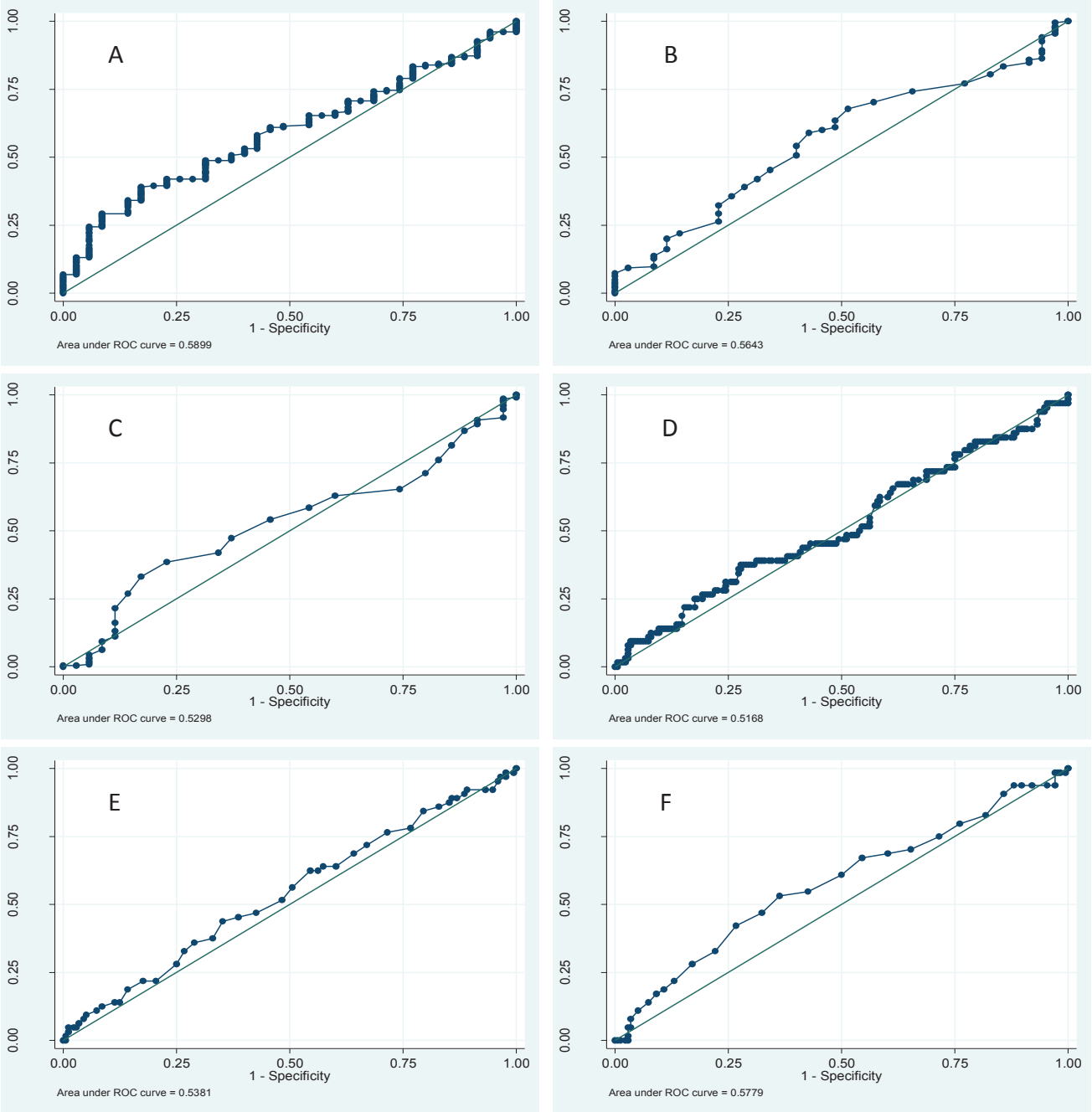

Figure 2. Area Under the Receiver Operating Curve (AUC) of the BMI, WC and WHR for predicting the presence of at least 1 and 2 CMDs in females. The AUCs were larger for all anthropometric indices for predicting the presence of at least 1 CMD compared to at least 2 CMDs. A, BMI and at least 1 CMD; B, WC and at least 1 CMD; C, WHR and at least 1 CMD; D, BMI and at least 2 CMDs; E, WC and at least 2 CMDs; and F, WHR and at least 2 CMDs.

Among females, the optimal BMI cut-off associated with the occurrence of each of the CMDs was 24 kg/m^2 with highest sensitivity for diabetes and specificity for hypertension (Table 5). In terms of the occurrence of at least 1 and 2 CMDs, the optimal cut-offs were 23 and 24 kg/m^2 respectively. The optimal WC cut-off associated with each of the CMDs ranged from 79–81 cm with highest sensitivity and specificity for occurrence of diabetes. The optimal cut-offs associated with the occurrence of at least 1 and 2 CMDs were 77 and 79 cm respectively. For the WHR, the optimal cut-off for each of the CMDs was 0.86 with highest sensitivity and specificity for diabetes. The optimal cut-offs for the occurrence of at least 1 and 2 CMDs were 0.85 and 0.86 respectively.

DISCUSSION

The BMI, WC and WHR have all been shown to be associated with CMDs particularly hypertension, diabetes and dyslipidemia. Most of the studies on the risk of developing CMDs associated with overweight and obesity have been deduced from Caucasians.[16,25] However, over the years, it is becoming clear that for Asians, the risk of developing these diseases related to excess amount of body

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fat occur at a lower BMI, WC and WHR.[14,17,26,27] The results of our study are consistent in showing that CMDs among Filipinos in these rural communities are associated with lower overweight and obesity anthropometric cut-offs compared to the WHO recommendations. Our results were derived from a population with no known CMDs, and free of medications that could alter their anthropometric and metabolic measurements. Our result is one of the first evidences that Filipinos living in the Philippines develop CMDs at lower anthropometric measurements.

Although our data do not represent all Filipinos, our study participants are representative of Filipinos in the rural communities: small-medium built, with moderate-high intensity physical activities and low-moderate caloric intake (consuming mostly rice, vegetables and fish). Despite their healthy physique and lifestyle, the percentage of population with CMDs in this rural community is higher compared to its latest prevalence reported in the National Nutrition and Health Survey 3 years ago (hypertension: 28.6 vs 20.6%; diabetes mellitus: 11.1 vs 6.0%; and dyslipidemia: 78.3 vs 72.0%).[5] This higher rate could be an overestimate of its true prevalence because of population (volunteer/selection) bias in our data due to inclusion of non-randomized participants (a limitation of doing the study in a rural setting as described above). However, the rate could also be an underestimate since 58% (192) of our population are <40 years when screening for CMDs like diabetes are not yet recommended in our country.[28] Our findings of elevated prevalence of CMDs despite low BMI are consistent with studies of Filipino-Americans who have higher diabetes prevalence, smaller WC, lower BMI but significantly more visceral adipose tissue (VAT) by computed tomography (CT) compared to obese Black women.[29] In the absence of CT-defined VAT measures, BMI, WC and WHR offer practical tools, particularly in rural settings to identify those at risk for CMD.

As in most studies, the optimal cut-offs have been identified based on the occurrence of at least 1[15,17-19] and 2[8,14] CMDs. That is, the cut-off with maximum sensitivity and specificity, where it is identified that the occurrence of a single or clustering of CMDs start to increase. Particularly for BMI, our optimal cut-off is for overweight and obesity combined. This is because there is no clear approach on how to delineate the two conditions based on occurrence of CMDs, unlike the well-established body fat percentage used in validation studies.[7]

Our results showed that for males, the optimal BMI, WC and WHR cut-offs were 24 kg/m^2, 84 cm and 0.91 respectively. These were determined from a higher sensitivity and specificity for the occurrence of at least 2 CMDs compared to at least 1 CMD. For females, the optimal BMI, WC and WHR cut-offs were 23 kg/m^2, 77 cm and 0.85 respectively. These were determined from a higher sensitivity and specificity for the occurrence of at least 1 CMDs compared to at least 2 CMDs. These cut-offs also showed larger AUCs for predicting the occurrence of at least 1 (for females) and 2 (for males) CMDs. Since anthropometric indices should serve as trigger to screen for CMDs, a cut-off with a higher sensitivity is preferable to include more and to minimize missing potential at-risk individuals especially if the tests are not costly and definitive.[29] Our results are more applicable to females. The small number of male participants (n=92) makes the recommendations weaker.

Using our optimal BMI cut-offs, the rate of overweight/obesity is 48.2% (40.2 and 51.3% in males and females respectively). This is higher by 15.1% higher and 2.1% lower than if the WHO and WHO-APP cut-offs respectively were used. On the other hand, using our optimal WC and WHR cut-offs, the rate of central obesity is 66.6% (56.5 and 70.4% in males and females respectively). This is higher by 49.9 and 7.4% if the WHO and WHO-APP cut-offs respectively were used. This underestimation of the existing cut-offs is also seen in other Asian countries.[15,19] It is clearly seen from our results that the balance between sensitivity and specificity of the optimal cut-off levels is better than that of the currently established cut-offs particularly the global WHO cut-offs.

Our results are also similar to other Southeast Asian and neighboring countries where the occurrence of CMDs appears at a lower BMI, WC and WHR compared to Western countries.[14-20] In countries like Taiwan,[15] Singapore,[17] Malaysia[18] and Cambodia[19] where cut-offs were identified based on the occurrence of at least 1 CMD, the BMI cut-off for overweight/obesity is approximately 23 kg/m^2 similar to our results except for Malaysian women whose cut-off was found to be higher at ~25 kg/m^2.[18] This lower BMI cut-off associated with the presence of any CMD for Asians seem to be true even for Asians living in America. In a recent study[27] on 1,663 Asian Americans which included 536 Filipinos, a BMI of 23 kg/m^2 was identified to be the optimal BMI cut-off point for screening diabetes similar to our results especially for females. However, a cut-off point with sensitivity of approximately 80% was used to determine this cut-off. In terms of WC, cut-offs were in the range of 80-83 cm except for Taiwanese women whose cut-off was found to be lower at 71.5.[15,17-19] Lastly, in terms of WHR, cut-offs were diverse. In Singapore, women have higher WHR cut-off than men (0.90 vs 0.80),[17] whereas the reverse is true in Taiwan (0.76 vs 0.85),[15] similar to our results.

Among the three anthropometric indices, our results showed that BMI, WC and WHR seem to best predict the occurrence of hypertension, diabetes and dyslipidemia respectively for both sexes since these indices have the largest AUCs. This was similarly found by Ko et al.,[16] and Aekplakorn et al.,[20] among Hong Kong Chinese and Thais respectively. They concluded that BMI and WHR were closely associated with various cardiovascular risk factors,

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complemented by other anthropometric indices. However, for the prediction of at least 1 and clustering of CMDs, AUCs of BMI has the largest among the three indices followed by WC among males. Among females, BMI has the largest AUCs for predicting the presence of at least 1 CMD, but for clustering of CMDs, WHR and WC were better than BMI. It may imply that BMI, WC and WHR are good indices that would predict the occurrence of any CMDs in both sexes especially for males (since the AUCs were always higher than for females). Among which of the three is better is a subject for debate. Among Malaysians, WC has been seen to predict obesity-related cardiovascular risk factors in men and women better than BMI.[18] Similar findings were reported by Zhu et al.,[30] among non-Hispanic black, Mexican Americans and Non-Hispanic whites, and Aekplakorn et al,.[20] among Thais. Li et al.,[31] further specified that for clustering of 2 or more cardiovascular risk factors among Chinese people, WC is the most important factor followed by age and BMI (both having the same impact). These results suggest that central obesity indices particularly WC is a better predictor of cardiovascular risk compared to BMI. This seems to be especially applicable to Asians who has been seen to be predisposed to central obesity, hence related to increased risk of the metabolic syndrome.[20] This predisposition is clearly seen in our population where the rate of central obesity is higher than overweight and obesity combined (70% vs 54%).

Our study is mainly limited by the volunteer bias during the recruitment for Phase II of DSME Program. However, this study aims to look for the relationship of anthropometric indices with the occurrence of CMDs, and not to report on prevalence data on CMDs. In essence, the same methodology has also been employed in other studies recruiting volunteers and not randomly selected participants.[14,16,18]

Since our study population are rural community dwellers, it is recommended that cut-offs for urban community dwellers are also determined. Second, body composition studies should be performed in relation to anthropometric indices to clarify whether Filipinos have equivalent levels of fatness of body size and BMI, and whether Filipinos preferentially deposit abdominal fat. Prospective studies on the relationship of obesity and the development of cardiovascular risk factors and occurrence of hard end points like mortality are recommended. Lastly, our study does not intend to recommend the appropriate anthropometric indices cut-offs for Filipinos. Our results simply provided evidence that CMDs occur at lower anthropometric indices cut-off levels. To change the screening practices in our country, national data must be evaluated using appropriate analysis.[27]

CONCLUSION

In our study, we have identified the levels of BMI, WC and WHR defining overweight and obesity associated with the occurrence of CMDs among Filipino adults in a rural community. Similar to other Asian countries, these cut-offs are lower than the current WHO recommendations.

Acknowledgements
The authors acknowledge the support of the Diabetes Study Group of the Section of Endocrinology, Diabetes and Metabolism of the University of the Philippines – Philippine General Hospital, Dr. Rosario Araneta for her help in editing the manuscript and Mr. Jundelle Romulo Jalique for analyzing our data.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
Phase II DSME Program is a recipient of research grants from Diabetes Philippines, the BRIDGES program (Bringing Research in Diabetes to Global Environments and Systems) of the International Diabetes Federation (IDF), and Department of Science and Technology (DOST)-Philippine Council for Health Research and Development (PCHRD).

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ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.05

JAFES

ORIGINAL ARTICLE

Validation of the Oral Health Screening Questionnaire in Predicting Serious Periodontitis among Adult Filipinos with Type 2 Diabetes Mellitus

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Abstract

Background. Periodontitis affects more than half of patients with diabetes. In resource poor areas in the Philippines, access to routine dental visits may be difficult and thus, a selective approach might be needed to identify those who need dental evaluation and management. An easy-to-administer oral health self-report questionnaire was developed in order to predict serious (moderate to severe) periodontitis.

Objective. The study aims to determine the validity of the Oral Health Screening Questionnaire for Persons with Diabetes (OHSQPD) in estimating the prevalence of serious periodontitis.

Methodology. A cross-sectional criterion-referenced study of 175 participants with T2DM were included in the study. They were asked to answer the questionnaire and then made to undergo a full dental examination to identify the presence and severity of periodontitis. The validity of the questionnaire was assessed by determining the sensitivity, specificity, positive predictive value, negative predictive value and area under the receiver-operating curve (AUROC) with the dental examination as the gold standard.

Results. Using the questionnaire, the prevalence of serious periodontitis was 61% (106) based on an optimal cut-off score of ≥12. At this score, the questionnaire yielded a sensitivity of 80.4% and a specificity of 70.6%, with an AUROC of 0.83.

Conclusion. The OHSQPD is a valid tool in detecting serious periodontitis.

Key words: questionnaire, type 2 diabetes mellitus, periodontitis, Filipino, oral health

INTRODUCTION

The estimated global prevalence of diabetes is 8.8%, with the majority living in low to middle income countries.[1] In 2013, the prevalence of diabetes in the Philippines among adults 20 years and above was at 5.4% and is increasing.[2] Persons with diabetes are predisposed to chronic infections and inflammation of the oral tissues, including periodontal diseases, which cause substantial oral functional disability.[3] Periodontitis has been considered as the sixth complication of diabetes.[4] It is a complex disease with numerous causal risk factors (including diabetes), characterized by the loss of connective tissues within the periodontium and the destruction of alveolar bone support.[5]

Recently, much has been published about periodontitis and its relationship with diabetes and vice-versa. In diabetes, the production of advanced glycated end-products (AGEs), which activate host cells such as monocytes/macrophages and endothelial cells, may lead to the release of pro-inflammatory cytokines and proteases which damage the gingival tissues and cause resorption of alveolar bone.[6] Studies have identified that the risk of periodontitis was 3 to 4 times higher in people with diabetes.[5,7] Susceptibility to periodontitis is increased with poor glycemic control and more severe forms of periodontitis are observed in those with poorly controlled diabetes.[5,8,9] The prevalence of periodontitis among Filipinos with type 2 diabetes mellitus (T2DM), 35 years old and above is observed to be as high as 68-94%.[10,11]

There is convincing evidence that there is a bidirectional association between periodontitis and diabetes.[6,7] Diabetes and periodontal disease share a common pathway in inflammation resulting in increased levels of

eISSN 2308-118x
Printed in the Philippines

Received: April 25, 2016. Accepted: May 25, 2016.
https://doi.org/10.15605/jafes.031.02.05

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ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.05

inflammatory mediators that can further increase insulin resistance.[12] Periodontal infection increases systemic inflammation by contributing to the cycle of hyperglycemia and AGEs binding accumulation thus the tendency for increasing the risk of developing diabetes or further increasing glycated hemoglobin (A1c) levels.[7] An improvement in glycemic control has been shown with early detection and treatment of periodontitis in both controlled and uncontrolled diabetes.[13-16]

Although prevalent, periodontitis is generally hidden, thus there is a need for routine oral evaluation in persons with diabetes.[7] While local and international guidelines recommend routine clinical screening and early referrals to dentistry, oral health awareness is lacking in the Philippines.[17] There is also a lack of access to public health care and the majority pay a larger out-of-pocket share.[1] Persons with diabetes have a higher utilization of dental procedures and may benefit from increased frequency of prophylactic services.[18] However, they are hesitant to see the dentist and probable reasons for not consulting is the cost of dental treatment as medications alone account for much of the patient's budget.[17] Thus, there is a need to develop strategies to promote prevention and control of periodontitis in settings were income is limited.

Untreated serious periodontitis (moderate to severe periodontitis) is associated with tooth loss and progression of pocket depths.[19] In those who underwent periodontal treatment, an initial pocket probe depth (PPD) range of 4-6 mm was a risk factor for tooth loss.[20,21] It is also recognized that due to untreated or inadequately controlled serious periodontitis, the systemic inflammatory burden may also be increased.[22]

The Centers for Disease Control and Prevention (CDC) in collaboration with the American Academy of Periodontology (AAP) has formulated self-report questionnaires that appear to be promising in predicting the prevalence and severity of periodontitis among the adult population.[23-25] These validated self-reported oral health questions were translated into Filipino and together with other relevant oral health, medical and demographic variables; multivariate logistic regression analyses were done to determine predictors of serious periodontitis.[11] Predictors of serious periodontitis among adult Filipinos with diabetes were low education status, tooth loss >6, poor gum health, history of loose teeth and poor tooth appearance. With these, revised questions in English as well a Filipino version and a scoring system predictive for serious periodontitis were formulated.

Currently, this questionnaire has not been validated and there are no other validated clinical oral health screening questionnaires available locally. The validation of such a questionnaire would be useful in our setting in which resources are limited and thus would lessen the costs of screening. This paper aims to do the following:

1. To determine the validity of the Oral Health Screening Questionnaire for Persons with Diabetes in estimating the prevalence of serious periodontitis.
2. To compute the cut off value for the Oral Health Screening Questionnaire for Persons with Diabetes that is most predictive for serious periodontitis using a receiver operator curve (ROC).

METHODOLOGY

Design/Setting

This is a cross-sectional criterion referenced study that was conducted at the tertiary outpatient clinics of the University of the Philippines - Philippine General Hospital (UP-PGH). The study was reviewed by the University of the Philippines Manila Research Ethics Board (UPMREB) Panel prior to commencement. The study participants were recruited consecutively from September 2015 – January 2016.

Study sample

Using Epi Info version 7, the minimum sample size requirement was estimated to be at least 138 based on an estimated sensitivity of 90% (unpublished data) by Lo et al., alpha (α) = 5%, and a margin of error = 5%.[11] The computed 138 minimum sample size was increased to 173 accounting for possible 20% non-response.

Selection Criteria

Inclusion Criteria

1. Adult (Age ≥35 years) Filipino diagnosed with type 2 diabetes mellitus for at least 1 year. Diagnosis of type 2 diabetes was based on the American Diabetes Association criteria as follows:[26]
   - Fasting Blood Sugar (FBS) ≥126 mg/dl on 2 determinations;
   - Symptoms of hyperglycemia and Random Blood Sugar (RBS) ≥200 mg/dl;
   - 2-hour plasma glucose ≥200 mg/dl after a 75 grams Oral Glucose Tolerance Test (OGTT);
   - Standardized A1c ≥6.5%
2. Dentulous persons with ≥6 teeth present
3. Recent A1c result done within the past 3 months
4. Able to read, comprehend and respond to the series of questions
5. Willing to undergo a dental examination

Exclusion Criteria

1. Patients with heart murmurs that would require antibiotics prior to dental examination

Withdrawal Criteria

1. Inclusion is voluntary. Withdrawal is allowed should the patient decide to stop participating even if consent was already given.

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Materials and Methods

The Oral Health Screening Questionnaire for Persons with Diabetes (OHSQPD) was used in this study (Appendix A). The questionnaire is composed of 5 questions that pertain to (Q1) low education status, (Q2) tooth loss >6, (Q3) poor gum health, (Q4) presence of loose teeth and (Q5) poor tooth appearance and a scoring system designed to predict serious periodontitis (Appendix B). It is self-reported with all questions answerable by YES or NO answers.

Participants included in the study were provided with an overview of the study and once eligibility status was determined, they were given the written informed consent and contact information was obtained. Information regarding gender, age, anthropometrics, smoking status, education level, duration of diabetes, frequency and last dental examination, co-morbidities, and A1c level were gathered. Socio-demographic and medical variables were collected using a standard data collection form (Appendix C).

The participants answered the OHSQPD (Appendix A) and were then referred to a dentist (co-investigator), who was unaware of the answers for a formal dental and periodontal evaluation. The participants answered the OHSQPD (Appendix A) and were then referred to a dentist (co-investigator), who was unaware of the answers for a formal dental and periodontal evaluation. The basic elements from the NHANES III protocol were used for the full-mouth periodontal examination.[27,28] The dentist reported variables relating to the measurement of periodontal supporting tissues such as attachment loss, probing depth and furcation involvement. This was done using a color-banded probe graduated at 2, 4, 6, 8, 10, and 12 mm. Measurements were carried out on six sites per tooth (mesio-buccal, buccal, distobuccal, mesio-lingual, lingual, disto-lingual, mesiofacial, mid-facial, and disto-facial) for all teeth (excluding 3rd molars). The number of lost teeth was also documented during the examination. Periodontal examination results were recorded using a separate Dental Sheet (Appendix D).

Participants were classified according to the severity of periodontal disease based on the criteria used in the NHANES III.[28] Periodontitis was defined as a disease state in which there is an active destruction of the periodontal supporting tissues as evidenced by the presence of at least 3 mm probing depth and periodontal attachment loss at the same site. It is classified as follows:

- Severe periodontitis: 1) two or more teeth (or 30% or more of the teeth examined) having ≥5 mm probing depth, or 2) four or more teeth (or 60% or more of the teeth examined) having ≥4 mm probing depth, or 3) one or more posterior teeth with grade II furcation involvement.
- Moderate Periodontitis: 1) one or more teeth with ≥5 mm probing depth, or 2) two or more teeth (or 30% or more of the teeth examined) having ≥4 mm probing depth, or 3) one or more posterior teeth with grade I furcation involvement and accompanied by ≥3 mm probing depth.
- Mild periodontitis: 1) one or more teeth with ≥3 mm probing depth, or 2) one or more posterior teeth with grade I furcation involvement.
- No periodontitis: participants with 6 or more teeth present who did not fulfill any of the above criteria.

In this study, serious periodontal disease was considered for participants fulfilling the criteria for moderate to severe periodontitis.[11,29] Results of the periodontal evaluation were given to the participant. Intervention and follow-up were advised accordingly to ensure proper treatment of periodontitis.

Data analysis

Data analysis was done using the software Stata SE version 13. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percentages. All responses on the oral health questionnaire were recorded according to the proposed scoring system (Appendix B).

The optimal cut-off value for detecting serious periodontitis was determined using a ROC. The value was determined using the point in which the sum of the sensitivity and specificity was highest.

The validity of the questionnaire in predicting serious periodontitis was assessed by determining its sensitivity, specificity, positive predictive value and negative predictive value (95% confidence interval) with the results of the full dental and periodontal examination as gold standard. The area under the receiver-operating curve (AUROC) (95% confidence interval) was computed to determine if the test is able to correctly classify those with and without the disease.

RESULTS

A total of 401 participants were consecutively seen in the UP-PGH outpatient clinics. One hundred seventy-seven (177) participants were not enrolled due to the exclusion criteria. The most common reason for exclusion was due to having fewer than 6 teeth left on examination. This accounted for 53% (93) of the excluded participants. Other leading reasons for exclusion were the 26% (47) who did not give consent and 16% (28) who had no recent A1c results. Figure 1 shows a flow diagram of the derivation of the participants available for the study.

Of the 224 enrolled, 49 (22%) did not undergo the full dental examination so that the final data set for analysis included a total of 175 participants. The mean age of the participants was 55.9±8.3 years old (range 36-74) of which 120 (69%) were females. One hundred twenty-six (72%) did not reach or finish college. The mean BMI and A1c were

ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.05

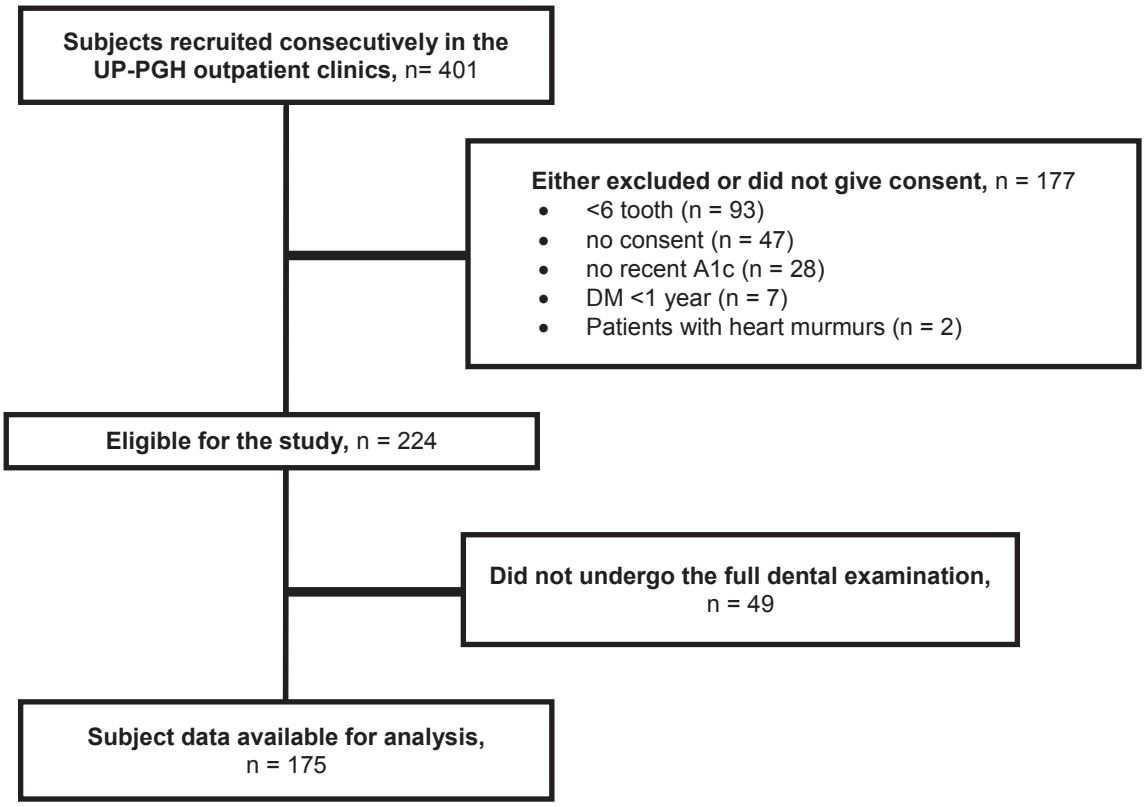

Figure 1. Flow diagram of the derivation of participants.

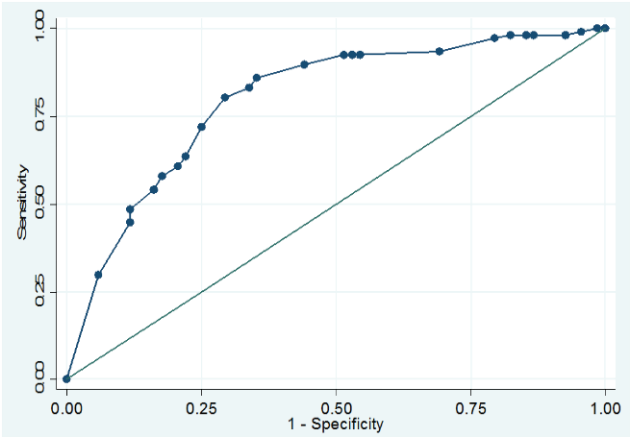

Figure 2. Area under the Receiver Operating Curve (AUROC) for identifying serious periodontitis using the self-reported Oral Health Questionnaire, N =175.

Table 1. Distribution of participants according to socio-demographic and clinical characteristics. Philippine General Hospital, Manila, N=175

Characteristics	(N = 175)
Gender (Female)	120 (69%)
Mean age ± SD (years)	55.86±8.34
Mean A1c ± SD (%)	7.43±1.65
Mean BMI ± SD (kg/m^2)	25.74±4.00
Mean lost tooth ± SD	12.92±6.97
Smoking history	28 (16%)
Educational attainment (High school or lower)	126 (72%)
Hypertension	132 (75%)
Dyslipidemia	127 (73%)
Dental visits per year (<1)	152 (87%)
Duration of diabetes ± SD (years)	9.03±7.67

25.7±4.0 kg/m^2 and 7.4±1.7% respectively with a mean duration of diabetes of 9.0±7.7 years. The majority of participants (87%) had no annual dental visits with a mean tooth loss on examination of 12.9±7.0. Only a minority of the participants were smokers or had ever smoked 28 (16%). Hypertension and dyslipidemia were the frequent co-morbidities observed. A summary of the distribution of the socio-demographic and clinical characteristics of the 175 participants included in the study is seen in Table 1.

Overall, 93% (162) of the participants had periodontitis, while the prevalence of serious periodontitis (moderate and severe) was 61% (107). The prevalence of mild, moderate, and severe periodontitis were 7.5% (13), 31% (55) and 54% (94) respectively. Only 7.5% (13) had no periodontitis on examination.

The optimal cut-off value for detecting serious periodontitis based on study criteria determined using the ROC was 12 (see Figure 2). With this cut-off score, the estimated prevalence of serious periodontitis was also 61% (106). The distribution of participants according to the oral health scores, seriousness of periodontitis, and the validity characteristics of the self-report questionnaire are seen in Tables 2 and 3. The questionnaire yielded a sensitivity [95% CI] of 80.4% [72.9-87.9] and a specificity [95% CI] of 70.6% [59.8-81.4]. Positive and negative predictive values were 81.0% [72.6-89.1] and 70% [58.7-80.4] respectively. The area under the receiver operating curve (AUROC) [95% CI] was 0.83 [0.69-0.97] (Figure 2).

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Table 2. Distribution of the participants according to the oral health score and seriousness of periodontitis

Oral Health Score	Serious periodontitis	Absent / Mild periodontitis	Total
≥12	86	20	106
<12	21	48	69
Total	107	68	175

Table 3. Validity characteristics of the Oral Health Screening Questionnaire for Diabetics at a derived cut-off score of 12

Performance measures	Result in % [Confidence Interval]
Sensitivity	80.4% [72.9-87.9]
Specificity	70.6% [59.8-81.4]
PPV	81.0% [72.63-89.10]
NPV	70.0% [58.7-80.43]

Note: Positive predictive value (PPV), Negative predictive value (NPV)

Table 4. Distribution of the participants according to the oral health score and seriousness of periodontitis

Study	Sensitivity	Specificity	Area under the ROC curve [95% CI]
Current Study	**0.80**	**0.71**	**0.83 [0.69-0.97]**
Khader Y 2015 [30]	0.61	0.83	0.77 [0.71, 0.82]
Zhan Y 2014 [31]	0.81	0.74	0.84 [0.82–0.86]
Lai H 2015 [32]	0.68	0.62	0.70 [0.67–0.74]

DISCUSSION

Periodontitis is a complication of diabetes and it causes a significant burden. There is still a lack of a certain degree of awareness regarding oral health and its relationship with diabetes. It is clear that routine oral health care in adults with diabetes is uncommon, as 152 (87%) of the participants had no regular dental visits.

While a full dental and periodontal examination remains the standard of care for persons with diabetes, it comes at a cost. Oral health is an important element of diabetes care and will contribute to the improvement in glycemic control.[15] Self-report measures can offer a practical alternative for periodontal disease evaluation. The OHSQPD was inexpensive and easy to administer in the outpatient setting. The importance of validating the questionnaire then, is to identify persons with diabetes having serious periodontitis who will potentially require urgent dental evaluation and treatment.

One hundred sixty two (93%) participants had periodontitis while more than half (107 or 61%) of the population had serious periodontitis. This prevalence of periodontitis based on the full dental and periodontal examination is similar to what was reported by Lo et. al., and this may be due to the similar population characteristics such as a lower level of education and poorer oral health care.[11]

The reported prevalence of serious periodontitis was 61% based on the OHSQPD when using the optimal cut-off score of 12, with a sensitivity of 80.4% and a specificity of 70.6%. The test had a good discriminating ability for detecting serious periodontitis based on the AUROC value.

Currently, there are no studies that used self-report questionnaires to detect periodontitis among persons with diabetes, however when compared to other self-reported periodontal disease scales that predicted periodontitis in those without diabetes, the questionnaire had comparable sensitivity and specificity.[30-32] The validity characteristics of these self-reported periodontal disease scales for detecting serious periodontitis are seen in Table 4.

As the study is done in a tertiary referral center, the questionnaire might perform differently in the community setting. Limitations stem from the setting of the study and are due to the educational and language barriers that may be encountered. Validity therefore may be dependent on the specific population characteristics. These population characteristics may affect the comprehensibility of the self-report questions hence may influence participant responses. The participants included in this study are also relatively older and already with established diabetes for almost ten years; thus, the sensitivity and specificity of the questionnaire in detecting serious periodontitis may be different in younger populations with a shorter duration of diabetes. Further evaluation is needed to determine the performance of the questionnaire in the community setting.

CONCLUSION

The Oral Health Screening Questionnaire for Persons with Diabetes is a valid tool with good sensitivity, specificity and predictive value for detecting serious periodontitis. In can potentially become an invaluable tool in settings in which routine and clinical oral examination for all diabetics is not feasible.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
None.

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APPENDIX

Appendix A. The Oral Health Screening Questionnaire for persons with diabetes

Oral Health Questions	Response
1. What is your highest educational attainment?	☐ High school or lower ☐ College or higher
2. How many teeth did you lose?	☐ ≥6 ☐ <6
3. Overall, how would you rate the health of your teeth and gums?	☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor
4. Have you ever had any teeth that became loose on their own, without an injury? (not baby teeth)	☐ Yes ☐ No
5. During the past 3 months, have you noticed that you have a tooth that doesn't look right?	☐ Yes ☐ No
Total Score	

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Appendix B. The recommended Oral Health Questionnaire and the scoring system predictive of serious periodontitis

Oral Health Questions	Response	Score
1. What is your highest educational attainment?	High school or lower	+ 3
	College or higher	0
2. How many teeth did you lose?	≥6	+ 4
	<6	0
3. Overall, how would you rate the health of your teeth and gums?	Excellent	- 5
	Very Good	- 4
	Good	- 3
	Fair	- 2
	Poor	- 1
4. Have you ever had any teeth that became loose on their own, without an injury? (not baby teeth)	Yes	+ 7
	No	0
5. During the past 3 months, have you noticed that you have a tooth that doesn't look right?	Yes	+ 7
	No	0
Total Score		

Appendix C. Patient data sheet

Part 1: General Data

Participant's Code: _____ Date Examined: _____

Age: _____ Civil Status: □ S □ M □ W

Sex: □ Male □ Female

Education Attainment: □ High school or lower □ College or higher

Occupation: _____ Family Monthly Income (Pesos): _____

Part 2: Medical History

Smoking history: □ Smoker (___ pack ___ years) □ Non-smoker

Comorbidities:

□ Hypertension □ Dyslipidemia

□ Bronchial Asthma □ Autoimmune disease

□ Liver disease □ Renal disease

□ Cardiac disease □ Others (specify)

Date of diagnosis with diabetes: _____

Date of last dental visit: _____

Number of dental visits per year: _____

Part 3: Clinical Data

BP: _____ Wt (kg): _____ Ht (cm): _____ BMI: _____ (kg/m^2)

Pertinent Physical Examination Findings:

_____

_____

_____

Part 4: Laboratory Data

A1c within the last 3 months: _____

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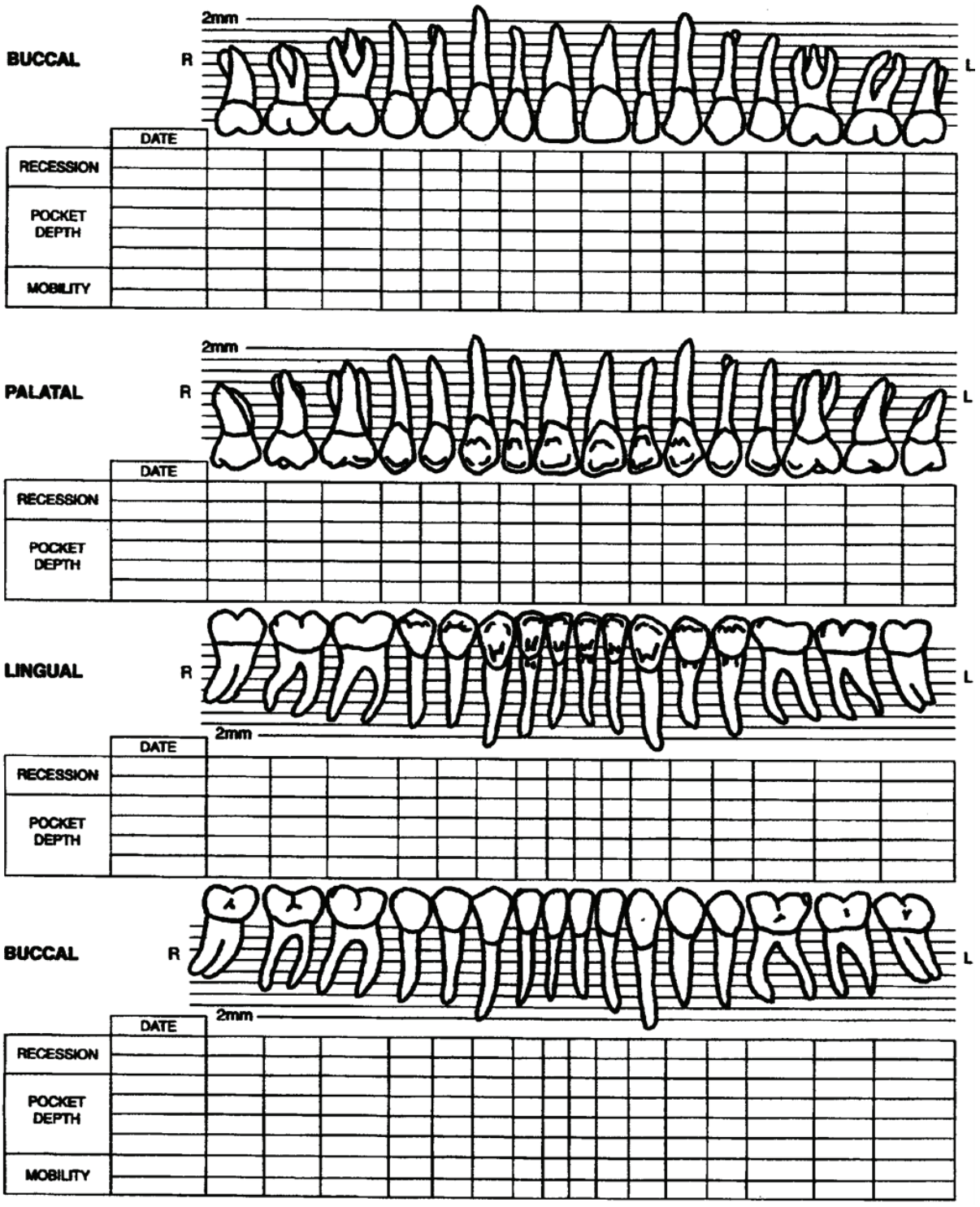
Appendix D. Dental sheet

Patient Number: _____

Periodontal Examination

Total Number of Teeth Present: _____ Total Number of Teeth Lost: _____
Periodontitis: _____ Present _____ Absent
Severity of Periodontitis: _____ Mild _____ Moderate _____ Severe
Other Findings: _____
Recommendation: _____
Assessed By: _____



ONLINE FIRST | August 18, 2016 | https://doi.org/10.15605/jafes.031.02.05

ONLINE FIRST | August 19, 2016 | https://doi.org/10.15605/jafes.031.02.06

ORIGINAL ARTICLE

JAFES

Validation of the Filipino-Translated Version of the Michigan Neuropathy Screening Instrument among Filipino Patients with Diabetes Mellitus Seen at the Philippine General Hospital*

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Abstract

Objectives. To assess the validity of the Filipino-translated version of the Michigan Neuropathy Screening Instrument (MNSI) in screening for diabetic neuropathy among Filipino patients with diabetes mellitus using nerve conduction velocity (NCV) as gold standard and to determine the most accurate cut-off score for the diagnosis of neuropathy using MNSI.

Methodology. A cross-sectional analytic study was done among adult diabetic patients. The original MNSI Questionnaire was translated and back-translated to the Filipino language. Each patient answered the Filipino version of MNSI Questionnaire followed by a lower extremity examination done by the investigator. All patients underwent NCV as reference standard. Sensitivity and specificity of MNSI were determined.

Results. We studied a total of 150 subjects. Eighty-seven (58%) were diagnosed to have diabetic neuropathy based on NCV. The sensitivity and specificity of the MNSI Questionnaire improved to 73.6% and 52.4% respectively when the cut off was reduced to ≥4, whereas for the MNSI Examination, the sensitivity and specificity improved to 86.2% and 55.6% respectively when the cut off was reduced to ≥1. Combining both MNSI Questionnaire and MNSI Examination further improves the sensitivity to 95.4% whereas specificity is at 39.7%.

Conclusion. The analyses in 150 subjects confirm that the Filipino-version of MNSI is a valid screening tool for diabetic neuropathy when compared with NCV as gold standard.

Key words: diabetic neuropathy, questionnaire, Filipino, diabetes mellitus

INTRODUCTION

Diabetic neuropathy is one of the most common complications of both Type 1 and Type 2 diabetes mellitus. In a population-based study done in Rochester, Minnesota, as many as 66% of patients with Type 1 diabetes mellitus and 59% in Type 2 diabetes mellitus has some form of neuropathy.[1] At the time of diagnosis of Type 2 diabetes a prevalence of 12.3% was reported in the United Kingdom Prospective Diabetes Study (UKPDS), and in the 15-year follow-up, prevalence of neuropathy increased to 36.8% despite treatment.[2]

Early diagnosis of diabetic neuropathy can decrease patient morbidity by allowing for potential therapeutic interventions, including patient education and regular foot surveillance. Traditionally, the diagnosis of diabetic neuropathy was based on subjective interpretation of clinical symptoms and specific signs such as reduced ankle reflexes and loss of vibratory sensation.[3] There has been no single diagnostic test for the detection of diabetic neuropathy. It is generally agreed that diabetic neuropathy should not be diagnosed on the basis of one symptom, sign or test alone. Dyck et al., recommended at least two abnormalities should be present in the diagnosis.[4] In 1988, the San Antonio Conference on Diabetic Neuropathy by the American Diabetes Association and the American Academy of Neurology proposed that in order to diagnose diabetic neuropathy, the patient must have at least one abnormal measurement among the following tests: clinical symptoms, clinical examination, electrophysiological studies, quantitative sensory testing and autonomic function testing.[5]

Electrophysiological testing which includes nerve conduction velocities, are objective, sensitive and reproducible tests used in clinical neuropathy trials.[6,7] Nerve conduction studies provide results with high

eISSN 2308-118x
Printed in the Philippines

Received: May 17, 2016. Accepted: July 11, 2016.
https://doi.org/10.15605/jafes.031.02.06

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**This paper was presented at the Philippine Society of Endocrinology, Diabetes, and Metabolism Annual Convention at EDSA Shangri-La Hotel, Mandaluyong City, March 17, 2016.*

ONLINE FIRST | August 19, 2016 | https://doi.org/10.15605/jafes.031.02.06

sensitivity of 92% for nerve dysfunction,[8] however, the test is not readily available in most centers in the country; it is time-consuming, expensive and requires equipment and training. Several diagnostic screening tools have been developed and validated abroad to aid clinicians and researchers in identifying patients with neuropathy. Instruments such as the McGill Pain Questionnaire, the NeuroQol, and the Neuropathy Symptom Score (NSS) and its derivatives have been used in clinical trials, however, these tools make use of clinical symptoms only either self-reported by the patients or queried in a standardized manner by a trained individual.[9-11] A neuropathic foot can be identified by simple clinical observation. Evidence might include small muscle wasting, clawing of toes, prominent metatarsal heads, dry skin, callus formation and body deformities. Two simple instruments have been developed for clinical practice and used in clinical trials that look into clinical signs of diabetic neuropathy – the Neuropathy Disability Score (NDS) and the Michigan Neuropathy Screening Instrument (MNSI) The NDS developed by Dyck and colleagues is a simple clinical examination that sums abnormalities of reflexes and sensory assessment.[10] The test is reproducible and easily performed by trained and experienced physicians, however, it does not include subjective symptoms which may have adverse effects on the quality of life in diabetic neuropathy.[12]

In 1994, Feldman and colleagues designed the Michigan Neuropathy Screening Instrument, an outpatient program to facilitate diagnosis of distal symmetrical peripheral neuropathy among diabetics. It includes two separate assessments – a brief 15-item self-administered questionnaire and a lower extremity examination composing of visual inspection, vibratory sensation, and ankle reflexes.[13] The instrument has the advantage of incorporating the patient's self-reported clinical symptoms and the physician's physical examination in one screening tool. The MNSI has a sensitivity of 80% and specificity of 95% and has been validated for patients with Type 1 diabetes included in the Diabetes Control and Complications Trial (DCCT)[14] and Type 2 diabetes in Iran.[15]

Although clinical practice guidelines recommend annual screening for neuropathy, they are unable to support specific recommendations for screening maneuvers because of a lack of evidence for the validity of screening tests in the medical literature.[16] Nerve conduction studies offer an objective and sensitive way to diagnose diabetic neuropathy however the availability of trained personnel and equipment is limited only to a few centers in the country. The MNSI or any other screening tool for diagnosis of diabetic neuropathy has not been validated in the Philippines. Some of the items in the questionnaire may not be culturally appropriate among Filipinos and modifications may be necessary. Thus, this study on the validity of MNSI in our local setting is of great importance for the prevention of diabetes-related foot problems especially in centers where means for early diagnosis of diabetic neuropathy is limited.

OBJECTIVES

1. To assess the validity of the Filipino-translated version of the Michigan Neuropathy Screening Instrument in screening for diabetic peripheral neuropathy among Filipino patients with Diabetes Mellitus using nerve conduction velocity studies as gold standard.
2. To determine the most accurate cut-off score for the diagnosis of neuropathy using MNSI among diabetic Filipino subjects.

METHODOLOGY

Study Design

Cross-sectional Analytic

Study Setting

This study was done at the Diabetes Clinic, General Medicine Clinic and Family Medicine Clinic, Out-Patient Department of the Philippine General Hospital, a tertiary hospital located in an urban setting.

Study Subjects

Patients with diabetes mellitus seen at the Diabetes, General Medicine and Family Medicine clinics were recruited through randomized sampling.

Inclusion Criteria

The study population is composed of patients aged >18 years, diagnosed with diabetes mellitus based on American Diabetes Association (ADA) 2014 criteria, able to read, write and understand the Filipino language, and consented to join in the study.

The study included patients with either type 1 or type 2 diabetes mellitus fulfilling the diagnosis based on the ADA 2014 criteria (fasting blood sugar ≥126 mg/dL, two hour plasma glucose of ≥200 mg/dL after an oral glucose tolerance test, random blood sugar ≥200 mg/dL with symptoms of diabetes, or HbA1c >6.5%).[17]

Exclusion Criteria

Patients recruited had their charts reviewed for the following exclusion criteria:

1. Had a history of stroke
2. With a co-morbid condition that predisposes them to somatic sensory dysfunction, namely:
   a. Uremia (creatinine clearance of <15 mL/min/1.73 m^2 with symptoms such as progressive weakness, fatigue, loss of appetite, nausea and vomiting, tremors, abnormal mental function, shallow respiration)

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b. Alcoholism (consumption of >100 g of alcohol per day for at least two years)[18]
c. Connective tissue diseases such as rheumatoid arthritis, systemic lupus erythomatosus, scleroderma and Sjögren's syndrome
d. Exposure to poisons such as heavy metals
e. Exposure to cancer medications
f. Infections such as leprosy, herpes zoster, and HIV
g. Neural Tumors such as neuromas, schwannomas, neurofibromas and malignant peripheral nerve sheath tumors
h. Thyroid diseases such as Graves's disease, Hashimoto's thyroiditis, and post-procedural hypothyroidism
i. Liver diseases such as cirrhosis, hepatitis and hepatocullar carcinoma

Withdrawal Criteria

Inclusion to the study was entirely voluntary. Withdrawal from the study was allowed should the patient decided to stop participating even if consent was already given.

Sample size

A total of 150 subjects will be recruited. Sample size computation was based on the formula specific for sensitivity and specificity studies where, sensitivity and specificity of MNSI from the original study,[13] 80% and 95% respectively, and prevalence of neuropathy of 66% were used.[1]

Sampling

Stratified Sampling was done on this study and that each clinic (Diabetes, General Medicine, and Family Medicine) represented one category. Randomized sampling was done on pre-specified clinic days - every Mondays and Wednesdays, recruitment was done at the General Medicine Clinics, Tuesdays and Thursdays at Family Medicine Clinics and Fridays at the Diabetes Clinic. All diabetic patients on a given clinic day were summarized in a list which served as the sampling frame where random sampling using Table of Random Numbers was done. At least 5 patients were recruited on a given day.

Development of MNSI Filipino Version

The original MNSI tool (Appendix A) was translated into the Filipino language by translators from *Sentro ng Wikang Filipino* (Center for Filipino Language), University of the Philippines, Manila.

Two physicians and one diabetic patient did back-translation from Filipino to English; all three were proficient in both the Filipino and English language and were blinded to the original English version. This was done to further examine the faithfulness and appropriateness to its original form. The back-translators were instructed to use simple language and provide a translation of what the item actually says, not interpret what he or she thinks the item is supposed to say, thereby capturing the literal meaning of the item.

Initial Reliability Testing and Cultural Validation

Twenty diabetic patients were recruited from the Diabetes Clinic and were asked to answer the Filipino MNSI tool after signing an informed consent. Responses were analyzed for reliability testing per item using Cronbach's alpha. Cultural validation was done by the same set of patients through cognitive debriefing interviews per item facilitated by the prinicipal investigator in a focused group discussion.[19] The following questions were asked per item, per patient:

- Did you have difficulty answering the question?
- What does the question mean to you?
- Is the question relevant to your condition?
- How would you have worded the question?

The tool was scrutinized for content, grammar, and cultural differences from the original questionnaire and then was modified to create the final translated version.

Training of the Principal Investigator

The principal investigator underwent a short-course training and certification from the supervising investigators, an Endocrinology consultant and a Neurology consultant on proper physical examination for diabetic neuropathy as prescribed by the original MNSI tool (Appendix B) prior to commencement of data collection so to ensure that proper techniques will be carried out.

Data Collection

After the final tool was created, recruitment of subjects started by randomized sampling followed by obtaining a signed consent. Demographic data was collected using a standardized data sheet. Chart review was done in each subject where comorbidities and diabetic complications such as nephropathy and retinopathy were noted. When indicated in the diagnosis and upon review of medications, the patient was on antihypertensive medications, then the patient was classified to be hypertensive. Results of previous lipid profile were also reviewed for presence of dyslipidemia. The latest body mass index (BMI) of each patient was also determined to classify obesity based on the WHO Asia-Pacific criteria.

Each patient filled out the 15-item questionnaire. The history questionnaire was self-administered by the patient. If a watcher accompanied the patient, the watcher was allowed to only assist the patient in answering the questions; but it was the patient himself who filled out the questionnaire. The questionnaire was estimated to be completely aswerable within 15 minutes or less, but the time spent on answering the questions was also recorded.

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Responses were added to obtain the total score. Responses of "yes" to items 1-3, 5-6, 8-9, 11-12, 14-15 were each counted as one point. A "no" response to items 7 and 13 counted as one point. Item #4 is a measure of impaired circulation and item #10 is a measure of general aesthenia and were not included in the scoring. To decrease the potential for bias, all scoring information was eliminated from the patient version. A score of ≥7 was considered abnormal.[20]

The principal investigator proceeded to do physical examination of the foot as indicated in the original MNSI (Appendix B).

Each patient was then sent to the EMG-NCV Station where a technician, blinded to the results, performed standard nerve conduction studies as reference standard. For the upper extremity, routine antidromic stimulations of the bilateral median, ulnar, and radial sensory nerves were done. In the lower extremity, bilateral stimulation of the sural and superficial peroneal sensory nerves and peroneal and tibial motor nerves were performed. In this test, the nerve was stimulated with several electrodes attached to the skin with tape or a special paste. Two electrodes were placed on the skin over the nerve. One electrode stimulates the nerve with a very mild electrical impulse and the other electrode records it. The resulting electrical activity was recorded by another electrode. This was repeated for each nerve being tested. The result was interpreted on the changes in latency, amplitude or nerve conduction from the given normal values. In peripheral neuropathy, there is slowing of all nerve conductions in more than one limb. Nerve conduction tests may take from 15 minutes to 1 hour or more. The co-investigators, a neurology resident and a neurology fellow, also blinded to the results of the screening tests, read and interpreted the nerve conduction velocity studies. One of the supervising investigators, a neurology consultant also blinded to the results, confirmed the readings.

Data Analysis

The performance of the MNSI questionnaire and examination in predicting confirmed clinical neuropathy was assessed by determining sensitivity, specificity, positive and negative predictive values. Sensitivity is the probability of having a positive questionnaire or examination in the presence of confirmed clinical neuropathy. Specificity is the probability of having normal (not positive) MNSI tests in the absence of confirmed clinical neuropathy. Positive predictive value is the proportion of subjects with neuropathy among those with positive MNSI questionnaires or examinations. Negative predictive value is the proportion of subjects without neuropathy among those with normal (not positive) MNSI tests.

All items in the questionnaire were coded as 0 for a negative response and 1 for a positive response (negative responses on items 7 and 13 counted as 1 point). For the examination, responses for the left and right feet were combined. For each measure of the examination (appearance, ulcer, reflex and vibration), a combined score ≥2.5 was classified as abnormal. The sensitivity and specificity of each item in predicting confirmed clinical neuropathy was evaluated. Chi-square values was used to determine the maximum discriminatory capability of each question.

Analysis was also done on different cut-off scores to determine the most accurate cut-off for the study population. Receiver operating characteristic (ROC) curves was used to illustrate the relationship between the true positive ratio (sensitivity) and the false positive ratio (1-specificity) of a test. Areas under the receiver operating characteristic curve (AUC) are a measure of the performance of a test in predicting the outcome of interest. An AUC value of 0.5 indicates that a test performs no better than chance. AUC values between 0.70 and 0.79 indicate fair test performance, values between 0.80 and 0.89 indicate good performance and values ≥0.9 indicate excellent performance.

Data were analyzed using Microsoft Excel and SPSS.

RESULTS

The English version of the MNSI Questionnaire was translated into the Filipino Version. An initial reliability testing was done on 20 diabetic patients showing a Crohnbach's alpha value of 0.747 indicating high testing reliability. The MNSI Filipino Version was modified based on the output of the focus group discussion with the patients for cultural validation thereby creating the final version (Appendix C).

A total of 171 patients were randomly selected, of which 150 consented to join the study and undergo nerve conduction velocity studies, equivalent to the target sample size.

Among the 150 subjects, 111 (74%) were females and 39 (26%) were males. The mean age was 56.7±12.0. The type of diabetes was not identified among the subjects as proper tests for diagnosis were not done for this study, but 42.7% were noted to be on insulin therapy. The mean duration of treatment for diabetes was 10.2±7.7 years at the time of inclusion.

The following comorbidities were noted to be present: hypertension 68.7%; dyslipidemia 71.3%; and obesity 44.7%. The mean BMI was 25.1±4.7. The presence of other microvascular complications of diabetes were also noted: diabetic nephropathy 21.3% and diabetic retinopathy 24.7%. The mean FBS and HbA1c were 138.8±54.8 mg/dL and 7.8±1.8%, respectively. Of the 150 subjects, 55 (36.6%) had good sugar control with an HbA1c of less than 7.0% as recommended by the ADA 2015 guidelines.

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MNSI Questionnaire scores and MNSI Examination scores were analyzed. Mean MNSI Questionnaire score was 4.5±2.6 whereas mean MNSI Examination score was 2.0±1.9. Eighty seven (58%) out of the 150 subjects were diagnosed to have diabetic neuropathy based on NCV. Each item of the MSNI Questionnaire was analyzed for sensitivity and specificity (Table 1). Sensitivity ranges from 3.4-85.1% and specificity ranges from 34.9%-98.4%. The two most sensitive questions were item #4 Do you get muscle cramps in your legs and/or feet? (*"Nagkakapulikat ka ba sa iyong mga binti at/o mga paa?")* and item #1 Are your legs and/or feet numb? (*"Namamanhid ba ang iyong mga binti at/o mga paa?")* with the sensitivity of 85.1% and 78.2% respectively. Whereas items #15 Have you ever had an amputation? (*"Naputulan ka na ba ng anumang bahagi ng iyong katawan?"*) and #13 Are you able to sense your feet when you walk? (*"Nararamdaman mo ba ang iyong mga paa kapag naglalakad*?") were the most specific questions with specificity of 98.4% and 93.7% respectively. Four of the questionnaire items (#1, #2, #4 and #9) had significant discriminatory capability to diagnose diabetic neuropathy as an independent question.

Sensitivity and specificity of each physical examination were also analyzed (Table 2). Sensitivity ranges from 13.8% - 74.7% and specificity ranges from 61.9-100%. Loss of ankle reflex had the most significant discriminatory capability with a sensitivity of 74.7% and specificity of 68.8%, p=<0.001.

Based on the original scoring algorithm, Item #4 and Item #10 were excluded, as they are more of a measure of impaired circulation and general asthenia respectively. Using the algorithm, only 14 (9.3%) had a score of ≥7, with the sensitivity of 13.8% and specificity of 96.8%. When the two questions were included in the scoring, sensitivity improved to 31.0%. ROC curves were generated to determine the AUC, which will measure the performance of the test in predicting the outcome of interest (Figure 1). AUC for the original algorithm was 0.677 and AUC for the new algorithm that includes the two questions was 0.687. Both indicated modest testing performance. Based on the coordinates of the curve, reducing the cut-off score to ≥4 further improves the sensitivity and specificity of the test to 73.6% and 52.4% respectively. Comparison of the accuracy of cut-off scores and ≥7 and ≥4 is shown in (Table 3).

An ROC curve was also generated for the MNSI Examination, which showed an AUC of 0.787, significantly indicating fair test performance, p=<0.001. (Figure 2) With the cut-off of ≥2.5 as indicated by the original MNSI algorithm, the sensitivity and specificity of the test are 52.9% and 84.1% respectively. Reducing the cut-off score to ≥1 would improve the sensitivity and specificity of the test to 86.2% and 55.6% respectively.

Combining both MNSI Questionnaire and MNSI Examination, with cut-off scores of ≥4 and ≥1 respectively, significantly improves the test performance of the tool to a sensitivity of 95.4% with a specificity of 39.7%, positive predictive value (PPV) of 81.3%, negative predictive value (NPV) of 59.3%, AUC=0.776, p=<0.001 (Figure 3).

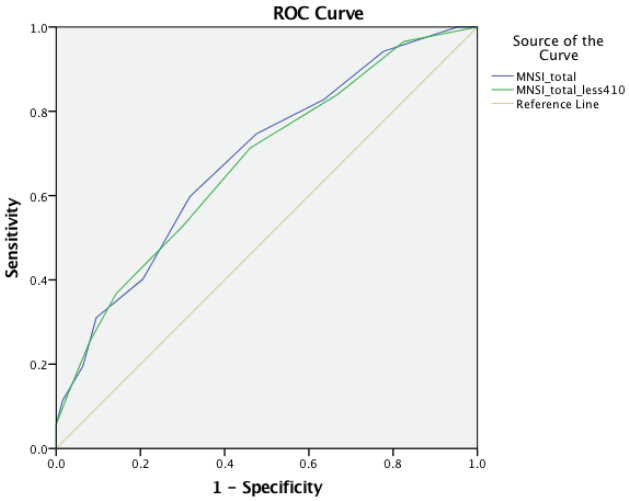

Figure 1. ROC Curves of the original MNSI algorithm vs the new MNSI algorithm (including item #4 and #10).

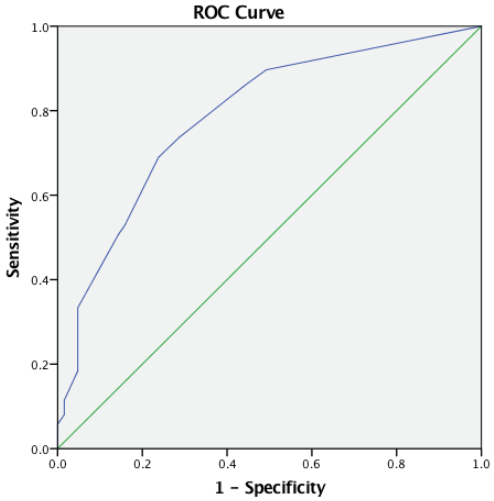

Figure 2. ROC Curve of the MNSI Examination.

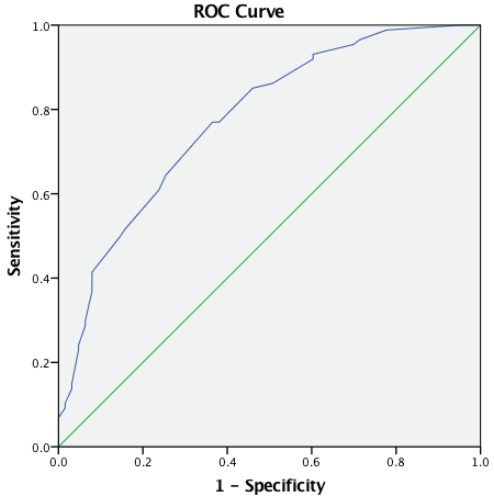

Figure 3. ROC Curve of Combined MNSI Questionnaire and MNSI Examination.

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Table 1. Performance of the individual components of the MNSI questionnaire in predicting confirmed clinical neuropathy

MNSI Questionnaire		With Neuropathy	Without Neuropathy	Total	Sensitivity	Specificity	X2 Test
Item 1	Yes	68	33	101	78.2%	47.6%	0.001
	No	19	33	49			
Item 2	Yes	39	15	54	44.8%	76.2%	0.008
	No	48	48	96			
Item 3	Yes	22	9	31	25.3%	85.7%	0.101
	No	65	54	119			
Item 4	Yes	74	41	115	85.1%	34.9%	0.004
	No	13	22	35			
Item 5	Yes	57	33	90	65.5%	47.6%	0.105
	No	30	30	60			
Item 6	Yes	4	4	8	4.6%	93.7%	0.638
	No	59	83	142			
Item 7	Yes	12	4	16	13.8%	93.7%	0.145
	No	75	59	134			
Item 8	Yes	20	8	28	23.0%	87.3%	0.110
	No	67	55	122			
Item 9	Yes	32	12	44	36.8%	81.0%	0.019
	No	55	51	106			
Item 10	Yes	41	22	63	47.1%	65.1%	0.135
	No	46	41	87			
Item 11	Yes	23	12	35	26.4%	81.0%	0.291
	No	64	51	115			
Item 12	Yes	45	24	69	51.7%	61.9%	0.098
	No	42	39	81			
Item 13	Yes	10	4	14	11.5%	93.7%	0.285
	No	77	59	136			
Item 14	Yes	22	11	33	25.3%	82.5%	0.253
	No	65	52	117			
Item 15	Yes	3	1	4	3.4%	98.4%	0.485
	No	84	62	146			

Table 2. Performance of the individual components of the MNSI Examination in predicting confirmed clinical neuropathy

MNSI Examination		With Neuropathy	Without Neuropathy	Total	Sensitivity	Specificity	X2 Test
Presence of abnormality on inspection	Yes	36	3	39	41.4%	95.2%	<0.001
	No	51	60	111			
Presence of ulcer	Yes	12	0	12	13.8%	100%	0.002
	No	75	63	138			
Loss of Ankle Reflex	Yes	65	25	90	74.7%	68.8%	<0.001
	No	22	38	60			
Loss of Vibration Sense	Yes	55	24	79	63.2%	61.9%	0.002
	No	32	39	71			

Table 3. Performance of MNSI Questionnaire at different cut-off values in predicting confirmed clinical neuropathy

MNSI Score	Sensitivity	Specificity	Positive PV	Negative PV
≥1	100.0%	4.8%	59.2%	100%
≥4	73.6%	52.4%	85.7%	44.9%
≥7	31.0%	90.5%	81.8%	48.7%

DISCUSSION

The early recognition of diabetic neuropathy is important for the following reasons: 1. Non-diabetic neuropathies may be present in a diabetic patient, which may be treatable; 2. Asymptomatic diabetic peripheral neuropathy may be present which puts the patient at risk for insensate injury to the foot; 3. Treatment options already exist which includes glycemic control and both pharmacologic and non-pharmacologic strategies to alleviate the symptoms.

Many medications are available for the treatment of diabetic neuropathic pain. Oral agents include antidepressants and anticonvulsant drugs such as gabapentin and pregabalin, and topical medication such as capsaicin and transdermal lidocaine for localized pain and for those with intolerance to oral medications, are available for addressing neuropathic pain. Vitamin B supplementation is also often prescribed to reduce paresthesias.[21]

The ADA Guidelines recommends annual screening of diabetic neuropathy, however, no single screening tool was mentioned. Screening is usually through a combination of symptom report from the patient and clinical tests done by the physician, such as ankle reflexes, vibration sense, pin-prick and light touch perception.[16] This approach is not standardized and lacks consistency and reproducibility. Electrophysiological testing, on the other hand, such as NCV is the gold standard, however, it is expensive, time-consuming, and available in certain centers only. Several tools have been developed and validated abroad which includes the MNSI; however, the tool has yet to be translated to the Filipino language and validated locally for clinical use here in the Philippines.

In this study, the MNSI tool was translated to the Filipino language and was validated using NCV as gold standard. When used separately, the MNSI questionnaire (AUC 0.687) and examination (AUC 0.787) performed similarly in predicting confirmed clinical neuropathy. We found, however, that the published cut-off point to define a positive test for the questionnaire (≥7) was very insensitive, missing many patients with confirmed clinical neuropathy.

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Changing the cut point to define a positive test for the questionnaire to ≥4 and ≥1 for the examination harmonized the sensitivity and specificity of both tools. When used in combination, the sensitivity improved to 95.4%, which is very suitable, as MNSI is just a screening tool to diagnose diabetic neuropathy. A highly sensitive test is more important for screening than it being more specific. For this study, the sensitivity of the tool is also more important that the PPV since PPV is not intrinsic to the test, and that the prevalence of DM neuropathy has to be considered for it to be useful. As of the moment, the prevalence of diabetic neuropathy among Filipino patients with diabetes has not been established yet. The prevalence of neuropathy in a tertiary hospital may be different from other institutions. However, it is notable that both the sensitivity and the PPV of the Filipino-version of MNSI are good (95.4% and 81.3%, respectively). Our findings are also similar to the validation of the MNSI tool among Type 1 diabetic patients enrolled in the DCCT, in which the questionnaire cut-off of ≥7 was found to be insensitive and the test performance of the test was optimized at the cut-off of ≥4.[14]

The performance of each item of the questionnaire in predicting the presence of diabetic neuropathy was analyzed. Item #4 Do you get muscle cramps in your legs and/or feet? (*"Nagkakapulikat ka ba sa iyong mga binti at/o mga paa?"*) and item #1 Are your legs and/or feet numb? (*"Namamanhid ba ang iyong mga binti at/o mga paa?")* were found to be the most sensitive, although both questions were found to be not significantly able to discriminate diabetic neuropathy if used independently. These questions are more frequently being reported by diabetic patients in the clinics in comparison to the other items in the questionnaire. There is a higher chance that these symptoms are already present in someone who has yet to be diagnosed with diabetic neuropathy. Item #6 Does it hurt when the bed covers touch your skin? (*"Nasasaktan ka ba kapag nadadampian ng kumot ang iyong balat?"*), item #13 Are you able to sense your feet when you walk? (*"Nararamdaman mo ba ang iyong mga paa kapag naglalakad?")* and item #15 Have you ever had an amputation (*"Naputulan ka na ba ng anumang bahagi ng iyong katawan?"*) were all very specific probably because these events rarely happen in comparison to the other items in the questionnaire.

CONCLUSION

The analyses in 150 subjects confirm that the Filipino-version of MNSI is a simple, non-invasive and valid measure of distal symmetrical peripheral neuropathy when compared with nerve conduction velocity as gold standard. The MNSI Questionnaire has to be used without excluding item #4 and item #10 with a cut-off score of ≥4 instead of ≥7, and the MNSI Examination cut-off should be ≥1 instead of ≥2.5. Combining the questionnaire and the examination increases the sensitivity of the tool. We recommend to use the combined Filipino-version of the MNSI questionnaire and the MNSI examination to screen for diabetic neuropathy in clinical practice using the cut points for abnormal findings mentioned.

Statement of Authorship

All authors have given approval to the final version submitted.

Author Disclosure

All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source

This study was chosen as the recipient of the P150,000 Philippine Society of Endocrinology, Diabetes and Metabolism (PSEDM) Research Grant in Diabetes for the year 2015.

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APPENDIX

Appendix A. Michigan Neuropathy Screening Instrument

A. History *(To be completed by the person with diabetes)*

Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check Yes or No based on how you usually feel. Thank you.

1.	Are your legs and/or feet numb?	☐ Yes ☐ No
2.	Do you ever have any burning pain in your legs and/or feet?	☐ Yes ☐ No
3.	Are your feet too sensitive to touch?	☐ Yes ☐ No
4.	Do you get muscle cramps in your legs and/or feet?	☐ Yes ☐ No
5.	Do you ever have any prickling feelings in your legs or feet?	☐ Yes ☐ No
6.	Does it hurt when the bed covers touch your skin?	☐ Yes ☐ No
7.	When you get into the tub or shower, are you able to tell the hot water from the cold water?	☐ Yes ☐ No
8.	Have you ever had an open sore on your foot?	☐ Yes ☐ No
9.	Has your doctor ever told you that you have diabetic neuropathy?	☐ Yes ☐ No
10.	Do you feel weak all over most of the time?	☐ Yes ☐ No
11.	Are your symptoms worse at night?	☐ Yes ☐ No
12.	Do your legs hurt when you walk?	☐ Yes ☐ No
13.	Are you able to sense your feet when you walk?	☐ Yes ☐ No
14.	Is the skin on your feet so dry that it cracks open?	☐ Yes ☐ No
15.	Have you ever had an amputation?	☐ Yes ☐ No

Total _____

B. Physical Assessment *(To be completed by health professional)*

1. Appearance of Feet

Right	Left
a. Normal ☐0 Yes ☐1 No	a. Normal ☐0 Yes ☐1 No
b. If no, check all that apply:	a. If no, check all that apply:
☐ Deformities	☐ Deformities
☐ Dry skin, callus	☐ Dry skin, callus
☐ Infection	☐ Infection
☐ Fissure	☐ Fissure
☐ Other	☐ Other
specify: _____	specify: _____

	Right		Left	
	Absent	Present	Absent	Present
2. Ulceration	☐0	☐1	☐0	☐1

	Right			Left		
	Present	Reinforcement	Absent	Present	Reinforcement	Absent
3. Ankle Reflexes	☐0	☐0.5	☐1	☐0	☐0.5	☐1

	Right			Left		
	Present	Decreased	Absent	Present	Decreased	Absent
4. Vibration Perception	☐0	☐0.5	☐1	☐0	☐0.5	☐1

Signature: _____ Total Score: _____

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Appendix B. How to Use the Michigan Screening Instrument

History

The history questionnaire is self-administered by the patient. Responses are added to obtain the total score. Responses of "yes" to items 1-3, 5-6, 8-9, 11-12, 14-15 are each counted as one point. A "no" response on items 7 and 13 counts as 1 point. Item #4 is a measure of impaired circulation and item #10 is a measure of general aesthenia and are not included in scoring. To decrease the potential for bias, all scoring information has been eliminated from the patient version.

Physical Examination

Foot Inspection. The feet were inspected for evidence of the presence of deformities,dry skin, calluses, infections, and fissures. Deformities include flat feet, hammer toes, overlapping toes, halux valgus, joint subluxation, prominent metatarsal heads, medial convexity (Charcot foot) and amputation. Each foot with any abnormality received a score of 1. Each foot was also inspected for ulcers and each foot with an ulcer received a score of 1.

Muscle Stretch Reflexes. The ankle reflexes were examined using an appropriate reflex hammer. The ankle reflexes were elicited in the sitting position with the foot dependent and the patient relaxed. For the reflex, the foot was passively positioned and the foot dorsiflexed slightly to obtain optimal stretch of the muscle. The Achilles tendon was percussed directly. If the reflex is obtained, it was graded as present. If the reflex is absent, the patient was asked to perform the Jendrassic maneuver (i.e., clenching the teeth and hooking the fingers together and pulling). Reflexes elicited with the Jendrassic maneuver alone were designated "present with reinforcement" and was scored as 0.5. If the reflex is absent, even in the face of the Jendrassic maneuver, the reflex was considered absent and was scored as 1.

Vibration Sense. Vibration sensation was performed with the great toe unsupported. Vibration sensation was tested bilaterally using a 128 Hz tuning fork placed over the dorsum of the great toe on the boney prominence of the DIP joint. The patient, whose eyes were closed, was asked to indicate when he can no longer sense the vibration from the vibrating tuning fork. In general, the investigator should be able to feel vibration in his hand for 5 seconds longer than a normal subject can at the great toe. If the examiner felt the vibration for 10 or more seconds on his or her finger, then vibration was considered decreased. A trial was given when the tuning fork is not vibrating to be certain that the patient is responding to vibration and not pressure or some other clue. Vibration was scored as present if the examiner senses the vibration on his or her finger for <10 seconds (scored as 0), reduced if sensed for ≥ 10 (scored as 0.5) or absent (no vibration detection) (scored as 1). The total possible score was 8 points and, in the published scoring algorithm, a score ≥ 2.5 was considered abnormal.

Appendix C. Michigan Neuropathy Screening Instrument (Filipino Version)

A. Kasaysayan *(Sasagutan ng taong may diabetes)*

Maglaan ng ilang minuto sa pagsagot ng mga sumusunod na tanong ukol sa mga nararamdaman sa binti at paa. Piliin ang Oo o Hindi batay sa madalas mong nararamdaman. Salamat.

1. Namamanhid ba ang iyong mga binti at/o mga paa?	☐ Oo	☐ Hindi
2. Nakararamdam ka ba ng nakapapasong kirot si iyong mga binti at/o paa?	☐ Oo	☐ Hindi
3. Masyado bang sensitibo ang iyong mga paa kapag nahihipo?	☐ Oo	☐ Hindi
4. Nagkakapulikat ka ba sa iyong mga binti at/o paa?	☐ Oo	☐ Hindi
5. Nakararamdam ka ba na parang may tumutusok-tusok sa iyong mga binti at/o paa?	☐ Oo	☐ Hindi
6. Nasasaktan ka ba kapag nadadampian ng kumot ang iyong balat?	☐ Oo	☐ Hindi
7. Habang naliligo, nararamdaman mo ba kung mainit o malamig ang tubig na ginagamit?	☐ Oo	☐ Hindi
8. Nagkaroon ka ba ng bukas na sugat na matagal gumaling sa iyong paa?	☐ Oo	☐ Hindi
9. Nasabihan ka ba ng iyong doktor na mayroon kang diabetic neuropathy?	☐ Oo	☐ Hindi
10. Madalas ka ba makaramdam ng panghihina ng buong katawan?	☐ Oo	☐ Hindi
11. Mas malala ba ang mga sintomas mo sa gabi?	☐ Oo	☐ Hindi
12. Sumasakit ba ang iyong mga binti kapag naglalakad?	☐ Oo	☐ Hindi
13. Nararamdaman mo ba ang iyong mga paa kapag naglalakad?	☐ Oo	☐ Hindi
14. Masyado bang tuyo ang balat sa iyong paa na nagkakaroon ito ng mga bitak-bitak?	☐ Oo	☐ Hindi
15. Naputulan ka na ba ng anumang bahagi ng iyong katawan?	☐ Oo	☐ Hindi

Total _____

ONLINE FIRST | August 19, 2016 | https://doi.org/10.15605/jafes.031.02.06

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.07

ORIGINAL ARTICLE

JAFES

Microvascular and Macrovascular Complications in Young-onset Type 2 Diabetes in a Tertiary Health Institution in Malaysia in Comparison with Type 1 Diabetes Patients*

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Abstract

Objectives. To compare the prevalence of diabetic complications in young-onset type 2 diabetes (T2DM) with type 1 diabetes (T1DM) patients and to examine the relationship between clinical or metabolic parameters with diabetic complications.

Methodology. This is a retrospective, cross-sectional comparative study based on electronic medical records review. Young-onset T2DM patients were defined as those with disease onset before the age of 40 and T1DM patients were included. Data were collected on demographic and clinical parameters, cardiovascular risks factors, macrovascular and microvascular complications.

Results. There were 194 young-onset T2DM and 45 T1DM subjects. Despite similar glycaemic profile, more subjects in the T2DM group had unfavourable cardiovascular risk factors and developed complications than the T1DM group (22 *vs*. 0%, $p<0.001$ for macrovascular, 68 *vs.* 27%, $p<0.001$ for microvascular). After adjustment of the confounders including age, gender, disease duration, HbA1c, obesity, blood pressure and lipid levels; young-onset T2DM instead of T1DM, hypertension, raised HbA1c and longer disease duration were independently associated with occurrence of diabetic complications.

Conclusion. Young-onset T2DM appeared to be a more aggressive disease compared to T1DM. An aggressive approach should be adopted in treating young-onset T2DM to optimise the cardiovascular risk factors and glycaemic control to prevent premature mortality and morbidity.

Key words: young-onset type 2 diabetes, diabetic complications, type 1 diabetes

INTRODUCTION

In the past few decades, there has been a progressive increase in the prevalence of young-onset type 2 diabetes (T2DM). T2DM was once considered a disease of older adults but the age of diagnosis is dropping and it is now increasingly diagnosed in adolescents and young adults.[1] The SEARCH for Diabetes in Youth Study highlighted the burden of DM in the youth in the United States of America while the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study illustrated the difficulty in achieving and maintaining a good glycaemic control in young-onset T2DM.[2,3] In clinical practice, a diagnosis of T2DM as opposed to type 1 diabetes (T1DM) in a young adult was often perceived as the milder form of diabetes by both the health care providers and the patients.[1,4] Thus, traditionally the focus of research of diabetes in young adults has been on T1DM.

Young-onset T2DM patients are predisposed to increased risk of complications at a younger age. Previous studies showed that young-onset T2DM was associated with more unfavourable cardiovascular risk factors, more aggressive phenotype with more complications and greater mortality when compared with T1DM.[4,5] This is a pilot study conducted in Malaysia with the objectives of comparing the prevalence of diabetic complications in young-onset T2DM with T1DM patients in a tertiary health care institution and to examine the relationship between the diabetic complications with various clinical and metabolic parameters.

eISSN 2308-118x
Printed in the Philippines

Received: March 2, 2016. Accepted: July 12, 2016.
https://doi.org/10.15605/jafes.031.02.07

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**This study was presented as an oral presentation at the 18th ASEANsean Federation of Endocrine Societies Congress on 10-13 December 2015 at Kuala Lumpur, Malaysia.*

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.07

METHODOLOGY

This was a retrospective, cross-sectional comparative study conducted at Selayang Hospital, a tertiary health care institution in the state of Selangor. Electronic medical records of all diabetic patients who were seen at the diabetes or medical clinic from January to June 2015 were reviewed retrospectively. The consecutive sampling was conducted over a six-month period in order to capture all active diabetic patients being treated at our hospital at three to six-monthly intervals. These patients were generally referred from primary or secondary care health facilities in the surrounding districts for optimisation of glycaemic control along with management of other cardiovascular risk factors and diabetic complications.

Young-onset T2DM patients were defined as those diagnosed as T2DM before 40 years old. They were differentiated from T1DM by the presence of the following: insidious disease onset, family history of T2DM, obesity, signs of insulin resistance such as acanthosis nigricans and other metabolic conditions commonly associated with T2DM including hypertension, dyslipidemia or polycystic ovarian syndrome.

T1DM patients were those diagnosed clinically as T1DM e.g., presence of diabetic ketoacidosis without significant precipitant, absence of acanthosis nigricans associated with T2DM with or without documented positive insulin autoantibodies. Exclusion criteria were patients given a clinical diagnosis of latent autoimmune diabetes of adults, monogenic diabetes mellitus, e.g., maturity onset diabetes of the young and secondary diabetes. This study was approved by Malaysia Medical Research and Ethics Committee and was done in adherence to the Helsinki Guidelines. Patient consent was not required because our study was retrospective and used deidentified data.

For each patient, data on demographic, anthropometry, clinical history, and laboratory biochemistry including glycated hemoglobin (HbA1c), lipid profile and renal function were collected. Associated cardiovascular risk factors including smoking, hypertension, dyslipidemia as well as their treatment were ascertained. Hypertension was defined as blood pressure ≥140/90 mmHg or on anti-hypertensive treatment. Dyslipidemia was defined as low density lipoprotein (LDL) ≥2.6 mmol/L, fasting triglyceride ≥1.7 mmol/L, high density lipoprotein (HDL) ≤1.0 mmol/L for males and ≤1.3 mmol/L for females or on lipid lowering therapy. Overweight or obesity was defined by a body mass index (BMI) of ≥23 kg/m^2 or waist circumference (WC) ≥90 cm for males and ≥80 cm in females. Adherence to medications, dietary modification and exercise were classified subjectively into good, fair, suboptimal or poor based on the documentation in the medical records of the last clinic visit.

Diabetic complications assessments involved elucidation of microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischemic heart disease, stroke and peripheral vascular disease) complications. Diabetic retinopathy assessment was based on serial ophthalmological findings by ophthalmologists at the ophthalmology clinic. Diabetic nephropathy was defined by the presence of persistent microalbuminuria or macroscopic proteinuria or impaired renal function not explained by other renal pathology. A urine albumin creatinine ratio (ACR) of 2.5 to 30.0 mg/mmol in males and 3.5 to 30.0 mg/mmol in females were considered microalbuminuric.[6] Proteinuria was determined by a urine dipstick of one plus or more. Renal function was evaluated by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula. Peripheral neuropathy was determined based on the presence of sensory symptoms and/or objective physical findings on neurological examination. Ischemic heart disease was defined as the presence of history of myocardial infarction, angina or previous coronary revascularization. Stroke was defined as history of ischemic or hemorrhagic stroke proven on a computed tomography (CT) of the brain or history of transient ischemic attack. Peripheral vascular disease was defined as history of intermittent claudication with ankle-brachial index <0.9, previous lower limb revascularization or amputation for ischemia. In order to examine the occurrence of diabetic complications in relation to the onset of diabetes, we stratified them into two categories, i.e., before or within the first five years or more than five years after the diagnosis of diabetes. All parameters were derived from the latest clinic visit.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Science version 19.0 for Windows (SPSS Incorporation, Chicago, Illinois, USA). Numerical values were expressed as mean±standard deviations (SD). Categorical data were expressed as percentage. Group means were compared with Student's t test or the Mann Whitney U test where appropriate. Categorical variables were compared using χ^2 test or Fisher's exact test. To examine the association between various clinical and metabolic parameters with the occurrence of microvascular and macrovascular complications, univariate followed by stepwise regression analyses were performed. The variables included in the regression analyses were type of diabetes; age; disease duration; gender; ethnicity; smoking status; adherence to medications, dietary modification and exercise; hypertension; systolic blood pressure (SBP); HbA_{1c}; dyslipidemia; total cholesterol; HDL level; LDL level; triglyceride level; BMI and WC. A p value of ≤0.05 was considered statistically significant.

RESULTS

Subject Characteristics

There were 194 young-onset T2DM and 45 T1DM subjects (Table 1). The young-onset T2DM subjects were older in

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.07

Table 1. Comparison of demographic and clinical characteristics between young-onset type 2 and type 1 diabetes patients

Parameters	Young-Onset T2DM (n=194)	T1DM (n=45)	*P* Value
Age (years)	42.6 (14.4)	27 (9.5)	<0.001
Age at Diagnosis (years)	28.5 (8.5)	16.1 (7.1)	<0.001
Disease Duration (years)	14.0 (10.6)	11.2 (7.8)	0.048
Gender (%) Male	48	29	0.015
Ethnicity (%) Malay	54	58	
Chinese	26	29	0.344
Indian	19	11	
Others	1	2	
HbA1c (%)	9.49 (2.42)	9.46 (2.06)	0.12
eGFR (ml/min/1.73m^2)	103.8 (80.6)	127.9 (46.6)	0.006
Body Mass Index (kg/m^2)	30.0 (5.7)	22.1(5.2)	<0.001
Waist Circumference (cm)			
Male	101.6 (11.3)	81.7 (16.7)	<0.001
Female	101.2 (11.5)	83.6 (9.9)	
Hypertension (%)	71	7	<0.001
Systolic BP (mmHg)	137.2 (19.9)	123.1 (15.8)	<0.001
Diastolic BP (mmHg)	78.6 (11.3)	74.5 (12.2)	0.026
Antihypertensive Drugs (%)	71	13	<0.001
Dyslipidemia (%) Yes	92	67	<0.001
Total Cholesterol (mmol/L)	4.89 (1.28)	5.08 (1.38)	0.393
Triglyceride (mmol/L)	1.83 (1.16)	1.24 (1.0)	0.001
HDL (mmol/L)	1.2 (0.3)	1.46 (0.33)	<0.001
LDL (mmol/L)	2.8 (1.07)	3.10 (1.06)	0.113
Lipid Lowering Drugs (%)	77	38	<0.001

*ND, no data; HbA1c, glycated haemoglobin; eGFR, estimated glomerular filtration rate; BP, blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein. Categorical data are expressed as percentage. Numerical data are expressed as absolute values or means ± standard deviation.

Table 2. Comparison of diabetic complications between young-onset type 2 and type 1 diabetes patients

Diabetic Complications	Young-onset T2DM (n=194)	T1DM (n=45)	*P* Value
Any Macrovascular (%)			
Yes	22	0	<0.001
No	78	100	
Ischemic Heart Disease (%)	19	0	<0.001
Stroke (%)	5	0	<0.001
Peripheral Vascular Disease (%)	3	0	<0.001
Any Microvascular (%)			
Yes	68	27	<0.001
No	32	64	
Nephropathy (%)	49	18	<0.001
Retinopathy (%)	44	18	0.003
Peripheral Neuropathy (%)	35	16	0.013

age and had slightly longer duration of disease compared to the T1DM subjects. The mean age of diabetes onset for young-onset T2DM and T1DM was 28.5±8.5 and 16.1±7.1 years (p<0.001) respectively. There was an excess of females, particularly in the T1DM cohort (71% *vs* 52%, p<0.05). There was no significant difference in ethnic distribution between the two groups. Majority (79%) of the young-onset T2DM patients had family history of diabetes. There was no significant difference in HbA1c between the two groups.

Cardiovascular Risk Factors

Young-onset T2DM subjects were more likely to have unfavourable cardiovascular risk factors compared with T1DM. These included the presence of hypertension (71% vs 7%, p<0.001), dyslipidemia (92% vs 67%, p<0.001), overweight or obesity (98% vs.55%, p<0.001). Among the young-onset T2DM subjects who were overweight or obese, 83% had the condition before or within the first five years of diagnosis of DM. The mean BMI for young-onset T2DM subjects was 30.0±5.7 kg/m^2 compared to 22.1±5.2 kg/m^2 among the T1DM subjects. Both systolic and diastolic blood pressures were significantly higher among the young-onset T2DM subjects despite being treated with antihypertensive drugs. The young-onset T2DM group also had significantly higher triglyceride and lower HDL levels, although 77% of them were already treated with lipid lowering drugs compared to only 38% in T1DM. Similarly, 64% of the young-onset T2DM subjects with hypertension or dyslipidemia already had the risk factors present before or within the first five years of diagnosis of diabetes.

Diabetic complications

Despite similar glycaemic profile, significantly more subjects in the young-onset T2DM group developed macrovascular and microvascular complications than the T1DM group (22% vs 0%, p<0.001for macrovascular, 68% vs.27%, p<0.001 for microvascular) (Table 2). The differences between the two groups were homogeneous for each individual macrovascular and microvascular complications. The onset of complications appeared to be earlier among the young-onset T2DM subjects. Among the 132 young-onset T2DM subjects who developed diabetic complications, 33% had the complications before or within the first 5 years of diagnosis of DM. As for the 12 T1DM subjects who developed microvascular complications, only 1 subject (8%) was affected within the first 5 years of diagnosis of DM.

Association between clinical or metabolic parameters and diabetic complications

Univariate regression analysis revealed a significant association between age, diabetes duration, types of

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.07

Table 3. Results of stepwise regression analysis for factors independently associated with macrovascular or microvascular complications

Parameters	Odds Ratio	95% Confidence Interval	*P* value
Disease duration (years)	1.12	1.07-1.18	<0.001
Hypertension	2.08	1.02-4.26	0.045
HbA1c	1.20	1.04-1.38	0.01
Type of DM (2 *vs.* 1)	2.64	1.15-6.04	0.022

*HbA1c, glycated haemoglobin; DM, diabetes mellitus.
Statistical Analysis: Stepwise regression
Variables included in the models:diabetes type, age, disease duration, gender, smoking history, hypertension, systolic BP, HbA1c, dyslipidemia, total cholesterol, HDL level , LDL level , triglyceride level, BMI, waist circumference, adherence to dietary modification, exercise and medications.

Table 4. Comparison of prevalence of diabetic complications among young-onset and adults-onset T2DM in Malaysia and other young-onset T2DM populations

	Lim KP et al.	Diabcare 2008[10]	JADE[11]	Soon HS[4]	Constatino et al.[5]
N	194	1670	7481	527	354
Age (years)	42.6 (4.4)	57.5 (10.9)	44.7	48.9	40.4
Disease Duration (years)	14.0 (10.6)	11.5 (8.0)	10	15	11.6
HbA1c (%)	9.49 (2.42)	8.66 (2.09)	8.32	8.95	8.1
Body Mass Index (kg/m^2)	30	27.8	26.5	35.3	32.2
Macrovascular Complication (%)					
Any	22.2	28.9	NA	NA	NA
Ischemic Heart Disease	18.5	18.4	2.3	14	12.6
Stroke	5.2	6.9	5.7	4.2	4.3
Microvascular Complication (%)					
Any	68	75	NA	NA	NA
Nephropathy	49	40.4	39	NA	47.4
Retinopathy	43.8	24.8	20	28.6	37
Neuropathy	34.5	29.2	11	29.6	NA

NA, Not available
Categorical data are expressed as percentage.
Numerical data are expressed as absolute values or means ± standard deviation.

diabetes, presence of hypertension, dyslipidemia, HbA1c, systolic BP and triglyceride level with diabetic complications. Stepwise regression analysis conducted to look for independent association between the clinical or metabolic parameters with diabetic complications revealed that being diagnosed with young-onset T2DM instead of T1DM, the presence of hypertension, a raised HbA1c and having longer duration of disease were independently associated with increased risk of diabetic complications (Table 3). Being diagnosed with young-onset T2DM as opposed to T1DM carried the highest odds ratio of 2.64.

DISCUSSION

In comparison to T1DM, our young-onset T2DM subjects had a more aggressive phenotype with more adverse cardiovascular risk factors. Despite similar glycaemic control, they developed more macrovascular and microvascular complications. A significant proportion of these complications occurred early in relation to the onset of T2DM, a pattern which was not observed in the T1DM group. The significant differences in prevalence of diabetic complications especially the macrovascular complications between our young-onset T2DM and T1DM patients (22% vs 0%) were most probably due to the earlier development of an atherogenic milieu among the young-onset T2DM patients in the presence of multiple adverse cardiovascular risk factors such as hypertension, atherogenic dyslipidemia with high TG and low HDL along with obesity. In the presence of prolonged period of asymptomatic dysglycaemia before the diagnosis of young-onset T2DM, they were predisposed to vascular damage which had probably commenced before the diagnosis of diabetes. The high prevalence of microvascular complications observed in the young-onset T2DM group despite similar glycaemic control could only be partially explained by the slightly longer disease duration and difference in age in comparison to the T1DM group. It was believed that the high prevalence of hypertension, atherogenic dyslipidemia and obesity among the young-onset T2DM patients which mostly were already present either before or within the first five years of diagnosis of diabetes also contributed significantly to the high prevalence of microvascular complications. The etiologic role of cardio-metabolic risk factors in the pathogenesis of microvascular complications have been implicated in several studies.[7-9] The overall findings of our study were consistent with the published literature demonstrating the adverse phenotype with high burden of cardiovascular disease associated with young-onset T2DM patients.[2,4,5]

We also found that being a young-onset T2DM patient (as opposed to T1DM), the presence of hypertension, a raised HbA1c and having longer duration of disease were independently associated with increased risk of macrovascular and microvascular complications. Dyslipidemia and obesity were not independent risk factors in our analysis. The lack of association was probably related to the fact that most of the patients with dyslipidemia were already well treated with a statin. The effect of obesity could not be ascertained due to the inability to calculate BMI with missing height data in 56% of our subjects. While hypertension, poor glycaemic control and long disease duration were expected to confer increased risk of diabetic complications and has been well described in the literature, this was the first study in Asia to demonstrate that being a young-onset T2DM patient independently confers an increased risk of diabetic complications up to 2.6 times above that of a type 1 DM. Similar findings had been reported in a United Kingdom

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.07

population.[4] In the presence of adverse cardio-metabolic phenotype among the young-onset T2DM patients, controlling glycaemia alone is not likely to attenuate the susceptibility to premature macrovascular and microvascular complications. Early detection of dysglycaemia via vigilant screening in young adult at risk followed by aggressive control of all the associated cardio-metabolic risk factors will be pertinent.

In the comparison of prevalence of diabetic complications of young-onset with the adult-onset T2DM population in Malaysia, our young-onset T2DM patients were younger, had slightly longer disease duration but poorer HbA1c (Table 5).[10] Although the overall prevalence of macrovascular and microvascular complications was lower than the adult-onset T2DM patients from Diabcare, the individual prevalence of diabetic complications was similar for macrovascular and higher for microvascular complications. This implies that multiple diabetic complications were more likely to occur within the same individual for our young-onset T2DM patients compared to the adult-onset T2DM. In the comparison of prevalence of diabetic complications with other young-onset T2DM populations, it was, higher overall for macrovascular and microvascular complications across all groups.[4,5,11] (Table 4) Compared to the Joint Asia Diabetes Evaluation (JADE) cohort in Asia,[8] our young-onset T2DM patients had longer disease duration despite being slightly younger in age indicating an earlier age of diabetes onset. The HbA1c was poorer while the BMI was higher. As a result, the prevalence of microvascular complications as well as ischemic heart disease was much higher. In comparison with the Caucasian populations from United Kingdom and Australia, our young-onset T2DM patients had similar disease duration and BMI but were younger in age.[4,5] Both the prevalence of macrovascular and microvascular complications was similar except for retinopathy. As glycaemia is the main contributor to the development of retinopathy, this finding was most probably driven by the higher HbA1c in our young-onset T2DM patients. Based on these observations, it appeared that our young-onset T2DM patients behaved more closely to the Caucasian than the Asian cohort in terms of macrovascular complications likely to be driven by the high BMI with associated cardiovascular risk factors. A similar pattern was also observed in a local study of newly diagnosed T2DM patients with predominance of insulin resistance over insulin secretary dysfunction largely driven by the high mean BMI.[12] As for microvascular complications, our young-onset T2DM patients reported the highest prevalence for all individual components likely to be attributable to poor glycaemic control.

According to the fifth Malaysia National Health and Morbidity Survey (NHMS) conducted in 2015, the prevalence of diabetes among individuals aged 39 and below has increased by more than double compared to the third NHMS in 2006.[13] One of the main implications of this trend is a substantial increase in the number of child bearing age women with young-onset T2DM. Apart from a higher risk of complications associated with diabetes during pregnancy such as miscarriage, preterm labour, macrosomia, birth injury, neonatal hypoglycaemia, congenital malformations and perinatal mortality; numerous studies have shown that diabetes during pregnancy also confers an increased risk of obesity and diabetes in the offspring.[14,15] This leads to a looming epidemic of young-onset T2DM associated with more aggressive phenotype and higher prevalence of macrovascular and microvascular complications. Ultimately, this phenomenon will pose a significant burden to the health and economic status at the individual as well as society level as these individuals are predisposed to increased risk of complications during their productive years.

This is a pilot study in Malaysia examining the young-onset T2DM population by comparing the burden of diabetic complications in reference to the T1DM population and exploring the association between various clinical or metabolic risk factors with diabetic complications. By examination of historical records, it allowed retrospective capture of all events. The limitations of this study included a potential bias in subject selection from a single tertiary health institution which was not representative of the overall diabetic population in Malaysia. The other limitations included the small number of subjects, gender imbalance especially in the T1DM group and a significant amount of missing data for BMI and WC. In the absence of macrovascular event registered in the T1DM group, this study was also not powered to demonstrate the potential differential effects of the individual clinical or metabolic risk factors on macrovascular and microvascular complications. The influence of genetic factors could not be excluded as there was no data on family history of cardiovascular disease. Ideally, a larger number of subjects from multiple centres including primary, secondary as well as tertiary health facilities should be examined to minimize the impact of selection bias, gender imbalance and incomplete data.

A national registry for young-onset T2DM should be created to establish a longitudinal prospective cohort. A comprehensive national young-onset T2DM cohort along with more data from the region will be essential to study the natural history of young-onset T2DM and to develop a strategic approach in management of young-onset T2DM.

CONCLUSION

This study highlighted the aggressive nature of young-onset T2DM compared to T1DM with higher prevalence of macrovascular and microvascular complications and earlier occurrence in relation to the onset of diabetes. Early detection of dysglycaemia via vigilant screening in young adults at risk followed by intensive and aggressive control

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.07

of the cardiovascular risk factors and glycaemic burden will be essential to prevent premature morbidity and mortality.

Acknowledgements
We would like to thank Adam bin Bujang, Statistician, Clinical Research Centre, Kuala Lumpur for the statistical analysis.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
This study was funded by Ministry of Health, Malaysia.

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ONLINE FIRST | October 4, 2016 | https://doi.org/10.15605/jafes.031.02.08

ORIGINAL ARTICLE

JAFES

The Effects of GCSF on the Recovery Time and Duration of Hospitalization in Patients with Anti-thyroid Drug-Induced Agranulocytosis in a Tertiary Hospital

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Abstract

Objectives. This study aims to determine if there is a significant difference in the recovery time and duration of hospital stay of patients with anti-thyroid drug-(ATD) induced agranulocytosis with and without granulocyte colony-stimulating factor (GCSF) therapy. It also aims to describe the clinical characteristics of patients who had anti-thyroid drug-induced agranulocytosis.

Methodology. This is a retrospective study of hyperthyroid patients on anti-thyroid drugs (ATD) who had an absolute neutrophil count (ANC) of less than 500/μL. Their charts were reviewed for collection of data on age, gender, body mass index (BMI), type and duration of ATD and use of antibiotic and steroid. Recovery time and length of hospital stay were compared between those who received and did not receive GCSF.

Results. With similar clinical features between the GCSF and non-GCSF groups, the recovery time from agranulocytosis and duration of hospitalization were significantly shorter in the GCSF group, despite lower ANC.

Conclusion. GCSF significantly decreased recovery time (4 versus 7 days, p=0.005) and duration of hospital stay (5 versus 7 days, p=0.009) of hyperthyroid patients with anti-thyroid drug-induced agranulocytosis compared to patients not given GCSF.

Key words: antithyroid drugs, agranulocytosis, granulocyte colony-stimulating factor, hyperthyroidism

INTRODUCTION

Anti-thyroid drugs are the first line therapy for treatment of hyperthyroidism since their discovery in 1941.[1] The ATDs are associated with a variety of minor side effects as well as potentially life-threatening complications such as agranulocytosis.[2] Agranulocytosis is defined as an ANC of less than 500 cells/μL or 0.5 x 10^9, which carries a very high risk for infection.[2,3] The occurrence of ATD-induced agranulocytosis is uncommon, in less than 0.1% to 0.5% of hyperthyroid patients on either thiamazole or propylthiouracil.[1,2] It has an incidence rate of 3 in every 10,000 patients per year.[4] In 2008, agranulocytosis was also found in 0.37% and 0.35% of hyperthyroid patients receiving propylthiouracil (PTU) and methimazole (MMI), respectively.[5] Although ATD-induced agranulocytosis is not commonly observed in hyperthyroid patients, it has a high mortality rate of 21.5% worldwide.[6] Among the drugs that can cause agranulocytosis, ATDs are among the medications with the highest relative risks of causing agranulocytosis, along with sulfasalazine and co-trimoxazole.[7]

The common ATDs used in the Philippines are MMI and PTU. Carbimazole, a precursor of MMI, is also widely used. It is rapidly converted to MMI in the serum and has the same mechanism of action.[8] In 2011, the American Association of Clinical Endocrinologists and the American Thyroid Association explained in their management guidelines that MMI should be used in virtually every patient who chooses ATD for Graves' disease (GD), except only during the first trimester of pregnancy, because it has the benefit of a once daily administration and a reduced risk of major side effects compared to PTU.[8] Also, the side effects of MMI are dose-related, whereas those of PTU are less clearly related to the dose. Minor side effects such as cutaneous reactions (usually urticaria or macular rashes), arthralgia and gastrointestinal upset occurred in approximately 5% of patients, with equal frequency for both drugs. Cross-reactivity between the 2 agents may be as high as 50%.[2] PTU may rarely cause agranulocytosis, and low doses of MMI may be less likely.[8] Another important finding is that agranulocytosis may still occur after a previous uneventful course of ATD, as re-exposure to the ATD may occur when patients have a relapse and

eISSN 2308-118x
Printed in the Philippines

Received: February 3, 2016. Accepted: May 26, 2016.
https://doi.org/10.15605/jafes.031.02.08

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ONLINE FIRST | October 4, 2016 | https://doi.org/10.15605/jafes.031.02.08

resume a second course of treatment.[2] The exact mechanism of ATD-induced agranulocytosis is still undetermined, but it is assumed to be related to autoimmunity as demonstrated by anti-granulocyte antibodies seen using immunofluorescence and cytotoxicity assays.[2]

A recent advancement on genetics showed 2 risk genotypes (HLA-B*38:02 and HLA-DRB1*08:03) that have independent association with ATD-induced agranulocytosis by human leukocyte antigen (HLA) genotyping and genome-wide association study (GWAS).[9] A study on GD included 42 patients with ATD-induced agranulocytosis and 927 with normal white blood cell count. HLA-B*38:02 was found in 59.52% of ATD-induced agranulocytosis, but only in 6.41% of those who did not experience agranulocytosis. HLA-DRB1*08:03 was seen in 52.38% of ATD-induced agranulocytosis, compared to only 15.22% of control patients. Although this is the largest research on the genetics of ATD-induced agranulocytosis with 2-stage study design, the researchers recommended to conduct another study using the same or other populations to support the validity of the result.[9]

Several studies have described the clinical characteristics of ATD-induced agranulocytosis. It was found to be more common in elderly patients using MMI in dosages more than 40 mg/day, while the prevalence with PTU was not dose-dependent.[10] Most cases were observed by to occur within 3 months following ATD initiation.[11] However, another study on a Japanese population found that the occurrence of ATD-induced agranulocytosis was not associated with dose, age and treatment duration.[12] Age, sex and type of ATD were not associated with any significant difference in the occurrence of agranulocytosis based on local data.[13]

In 1990, granulocyte colony-stimulating factor, a recombinant human hematopoietic growth factor used to decrease infection associated with neutropenia caused by the myelosuppression from chemotherapy of cancer patients, was found to improve the ANCs of some patients with ATD-induced agranulocytosis.[14] It is a hematopoietic growth factor that acts on hematopoietic cells to stimulate production, maturation and activation of neutrophils. It also increases migration and cytotoxicity of neutrophils. The actions of GCSF include stimulation and differentiation of myeloid granulocyte progenitors, squeezing mature granulocytes from bone marrow and shifting neutrophils from the perivascular to the vascular space.[15]

Studies on the benefits of GCSF on ATD-induced agranulocytosis are mostly non-randomized and retrospective because of its low incidence rate. A randomized prospective study done in 1999 studied 24 GD patients with ATD-induced agranulocytosis in Japan: 14 patients were given GCSF and 10 were controls.[15] The objective was to examine whether GCSF was effective for ATD-induced agranulocytosis. They defined agranulocytosis as ANC less than 500/mm^3, and agranulocytosis recovery time as number of days required for ANC to exceed 500/mm^3. The mean age and ANC were not statistically significant between the 2 groups. Recovery time in the GCSF-treated group did not differ from that of the untreated group in those patients with moderate and severe agranulocytosis. It was concluded that GCSF was generally ineffective for ATD-induced agranulocytosis.[15]

In 2001, contrary findings were reported by a retrospective cohort study done in France. The mean duration of hematological recovery (6.8±4 days for GCSF versus 11.6±5 days for non-GCSF), mean treatment duration of antibiotic therapy (7.5±3.8 days versus 12±4.5 days) and length of hospitalization (7.5±3.8 days versus 12±4.5 days) were significantly reduced with GCSF.[16] The different findings of the Japanese study by Fukata and colleagues were attributed to the use of inappropriate GCSF doses at 100 to 200 μg/day subcutaneously and the absence of a well-defined target population.[16] On the other hand, the French study observed the effect of 300 μg/day of subcutaneous GCSF in a well-defined population.

A retrospective study done on 109 patients with ATD-induced agranulocytosis by Tajiri and colleagues in 2005 designated patients as symptomatic and asymptomatic.[14] GCSF therapy was found to shorten the period of recovery from ATD-induced agranulocytosis in asymptomatic patients and symptomatic patients with ANC above 0.1 x 10^9/L, and not those with symptoms and ANC below 0.1 x 10^9/L.[14]

A recent retrospective cohort study done by Watanabe and colleagues in 2012 involved 55 patients with ATD-induced agranulocytosis alone (n=50) and with pancytopenia (n=5). GCSF was given in 35 patients with agranulocytosis alone and in 2 with pancytopenia. The remaining received either steroids (n=10) or supportive care (n=8 patients). Of those with agranulocytosis alone, the recovery time was 7 days (range, 2 to 22 days) in the GCSF group, 9 days (5 to 11 days) in those given steroids, and 9 days (4 to 21 days) for supportive care alone. Fifty-four patients treated with GCSF recovered significantly earlier (7 days, range 2 to 22 days) than those who did not receive GCSF (9 days, 4 to 21 days) (p=0.004).[1]

A local retrospective analysis done in 2008 by Macaballug studied the severity of ATD-induced agranulocytosis in 14 patients. Two out of the 14 patients were given GCSF. Doses of PTU greater than 300 mg/day were correlated

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with agranulocytosis. The ANCs of patients with normal BMI were higher compared to those who were underweight, but the difference was not statistically significant. A mean ANC less than 24 was correlated with poor outcome. The use of GCSF improved the outcome in the 2 patients with ATD-induced agranulocytosis.[17]

The benefits of GCSF on ATD-induced agranulocytosis do not seem to be consistent across studies.[14-20] In studies done by Watanabe, Andres and Tamai, GCSF shortened the recovery period from agranulocytosis.[1,16,18,19] GCSF was ineffective against ATD-induced agranulocytosis in a prospective controlled study.[15]

The cost of GCSF is also an important issue for both the patient and physician, particularly in emerging countries such as the Philippines. GCSF is an expensive treatment modality. With the recommended dose of GCSF at 5 μg/kg/day, this typically requires an average of 300 μg per 1 mL vial injected subcutaneously once a day.[21] The physician's decision to treat rests on careful assessment of benefit from treatment.

In 2006, the American Society of Clinical Oncology (ASCO) provided updated recommendations for GCSF use in non-cancer or non-chemotherapy-related neutropenic patients. The ASCO recommended that GCSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. They emphasized that GCSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (more than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia, age older than 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.[21] The prognostic factors for poor clinical outcomes can be used in considering GCSF treatment, since there is no existing standard of care, clinical practice guideline nor consensus specifically for ATD-induced agranulocytosis at this time. These high-risk features were included in the inclusion criteria so that all the patients in this study have similar indications for recommending GCSF therapy.

Given the lack of evidence on the efficacy of GCSF in drug-induced neutropenia and agranulocytosis for non-oncologic conditions and the paucity of local data, its utility and practicality in our setting has yet to be established.[2] This study sought to present data from our institution to describe the clinical characteristics of patients who had anti-thyroid drug-induced agranulocytosis, and to determine if there is a significant difference in the recovery time and duration of hospital stay of patients with with and without GCSF therapy.

METHODOLOGY

Study Design

A retrospective cohort study was performed.

Inclusion and Exclusion Criteria

Admitted patients with diagnosed hyperthyroidism on anti-thyroid medication, age 18 years old and older, documented temperature ≥37.8 °C, ANC upon admission below 500 cells/μL or below 0.5 x 10^9/L, with at least one of the prognostic factors predictive of poor clinical outcomes where GCSF administration can be considered [age greater than 65 years old, uncontrolled primary disease (uncontrolled hyperthyroidism), expected prolonged (more than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia, pneumonia fungal infection, hypotension, sepsis or multi-organ dysfunction] were included. Patients being worked-up for or previously diagnosed with anemia; with hematologic disorder, malignancy, history of chemotherapy and radiation therapy; or on treatment with methotrexate, cyclophosphamide, colchicine, azathioprine, ganciclovir, clozapine, sulfasalazine, amodiaquine, deferiprone, dapsone, dypirone, penicillin G, rituximab, sulfasalazine, ticlopidine, anti-arrhythmic drugs such as tocainide, procainamide and flecainide were excluded.

Sample Size

The sample size was calculated using the computation for difference between 2 means, with the level of significance and power set at 0.05 (Z_α=*1.96*) and 80% (Z_β=*0.84*), respectively. Values for the difference in mean and standard deviation were based on The Medical City's census on recovery days between patients who were given GCSF therapy and patients who were not given GCSF therapy from January 2005 to June 2014, wherein *D=8.466* and σ=*7.5*. The sample size computed for each group was 14 (N=28).

Study Procedure

Prior to data collection, the study was reviewed and approved for implementation by the Institutional Review Board of The Medical City. The Department of Medicine census and the Medical Records Department database were used to search the terms hyperthyroidism, Graves' disease, agranulocytosis, neutropenia and febrile neutropenia in the diagnosis of patients admitted from January 1, 2005 to June 30, 2014. Clinical characteristics such as age, sex, BMI, type and duration of anti-thyroid drug use, ANCs and their

ONLINE FIRST | October 4, 2016 | https://doi.org/10.15605/jafes.031.02.08

dates upon admission and upon reaching 500/μL or above, and use of antibiotics and/or steroids were obtained. Patients were classified into two groups according to treatment or non-treatment with GCSF. Clinical outcomes taken were recovery time from agranulocytosis (number of days from the date of ANC upon admission until ≥500/microL was reached) and the duration of hospital stay (excluding the days needed for the RAI treatment) were compared between the two groups.

Data Analysis

Data were analyzed using Stata® version 11. Continuous variables were described using median and range. Categorical variables were expressed as frequency and percentage. Comparison of age, BMI, duration of ATD use, ANC level upon admission, recovery time and duration of hospital stay between the two groups were analyzed using Mann-Whitney U-test, assuming that the difference across samples were not normally distributed. Categorical variables were analyzed using Fisher exact test. Significance was set at 0.05.

Ethical Considerations

This manuscript has been duly approved by the Institutional Review Board of The Medical City.

RESULTS

A total of 30 medical records of patients with anti-thyroid drug-induced agranulocytosis admitted in from January 2005 to June 2014 were reviewed. Two patients were excluded: one due to concomitant anemia, while the other had no prognostic factor predictive of poor clinical outcome. Of the remaining 28 patients, 14 patients were given GCSF therapy and the remaining 14 patients were not given GCSF.

The median ages were 39.5 and 28 years for the GCSF and non-GCSF group, respectively. Age (p=0.197), sex (p=1.0) and BMI (p=0.826) were not significantly different between the 2 groups (Table 1). Thirteen patients (93%) were on imidazoles (either methimazole or carbimazole) and one (7%) on PTU in each of the GCSF and non-GCSF groups. The shortest duration of ATD use prior to the development of agranulocytosis was 2 weeks in the GCSF group, compared to one week in the non-GCSF. The longest duration of ATD use was 36 weeks in the GCSF group and 16 weeks in the non-GCSF. The median duration of ATD was 5 weeks and 4 weeks for the GCSF and the non-GCSF groups, respectively, with no significant difference (p=0.424). The lowest ANC was 14 cells/μL in the GCSF group and 65 cells/μL in the non-GCSF. The median ANC was lower in the GCSF group (62.5 cells/μL) than the non-GCSF (258 cells/μL) (p=0.002). All patients in the GCSF group were given antibiotics compared to only 12 (86%) in the non-GCSF group. Steroids were given in 4 patients (29%) in the GCSF group, and 5 (36%) in the non-GCSF. There was no significant difference in the number of patients treated or untreated with antibiotics and steroids, with a p value of 0.4815 and 1.0, respectively.

The most common infection in both groups was acute tonsillopharyngitis (64.3% in the GCSF, 57.1% in the non-GCSF) (Table 2). Thirteen of the 14 patients had confirmed uncontrolled hyperthyroidism in each of the GCSF and non-GCSF groups. The remaining patients with undocumented thyroid function had pneumonia. Both uncontrolled hyperthyroidism and pneumonia were prognostic factors for poor clinical outcomes.

There was a significantly shorter recovery time in the GCSF compared to the non-GCSF group (4 versus 7 days, p=0.005. Duration of hospital stay was significantly shorter in the GCSF-treated group (5 versus 7 days, p=0.009), despite the significantly lower ANC level on admission (Table 1).

Table 1. Clinical characteristics of patients with anti-thyroid drug-induced agranulocytosis

Characteristic	GCSF[a] treated (n=14)	Non-GCSF[a] treated (n=14)	*p* value
Median age, year (range)	39.5 (21–55)	28 (18–64)	0.197
Female gender (%)	12 (86%)	11 (79%)	1.0
Median body mass index, kg/m^2 (range)	20.3 (17.9–27.3)	21.4 (15.5–28.2)	0.826
Type of ATD[b] (%)			
Propylthiouracil	1 (7%)	1 (7%)	1.0
Imidazoles	13 (93%)	13 (93%)	
Median duration of ATD[b] use, week (range)	5 (2-36)	4 (1-16)	0.424
Use of antibiotics (%)			
With antibiotic	14 (100%)	12 (86%)	0.4815
Without antibiotic	0	2 (14%)	
Use of steroids (%)			
With steroids	4 (29%)	5 (36%)	1.0
Without steroids	10 (71%)	9 (64%)	
Median ANC[c] upon admission, cells/ μL (range)	62.5 (14–408)	258 (65–432)	0.002
Median recovery time, days (range)	4 (1-8)	7 (5-22)	0.005
Median duration of hospital stay, days (range)	5 (3-8)	7 (4-22)	0.009

[a]GCSF, granulocyte colony-stimulating factor
[b]ATD, anti-thyroid drug
[c]ANC, absolute neutrophil count

Table 2. Frequency of infection on admission

Infection	GCSF[a] (n=14)	Non-GCSF[a] (n=14)
Acute tonsillopharyngitis	9 (64.3%)	8 (57.1%)
Pneumonia	2 (14.3%)	2 (14.3%)
Sepsis	1 (7.1%)	0
Acute bronchitis	0	1 (7.1%)
Urinary tract infection	0	1 (7.1%)
Cellulitis	1 (7.1%)	0
Oral candidiasis	1 (7.1%)	0
Systemic viral infection	0	2 (14.3%)

[a]GCSF, granulocyte colony-stimulating factor

ONLINE FIRST | October 4, 2016 | https://doi.org/10.15605/jafes.031.02.08

DISCUSSION

Clinical features, such as ANC less than 500 cells/μL or less than 0.5 x 10^9/L and high risk for infection, were similar in all the included patients. These were also found in the studies of Fukata and Andres.[15,16] With the exception of ANCs upon admission, there were no significant differences between the GCSF-treated and non-treated groups in all of the characteristics, particularly age (p=0.197), sex (p=1) and BMI (p=0.826), type (p=1) and duration (p=0.424) of ATD, use of antibiotic (p=0.4815) and steroid treatment (p=1). The predominantly female composition of both groups was consistent with studies on ATD-induced agranulocytosis done in Japan, France and the Philippines.[1,14-17] This may be attributed to the 1:5 male-to-female ratio of hyperthyroidism worldwide.[22]

Most of the hyperthyroid patients who developed anti-thyroid drug-induced agranulocytosis were on imidazoles, as only a small proportion were on PTU.[1,14-16] Imidazoles are preferred over PTU due to their ability to rapidly achieve euthyroidism, once daily dosing assuring better compliance and less reported toxicity.[23]

The most common initial adverse reactions to ATDs are pruritus and rashes. This can occur within 24 hours after taking the anti-thyroid drug. Agranulocytosis, the more life-threatening side effect, is usually seen within 2 months of anti-thyroid drug use.[1] The median duration of ATD use was not significantly different between the two groups (5 weeks in the GCSF versus 4 weeks in the non-GCSF, p=0.424).

In our study, all patients were febrile with ANC less than 500 cells/μL. The ASCO recommends against the routine use of GCSF in febrile neutropenia.[21] Its use should be considered, however, in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. These prognostic factors were in our inclusion criteria to ensure that the patients in both groups were all candidates for GCSF therapy. High-risk features include expected prolonged (more than 10 days) and profound (less than 0.1 x 10^9/L) neutropenia, age greater than 65 years, uncontrolled primary disease (uncontrolled hyperthyroidism documented in 26 patients), pneumonia (2 patients each in GCSF and non-GCSF groups), fungal infection (1 patient), hypotension and multi-organ dysfunction or sepsis syndrome (1 patient) or being hospitalized at the time of the development of fever.[21] Two patients with undocumented hyperthyroidism had pneumonia. All of the patients in the 2 groups have at least one prognostic factor predictive of poor clinical outcomes.

Antibiotics and steroids were considered as supportive management for ATD-induced agranulocytosis. Antibiotic use was described but not correlated to GCSF treatment in the studies of Watanabe, Andres and Macaballug.[1,16,17] The studies generally stated that antibiotics and steroids improved the prognosis of the ATD-induced agranulocytosis, without reference to its effect on recovery time and duration of hospital stay in the GCSF or non-GCSF group. Glucocorticoids are thought to have 3 mechanisms for causing neutrophilic granulocytosis: (1) induction of detachment of neutrophils from the endothelial lining of blood vessels, (2) delay in migration of neutrophils from circulation into tissues, and (3) improvement of neutrophil survival by suppression of apoptosis.[24] In our study, there was a balance between patients given antibiotic and steroids in the GCSF and non-GCSF groups, somewhat reducing their confounding effects.

Fukata and colleagues found that the recovery time in the GCSF-treated group did not differ from the untreated when ANCs were less than 500 cells/μL.[15] The disparity with our findings may be due to the different dosage of GCSF (300 μg/day) given in our institution, as per the current recommended dose of 5 μg/kg body weight/day.[21] The significantly shorter recovery time (p=0.005) and duration of hospital stay (p=0.009) despite lower ANC levels of the GCSF group in this study was consistent with the findings of Andres and colleagues.[16]

CONCLUSION

GCSF significantly shortened the recovery time and duration of hospitalization of hyperthyroid patients with ATD-induced agranulocytosis. Physicians may use GCSF in patients with anti-thyroid drug-induced agranulocytosis who have prognostic factors that are predictive of poor clinical outcomes.

Recommendation

The generalizability of the results is limited by the reported experience in a single tertiary level hospital. Collaborative research with other institutions to compare clinical experiences may help initiate the formulation of evidence-based local guidelines for the care of patients with anti-thyroid drug-induced agranulocytosis.

Acknowledgements

The authors express their appreciation to the staff of the Medical Information Department of The Medical City for their assistance in the retrieval of medical records, and to the Pharmacy Department for providing the essential data on GCSF in their In-Patient Drug Dispensing System.

Statement of Authorship

All authors have given approval to the final version submitted.

Author Disclosure

All the authors have declared no conflict of interest.

ONLINE FIRST | October 4, 2016 | https://doi.org/10.15605/jafes.031.02.08

Funding Source
None.

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ONLINE FIRST | October 24, 2016 | https://doi.org/10.15605/jafes.031.02.09

ORIGINAL ARTICLE

JAFES

Prevalence of Sensorineural Hearing Loss and its Association with Glycemic Control in Filipino Patients with Diabetes at the Philippine General Hospital

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Abstract

Background. Sensorineural hearing loss (SNHL) is a form of diabetic neuropathy. Its prevalence rate varies from 21.7-73.3% among different populations. The association of this complication with long-term glycemic control has not been described extensively.

Objectives. The study aims to determine the prevalence of SNHL in Filipino patients with diabetes consulting in a tertiary hospital; and to determine the association of SNHL with the degree of blood sugar control as measured by the mean hemoglobin bA1c (HbA1c) for the last five years.

Methodology. A cross-sectional study of 128 patients in a tertiary hospital was done. Patients were recruited via stratified random sampling with the different clinics as the stratifying variable. They underwent physical examination and pure tone audiometry (PTA) to detect presence of SNHL and presence of distal peripheral neuropathy. Chart review was done to gather the HbA1c levels for the last five years, as well as data on the presence of retinopathy and nephropathy. The average HbA1c levels, and other clinical and demographic factors and their association with SNHL were analyzed using logistic regression.

Results. The prevalence of SNHL among patients with diabetes is 45.31%. Glycemic control does not seem to be associated with SNHL (p value 0.451, OR 1.447). Age was found to be significantly associated with SNHL (p value=0.046, OR=1.035). Among patients age 60 years old and below, retinopathy was significantly associated with SNHL (p value 0.023, OR=3.564). Multivariate analysis did not show any significant predictor for SNHL. There was no observed difference in the proportion of patients with SNHL among males (48.94%) compared to females (43.21%), p value of 0.530. A more advanced age is associated with SNHL among males (p value 0.024, OR=1.095) and a family history of hearing loss is an independent predictor of SNHL (p value 0.047, OR=1.088).

Conclusion. There is a high prevalence rate of SNHL among Filipino patients with diabetes. SNHL does not seem to be associated with glycemic control. Screening for SNHL maybe warranted for patients with diabetes due to its high prevalence rate regardless of glycemic control. Hearing care, focusing on prevention of hearing loss, should be advocated for patients with diabetes mellitus.

Key words: Sensorineural hearing loss, prevalence rate, pure-tone audiometry, HbA1c

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia.[1] One of its disabling complications is sensory neuropathy including hearing loss. Sensorineural hearing loss (SNHL) is one form of hearing loss, which is caused by damage in the inner ear, involving the cochlea and its haircells.[2] Diabetes is thought to be an important causative factor for SNHL. It was described in one retrospective study that SNHL was more common in patients with diabetes than those without the disease.[3] The pathogenesis involves oxidative stress, microangiopathy and auditory neuropathy.[4] The prevalence of SNHL in diabetics varies widely in different studies and the data regarding its association with glycemic control are inconsistent. Studies on different populations have shown a prevalence range of 21.7% to as high as 73.3%.[5-7] These results support the finding that the prevalence of SNHL varies among different racial ethinicities.[8] A few studies tried to determine the association of SNHL with the degree of glycemic control. Fasting blood sugar was noted to be correlated with the severity of SNHL, however conflicting results have been noted in the association of hearing loss and HbA1c levels.[7-9]

eISSN 2308-118x
Printed in the Philippines

Received: May 30, 2016. Accepted: July 13, 2016.
https://doi.org/10.15605/jafes.031.02.09

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ONLINE FIRST | October 24, 2016 | https://doi.org/10.15605/jafes.031.02.09

According to the Philippines' latest National Health and Nutrition Survey (NNHeS) in 2013, the prevalence rate of diabetes by oral glucose tolerance test is 5.4%.[10] However there is no local data available describing the prevalence of SNHL in Filipino patients with diabetes. It seems that SNHL is a less recognized complication of diabetes.

The World Health Organization (WHO) defines hearing impairment as pure-tone thresholds of more than 25 dB hearing loss in the better ear.[11] Hearing loss may be mild (threshold of 26-40 dB), moderate (threshold of 41-55 dB), moderately severe (threshold of 56-70 dB), severe (threshold of 71-90 dB), and profound (threshold of >90 dB).[12] Disabling hearing loss refers to thresholds greater than 40 dB in the better ear. Above this threshold, hearing impairment makes it difficult to hear speech sounds lower than normal voices and may cause individuals to miss parts of or all of the words in ordinary conversation.[11] Hearing loss is thus considered a disabling problem.

This study aims to ascertain the prevalence of SNHL among adult Filipinos with diabetes consulting in a tertiary urban hospital. It also aims to determine the association between the presence of SNHL and poor glycemic control.

METHODOLOGY

A cross-sectional analytic study was done among 128 patients with diabetes mellitus consulting at the outpatient departments of Philippine General Hospital, a tertiary hospital in Manila. Included were adults aged 19 and above, with Type 1 or Type 2 diabetes mellitus with disease duration of at least five years, diagnosed with the disease based on Philippine practice guidelines for diagnosis and management of diabetes and with at least one HbA1c result per year during the last five years.[12] Exclusion criteria were presence of risk factors for SNHL such as history of ototoxic drug exposure (aminoglycosides, loop diuretics such as furosemide, salicylates, and chemotherapeutic drugs) within the last 5 years, history of radiation exposure in the head within the last 5 years, occupational noise exposure, congenital/structural deformity in the ear, abnormal otoscopy findings, conductive hearing loss of unknown etiology, and infections (otitis media, syphilis, herpes zoster). Those with conditions that preclude accurate pure tone testing such as claustrophobia were also excluded.

Using Epi Info version 7, the minimum sample size requirement is at least 128 based on the prevalence of SNHL in this population=21.7% with 95% confidence level, 7.5% margin of error, and 10% non-response rate (possibility of incomplete patient charts during review of records).[13] Stratified random sampling was done to recruit patients from the family medicine, internal medicine, and diabetes clinics. The three different clinics were used as strata. The list of patients scheduled for consult for the day was used as the sampling frame. Proportionate allocation was implemented in recruiting patients from each stratum. We randomly selected 15 patients from the family medicine clinic, 24 from the internal medicine clinic, and 89 from the diabetes clinic. Patients who met the inclusion criteria and gave their informed consent were included in the study. If the invited subject declined, then he or she was replaced by randomly selecting a patient consulting in that clinic. The University of the Philippines Manila Research Ethics Board approved the study for implementation.

The following data were collected from each patient by interview and physical exam: date of birth, approximate date (nearest month and year) of diagnosis of diabetes. Weight (kilograms) and height (centimeters) were obtained using a standard weighing scale with stadiometer without shoes. Systolic and diastolic blood pressures were obtained uniformly using the right arm with the subject seated and using a digital sphygmomanometer. A blood pressure ≥140/90 is considered hypertensive, and below that level, non-hypertensive. Chart review was done to retrieve the HbA1c values for the last five years, and then the average HbA1c was computed. An average of <7% was classified as controlled diabetes, and an average of ≥7% was classified as uncontrolled diabetes.

The presence of diabetic complications in each participant was determined by reviewing chart data. The presence of albuminuria was obtained from the latest urinalysis within a year from inclusion. The most recent creatinine during the latest consult was used to calculate the creatinine clearance using the Cockroft and Gault formula. The presence of retinopathy was based on the most recent consult with the ophthalmologist within the past year. Peripheral neuropathy was screened using the Neuropathy Disability Score (NDS).

Recruited patients underwent PTA-ST using the Madsen Itera II Diagnostic Audiometer at the Ear Unit of the Philippine General Hospital. These machines were ISO certified and are regularly calibrated. Air conduction and bone conduction were tested. The threshold expressed in decibels (dB) were measured for sound frequencies 250, 500, 1000, 2000, 4000, and 8000 hertz (Hz) for air conduction and 500, 1000, 2000, and 4000 Hz for bone conduction. The average of the air conduction threshold for the 500, 1000, and 2000 Hz was used to determine the pure tone average. The presence of a threshold of PTA >25 db in at least one ear, with bone conduction average not more than 10db from the PTA is diagnostic of SNHL.

Data Analysis

Data analysis was performed using STATA version 13 statistical software. Quantitative variables were presented as mean and standard deviation, while qualitative variables were presented as frequency and percentage. Logistic regression analysis was done to analyze factors associated with SNHL among patients with diabetes. Independent predictors of SNHL among patients with

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diabetes were determined using multiple logistic regression analysis with backward elimination. The level of significance was set at 5%.

RESULTS

A total of 148 patients were recruited to participate in the study, however 20 were excluded due to a history of chemotherapy, history of exposure to loud noises, impacted cerumen, presence of ear infection, and no consent. There were 128 patients eligible for the study. The clinical and demographic characteristics of all participants are shown in Table 1. These individuals underwent PTA-ST. Data on the presence of diabetic complications were gathered. Eight patients had no data on albuminuria, three patients did not have creatinine values, and six patients did not have screening for retinopathy at the time of inclusion in the study.

Table 1. Demographic and clinical profile of all participants. (n=128)

Variable	Mean±SD or n(%)
Age (mean in years±SD)	57.52±11.10
HBA1c (mean (mean±SD)	7.88±1.45
Duration of Diabetes (years)	13.27±7.57
BMI (kg/m^2)	26.21±6.48
Male n (%)	47 (36.72)
Type of Diabetes	
Type 1 n (%)	8 (6.25)
Type 2 n (%)	120 (93.75)
Systolic BP (mean mmHg±SD)	122.34±15.82
Diastolic BP (mean mmHg±SD)	75.26±9.02
Insulin Therapy, no. n (%)	67/128 (52.34)

Among the 128 patients included in the study, 58 or 45.31% had SNHL. Twenty-one patients had unilateral SNHL and 37 patients had bilateral SNHL. Among those with bilateral SNHL, 26 patients had symmetric SNHL and 11 patients had asymmetric SNHL. Among patients who had SNHL, 41 patients had mild hearing loss, 12 had moderate hearing loss, 4 patients had moderately severe hearing loss, none had severe hearing loss, and 1 had profound hearing loss. The demographic and clinical characteristics of the participants with SNHL and without SNHL are compared in Table 2.

There were 87 (70.16%) participants with a five-year average HbA1c ≥7%. Among these patients, 38 (43.68%) had SNHL and 49 (56.32%) did not have SNHL. The proportion of patients with SNHL with a five-year average HbA1c <7% compared to those patients with a five-year average HbA1c ≥7%, were 48.78% (20/41) and 43.68% (38/87) respectively, p value=0.588.

There were 23 (33.33%) patients age 60 years old and below who had SNHL and 35 (59.32%) patients above 60 years old who had SNHL (p value=0.003). Among the 47 males, 23 (48.94%) had SNHL and among the 81 females, 35 (43.21%) had SNHL (p value=0.530).

Multiple logistic regression analyses of the 128 participants are shown in Table 3. The clinical and demographic profiles of the participants grouped according to age and sex are shown in Tables 4 and 5 respectively. The multiple regression analysis according to age group and sex are shown in Tables 6 and 7.

DISCUSSION

Prevalence of Sensorineural Hearing Loss and Clinical Characteristics of Participants

Almost half of the patients included in our study have hearing loss. The observed prevalence rate of SNHL in our hospital is 45.31%, which is within the range of the observed prevalence rates in different studies.[6-7] It is very similar to the reported 44% rate in a study done in Turkey and 45% prevalence rate in a study done in Iran.[4,14]

Among the demographic and clinical characteristics of patients investigated in our study, mean age was the only variable that was associated with SNHL (p=0.046, OR 1.035). The group with SNHL tended to be older than those without SNHL (Table 2). A more advanced age seemed to be associated with the presence of SNHL. This might be due to the development of presbycusis, since the risk for hearing loss increases steadily with increasing age.[15]

The groups of patients with SNHL and without SNHL are similar in terms of diabetes control, BMI, presence of hypertension and diabetes duration. The two groups are also comparable in terms of proportion of males, insulin treatment, smoking history and family history of hearing

Table 2. Association of demographic and clinical characteristics of patients with sensorineural hearing loss, (N=128)

Variable	With SNHL (n=58)	Without SNHL (n=70)	Odds Ratio	P value
Age (mean ±SD)	59.71±11.19	55±10.78	1.035	0.046
BMI (mean ±SD kg/m^2)	27.63±9.45	25.60±4.45	1.025	0.527
Duration of Diabetes (Years, mean±SD)	13.57±8.00	13.03±7.25	1.001	0.687
Male n(%)	23 (39.66)	24 (34.29)	1.260	0.531
Type 2 Diabetes n (%)	54 (91.53)	66 (94.29)	1.222	0.784
Uncontrolled Diabetes n(%)	38 (65.52)	49 (70)	0.814	0.589
Hypertension n(%)	6 (10.34)	7 (10.00)	1.038	0.949
Insulin Therapy, n (%)	26/58 (44.83)	41/70 (58.57)	0.575	0.122
Albuminuria n (%)	15/56 (26.79)	21/64 (32.81)	0.749	0.473
Nephropathy n (%)	32/58 (55.27)	33/67 (49.25)	1.231	0.562
Retinopathy n (%)	17/57 (29.82)	19/65 (29.23)	1.051	0.900
Peripheral Neuropathy Present n (%)	20/58 (34.48)	25/70 (35.71)	0.947	0.885
Smoking, n (%)	6/58 (10.34)	12/70 (17.14)	0.557	0.275
First-degree relative with hearing loss, n (%)	5/58 (8.62)	6/70 (8.57)	1.006	0.992

ONLINE FIRST | October 24, 2016 | https://doi.org/10.15605/jafes.031.02.09

Table 3. Multiple Logistic Regression Analysis (N=128)

Variable	p value	Odds Ratio
DM control	0.451	1.447
Age	0.195	1.032
Sex	0.239	1.798
BMI	0.445	1.039
DM type	0.307	2.728
DM duration	0.816	1.006
Hypertension	0.922	1.070
Insulin Therapy	0.298	0.620
Albuminuria	0.441	0.686
Nephropathy	0.849	0.916
Retinopathy	0.944	1.033
Peripheral Neuropathy	0.385	0.673
Smoking status	0.303	0.484
Family history of hearing loss	0.302	2.272

loss. The presence of diabetic complications such as retinopathy, nephropathy and retinopathy also does not seem to be associated with having SNHL. There was no statistically significant difference in the presence of these complications in both groups of patients (Table 2). The results are consistent with the findings of De Leon-Morales among 94 patients with diabetes, wherein the presence of SNHL is independent of the presence of other diabetic complications such as peripheral neuropathy, retinopathy and neuropathy.[16] However, these results are different from the large retrospective study done by Kakarlapudi, where patients with increasing creatinine correlated with progressive hearing loss.[3]

Other factors have been described in literature to be associated with SNHL such as hypertension and duration of diabetes. It was described that a higher prevalence of SNHL is observed in patients with higher blood pressure[17,18] In our study, patients with SNHL did not have higher blood pressure levels than those who did not have SNHL. Diabetes duration was also not statistically significant between those patients with SNHL and without SNHL. Our finding is consistent with the findings of Rajendran, where there was a higher prevalence of SNHL which was not associated with longer diabetes duration. This finding however is in contrast with the results of the study of Mozzafari and Austin.[6,14,20]

Sensorineural Hearing Loss and Glycemic Control

Two different studies described the association of SNHL with fasting blood sugar level (FBS). One study showed a statistically significant higher rate of SNHL among patients with elevated FBS levels and another also showed a higher proportion of patients with SNHL among patients with elevated FBS levels but was not statistically significant.[9,10] These studies used FBS instead of HbA1c in determining glycemic control, which is the ideal test in assessing blood sugar control. One study used HbA1c level in assessing

Table 4. Demographic and clinical factors associated with SNHL stratified by age

Variable	Patients Aged ≤ 60 yo (n=69)				Patients Aged >60 yo (n=59)			
	With SNHL (n=23)	Without SNHL (n=46)	Odds Ratio	P value	With SNHL (n=35)	Without SNHL (n=24)	Odds Ratio	P value
Age (mean ±SD)	49.39±10.75	50.17±8.94	0.991	0.746	66.49±3.37	66.33±3.63	1.011	0.879
Male n (%)	4 (17.39)	14 (30.43)	0.481	0.251	19 (32.20))	10 (41.67)	1.663	0.342
BMI (mean ±SD kg/m^2)	26.38±6.43	24.98±4.73	1.049	0310	25.95±3.59	26.78±3.67	0.937	0.382
Duration of Diabetes (Years, mean±SD)	13.13±6.65	11.65±6.63	1.034	0.385	13.86±8.86	15.67±7.78	0.974	0.418
Type 2 Diabetes n (%)	21 (91.30)	42 (60.87)	1.00	1.00	33 (94.28)	24 (100)	*	*
Uncontrolled DM	20 (86.96)	34 (73.91)	2.352	0.224	18 (51.43)	15 (62.5)	0.635	0.401
Hypertension	2 (8.70)	4 (8.70)	1.000	1.000	4 (11.43)	3 (12.5)	0.903	0.901
Insulin Therapy, n (%)	14/23 (60.87)	27/46 (58.70)	1.095	0.862	12/35 (34.29)	14/24 (58.33)	0.373	0.071
Albuminuria n (%)	5/23 (21.74)	13/42 (32.81)	0.629	0.430	10/33 (30.30)	8/22 (36.36)	0.761	0.639
Nephropathy n (%)	8/23 (34.78)	33/67 (30.95)	0.702	0.507	6/35 (17.14)	15/24 (62.50)	1.309	0.629
Retinopathy n (%)	11/23 (47.83)	2/44 (4.54)	**3.564**	**0.023**	6/34 (17.65)	10/22 (45.45)	0.257	0.029
Peripheral Neuropathy Present n (%)	6/23 (26.09)	13/46 (28.26)	0.896	0.849	14/35 (40.00)	12/24 (50.00)	0.667	0.448
Smoking, n (%)	1/23 (4.35)	7/46 (15.22)	0.253	0.213	5/35 (14.29)	5/24 (20.83)	0.633	0.512
First-degree relative with hearing loss, n (%)	1/23 (4.35)	5/46 (10.87)	0.373	0.381	4/35 (11.43)	1/24 (4.67)	2.968	0.345

*Cannot be computed

Table 5. Demographic and clinical factors associated with SNHL stratified by sex

Variable	Males (n=47)				Females (n=81)			
	With SNHL (n=23)	Without SNHL (n=24)	Odds Ratio	P value	With SNHL (n=35)	Without SNHL (n=46)	Odds Ratio	P value
Age (mean ±SD)	64.13±16.18	55.79±13.50	**1.095**	**0.024**	56.80±12.77	55.67±9.22	1.010	0.642
BMI (mean ±SD kg/m^2)	25.16±3.15	24.70±3.48	1.088	0.355	26.74±5.68	26.29±4.77	1.017	0.693
Type 2 Diabetes n (%)	21 (91.30)	21 (87.50)	0.318	0.338	32 (91.43)	1/46 (2.17)	4.219	0.222
Duration of Diabetes (Years, mean±SD)	13.52±7.91	14.58±6.18	0.978	0.601	13.60±8.17	12.22±7.69	1.023	0.436
Uncontrolled DM	14 (60.87)	15 (62.5)	0.933	0.908	24 (68.57)	34 (73.91)	0.770	0.598
Hypertension	3 (13.04)	6 (25)	3.450	0.300	3 (8.57)	6 (13.04)	0.625	0.529
Insulin Therapy, n (%)	11/23 (23.40)	17/24 (70.83)	0.377	0.112	12/35 (34.29)	24/46 (52.17)	0.688	0.407
Albuminuria n (%)	6/23 (26.08)	10/23 (43.48)	0.488	0.260	9/34 (26.47)	11/46 (23.91)	0.982	0.972
Nephropathy n (%)	15/23 (65.22)	12/23 (56.52)	1.442	0.546	17/35 (48.57)	21/45 (46.67)	1.079	0.866
Retinopathy n (%)	6/22 (27.27)	8/21 (38.10)	0.609	0.451	11/35 (31.43)	11/45 (24.44)	1.417	0.489
Peripheral Neuropathy Present n (%)	9/23 (39.13)	14/24 (58.33)	0.459	0.191	11/35 (31.43)	11/46 (26.08)	1.458	0.452
Smoking, n (%)	6/23 (26.09)	10/24 (40.00)	0.494	0.263	0 (0.00)	2/46 (4.35)	*	*
First-degree relative with hearing loss, n (%)	4/23 (17.39)	2/24 (8.33)	2.316	0.362	1/35 (2.86)	4/46 (8.70)	2.968	0.345

*Cannot be computed

ONLINE FIRST | October 24, 2016 | https://doi.org/10.15605/jafes.031.02.09

Table 6. Multiple regression analysis of subgroups according to age

Variable	Patients Aged ≤ 60 yo (n=69)		Patients Aged >60 yo (n=59)	
	p value	Odds Ratio	p value	Odds Ratio
DM control	0.214	3.28	0.600	1.517
Age	0.056	0.892	0.831	1.022
Sex	0.707	0.707	0.088	4.953
BMI	0.889	1.009	0.750	1.038
DM type	0.619	0.416	*	*
DM duration	0.139	1.103	0.339	0.960
Hypertension	0.385	2.835	0.377	0.328
Insulin Therapy	0.727	0.749	0.063	0.188
Albuminuria	0.041	0.124	0.904	1.120
Nephropathy	0.072	0.169	0.592	0.636
Retinopathy	**0.009**	**12.163**	0.022	0.978
Peripheral Neuropathy	0.418	2.006	0.933	0.924
Smoking status	0.556	0.439	0.666	0.584
Family history of hearing loss	0.783	0.643	0.078	13.875

*Cannot be computed

Table 7. Multiple regression analysis of subgroups according to sex

Variable	Male (n=47)		Female (n=81)	
	p value	Odds Ratio	p value	Odds Ratio
DM control	0.195	4.619	0.944	1.044
Age	0.063	0.777	0.905	0.996
BMI	0.870	1.033	0.625	1.026
DM type	0.949	0.859	0.364	3.657
DM duration	0.478	1.058	0.679	1.015
Hypertension	0.144	50.740	0.643	0.685
Insulin Therapy	0.370	0.408	0.333	0.580
Albuminuria	0.128	0.204	0.825	0.864
Nephropathy	0.724	0.686	0.810	0.872
Retinopathy	0.626	0.594	0.918	1.065
Peripheral Neuropathy	0.163	0.215	0.060	1.036
Smoking status	0.085	0.154	*	*
Family history of hearing loss	**0.029**	**24.070**	0.768	0.675

*Cannot be computed

glycemic control showed a positive correlation of SNHL and glycemic control. The study showed a higher prevalence of SNHL in patients with higher HbA1c level. Those with SNHL had an average HbA1c of 12.2±3.2% and those without SNHL had an average HbA1c of 9.8±2.6% with a p value of 0.02.[7] This study however included only 46 patients with diabetes and correlated SNHL with only a single, most recent HbA1c result. Our study included a bigger number of patients and correlated the presence of SNHL with the average glycemic control over a longer period of time. Those with SNHL had a five-year average HbA1c of 7.78±1.51 and those without SNHL had a five-year average HbA1c of 7.96±1.41. There was no statistically significant difference in the HbA1c levels in both groups with a p-value of 0.476. The results of our study show that there seems to be no association of long term glucose control with the presence of SNHL.

Multiple logistic regression analysis with backward elimination was done to determine independent predictors of SNHL among all the 128 patients recruited. However, none of the clinical characteristics investigated in our study are independent predictors of SNHL. After the multiple logistic regression analysis, age does not seem to be a predictor of SNHL among our patients, p value=0.195 (Table 3).

Analysis by Age

In our study there were more patients with SNHL in the age group above 60 years old compared to the age group of 60 years old and below (p value=0.003). Therefore, segregating the results according to age might help lessen the effect of presbycusis. Simple bivariate analysis of the presence of SNHL and diabetes control in patients age 60 years old and below, showed no association, as well as in the age group above 60 years old with p values of 0.224 and 0.401 respectively (Table 4). Our results show that there seems to be no association of the presence of SNHL and long-term glycemic control regardless of age.

Those patients with SNHL in the age group 60 years old and below had a greater proportion of retinopathy than those who did not have SNHL. The difference between the two groups is significant (p value of 0.023 and OR of 3.564). However, in the age group above 60 years old, there were more patients without SNHL who had retinopathy, than those patients with SNHL who had retinopathy (p value of 0.029). After multiple regression with backward elimination analysis, retinopathy was not an independent predictor of SNHL (Table 6). There were no other variables that are predictors of SNHL among patients 60 years old and below and those above 60 years old.

Analysis by Sex

In our study there was no difference in the proportion of males and females with SNHL. Our findings are consistent with the studies of Rajendran and Srinivas, wherein the association of hearing loss in patients with diabetes and sex is insignificant.[6,21] In the male population, a more advanced age was associated with SNHL (Table 5). However on multiple regression analysis, it was a family history of hearing loss that is an independent predictor of SNHL with a p value=0.047, OR=1.088 (Table 7). Among females, there were no clinical factors that have been identified to be

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associated with having SNHL in the bivariate and multiple regression analysis (Table 5 and Table 7).

It seems that patients with diabetes are at risk of having SNHL regardless of their blood sugar control. Limiting exposure to ototoxic drugs and loud noises may help decrease the risk of having SNHL among patients with diabetes. Screening for SHNL may be necessary so appropriate treatment maybe given since hearing loss is a disabling complication that may significantly affect the quality of life of patients with diabetes.

CONCLUSION

There is a high prevalence rate of SNHL among Filipino patients consulting in our hospital. There seems to be no association between the presence of SNHL and long-term glycemic control. Therefore patients with diabetes are at risk of having SNHL regardless of blood sugar control. Among the clinical variables investigated in our study, a family history of hearing loss increases the odds of having SNHL among male patients with diabetes. Screening for SNHL among patients with diabetes may be warranted, regardless of blood sugar control, especially in patients with age 60 years old and below with retinopathy. Hearing care, focusing on prevention of hearing loss should be advocated for patients with diabetes mellitus.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
None.

Acknowledgement
We would like to recognize Maria Luz M. San Agustin RN, audiometrician at the Philippine National Ear Institute, National Institutes of Health, for performing the PTA on all the participants.

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ONLINE FIRST | October 24, 2016 | https://doi.org/10.15605/jafes.031.02.09

APPENDIX

Appendix A. Data Collection Forms

Date:	
Patient Code:	
Birthday:	
Sex:	
Weight (kg)	
Height (cm)	
BP (mmHg)	1.
	2.
	3.
	Average:
HBA1c levels	1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20.
Average HBA1c	
Diabetes Duration (years)	
Insulin Therapy (Y/N)	
Presence of Diabetic Retinopathy? (Y/N?) Proliferative (Y, Mild, Moderate, or Severe) Non-proliferative (Y/N)	
Presence of Nephropathy eGFR? (by Cockroft and Gaunt Formula)	
Presence of Albuminuria without pyuria (Y/N)	
Presence of peripheral neuropathy (Y/N)	
Presence of Neuropathy (Y/N) (NDS score ≥3)	
Smoking (Y/N)	
First Degree Relatives with Hearing loss before (Y/N)	

Neuropathy Disability Score		
Date:		
Patient Code:		
Test:	Right	Left
Vibration		
Temperature		
Pinprick		
Achilles Reflex		
Total Score:		

ONLINE FIRST | November 7, 2016 | https://doi.org/10.15605/jafes.031.02.10

JAFES

ORIGINAL ARTICLE

Assessment of Physical Activity Level among Patients with Type 2 Diabetes Mellitus at the UP – Philippine General Hospital Diabetes Clinic

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Abstract

Introduction. Physical activity is an important factor in reducing morbidity from type 2 diabetes mellitus and maintaining quality of life. There is no available data on physical activity among Filipino patients with type 2 diabetes mellitus.

Objectives. The objectives are to assess the physical activity level of patients with type 2 diabetes mellitus at the UP-PGH Diabetes Clinic using Global Physical Activity Questionnaire and to determine the relationship between physical activity, health profiles and socio-demographic characteristics.

Methodology. A cross-sectional study was conducted to assess the physical activity levels of 151 patients with type 2 diabetes mellitus (46 men and 105 women) using GPAQ. Anthropometric measurements, socio-demographic profiles and HbA1c were also taken.

Results. Majority of subjects had moderate to high physical activity (68.9%) and most of the patients had poor glycemic control based on HbA1c of ≥7% (68.2%). Subjects aged 60 years and above (68.1%; p=0.022) and with poor glycemic control (89.4%; p=<0.001) had low physical activity level. There is no significant statistical correlation between physical activity, anthropometric profile and other socio-demographic characteristics.

Conclusion. Majority of the patients with type 2 diabetes mellitus at the UP-PGH Diabetes Clinic had moderate to high physical activity level. Subjects with poor glycemic control and older age group were associated with low physical activity.

Key words: physical activity level, diabetes mellitus, glycemic control

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, contributing to more than 90% of diabetes mellitus cases worldwide.[1] The prevalence of diabetes mellitus in the Philippines according to the National Nutrition and Health Survey of 2008 is 7.2%.[2] The increasing prevalence of diabetes mellitus creates both medical and social problems due to the diabetic complications. If hyperglycemia, hypertension, dyslipidemia and obesity are appropriately addressed, prevention of these complications is possible. Physical activity, dietary modifications and behavioral therapy are part of the comprehensive treatment strategy in patients with T2DM.[3]

Regular exercise can offer both general health benefits and diabetes-specific health benefits. It can decrease the cardiovascular risk by improving lipid profile, lowering the blood pressure and inducing weight loss.[4] It also affects overall glycemic control through improved insulin sensitivity and lowered insulin requirements. All of these health benefits may have a great impact to decrease the risk for diabetes complications, reduce the progression of existing complications, and improve quality of life. Many metabolic adaptations occur in response to physical activity and these may lead to improvement of glycemic control for individuals with T2DM.[5]

Physical inactivity is one of the established risk factors that is responsible for about one-third of deaths due to diabetes.[6] Given the multiple health benefits that physical activity confers, the World Health Organization (WHO) recommends that all adults engage in moderate intensity physical activity for at least 150 minutes per week or vigorous-intensity physical activity for at least 75 minutes per week or an equivalent combination of moderate- and vigorous-intensity physical activity achieving at least 600 MET-minutes throughout a week, including activity for work, during transport and leisure time.

Physical activity level of patients with T2DM in this study was assessed using a WHO validated Global Physical Activity Questionnaire (GPAQ).[7] The GPAQ was selected above other physical activity tools because it provides summary of activities by recreation, occupation, and transportation domains. The questionnaire was used in the

eISSN 2308-118x
Printed in the Philippines

Received: May 17, 2016. Accepted: October 10, 2016.
https://doi.org/10.15605/jafes.031.02.10

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ONLINE FIRST | November 7, 2016 | https://doi.org/10.15605/jafes.031.02.10

national nutrition survey and in a previous study with specific examples of local activities to help participants understand the questions in GPAQ; and a validity testing of self-administered GPAQ was conducted among non-diabetic Filipino adults.[8,9] A study among adult individuals of either gender aged 21 years and older was conducted to compare self-administered and original interviewer-administered versions of the GPAQ. For validity, GPAQ demonstrated fair-to-moderate correlations for moderate-to-vigorous physical activity (MVPA) for interviewer-administration (rs=0.46). Reliability for MVPA revealed moderate correlations (rs=0.63) for interviewer-administration.[10] Another study conducted to assess the test–retest reliability and concurrent validity of GPAQ against the other internationally acceptable physical activity questionnaire called International Physical Activity Questionnaire (IPAQ) and the criterion validity of the GPAQ instrument against objective measures like pedometer or accelerometer over 7 days which demonstrated reliability coefficients of moderate to substantial strength (Spearman's rho 0.67 to 0.81; Kappa 0.67 to 0.73). Findings on concurrent validity between IPAQ and GPAQ also showed a moderate to strong positive relationship (range 0.45 to 0.65). The criterion validity were in the low-to-moderate correlations (range 0.06 to 0.35).[11]

Measuring levels of physical activity is an important initial step and a public health priority. However, currently, there is no available data on physical activity among Filipino patients with type 2 diabetes mellitus. Assessment for physical activity was only conducted among non-diabetic Filipino adults and school children. Thus, this study aims to assess the physical activity level among individuals with T2DM at Philippine General Hospital (PGH), Manila, Philippines using GPAQ. Other specific objectives are to describe the socio-demographic characteristics and health profiles of patients with T2DM at UP-PGH diabetes clinic and to determine their correlation to physical activity level.

METHODOLOGY

Sampling and Design of the Study

This is a cross sectional study of adult patients diagnosed with T2DM seen at the PGH diabetes out-patient clinic during the study period of 6 months from September 2015 to February 2016. A total of 151 participants were included (46 males and 105 females). The study subjects were selected on the basis of the inclusion criteria which include age 30 years and above, diagnosed with T2DM and receiving treatment for diabetes, with or without major complications, and willing to participate in the study with the ability to comprehend relevant information. Patients with impaired mental function who were unable to comprehend relevant information, who had life-threatening illnesses, disability, proliferative retinopathy, pregnant women and those who had type 1 diabetes mellitus or other chronic conditions that may influence physical activity such as stroke and cancer were excluded. The study was approved by the PGH Expanded Hospital Research Office (EHRO). Informed consent was obtained from patients before the study began.

Eligible study subjects were interviewed to obtain information on socio-demographic parameters which include age, gender, marital status, educational level, occupational status, and place of residence. HbA1c values were obtained from medical records. Only values recorded for the past three months were used for the study. Measurements of the weight and height were obtained. A face-to-face interview was then made using a validated physical activity questionnaire to assess the physical activity level of the study population.

Study Sample

A total of 151 study subjects were included in the study. The minimum sample size requirement was estimated to be at least 96 based on the proportion (45.2%) of physical inactivity in the Philippines among adults (NNS 2013) with a 95% confidence interval, 10% margin of error and 5% level of significance.[12]

Physical Activity Measurement

Physical activity level of patients with T2DM were assessed using a WHO validated Global Physical Activity Questionnaire (GPAQ). It is composed of 16 questions about physical activity in a typical week and assesses physical activity in three domains, namely, work, transportation and recreational activities. The ratio of a person's working metabolic rate relative to the resting metabolic rate is called metabolic equivalent (MET). In the calculation of a person's overall energy expenditure, 4 METs was given to the time spent in moderate activities, and 8 METs to the time spent in vigorous activities. The total time spent on physical activity during a typical week, the number of days as well as the intensity of physical activity is taken into account to calculate for the categorical indicator. The three levels of physical activity suggested for classifying patients are low, moderate, and high. High if 7 or more days of any combination of walking, moderate or vigorous intensity activities achieving a minimum of at least 3,000 MET-minutes per week; moderate if 5 or more days of any combination of walking, moderate or vigorous intensity activities achieving a minimum of at least 600 MET-minutes per week; and low if a person is not meeting any of the above mentioned criteria.

Anthropometric Measurements

Anthropometric measurements that were taken include weight and height. Body weight was measured without shoes and with light clothing using a mechanical weighing scale (Detecto, USA). Standing height was measured

ONLINE FIRST | November 7, 2016 | https://doi.org/10.15605/jafes.031.02.10

barefooted with light clothing using a stadiometer. The reading of the weight was recorded to the nearest 0.1 kg whereas the height was recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated using the following formula: weight (kg)/height(m^2) and classified accordingly based on Asian criteria: underweight - <18.5 kg/m^2, normal – 18.5-22.9 kg/m^2, overweight/pre-obese – 23-29.9 kg/m^2 and obese - ≥30 kg/m^2.

Statistical Analysis

The results were presented as means, percentages and standard deviations. The Chi-square test was used to determine the relationship between socio-demographic information, glycemic control and levels of physical activity. Independent t-test was used to determine the differences in age, BMI and HbA1c in relation to physical activity level.

Ethical Consideration

All subjects were informed of the purpose of the study and were asked to sign a standard written consent form prior to data collection. The participation of the eligible subjects was voluntary and without financial compensation. Information was recorded anonymously and confidentiality was assured throughout the study period. This cross-sectional study has been duly reviewed and approved by the Technical Review Board (TRB) and University of the Philippines Manila Research Ethics Board (UPMREB).

RESULTS

A total of 151 subjects (46 men and 105 women) participated in the study (Table 1). The mean age for the subjects was 59.1 ± 9.5 years and ranged from 31 to 79 years old. Most of the subjects were married (74.2%) and are living in urban areas (74.8%). The majority of the subjects completed secondary education (45%) and were unemployed or housewives (70.2%). About 68.2% of subjects had poor glycemic control based on HbA1c of ≥7%. According to BMI category (Asian criteria), most of the subjects were obese (42.4%).

As depicted in Table 2, majority of the patients in UP-PGH Diabetes Clinic had moderate to high physical activity (68.9%). A higher percentage of subjects aged 60 years and above (68.1%; p=0.022) and with poor glycemic control (89.4%; p=<0.001) had low physical activity level as compared to subjects aged 30 to 59 years (31.9%) and with good glycemic control (10.6%) respectively.

Table 1. Socio-demographic and clinical profile of study population

Variable	Total (n=151)	Percent (%)
Age		
30-59	69	45.7
≥ 60	82	54.3
Sex		
Men	46	30.5
Women	105	69.5
BMI		
Underweight	3	2.0
Normal	49	32.4
Overweight	35	23.2
Obese	64	42.4
Occupational status		
Working/working retirees	45	29.8
Not working/housewife	106	70.2
Educational level		
Primary	30	19.9
Secondary	68	45.0
Vocational/College	53	35.1
Marital Status		
Single	14	9.3
Married	112	74.2
Divorcee/Widow/Widower	25	16.5
Residence		
Urban	113	74.8
Rural	38	25.2
Glycemic Control		
Good HbA1c (<7%)	48	31.8
Poor HbA1c (≥7%)	103	68.2

Table 2. Socio-demographic and clinical profile of study population

Variable	Low (n=47, 31.1%)		Moderate and High (n=104, 68.9%)		p-value
	n	%	n	%	
Age					
30-59	15	31.9	54	51.9	0.022*
≥ 60	32	68.1	50	48.1	
Gender					
Men	15	31.9	31	29.8	0.794
Women	32	68.1	73	70.2	
BMI					
Underweight/Normal	18	38.3	34	32.7	0.502
Overweight/Obese	29	61.7	70	67.3	
Occupational status					
Working/working retirees	12	25.5	33	31.7	0.441
Not working/housewife	35	74.5	71	68.3	
Educational level					
Primary/Secondary	29	34.0	69	50.0	0.580
Vocational/College	18	38.3	35	33.7	
Marital Status					
Married	35	74.5	77	74.0	0.955
Single/Divorcee/widow/widower	12	25.5	27	26.0	
Residence					
Urban	34	72.3	79	76.0	0.635
Rural	13	27.7	25	24.0	
Glycemic Control					
Good HbA1c (<7%)	5	10.6	43	41.3	<0.001*
Poor HbA1c (≥7%)	42	89.4	61	58.7	

*Significant differences p-values ≤ 0.05.

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Analysis revealed no statistically significant relationship between the level of physical activity, anthropometric profile and other socio-demographic profiles. Table 3 presents the means and standard deviations for age, BMI and glycemic control in relation to physical activity level. The mean age for men and women were 60.9±8.6 years and 57.8±9.9 respectively (p=0.053). Study population with low physical activity had significantly higher HbA1c than those with moderate to high physical activity (7.8±1.6; p=0.001).

Table 3. Means and standard deviations for age, BMI and HbA1c in relation to physical activity level

Variable	Low (n=47)	Moderate and High (n=104)	p-value
Age	60.9 ± 8.6	57.8 ± 9.9	0.053*
BMI	25.6 ± 5.0	24.7 ± 4.7	0.287
HbA1c	7.8 ± 1.6	6.9 ± 1.5	0.001*

*Significant differences p-values ≤ 0.05.

DISCUSSION

Most of the subjects in the study had moderate to high physical activity level (68.9%). Based on the results of the study among adults with diabetes in America, half of the subjects (52.5%) had a moderate physical activity level.[13] A study among adults with T2DM also showed that 64.4% of the patients had moderate physical activity and were not participating in regular exercise.[14] These support the fact that moderate physical activity level is more common among T2DM patients which could be due to the information dissemination of health care providers about the health benefits of doing regular physical activity. It is necessary that physicians, health care workers or educators know about the socio-cultural habits and expected barriers in giving advice to patients with T2DM to enhance adherence to lifestyle modification by developing a diversified and appropriate health education programmes for these high risk group.

In the present study, poor glycemic control was associated with low physical activity level. A study among diabetic patients showed that moderate and vigorous physical activity provides good glycemic control by reducing the value of HbA1c.[15] Physical activity helps in glycemic control by improving insulin sensitivity thus improving glycemic control. In a meta-analysis of 14 clinical controlled trials of physical activity intervention among middle-aged diabetic individuals lasting for about 8 weeks or more demonstrated that regular exercise resulted to a decrease in HbA1c levels.[16] Findings of the available clinical research in knowing the physiologic relationship between diabetes and physical activity still remains insufficient. Aside from searching for complete data of the applicable physiology, we should also give priority towards identifying the strategies on how to encourage our patients to have a sustained exercise that will offer health improvement.

A significantly higher percentage of those aged 60 years and above (68.1%) had lower physical activity than those with younger age group (31.9%). Older age group prefers to do low intensity physical activity because of their perception that diabetes 'weakened' and 'aged' the body causing them to have some demotivational effect in involving or maintaining a regular exercise regimen and more intense physical activity.[17] Health education plays an important role with emphasis on the necessity of doing regular exercise in preventing and delaying diabetic complications.

The study did not show any association between anthropometric profile and physical activity which was consistent with other similar studies. This might be due to obese individuals who are being motivated to increase their physical activity in order to have weight loss. No significant correlation was also noted between physical activity and other socio-demographic characteristics of the study population.

The limitation of this study is that physical activity was assessed by using a questionnaire which provides a crude measurement of physical activity and is subjected to recall bias. Participation to physical activity itself might be under-reported or over-reported because most of the patients were not able to recall exactly the type and duration of the activity done. Another limitation was the study population was recruited from one diabetes clinic only, which limits the generalizability of the study findings. The results only showed the association of each of the independent variables with the physical activity levels. It is advisable to include dietary history or caloric expenditure and to incorporate accelerometers or pedometers in future studies. Further study is recommended in a multicenter setting with a larger sample size in order to perform a multivariate logistic regression analysis to determine significant associations with different physical activity levels.

CONCLUSION

The majority of the patients in UP-PGH Diabetes Clinic have moderate to high physical activity. There is no significant relationship between the level of physical activity, anthropometric measurements and other socio-demographic profiles. Subjects with poor glycemic control and older age had low physical activity. Thus, we should promote regular physical activity among diabetic patients with sedentary lifestyle in order to achieve optimal glycemic control and prevent diabetic complications.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
None.

ONLINE FIRST | November 7, 2016 | https://doi.org/10.15605/jafes.031.02.10

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APPENDIX

Global Physical Activity Questionnaire (GPAQ)

Physical Activity

Next I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person. Think first about the time you spend doing work. Think of work as the things that you have to do such as paid or unpaid work, study/training, household chores, harvesting food/crops, fishing or hunting for food, seeking employment. In answering the following questions 'vigorous-intensity activities' are activities that require hard physical effort and cause large increases in breathing or heart rate, 'moderate-intensity activities' are activities that require moderate physical effort and cause small increases in breathing or heart rate.

Questions		Response	Code
Activity at work			
1	Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate like [carrying or lifting heavy loads, digging or construction work] for at least 10 minutes continuously? (SHOW THE LIST)	Yes 1 No 2 (If No, go to P 4)	P1
2	In a typical week, on how many days do you do vigorous intensity activities as part of your work?	Number of days: _____	P2
3	How much time do you spend doing vigorous-intensity activities at work on a typical day?	Hours : _____ minutes: _____	P3 (a-b)
4	Does your work involve moderate-intensity activity that causes small increases in breathing or heart rate such as brisk walking [or carrying light loads] for at least 10 minutes continuously? (SHOW THE LIST)	Yes 1 No 2 (If No, go to P 7)	P4
5	In a typical week, on how many days do you do moderate intensity activities as part of your work?	Number of days: _____	P5
6	How much time do you spend doing moderate-intensity activities at work on a typical day?	Hours : _____ minutes: _____	P6 (a-b)

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Travel to and from places			
The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way you travel to and from places. For example to work, for shopping, to market, to place of worship.			
7	Do you walk or use a bicycle (pedal cycle) for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 (If No, go to P 10)	P7
8	In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days: _____	P8
9	How much time do you spend walking or bicycling for travel on a typical day?	Hours : _____ minutes: _____	P9 (a-b)
Recreational activities			
The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities (leisure).			
10	Do you do any vigorous-intensity sports, fitness or recreational (leisure) activities that cause large increases in breathing or heart rate like [running or football,] for at least 10 minutes continuously? (SHOW THE LIST)	Yes 1 No 2 (If No, go to P 13)	P10
11	In a typical week, on how many days do you do vigorous intensity sports, fitness or recreational (leisure) activities?	Number of days: _____	P11
12	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Hours : _____ minutes: _____	P12
13	Do you do any moderate-intensity sports, fitness or recreational (leisure) activities that causes a small increase in breathing or heart rate such as brisk walking,(cycling, swimming, volleyball)for at least 10 minutes continuously? (SHOW THE LIST)	Yes 1 No 2 (If No, go to P 16)	P13
14	In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational (leisure) activities?	Number of days: _____	P14
15	How much time do you spend doing moderate-intensity sports, fitness or recreational (leisure) activities on a typical day?	Hours : _____ minutes: _____	P15 (a-b)
Sedentary behaviour			
The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent [sitting at a desk, sitting with friends, travelling in car, bus, train, reading, playing cards or watching television], but do not include time spent sleeping.			
16	How much time do you usually spend sitting or reclining on a typical day?	Hours : _____ minutes: _____	P16 (a-b)

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ONLINE FIRST | August 24, 2016 | https://doi.org/10.15605/jafes.031.02.11

CASE REPORT

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De La Chapelle Syndrome: A Rare Case of Male Infertility

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Abstract

A 25-year-old Indian male presented to Endocrine Outpatient Department of PGIMS Rohtak with chief complaints of inability to father a child in spite of 2 years of unprotected sexual intercourse. Patient had a normal male phenotype, however seminal fluid analysis was suggestive of azoospermia. Karyotyping chromosomal analysis showed 46,XX chromosomes. The frequency, etiology and diagnosis of this syndrome are reviewed here.

Key words: male phenotype, 46,XX chromosomes, azoospermia

INTRODUCTION

De La Chapelle, also known as XX Male syndrome is a rare cause of male infertility.[1] Testis Determining Factor (TDF), located on the short arm of the Y chromosome, is responsible for testicular development in males. Sertoli cells secrete Müllerian Inhibiting Factor which is responsible for the agenesis of Müllerian structures. That action, along with Leydig cells that secrete testosterone, ultimately lead to male internal genitalia development. The presence of the SRY gene on X chromosome is responsible for the male phenotype in the majority of XX males, but a few of these males do not bear this chromosome. The role of certain key genes that could be implicated in abnormal sexual differentiation is known, but the complexity and heterogeneous nature of this syndrome leaves many questions unanswered. The basis of therapy is testosterone supplementation at an early stage. The objective of the case report is to highlight the importance of karyotyping during the work up of infertility in males, if azoospermia is seen on semen analysis.

CASE

A 25-year-old Indian man, nonsmoker, occasional alcoholic beverage drinker, vegetarian by diet, married for the last 2 years, presented to Endocrine OPD with complaint of inability to father a child. He had history of bilateral mastectomy a year back for gynaecomastia (Figure 1a). There were no previous records available about the work up of gynaecomastia. According to the patient, he underwent mastectomy for cosmetic purposes after his marriage. He was born as a result of non-consanguineous marriage by full term normal vaginal delivery and cried immediately after birth. His developmental milestones were normal according to age. His height was 170 cm, weight 85 kg (BMI-29.4 kg/m^2) and arm span 173 cm. His facial, axillary and pubic hair were normal in density and distribution (Figures 1b, 1c). The stretched penile length was 7 cm and testicular volume was 3 ml each (Figure 2). Respiratory, CVS, CNS, and abdominal examinations were normal.

Ultrasonography and CT abdomen were normal and failed to find the uterus and adnexa. Azoospermia was reported on seminal fluid analysis. Serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) were at 10.16 and 13.69.7 mIU/ml respectively (normal 2–9.6 mIU/ml and 1.2–5.0 mIU/ml respectively). Serum testosterone concentration was 180.32 ng/dl (normal ranges are 270–1070 ng/dl), serum prolactin concentration was 6.32 ng/ml (normal ranges are 2.5–17 ng/ml). Karyotyping revealed a female pattern i.e., 46,XX (Figure 3). Fluorescent in situ hybridization (FISH) to determine presence of SRY gene on X chromosome of patient was planned but patient could not get it done due to financial constraints.

The authors committed to the Helsinki Convention at all stages of the investigation. An informed consent form was taken from the patient.

DISCUSSION

Infertility has traditionally been defined as the inability to conceive after 12 months of unprotected sexual intercourse. Infertility can be attributed primarily to male

eISSN 2308-118x
Printed in the Philippines

Received: March 13, 2016. Accepted: July 18, 2016.
https://doi.org/10.15605/jafes.031.02.11

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ONLINE FIRST | August 24, 2016 | https://doi.org/10.15605/jafes.031.02.11

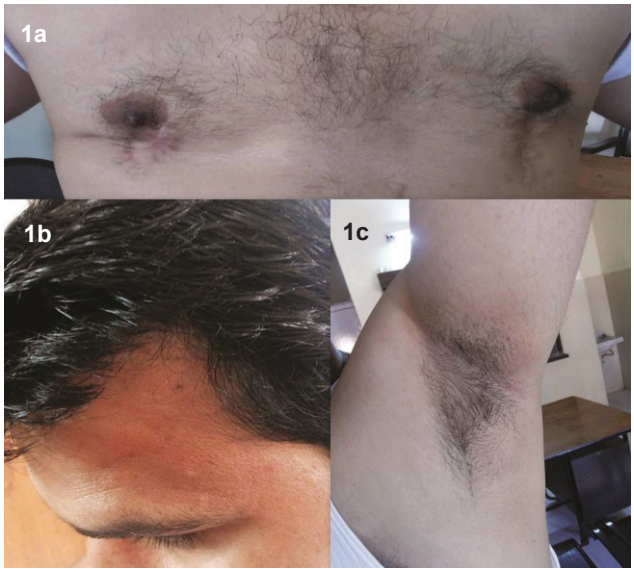

Figure 1. Patient characteristics.

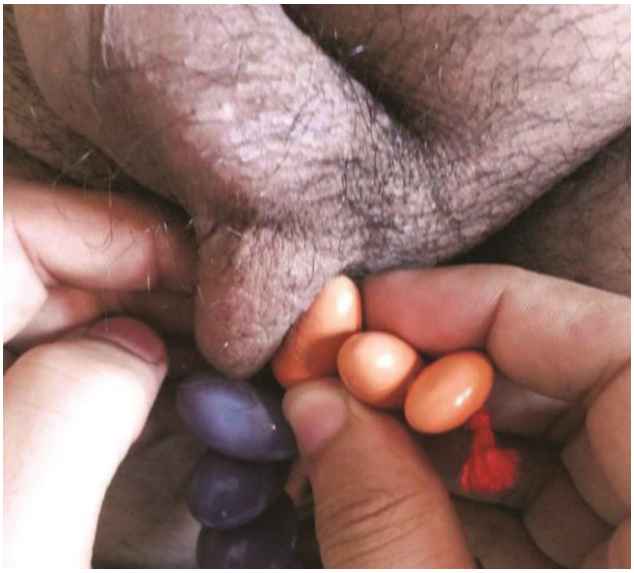

Figure 2. Stretched penile length and testicular volumes of patient.

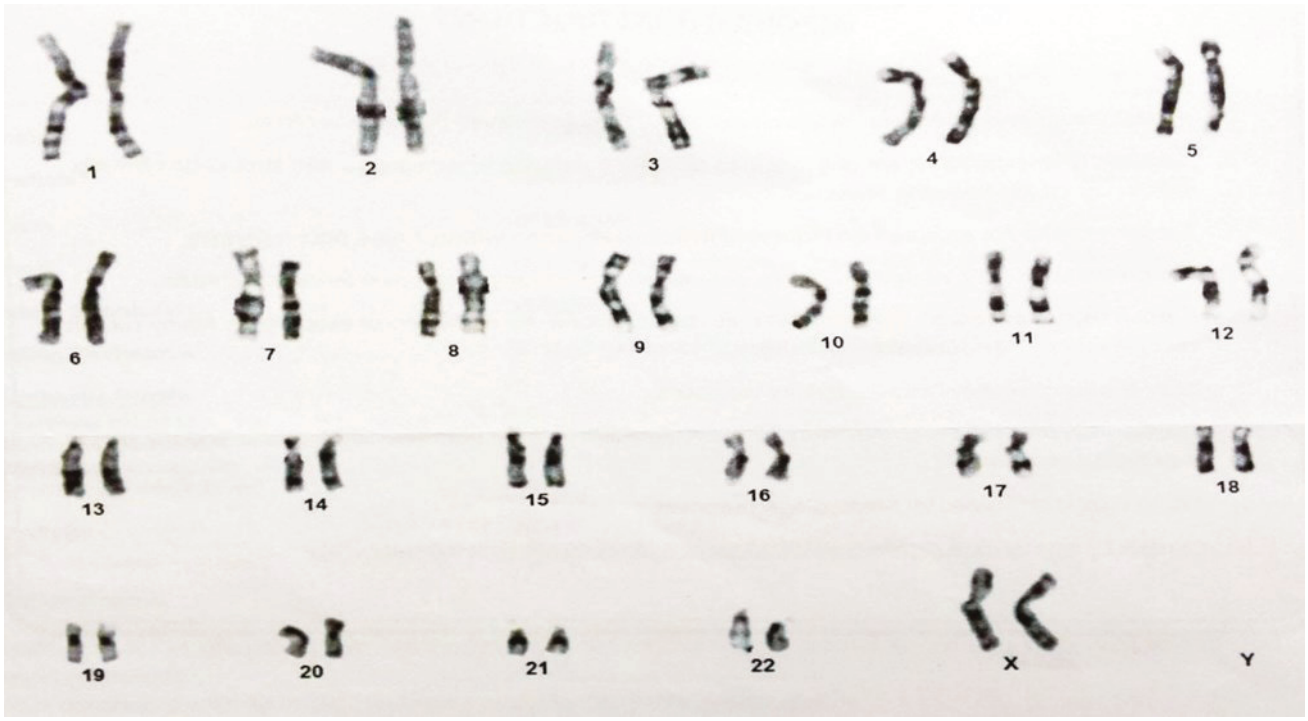

Figure 3. Karyotyping of patient.

factors in 25% of couples and female factors in 58% of couples and is unexplained in about 17% of couples. Out of 25% of male factor infertility, primary hypogonadism accounts for 30-40% of cases, secondary hypogonadism 2% of cases, sperm transport disorders 10-20% of cases and unknown in 20-50% of cases.

Male infertility can be classified as disorders of chromosomal sex development (most common being 47XXY; Klinefelter syndrome), 46,XY disorders of sex development which include disorders of testicular development or disorders of androgen synthesis/action, primary testicular disease (uncorrected cryptorchidism, cancer chemotherapy, trauma, infectious orchitis, torsion etc.), secondary hypogonadism or hypothalamo-pituitary disease, disorders of sperm transport and aging.

Human males with a 46,XX karyotype are infertile. The incidence in newborn males is around 1 in 20,000. This syndrome accounts for 2% of cases of male infertility. Most cases are sporadic.[1] According to a proposed revised nomenclature (the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology, 2006), the diagnosis of XX male or XX sex reversal is renamed as 46,XX testicular disorder of sex development.[2] Clinical presentation depends on the

ONLINE FIRST | August 24, 2016 | https://doi.org/10.15605/jafes.031.02.11

presence of the SRY gene. The majority are SRY positive cases, which present as normal men after puberty with normal pubic hair and penile size but with small testes, gynaecomastia and azoospermia-related sterility. The testes size of our patient was 3 ml which was in prepubertal range as per Tanners staging. Similar presentation was seen in our patient which probably makes our patient SRY positive.

SRY-negative cases present at birth with features such as hypospadias and cryptorchidism. All males with this phenotype genotype mismatch are azoospermic, due to the absence of long arm of Y chromosome containing Azoospermia Factor gene (AZF), which is responsible for normal spermatogenesis. Studies have suggested that Y chromosomal genes such as the AZF are not only crucial for spermatogenesis but also pivotal for the maintenance of normal somatic cell function.[3]

Majority of these patients have Y chromosomal material along with SRY gene which is responsible for normal testicular development. It has been suggested that an unequal Y-to-X interchange occurs during paternal meiosis,[4] which was corroborated by more recent studies.[5] Less common causes for XX males who are SRY negative include autosomal or X chromosome gene mutations, which are responsible for testicular determination in absence of TDF, and undetermined mosaicism in Y bearing cell line.[6-7]

Reports from a Mexican family having two siblings without genital ambiguity were found to be SRY negative, which was suggestive of the possibility that inherent loss of function mutation of the gene participating in sex determining cascade could result in normal male sexual differentiation in absence of normal SRY gene.[8] Although incomplete masculinization is a result of the absence of Y DNA, exceptions could occur. Another possible reason for the presence of male phenotype is the influence of X inactivation on a downstream gene on the X chromosome.[9] Lastly, it has been hypothesized that this phenotype genotype mismatch is due to a defect in X-linked or autosomal sex-determining gene.[10]

Although FISH, the gold standard to determine presence of the SRY gene on X chromosome, was not done, the male phenotype and presence of gynaecomastia, azoospermia, male infertility with chromosomal pattern of XX led us to our diagnosis of 46,XX testicular disorder of sex development. Differentials of this syndrome include Klinefelter syndrome and 46,XX ovotesticular DSD. Klinefelter syndrome was ruled out as Y chromosome was not identified. 46,XX ovotesticular DSD was unlikely because of characteristic findings and no evidence of Müllerian structures on ultrasonography and CT abdomen.

As most of the males develop normal male phenotype, they are raised as males. Those who fail to develop adequate secondary sexual characteristics are given testosterone replacement which improves libido and overall sexual activity, increases energy, lean muscle mass and bone density and decreases fat mass. Patients remain infertile and the only option available is by obtaining donor sperm and subsequent IUI or child adoption.

After the disclosure of the diagnosis, our patient went into denial and was not ready to accept the diagnosis. With counseling, he eventually came to terms with the fact that he cannot father a child. So, infertility being a stressful event for the couple seeking treatment, psychosocial counselling is helpful for them.

The aim of reviewing the current literature is to highlight the value of karyotyping in all males with congenital azoospermia or severe oligospermia who present for evaluation of infertility, since the male phenotype does not always guarantee the presence of Y sequence in the genome.

CONCLUSION

We conclude that owing to the rarity of this syndrome, it is easy to miss it in the differential diagnosis of phenotypically normal males with complete azoospermia. Without proper karyotyping, these patients would be subjected to financial and psychological constraints of unwanted invasive procedures. Once diagnosed, long term androgen therapy and counseling with a cooperative interdisciplinary approach would be required.

Ethical Consideration
Patient consent form has been procured prior to the case report study.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
None.

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ONLINE FIRST | August 25, 2016 | https://doi.org/10.15605/jafes.031.02.12

CASE REPORT

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Turner Syndrome with Pseudohypoparathyroidism: A Case Report

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Abstract

The association of Pseudohypoparathyroidism (PHP) with Turner syndrome is very rare and only a single case has been reported so far. Both manifest with short stature and lack of secondary sexual characteristics along with other stigmata similar to each other, creating a diagnostic dilemma.

We describe a case of a 15-year-old Asian Indian female who presented with short stature and delayed puberty with overlapping phenotype of PHP and Turner syndrome. The diagnosis of Turner syndrome was made easily on the basis of typical history, clinical features and karyotype but the diagnosis of PHP was suspected only after radiological and biochemical investigations. The association of Turner syndrome with PHP can be easily missed due to similar phenotypes and subtle manifestations.

Key words: pseudohypoparathyroidism, Turner syndrome, Albright's hereditary osteodystrophy

INTRODUCTION

Pseudohypoparathyroidism (PHP) is a rare heterogeneous disorder. It is divided into Type 1 PHP, Type 2 PHP and pseudo-pseudohypoparathyroidism on the basis of presenting signs and investigations. Type 1 PHP presents with elevated PTH in the presence of hypocalcemia, hyperphosphatemia along with blunted phosphaturic and cAMP response to exogenous PTH infusion.[1] Type 1 PHP is further subdivided into subcategories PHP 1a, 1b and 1c. Types PHP 1a and 1c both have associated features of Albright's Hereditary Osteodystrophy (AHO) characterized by heterogeneous clinical findings such as brachydactyly, rounded face, short stature, central obesity, subcutaneous ossifications and variable degrees of mental retardation.[2,3] Type PHP 1b can be easily differentiated clinically from PHP 1a and 1c by the absence of AHO in the former subtype. Patients with PHP 1a and 1c also have resistance to other hormones acting through G protein coupled receptors like TSH, GHRH and gonadotropins. Differentiation between PHP 1a and PHP 1c requires genetic analysis of erythrocyte Gsα activity which is reduced in PHP 1a while it is normal in PHP 1c.[1] Type 2 PHP is characterized by resistance to PTH in the absence of AHO along with resistance to other hormones, while pseudo-PHP is characterized by the presence of AHO and the absence of any hormone resistance.[1]

Turner syndrome is characterized by the absence of the complete or a part of a normal sex chromosome in females and associated features including congenital lymphedema, short stature and gonadal dysgenesis.[4] Approximately half of the patients with Turner syndrome have monosomy X while the rest have other abnormalities.[4]

Since both these disorders usually present with short stature and delayed puberty, the diagnosis and management can be challenging if both disorders are present in the same patient. We describe a case of an Asian Indian female who presented with short stature and delayed puberty along with other physical features suggestive of overlapping of PHP and Turner's syndrome.

CASE

A 15-year-old Asian Indian girl presented in the Endocrinology outpatient department with chief complaints of short stature and delayed puberty. She also complained of small 3rd, 4th, 5th toes and fingers. She was born of a non-consanguineous marriage with full term normal vaginal delivery. She attained all developmental and social milestones at the same age as her peers. At the age of 8 years, her parents noticed growth retardation along with abnormality in the shape of her toes and fingers. There was no significant history of repeated childhood hospitalizations, seizures, obesity, mental sub-normality, head trauma, abnormal calcifications or edema of extremities, delayed dentition and enamel hypoplasia.

Clinical evaluation revealed a round small face, brachydactyly (shortening of 3rd, 4th, 5th fingers and toes)

eISSN 2308-118x
Printed in the Philippines

Received: March 17, 2016. Accepted: May 23, 2016.
https://doi.org/10.15605/jafes.031.02.12

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ONLINE FIRST | August 25, 2016 | https://doi.org/10.15605/jafes.031.02.12

Figure 1. Round face with typical AHO facies with short stature seen in the elder sister (right) suffering from pseudohypoparathyroidism with Turner syndrome looking shorter than 12 years. On the left is her younger sister.

[Figure 2a,b] and cubitus valgus. Anthropometry showed proportionate short stature (Figure 1) with a height of 127 cm (<3rd percentile, Standard deviation score: -4.44, mean parental height: 156 cm), arm span of 120 cm while her upper segment: lower segment ratio was 1.01. Her body mass index (BMI) was 14.17 kg/m^2. Her Tanner's staging was pre-pubertal with no axillary and pubic hair and no evidence of thelarche. Her blood pressure was normal in all four limbs. There was no evidence of any subcutaneous ossification. Her thyroid gland was not palpable. Her systemic examination was unremarkable.

Biochemical evaluation revealed microcytic hypochromic anemia, hypocalcemia and hyperphosphatemia (Table 1). The hormonal investigations were done through chemiluminescence immunoassay by Abbott ARCHITECT i1000sr immunoassay analyzer USA using fasting plasma sample which revealed elevated parathormone level, autoimmune hypothyroidism, hypergonadotropic hypogonadism along with raised prolactin (Table 2). Roentgenographical assessment revealed bilateral short 3rd, 4th and 5th metacarpals and metatarsals with positive Archibald sign [Figure 3a,b] while the rest of the skeletal survey was normal. Ultrasonography of the abdomen showed streak ovaries along with pre-pubertal uterus. Her karyotype showing 45 (X,O) confirmed the diagnosis of Turner syndrome. Electrocardiography, 2D echocardiography and pure tone audiometry were unremarkable while thyroid ultrasonography revealed hypo-echogenicity of the thyroid gland.

On the basis of clinical history, examination and investigations, the diagnosis of Turner syndrome along

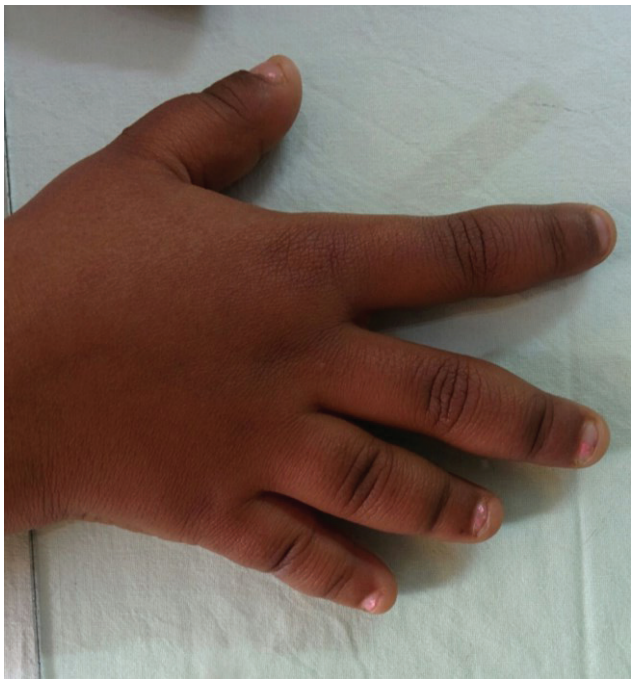

Figure 2a. Right hand showing brachydactyly.

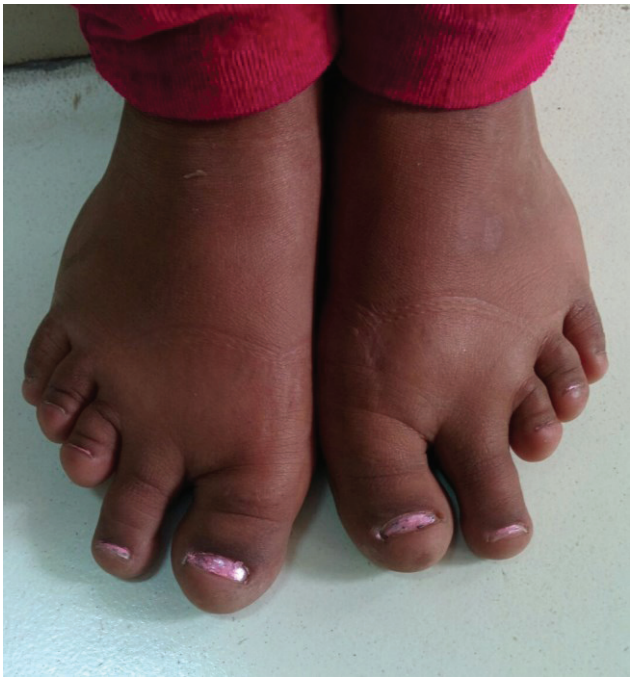

Figure 2b. Showing shortening of 3rd, 4th & 5th toes bilaterally.

ONLINE FIRST | August 25, 2016 | https://doi.org/10.15605/jafes.031.02.12

with PHP with autoimmune hypothyroidism and nutritional deficiency anemia was made. The patient was started on treatment with thyroxine replacement, calcium, estradiol, haematinics and 1,25(OH)$_2$ vitamin D and follow up advice after 2 months.

After 2 months of therapy, the patient showed significant clinical and biochemical improvement. On follow up visit after 2 month, her hemoglobin was 11.2 gm/dl. Her thyroid functions were improved with TSH 6.4329 μIU/m and T_4 5.85 μg/dl along with normalization of serum prolactin (S. Prolactin: 5.5 ng/ml). The patient became normocalcemic and normophosphatemic with serum calcium 9.2 mg/dl and serum phosphorus 6.47 mg/dl and her parathormone level was 74.2 pg/ml.

Table 1. Hematological and biochemical profile

S. No.	Parameter	Observed Value	Reference Range
1	Hemoglobin	8.2 gm/dl	12-15.8 gm/dl
2	MCV	85 f/L	79-93.3 f/L
3	MCH	25.9 pgm	26.7-31.9 pgm
4	MCHC	28.2%	32.3%-35.9%
5.	TLC	9800/cumm	4000-11000/cumm
6.	DLC	$P_{560}L_{42}E_{02}$	$P_{40-70}L_{20-50}E_{0-6}$
7.	Platelet count	2.0 lac	1.65-4.15 lac
8.	ESR	22 mm Isthr	0-20 mm Isthr
9.	Blood Urea	27 mg/dl	30-40 mg/dl
10.	S. Creatinine	0.88 mg/dl	0.5-0.9 mg/dl
11.	S. Bilirubin	0.6 mg/dl	0.37-1.3 mg/dl
12.	SGOT	24 IU/L	12-38 IU/L
13.	SGPT	12 IU/L	7-41 IU/L
14.	S. Sodium	139 mEq/L	136-146 mEq/L
15.	S. Potassium	4.07 mEq/L	3.5 -5.0 mEq/L
16.	S. Phosphorus	12 mg/dl	2.5-4.3 mg/dl
17.	S. Calcium	7.9 mg/dl	8.7-10.2 mg/dl
18.	ALP	367 IU/L	44-147 IU/L
19.	Total protein	8.17 gm/dl	6.7-8.6 gm/dl
20.	Albumin	4.6 gm/dl	3.5-5.5 gm/dl
21.	Globulin	3.57gm/dl	2.0—3.5 gm/dl

Table 2. Hormonal and serological profile

S. No.	Parameter	Baseline value	Reference range
1	TSH	520.0000 μIU/ml	0.5-4.3 μIU/ml
2	T4	<1.00μg/dl	4.7-10.4 μg/dl,
3	Anti TPO	1300 IU/ml	<35 IU/ml
4	FSH	40.89 IU/L	3.0-20.0 IU/L
5	LH	34 IU/L	2.0-15.0 IU/L
6	Prolactin	102.8 ng/ml	3.6-12 ng/ml
7	Estradiol	2.0 pg/ ml	<20-145 pg/ml
8	Cortisol	9.5 μg/dl	2-17 μg/dl,
9	iPTH	185.1 pg/ml	8-51 pg/ml
10	25 (OH) vit.D	44.75 ng/ml	30-100ng/ml

DISCUSSION

PHP is a heterogeneous disorder with a variety of manifestations. The prevalence of the disorder is about 0.79 per 100,000.[1] It was the first hormone resistance syndrome ever described. The first description of pseudohypoparathyroidism with Albright hereditary osteodystrophy was made in 1942 by Fuller Albright.[5] In his original work, Albright described a person with hypocalcemia and hyperphosphatemia with normal renal function who had no calcemic and phosphaturic response to bovine parathyroid extract as compared to hypoparathyroid patients, hence the concept of hormone resistance came into being.[5] Later on, with the discovery of the PTH receptor and its mechanism of action, the basic pathophysiology of the disorder was described and the syndrome was further subdivided into various types.[1] The primary pathological mechanism was described as a GNAS mutation which leads to defective activity of $G_{s\alpha}$ (stimulatory subunit of G protein coupled receptors).[1] PHP has various manifestations due to the involvement of maternal imprinting of the genes.[1] PHP 1a is characterized by parathormone resistance (elevated PTH in spite of hypocalcemia and hyperphosphatemia; poor cAMP and phosphaturic response to exogenous PTH administration) along with features of Albright's hereditary osteodystrophy (AHO), characterized by brachydactyly, rounded face, short stature, central obesity, subcutaneous calcifications in conjunction with variable mental retardation.[1] Together with variable PTH resistance, resistance to other hormones operating through G protein

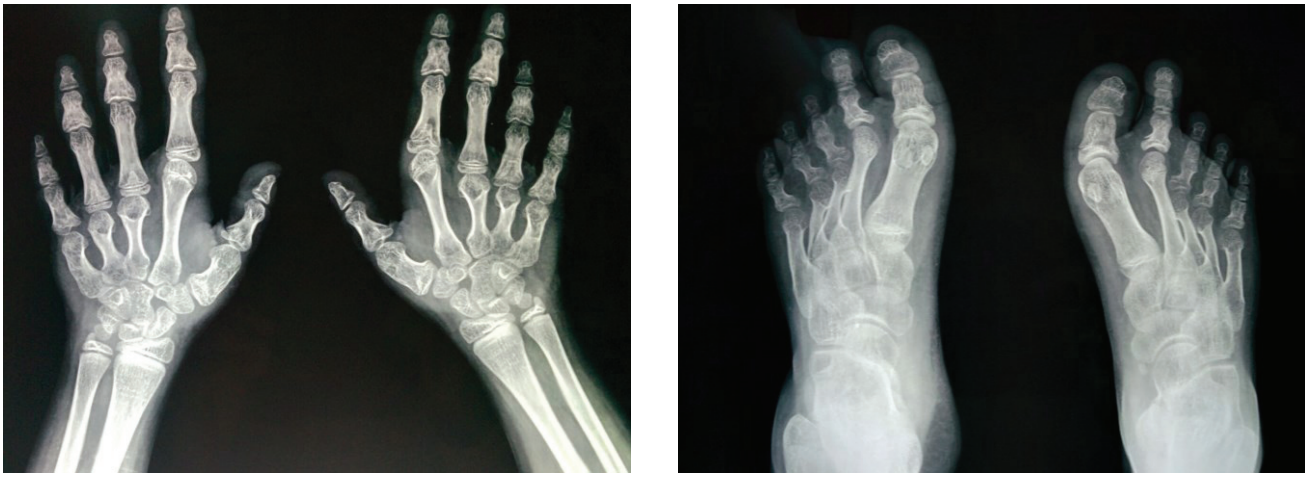

Figure 3a. X-ray both hands and feet showing short 3rd, 4th and 5th metacarpals; **3b.** Metatarsals in both limbs with positive Archibald sign.

ONLINE FIRST | August 25, 2016 | https://doi.org/10.15605/jafes.031.02.12

coupled receptors can also be present in PHP.[1] The patient in the present case had short stature, a round face, brachydactyly [Figures 1 and 2a,b] and elevated PTH in spite of hypocalcemia and hyperphosphatemia (Table 1). Along with these features, the patient also had delayed puberty and no development of secondary sexual characteristics due to hypergonadotropic hypogonadism. Her skeletal survey showed specific changes associated with AHO such as short 3rd, 4th and 5th metacarpals with short distal phalange of her thumb but the absence of heterotropic calcification.

Turner syndrome is characterized by a combination of typical physical features in phenotypic females and a complete or partial absence of the second sex chromosome, with or without cell line mosaicism.[6] Short stature is the most common physical finding in the patient with Turner syndrome and is caused by haplo-insufficiency of the SHOX gene.[7] Other physical features of Turner syndrome are short fourth metacarpal, shield chest, cubitus valgus, high arched narrow palate, epicanthal folds, genu valgum, etc. Together with these features, patients with Turner syndrome are prone to develop hypertension, diabetes mellitus, coarctation of the aorta, aortic dissection, inflammatory bowel disease, hypothyroidism and many autoimmune diseases.[6,7] Our patient presented with short stature, delayed puberty, cubitus valgus and brachydactyly. On investigation, she was found to have hypergonadotropic hypogonadism and autoimmune hypothyroidism. Her karyotype revealed X chromosome haplo-insufficiency.

So far in medical literature, only one case of pseudohypoparathyroidism 1a with Turner syndrome has been described.[8] Another case of pseudo-pseudohypoparathyroidism with Turner syndrome and one case with pseudohypohyperparathyroidism have been reported.[9,10] The only case of pseudohypoparathyroidism with Hashimoto's thyroiditis with Turner syndrome was described by Wen Heng-Zeng et al., in 2014 in which they described the case of a 16-year-old female presenting with short stature. On examination, round chubby face, short neck, short stature and obesity were observed. Biochemical investigations revealed elevated parathormone, thyroid stimulating hormone (TSH), prolactin, follicle stimulating hormone (FSH), antithyroid peroxidase antibody and anti-thyroglobulin antibody levels. The radiological examination showed delayed bone age, immature uterus along with shortening of metacarpals and metatarsals of the 3rd, 4th and 5th digits. Karyotyping revealed 46, X, i (Xq10), while molecular analysis unmasked a silent codon change in exon 5 of *GNAS* (ATC → ATT, Ile).[8]

In our case, the patient had similar finding on clinical examination except for obesity and heterotrophic subcutaneous calcifications. Biochemical findings were also similar except the patient had microcytic hypochromic anemia. Radiological findings of our case completely correlate with the findings described by Wen Heng-Zeng. Karyotype of our patient showed complete absence of one X chromosome [45,XO].

In our patient, the presence of hypocalcemia, hyperphosphatemia, elevated PTH level along with the normal renal functions and 25(OH) vitamin D levels clearly point towards PHP as the differential diagnosis. Presence of the AHO phenotype points towards the possibility of PHP 1a, 1c and pseudo-pseudohypoparathyroidism. The presence of AHO along with biochemical abnormalities, presence of renal PTH resistance leaves no other differential diagnosis except PHP 1a and 1c.[1] The Gs_{α} activity analysis further differentiates between PHP 1a and PHP 1c but in the present case, genetic analysis and response to exogenous parathormone could not be done due to financial constraints and lack of available facilities. In the view of clinical history, examination, biochemical, radiological and karyotypic findings, the diagnosis of Turner syndrome with PHP with autoimmune hypothyroidism and microcytic hypochromic anemia was made. The patient was started with calcium, calcitriol, haematinics, thyroxine and estradiol with follow up advice after 2 months. After 2 months of starting therapy, the patient improved clinically and biochemically.

CONCLUSION

The association of PHP and Turner syndrome is rare. Several heterogeneous and overlapping features like short stature, delayed puberty, hypothyroidism and shortening of metacarpals can lead to a diagnostic dilemma. If unusual features in phenotype like absence of typical facies, shortening of 3rd, 4th and 5th metacarpals and metatarsals etc., then phenotypic features of PHP should be looked for and confirmed biochemically. A thorough clinical history and examination along with judicious use of diagnostic tests can make the diagnosis quite straight forward.

Ethical Consideration

Patient consent form has been procured prior to the case report study.

Statement of Authorship

All authors have given approval to the final version submitted.

Author Disclosure

All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source

All expenditures were done by the Department of Endocrinology and Human Metabolism, L.L.R.M. Medical College, Meerut, Uttar Pradesh, India and no external funding organization was involved.

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ONLINE FIRST | August 25, 2016 | https://doi.org/10.15605/jafes.031.02.13

JAFES

CASE REPORT

Managing Periodontitis in Type 1 Diabetic Patients Improves Glycemic Control: A Case Report

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Abstract

This case report describes the long-term follow-up of a 22-year-old, female patient with type 1 diabetes managed by conservative oral care and glycemic control measures. She is on a twice a day insulin regimen. Tooth numbers 13 and 37 had pockets less than 6 mm while all remaining teeth had greater than 6 mm. Periodontal management consisted of root planing combined with instructions on diabetes self-management skills at home. Nine weeks after the first sextant was treated, Pocket depth measurements in 93 (81.6%) out of 114 sites and bleeding on probing (BOP) scores in 11 (57.9%) out of 19 teeth decreased. There was a 50% reduction in the C reactive Protein and a 46.7% decrease in the fructosamine assay levels. Initial glycohemoglobin level of 8.3% decreased substantially to 7.1%. The goal of the dentist is no longer just the improvement of oral health but ultimately the overall health of the patient and the physician's goal is to include oral health in the promotion of overall health.

Key words: diabetes, periodontitis, glycated hemoglobin assay, diabetes camp, Diabetes Self-Management Education

INTRODUCTION

Glycemic control is at the core of diabetes management. The Diabetes Control and Complications Trial Research Group has shown that strict blood sugar control can reduce the risk of long-term complications.[1] The clinical practice recommendations of the American Diabetes Association for the standards of medical care in diabetes suggest that the glycated hemoglobin (HbA1c) goal for patients in general is <7%, but <6% is preferred if this can be accomplished without significant hypoglycemia.[2] Even if most patients are unsuccessful in bringing their blood sugar levels to near normal values, a 1% reduction in HbA1c level is associated with a relative risk reduction of 21% for any diabetes-related endpoint, 21% for diabetes-related deaths, 14% for myocardial infarction and 37% for microvascular complications.[3] Because of these findings, great emphasis is placed on controlling blood sugar levels.

Treatment of periodontal disease has been shown to improve glycemic control in diabetic patients. A meta-analysis on the effect of periodontal therapy on glycemic control showed a mean 0.4% reduction in HbA1c in diabetic patients.[4] Data from this meta-analysis mostly came from studies involving patients with type 2 diabetes. Several studies on type 1 diabetics reported significant improvement in periodontal health but not in HbA1c levels after periodontal therapy.[5-7] One group, however, found no significant changes even in patients with the best response to periodontal treatment. Interestingly, Williams and Mahan, long ago reported reductions in insulin requirements following periodontal therapy and tooth extraction in seven of nine patients, with eight of the nine patients having type 1 diabetes.[9] Miller and colleagues, studying a group of nine poorly controlled type 1 diabetics with moderate-to-severe periodontitis, reported a decrease in mean HbA1c level from 8.7 percent pre-treatment to 7.8 percent post-treatment.[10]

Periodontitis is an inflammatory disease initiated by infection. It clinically appears as gingival bleeding and swelling, with an increase in pocket probing depths (PPD). The success of periodontal treatment is usually gauged by the return of tissues to normal appearance and characteristics, e.g., decreased bleeding and reduction in PPD. Recently however, local inflammation observed in periodontal tissues was shown to have a systemic dimension following findings that plasma C-reactive protein (CRP) levels are elevated in patients with periodontitis.[11-13] CRP is generally regarded as a valuable biomarker of systemic inflammation and cardiovascular disease. Periodontal treatment in type 2 diabetics has shown a weighted mean difference of reductions in CRP after therapy of 0.50 mg/L.[14] More important, CRP is found to be elevated in patients with type 1 diabetes of long duration.[15] The purpose of the current report is to describe the long-term follow-up of a young adult patient with type 1 diabetes managed by intensive oral care and glycemic control measures.

eISSN 2308-118x
Printed in the Philippines

Received: April 20, 2016. Accepted: May 23, 2016.
https://doi.org/10.15605/jafes.031.02.13

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ONLINE FIRST | August 25, 2016 | https://doi.org/10.15605/jafes.031.02.13

Clinical Relevance

Scientific rationale for study

Intensive insulin therapy improves metabolic control in diabetic patients, but does not result in improved clinical periodontal status. Periodontal intervention in type 1 diabetics improves periodontal parameters but not glycosylated hemoglobin levels.

Principal finding

The use of both periodontal intervention and motivation to reinforce diabetes self-management skills resulted in: 46.7% decrease in the fructosamine levels, a net decrease of 1.2% in glycated hemoglobin levels, and a 50% reduction in the C reactive Protein levels

Practical implications

Integrating dental care in the comprehensive management of diabetes promotes better glycemic control and compliance among type 1 diabetic patients.

CASE

The patient is a female diagnosed with type 1 diabetes at age 7. She was first examined on March 3, 2012. She injects insulin twice a day, using a combination of isophane and regular insulin. She frequently has to adjust her dose as she experiences hypoglycemia in the morning frequently. The patient owns a glucose meter, but seldom monitored her blood sugar due to the high cost of glucose strips. She went to a dental facility when newly diagnosed, but was apparently turned away because the dentist felt inadequate to treat pediatric diabetic patients. She has not returned for dental care until her visit to this clinic. Scaling and polishing was performed in 3 visits to remove supragingival calcular deposits. Oral hygiene instructions were given and photographs of her teeth were taken (Figure 1). The patient did not return to continue treatment due to lack of money for transportation expenses (Figure 2).

Definitive Treatment

When the patient returned on September 25, 2013, pocket probing depth (PPD) was measured and recorded (Table 1). The PPD is measured in six sites around the tooth, using a periodontal probe with calibrated marking to indicate depth in millimeters (Figure 3). PPD is the distance between the marginal gingiva and the bottom of the gingival sulcus. A pocket probing depth of 4 mm and above is indicative of the presence of periodontitis. Bleeding on probing (BOP) is indicative of the degree of inflammation that is present. A tooth was given a BOP score of: 0 when no bleeding was observed, 1 when a dot of blood appeared on the gingival margin following probing, 2 when a line of blood appeared, and 3 when blood overflowed from the gingival margin (Figure 3). Tooth Mobility is indicative of the amount of alveolar bone loss around the tooth. Mobility was given a score of: 0 when no mobility was detected, 1 when there was less than a millimeter (mm) of mobility detected, 2 when there was a >1 mm mobility detected (Table 1). Caries or tooth decay was found on the following teeth: 15, 26, 27, 36, 46, and 47. Tooth numbers 18 and 28 were impacted. Tooth numbers 13 and 37 had periodontal pockets less than 6 mm while all remaining teeth had pockets greater than 6 mm (Table 1). Except for tooth numbers 47, 46, 36, and 37, all the other teeth had 50% or less remaining bone support based on the panoramic x-ray (Figure 4).

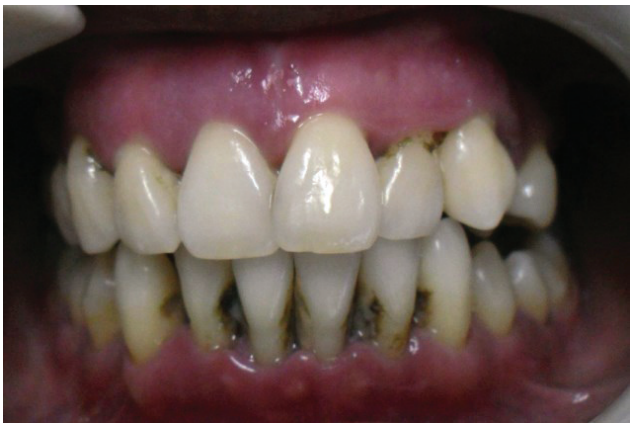

Figure 1. Patient's initial appearance, March 3, 2012.

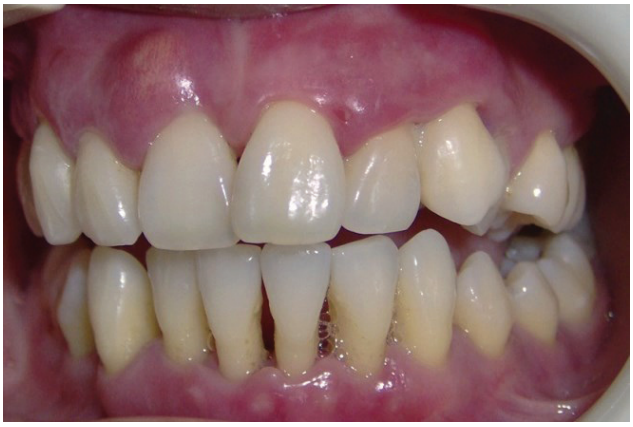

Figure 2. After 3 rounds of scaling.

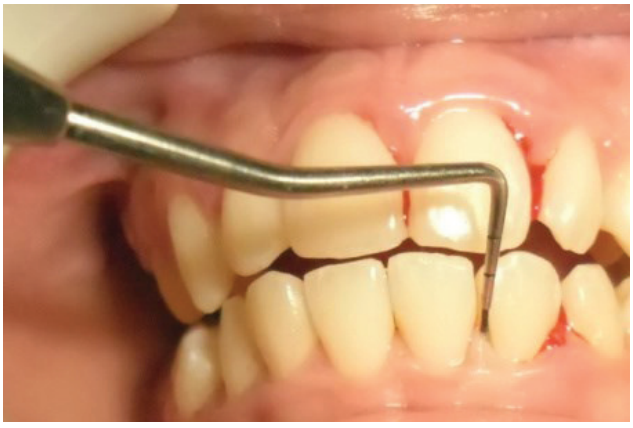

Figure 3. Example of recording pocket probing depth and bleeding on probing.

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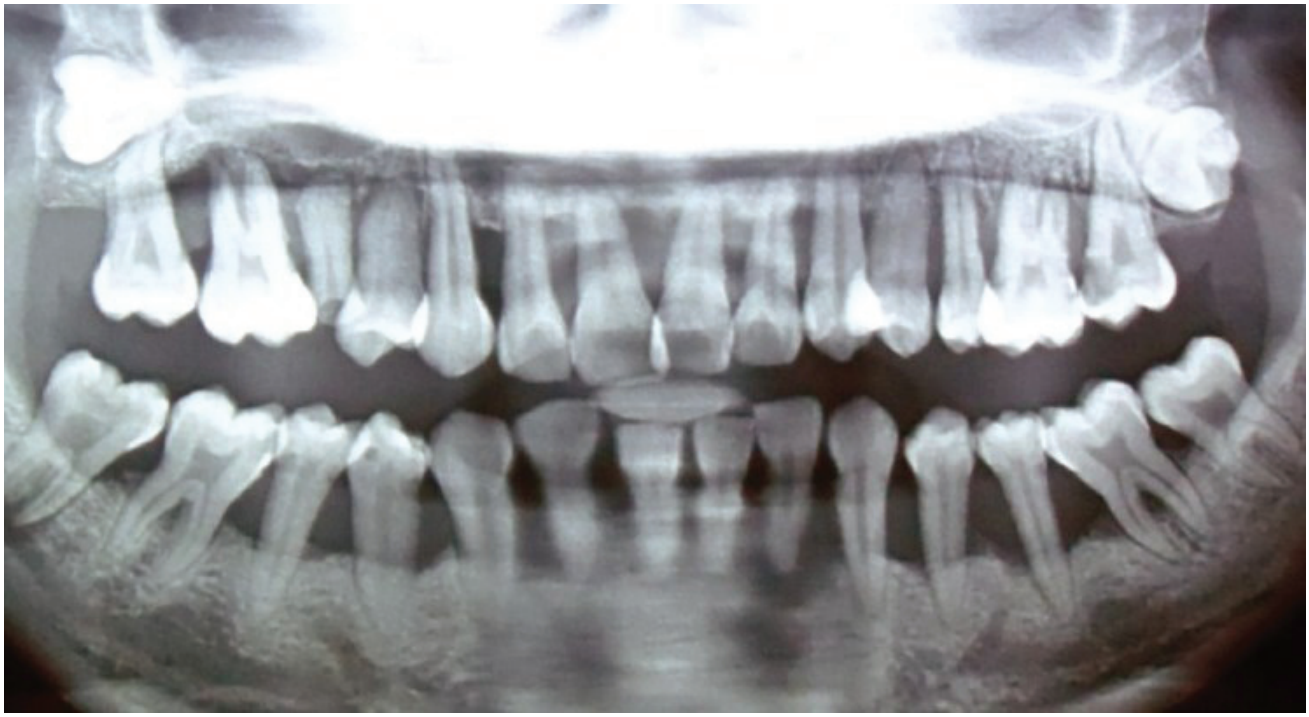

Figure 4. Patient's panoramic radiograph September 25, 2013.

Table 1. Patient's initial periodontal status September 25, 2013

Furcation Involvement	+			+			-			-			-			-			-												
Mobility	2			2			2			2			0			1			2												
Bleeding on Probing	2			2			2			2			2			2			2												
Pocket Probing Depth	5	5	6	5	5	8	6	6	6	7	1	6	4	1	5	4	1	6	7	1	8										
	4	6	6	5	6	6	8	6	6	9	4	6	5	3	4	4	4	6	8	7	9										
Tooth no.	2nd Molar			1st Molar			2nd Premolar			1st Premolar			Cuspid			Lateral Incisor			Central Incisor												
RIGHT MAXILLARY TEETH																															
RIGHT MANDIBULAR TEETH																															
Tooth no.	2nd Molar			1st Molar			2nd Premolar			1st Premolar			Cuspid			Lateral Incisor			Central Incisor												
Pocket Probing Depth	4	2	4	4	4	6	4	6	6	5	6	7	4	2	6	6	2	6	5	5	5										
	4	8	5	5	2	4	5	3	6	6	1	5	2	2	7	6	5	6	5	5	6										
Bleeding on Probing	0			3			3			2			2			3			2												
Mobility	0			1			2			2			2			2			2												
Furcation involvement	-			+			-			-			-			-			-												

MIDLINE

Furcation Involvement	-			-			-			-			+			-														
Mobility	2			2			2			2			2			0														
Bleeding on Probing	2			3			3			3			3			3														
Pocket Probing Depth	8	1	9	6	2	6	9	9	6	8	5	8	6	1	9	3	5	7	5	5	6										
	8	7	9	8	8	8	8	6	6	6	6	8	8	8	7	7	6	6	5	2	3										
Tooth no.	Central Incisor			Lateral Incisor			Cuspid			1st Premolar			2nd Premolar			1st Molar			2nd Molar												
LEFT MAXILLARY TEETH																															
LEFT MANDIBULAR TEETH																															
Tooth no.	Central Incisor			Lateral Incisor			Cuspid			1st Premolar			2nd Premolar			1st Molar			2nd Molar												
Pocket Probing Depth	5	5	6	6	9	6	4	6	9	7	4	5	6	6	6	5	6	5	4	2	4										
	5	2	5	7	4	6	6	2	7	6	2	6	6	2	6	6	2	3	3	2	2										
Bleeding on Probing	2			3			2			2			2			2			3												
Mobility	2			2			2			2			2			2			0												
Furcation involvement	-			-			-			-			-			+			-												

Table 2. Laboratory results

	Ref Value	26-Sep-13	5-Nov-13	29-Nov-13	27-Dec-13
HbA1c	<5.7%	8.30%			7.10%
Fructosamine test	<285 µmol/L	336.11 umol/L	238.65 umol/L	209.00 umol/L	
High Sensitive C Reactive Protein	0.00-0.5 mg/dl	0.56 mg/dL		0.28 mg/dL	

The patient is 151 cm tall and weighs 43.1 kg, with a body mass index of 19 kg/cm^2. The following laboratory tests were performed over the course of treatment (see Table 2): glycated hemoglobin assay (HbA1c), fructosamine test, and high sensitive CRP. HbA1c reflects the mean blood glucose concentration over the preceding 1–3 months and has been found in studies to correlate well with the development of diabetes complications.[16] The fructosamine test is a measure of glycated albumin. It reflects glycemic control over a 2-3 week period. It can be helpful in evaluating the effects of periodontal therapy on glycemic control.[17] Evidence from cross-sectional studies have shown that plasma CRP is elevated in periodontitis compared with controls and there is modest evidence on the effect of periodontal therapy in lowering the levels of CRP.[14]

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Table 3. Periodontal status after root planing

	Prior to Root Planing	6 weeks after Root Planing
Number of erupted teeth	28	19
Teeth with BOP = 0 (n=19)	0 (0%)	9 (47.4%)
Teeth with BOP = 1 (n=19)	0 (0%)	1 (5.3%)
Teeth with BOP = 2 (n=19)	11 (57.9%)	7 (36.8%)
Teeth with BOP = 3 (n=19)	8 (42.1%)	2 (10.5%)
Teeth with BOP that remained the same after therapy (n=19)		7 (36.8%)
Teeth with decreased BOP after therapy (n=19)		11 (57.9%)
Teeth with increased BOP after therapy (n=19)		1 (5.3%)
Sites with <4mm PPD (n=114)	22 (19.3%)	80 (70.2%)
Sites with 4-6 mm PPD (n=114)	62 (54.4%)	34 (29.8%)
Sites with >6 mm PPD (n=114)	30 (26.3%)	0 (0%)
Sites with PPD that remained the same (n=114)		12 (10.5%)
Sites with PPD that decreased in depth (n=114)		93 (81.6%)
Sites with PPD that increased in depth (n=114)		9 (7.9%)

Box 1. Diabetes Self-Management Education topics learned in camp reiterated

1. Oral Health and Diabetes
   a. Oral hygiene practices
   b. Caries and periodontitis.
   c. Oral–systemic health connection
2. Medical nutrition therapy
   a. Carbohydrate counting
   b. Food exchange
   c. Reading nutritional facts
3. Blood glucose monitoring
   a. Proper use of the meter and strips
   b. Interpreting results in relation to food intake and activity
   c. Hyperglycemia, hypoglycemia and diabetes ketoacidosis
4. Insulin
   a. Carbohydrate counting
   b. Dose and duration of action
   c. Rescue dose
5. Exercise
   a. Adjusting food intake and insulin prior to activity
   b. Proper hydration
   c. Emergency procedures in case of hypoglycemia
6. Diabetes complications

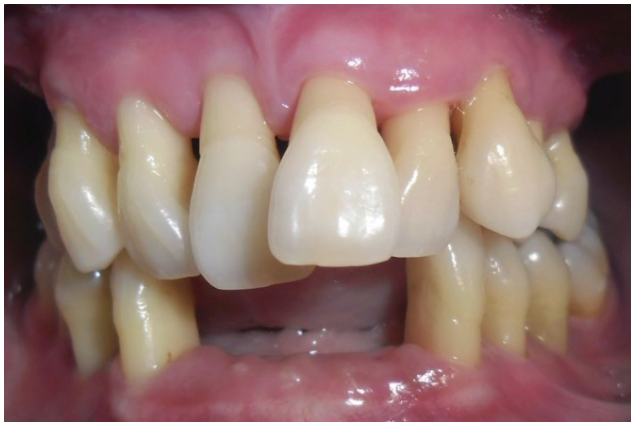

Figure 5. Marked resolution of inflammation with marked gingival recession.

The patient was provided with insulin and glucose strips for blood glucose home monitoring up to November. The patient was also provided with a toothbrush, triclosan/ copolymer toothpaste, dental floss, an interdental toothbrush, 0.12% chlorhexidine gluconate mouthwash (up to 6 weeks post-root planing) and a 0.075 cetylpridinium chloride mouthwash (after 6 weeks post-root planing). Oral hygiene instructions were again given. The teeth were then divided into sextants and treatment (scaling and root planing) was performed beginning with the anterior teeth. The following teeth were extracted: 16, 15, 26, 27, 32, 31, 41, 42 and 47. During the course of treatment, the patient was given repeat instructions on oral hygiene and diabetes (see Box 1).

The patient was also asked to keep a food diary, a record of daily blood glucose readings and insulin doses. Additionally, the patient was provided with transportation money and a small allowance.

Overall, the patient's oral health significantly improved following treatment (Figure 5). Of the patients 28 erupted teeth, 9 (32%) were extracted due to severe mobility, furcation involvement, or pulpal involvement. The patient was unwilling and lacked the resources to return for endodontic treatment. The remaining 19 teeth showed a decrease in PPD measurements [93 (82%) out of 114 sites] and BOP scores [11 (58%) out of 19] (Table 3). Significantly, there was a 50% reduction in the High Sensitive C reactive Protein levels and a 46.7% decrease in the fructosamine assay levels. Initial glycohemoglobin level of 8.3% decreased substantially to 7.1 % (Table 2).

DISCUSSION

The Institute of Medicine recommends that all health professionals should be educated to deliver patient-centered care as members of an interdisciplinary team, emphasizing evidence-based practice, quality improvement approaches, and informatics.[18] As early as the beginning of the nineteenth century, the call for the integration of medicine and dentistry can be found in the Flexner[19] and Gies[20] Reports. Scientific and technological advances in molecular biology, immunology, and genetics, along with an aging population with more complex health needs, has increasingly linked dentistry and medicine, i.e., the knowledge and skills physicians need related to clinical dentistry and the knowledge and skills dentists need related to clinical medicine are progressively overlapping.[21] Management of oral problems in children with diabetes affords one of the best examples of interprofessional collaboration. The dentist, physician, dietitian and diabetes nurse educator need to coordinate efforts take care of patients effectively.

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Summer camps for children with diabetes have the objective of teaching children how to manage their diabetes at home. It encourages children to be independent, self-sufficient, and knowledgeable about their diabetes. It promotes empowerment and at the same time compliance to recommended regimen in oral hygiene, diet, medication, blood sugar monitoring and visits to health professionals. During these camping sessions, interprofessional education occurs among the different health professionals acting as facilitators or counselors during the camp. It allows for sharing of information, strategies, and most of all, it allows health professionals from one discipline to appreciate the role of other health professionals.

Management of periodontal disease for the patient described herein relied heavily on mechanical debridement of crown and root surfaces; still the most reliable way of reducing plaque and calcular deposits. In addition, improved oral hygiene practices (toothbrush and dental floss) and chemotherapeutic agents (cetylpyridinium chloride; chlorhexidine) were employed to prevent recolonization by bacterial pathogens and to reduce gingival inflammation.

An earlier report suggested that type 1 diabetic patients show much improvement in metabolic control after intensive insulin therapy, but no improvement in clinical periodontal status and no changes in the subgingival levels of periodontitis-associated bacteria.[22] Other studies employing periodontal intervention in type 1 diabetics, showed significant improvement in periodontal parameters but not in glycosylated hemoglobin levels.[5-8]

What was unique in the management of the patient was the use of both periodontal intervention and motivation to reinforce diabetes self-management skills. Klein and colleagues cited 3 meta-analyses of the effectiveness of Diabetes Self-Management Education in reducing glycated hemoglobin values and reported reductions from 0.32% to 0.76%.[23] The net decrease of 1.2% in glycated hemoglobin levels in this patient, compared to results of previous studies, on type 1 diabetic patients, is considerable. Perhaps the reason for little improvement in glycemic control after periodontal treatment in previous studies was due to the neglect of other factors that affect glycemic control. This suggestion is supported by (i) the improvement in clinical periodontal disease parameters following mechanical cleaning of the teeth, (ii) the initial 30% reduction in fructosamine levels 4 weeks following periodontal therapy, and the 50% reduction in CRP achieved with this patient. However, these results, while encouraging, are based only on a single patient. Thus, it seems reasonable to propose direct testing of this hypothesis in a large interventional study of type 1 diabetics.

Lessons learned in diabetes camps regarding insulin dose adjustment, traditionally taught by physicians, are important tools in curbing rising blood sugar levels. However, most pediatric patients are reluctant to do this at home on their own. Calorie counting and food exchange, taught by dietitians, are effective methods of lowering carbohydrate intake but depends a lot upon the patient's desire and motivation to follow. Insulin injection and glucose monitoring, taught by diabetes nurse educators, is part of the daily routine of children with diabetes. But, the daily repetitious act becomes monotonous that long term compliance eventually becomes poor. All these are important tools that the diabetic patient can employ to achieve optimum health. The dentist, acting as a diabetes educator, can help improve patient compliance by reinforcing lessons learned in camp during dental visits.

CONCLUSION

Caries and periodontal disease are the most common oral problems. It is highly preventable, but if left untreated, it can lead to functional problems that can affect dietary needs, psychological problems that can affect self-esteem, and systemic problems that can impair blood glucose control in diabetic patients.

The goal of the dentist is no longer just the improvement of oral health but ultimately the overall health of the patient; and the physician's goal is to include oral health in the promotion of overall health. Science and patient needs have erased professional boundaries. It is now time to change traditional paradigms regarding oral health and disease so that oral health becomes an integral component of general health. It is now time for the dentist and the physician to share in the responsibility for the oral health and overall health of the patient.

Laboratory tests were sent to the Hi-Precision laboratories. HbA1c was determined using high performance liquid chromatography while fructosamine was determined using a colorimetric reaction with nitrobluetetrasolium. CRP was determined by the agglutination method.

Acknowledgements

I would like to thank the following: the staff of Rainbow Camp, Camp Cope, and Davao Diabetes Camp for inviting me to their camp to share my knowledge in dentistry and learn about diabetes; Dr. AC Dampil and the St. Luke's Medical Center for providing much needed examination and laboratory tests to rule out any diabetes complications; Mr. Iam Guerrero of Colgate who suggested the idea of making a case report and at the same time helping this particular patient obtain the necessary treatment she needed; Mrs. Liberty Amos Nichols and her daughter Macky Mendoza for donating the glucose strips used by the patient for the duration of the study; and Ms Monica Solis of SciGen and Caesarah Taboada formerly of Novo Nordisk for the insulin used by the patient; Mrs. Becky Fuellos of Children International Philippines, for the insulin syringes, and Dr. Raphael Silva and Dr. Bruce Baum for reviewing the manuscript. Most of all I would like to thank all the children with diabetes who have shared their life and experience with me since 1996.

ONLINE FIRST | August 25, 2016 | https://doi.org/10.15605/jafes.031.02.13

Ethical Consideration

Patient consent form has been procured prior to the case study report.

Author Disclosure and Source of Funding

The patient received an honorarium and money from Colgate Palmolive, Philippines for various needs including laboratory tests, panoramic x-ray, and oral hygiene products consisting of toothpastes, toothbrushes, interdental toothbrushes, dental floss, chlorhexidine and cetylpridnium mouthwashes.

The author received an honararium for writing this case report from Colgate Palmolive, Philippines.

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ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.14

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CASE REPORT

Unusual Presentation of Sheehan's Syndrome with Severe Hyponatremia and Recurrent Symptomatic Hypoglycemia: A Case Report

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Abstract

Sheehan's syndrome (SS) is postpartum hypopituitarism caused by necrosis of the pituitary gland. The onset in most cases is several months or even years after the inciting delivery, so it is often unrecognized and not adequately treated. Because SS often evolves slowly, it is usually diagnosed late. We report a 47-year old woman with loss of consciousness. Fourteen years ago, she had postpartum hemorrhage with subsequent amenorrhea and failure to lactate. Laboratory investigation showed low blood sugar and serum sodium levels, amid normal cortisol and thyroid function tests. Magnetic resonance imaging (MRI) of the pituitary revealed an empty sella consistent with SS. The presentation of hypoglycemia and hyponatremia are less known complications of Sheehan's syndrome with only a few documented in case reports.

Key words: Sheehan's syndrome, hyponatremia, hypoglycemia, empty sella

INTRODUCTION

In his publications from 1938 to 1968, Sheehan elegantly described the natural history, clinical signs and pathologic findings of the syndrome that results from postpartum necrosis of the anterior lobe of the pituitary gland. The exact pathogenesis of the disease is not well understood, since many women who suffer severe hemorrhage at delivery apparently escape damage to the anterior pituitary.[1,2,3] Many of the cases remain undetected until years later, when hypothyroidism or secondary adrenal insufficiency become evident in a woman who had postpartum hemorrhage.[4]

A recent epidemiologic study from the Kashmir Valley of the Indian subcontinent estimated the prevalence of SS to be about 3% for women above 20 years of age, almost two-thirds of whom had home deliveries. However, SS is a rare cause of hypopituitarism in developed countries. In a study of 1,034 adults with hypopituitarism, SS was the sixth most frequent cause of growth hormone (GH) deficiency, being responsible for 3.1% of cases.[5] In a retrospective nationwide analysis in Iceland, the prevalence of SS in 2009 was estimated to be 5.1 per 100,000 women.[6] The clinical presentation of Sheehan's syndrome varies from nonspecific manifestations such as weakness, anemia and fatigue, to severe pituitary dysfunction resulting to coma and even death. A medical history of postpartum hemorrhage, failure to lactate and cessation of menses are helpful clues to the diagnosis.[7-10]

Sheehan's syndrome that initially presents with hyponatremia and hypoglycemia is rarely reported in literature.[11] Hypothyroidism and glucocorticoid deficiency decrease free water clearance independent of vasopressin and subsequently cause hyponatremia. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) and volume depletion are other factors that also lead to hyponatremia.[12,13] Recurrent hypoglycemia due to growth hormone, adrenal and other counter-regulatory hormone deficiencies is a less known complication of SS.[14] In this study, we present a case of Sheehan's syndrome with hyponatremia and hypoglycemia that improved after replacement with glucocorticoids.

CASE

A 47-year old Indonesian housewife was admitted to our hospital in December 2013 due to sudden loss of consciousness (Figure 1). She was found to have recurrent episodes of loss of consciousness in the last 6 months, accompanied by symptoms of generalized fatigue, weakness and anorexia. She noticed dry skin and thinning of hair starting 3 years ago. She had no history of

eISSN 2308-118x
Printed in the Philippines

Received: September 20, 2015. Accepted: July 12, 2016.
https://doi.org/10.15605/jafes.031.02.14

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ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.14

Table 1. Basal hormonal parameters

Hormone	Results	Normal range
Free triiodothyronine, pmol/L	< 0.70	4-8.3
Free thyroxine, pmol/L	28.54	9-20
Thyroid stimulating hormone, µIU/mL	1.026	0.25-5
Serum cortisol, morning, µg/dL	8.90	4.3-22.40
Luteinzing hormone, mIU/mL	3.21	5.16 - 61.99 (post-menopause)
Follicle-stimulating hormone, mIU/mL	7.33	26.72-133.41 (post-menopause)
Prolactin, ng/mL	1.64	5.18-26.53
Growth hormone, ng/mL	0.163	≤ 10

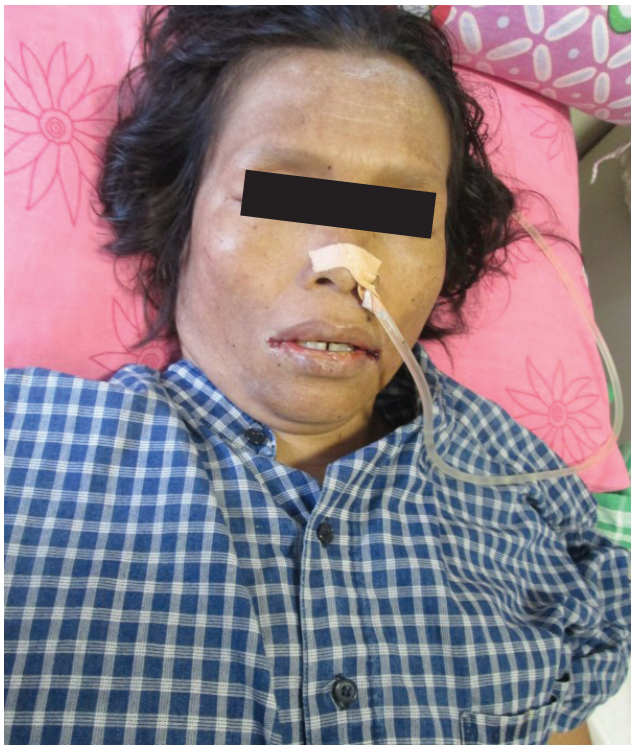

Figure 1. Image of the patient at presentation with sudden loss of consciousness.

fever, headache, vomiting, seizure, head injury or loose stools. She was multigravid (G7P6), with her last baby delivered at home by a midwife at the age of 33 years. She had severe postpartum hemorrhage necessitating hospitalization and transfusion with six units of blood. After the eventful delivery, she was unable to produce breastmilk and subsequently had irregular menstrual cycles in the last 14 years. She had been amenorrheic for one year.

On physical examination, the patient appeared chronically ill with depressed sensorium (Glasgow coma scale E3V3M5). She was afebrile, with stable vital signs (pulse rate 72 beats/min, regular; blood pressure 100/70; respiratory rate 20 cycles/min). She had dry, rough and cold skin, with good turgor. She had pale palpebral conjunctivae and absent axillary and pubic hairs. Laboratory tests revealed normocytic, normochromic anemia with low hemoglobin concentration (7.8 g/dL). She had hyponatremia (109 mmol/L) and hypoglycemia (40 mg/dL), normal potassium (3.9 mEq/L) and creatinine (0.6 mg/dL), top normal urea (20 mg/dL) and low serum osmolality (233 mOsm/kg). Arterial blood gas analysis

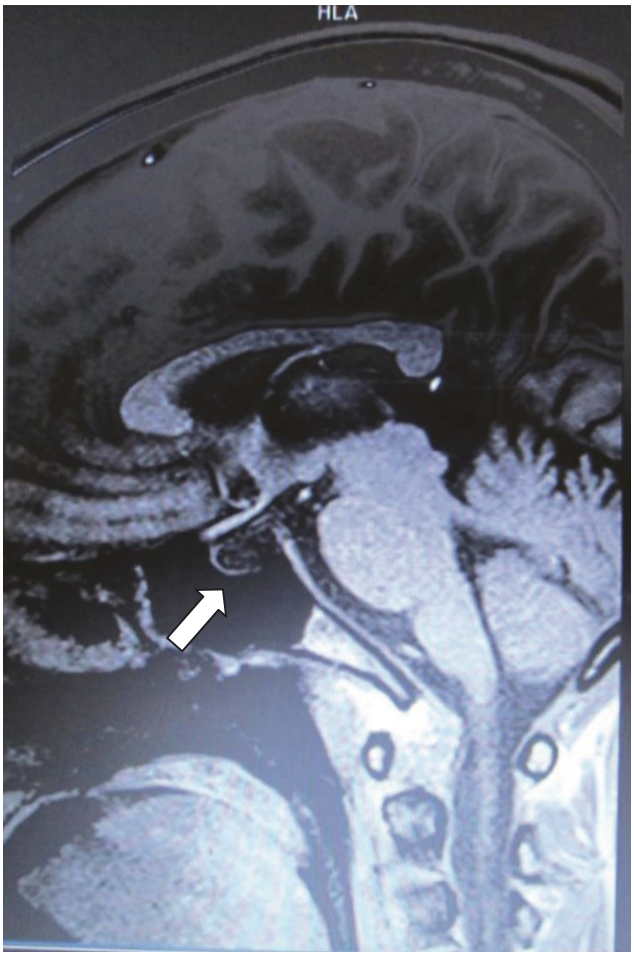

Figure 2. Sagittal enhanced T1-weighted magnetic resonance image showing empty sella appearance, with the pituitary gland flattened against the sellar floor.

revealed pH 7.424, PO_2 146.9 mmHg and PCO_2 24.9 mmHg. Urine electrolytes showed natriuresis (urinary sodium 273 mmol/24 hours, normal value 40-220 mmol/24 hours) and normal potassium excretion (urinary potassium 20.3 mmol/24 hours, normal value 15-125 mmol/24 hours). Basal hormonal workup showed low levels of growth hormone (GH), prolactin (PRL), luteinizing hormone (LH) and follicle stimulating hormone (FSH); and normal cortisol. She also had low free triiodothyronine (FT3) and normal thyroid stimulating hormone (TSH) (Table 1). Magnetic resonance imaging (MRI) of the brain showed an empty sella appearance, with the small-volume pituitary gland flattened against the sellar floor (Figure 2). These findings confirmed the diagnosis of Sheehan's syndrome.

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.14

Following the clinical and laboratory findings, she was given saline infusion and glucocorticoid replacement with intravenous methylprednisolone at 125 mg/day for 3 days. There was improvement of hypoglycemia, hyponatremia and clinical symptoms. She was managed with oral steroids subsequently.

DISCUSSION

Sheehan's syndrome is characterized by pituitary necrosis after severe postpartum hemorrhage and hypovolemia. Vasospasm, thrombosis and vascular compression of the hypophyseal arteries have also been described as possible causes of the syndrome. Enlargement of the pituitary gland, small sellar size, disseminated intravascular coagulation and autoimmunity have been suggested to play a role in the pathogenesis of SS. The syndrome is characterized by varying degrees of anterior pituitary dysfunction. It may cause hypopituitarism either immediately or after a delay of several years, depending on the degree of tissue destruction. Some degree of hypopituitarism occurs in nearly one-third of patients with severe postpartum hemorrhage. Although symptomatic posterior pituitary dysfunction is uncommon, many patients have impaired neurohypophyseal function tests.[5,16,17]

Forty years ago, it was estimated that the prevalence of Sheehan's syndrome was about 100 to 200 per 1,000,000 women.[5] It is now considered a very rare obstetric complication. The clinical presentation of Sheehan's syndrome ranges from long-standing non-specific features such as weakness, fatigue and anemia, to profound abrupt hypopituitarism resulting in coma and death.[18]

A retrospective study of 20 patients with SS, which included patients aged 28 to 71 years, showed that the interval between the beginning of the disease and the definitive diagnosis varied between 5 to 25 years. All of the patients had a history of a serious bleeding during or after delivery. Six patients had received blood transfusion for severe bleeding. All of the patients described inability to nurse and subsequent failure of menstrual cycles to return to normal patterns.[2] Sunil and colleagues reported that failure to resume menstruation and agalactia were the most common symptoms, found in 100% and 72% of the patients, respectively.[19] Sert and colleagues reported that 9 of their 28 patients presented with disturbance in consciousness.[3] In the report by Ozkan and colleagues, they found 3 patients referred to the emergency service for hypoglycemia, 3 for hypothyroidism and one for hyponatremia.[2] Our patient experienced altered consciousness associated with weakness beginning 6 months before admission. A detailed obstetric history revealed severe hemorrhage following delivery of her seventh pregnancy, with ensuing failure to produce breast milk and irregular menstrual cycles.

As a presenting manifestation of Sheehan's syndrome, severe hyponatremia causing altered sensorium has rarely been described in the literature. This is probably due to the slow evolution of the disease into its chronic form.[14] Punwell and colleagues found mild to severe hyponatremia in 9 of 13 patients with Sheehan's syndrome.[20] The cause of hyponatremia in Sheehan's syndrome is still open to debate. Cases of severe hyponatremia, with serum sodium levels below 125 mmol/L, developing 16 years after postpartum bleeding have been reported. Adrenal insufficiency is one of the most likely causes of hyponatremia in SS. SIADH may also be responsible for hyponatremia in patients with Sheehan's syndrome.[21,22] Inappropriate secretion of antidiuretic hormone is known to occur in states of adrenocorticotropin deficiency. The mechanism by which hypopituitarism leads to decreased sodium concentration is complex and only partially understood. There is evidence of water retention as a result of inappropriately high levels of vasopressin. Animal experiments and clinical observations suggest that glucocorticoids tonically inhibit the secretion of vasopressin. A sudden loss or decrease in the inhibitory control may lead to rapid serum elevations of vasopressin. Another potential mechanism for the elevation in vasopressin is the uncontrolled release of the hormone from the posterior hypophysis in the setting of ischemia.[23] In our patient's case, we found severe hypoosmolar hyponatremia with normovolemia, and increased urinary sodium. Low serum osmolality and elevated urine osmolality suggested SIADH.

Hypoglycemia in a case of hypopituitarism is more often seen in pituitary apoplexy than Sheehan's syndrome. Endocrine deficiency is the next most common cause of hypoglycemia (20%), second only to diabetes treatments (42%). Of these deficiencies, hypopituitarism is the leading cause, with Sheehan's syndrome being the most common underlying etiology (44%).[15] In a case review conducted by Ozkan and Colak, 3 out of 20 Sheehan's syndrome patients (15%) presented with hypoglycemia.[2] Cortisol deficiency results in glycogen depletion by causing anorexia and weight loss. This increases reliance on the gluconeogenesis pathway. Glycogen depletion and low levels of gluconeogenetic precursors due to cortisol deficiency result to an impaired ability to tolerate fasting. Growth hormone deficiency also contributes to hypoglycemia. In some cases where there is only partial pituitary necrosis, the syndrome can present in an atypical and incomplete manner, further complicating the diagnosis.[24] Our patient presented with low blood glucose during hospitalization prior to the diagnosis of Sheehan's syndrome. Hormonal studies showed decreased growth hormone and normal cortisol.

Murat and colleagues reported that the pattern of hormone deficiency in Sheehan's syndrome is variable. Hormone deficiencies following ischemic infarction of pituitary include GH (88%), gonadotropin (58 to 76%), and

ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.14

corticotropin (66%). Secondary hypothyroidism occurs was found in 42 to 53% of patients, and prolactin deficiency in 67 to 100% of patients.[3] In a review of 18 cases of SS at diagnosis, Sanval noted that lactotroph and gonadotroph failure were present in all patients, but corticotroph preservation was documented in 3 (16.7%) and thyrotroph in 2 (11.1%) patients. The anatomical location of GH and prolactin cells in the lower lateral region of the adenohypophysis make them most susceptible to ischemic damage.[25] In our patient's case, we found low FT3 with normal TSH, supporting the diagnosis of central hypothyroidism. We also found low plasma levels of FSH, LH and prolactin.

The main radiologic finding of SS is the image of an empty sella (seen in 70% of patients) or partially empty sella (30%). The time-dependent evolution of the findings on MRI in SS has been observed to begin acutely with non-hemorrhagic changes in signal intensity consistent with central infarction, along with peripheral and heterogeneous central enhancement in an enlarged pituitary gland. The findings are consistent with patchy central ischemic necrosis in an enlarged gland and are followed by pituitary gland atrophy and an empty sella. These findings on MRI characterize SS and provide early confirmation of the clinical diagnosis.[26-28] In our patient, we found a widened sella turcica with a flattened pituitary gland consistent with an empty sella.

The treatment of Sheehan's syndrome is replacement of the deficient hormones. ACTH and TSH deficiencies should be replaced with glucocorticoids and thyroxine respectively; mineralocorticoid replacement is usually not required.[18,29] Our patient improved clinically after methylprednisolone was given.

CONCLUSION

We encountered a rarely reported presentation of Sheehan's syndrome, with documented hyponatremia and hypoglycemia in a patient with loss of consciousness. Her history of postpartum hemorrhage, failure to lactate and cessation of menses provided important clues to the diagnosis. Supported by hormonal studies and neuroimaging, we diagnosed the patient with SS and treated the patient appropriately. Some SS patients have been reported to have partial hypopituitarism, with preserved thyrotroph and corticotroph functions. Some are diagnosed late in the disease because the clinical features of SS are often subtle. Early diagnosis and appropriate treatment are necessary to reduce morbidity and mortality.

Ethical Consideration
Patient consent has been procured prior to the case report study.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
None.

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ONLINE FIRST | September 2, 2016 | https://doi.org/10.15605/jafes.031.02.14

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ONLINE FIRST | November 8, 2016 | https://doi.org/10.15605/jafes.031.02.15

CASE REPORT

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Case Report of Tumour-induced Osteomalacia with Parotid Gland Tumour as a Focus

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Abstract

Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome, which is characterized by overproduction of FGF23 as a phosphaturic agent leading to chronic phosphaturia and hypophosphatemia, associated with inappropriately normal or low levels of vitamin D. We describe a rare case of a 57-year-old Indian female who presented with bone pains, muscle pains and lower limb weakness. On examination she was found to have hypophosphatemia. Our work up led to the identification of a FGF23 secreting parotid tumour. The tumour responsible for symptoms was a pleomorphic adenoma of the parotid gland. Its complete resection resulted in normalisation of patient's symptoms. Laboratory parameters and microsopic examination further revealed a mesenchymal tumour of mixed connective tissue type.

Key words: TIO, hypophosphatemia, FGF23

INTRODUCTION

Hypophosphatemic osteomalacia comprises hereditary and acquired disturbances. Main syndromes described as causing this disease are x-linked hypophosphatemic rickets (XHR), Autosomal Dominant Hypophosphatemic Rickets (ADHR) and Fibrous dysplasia.

TIO is an acquired condition and is related to mesenchymal or mixed connective tissue tumour(s) that markedly expresses FGF23 RNA protein, which cannot be adequately degraded by specific endopeptidases. Other clinical syndromes have been also associated with FGF-23 overproduction, such as NF–1, Mc Cune-Albright Syndrome (MAS).[1]

The FGF-23 protein inhibits type II a and II c sodium – phosphate co-transport in proximal convoluted tubules and inhibits renal 1-α hydroxylation of vitamin D.

Although these conditions exhibit different etiopathogenic mechanisms, they share the same pathophysiological pathways i.e., secretion of FGF23 that acts on proximal tubules, and increases renal excretion of phosphate, leading to hyperphosphaturia, and hypophosphatemia with impaired vitamin D metabolism, as FGF23 inhibits 1-alpha hydroxylase.[2,3]

The diagnosis is often delayed, as the patient presents with multiple complaints, such as bone and muscle pain and muscle weakness. The tumour itself is small and slow growing, and often missed during the clinical examination. As clinical and biochemical changes of TIO are potentially reversible by tumour removal, its localization is essential.

We report a case of chronic hypophosphatemic osteomalacia, characterized by severe muscle weakness, pain and multiple bone fractures. Our aim is to register the case, and also discuss the diagnostic approach and therapeutic management of TIO.

CASE

A 57-year-old Indian woman, presented with the chief complaints of bilateral leg pains on walking since 15 months, limping to either side since 3 months and currently walking with support of a stick since 1 month. The patient also complained of pain in both upper limbs since 1 month. She had past history of Chikungunya infection 4 years ago and history of left superficial parotidectomy in 2011. Before coming to our OPD, she was treated for Rheumatoid Arthritis, evaluated for multiple myeloma and connective tissue disorder due to intense pain in lower limbs. She had received oral calcitriol before coming to hospital. However, the patient was not given phosphorous supplement. There was no family history of metabolic bone disease. There was no history of loss of weight, decreased appetite, and swelling or mass anywhere in the body except a left parotid enlargement.

eISSN 2308-118x
Printed in the Philippines

Received: April 29, 2016. Accepted: July 20, 2016.
https://doi.org/10.15605/jafes.031.02.15

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ONLINE FIRST | November 8, 2016 | https://doi.org/10.15605/jafes.031.02.15

On physical examination, the patient had antalgic gait, and left parotid enlargement 3 x 4 cm. She had localized tenderness over multiple ribs and multiple tender points over the lower limbs. She had left sided lower motor neuron facial palsy. Motor strength in the lower limbs was grade 5, but she had intense pain (numerical response scale 8/10) in both the feet and right hip.

Initial laboratory testing revealed a calcium 9.6 mg/dl (8.8-10.2 mg/dl), phosphorus level 2 mg/dl, alkaline phosphatase was marginally elevated 179 U/L, creatinine 0.6 mg/dl, SGOT 22.1(U/L) SGPT 23.8(U/L) PTH 5.6 pg/ml, and vitamin D 17.5 ng/ml. Complete blood count, liver function tests, renal function tests, TSH, serum protein electrophoresis and CPK were normal (Table 1). We were unable to measure 1,25 vitamin D as the test was not available. The patient's ANA and Rheumatoid factor was negative. Her EMG and Nerve conduction studies were normal.

Table 1. Laboratory Test Results

	Patient value	Normal value
Calcium	9.6 mg/dl	8.8-10.2 mg/dl
Phosphorous	2 mg/dl	2.7-4.5 mg/dl
Creatinine	0.6 mg/dl	.67-1.17 mg/dl
SGOT	22.1 U/L	10-50 U/L
SGPT	23.8 U/L	0-41 U/L
PTH	5.6 pg/ml	15-65 pg/ml
VIT D	17 ng/ml	> 30 ng/ml - < 100 ng/ml

Radiological studies showed bilateral tibial shaft fractures, multiple fractures in bilateral tarsals (Figures 1 to 3). A PET Scan showed multiple insufficiency fractures of bilateral tibia, neck of right femur, metacarpal bones and scapula (Figures 4 to 7).

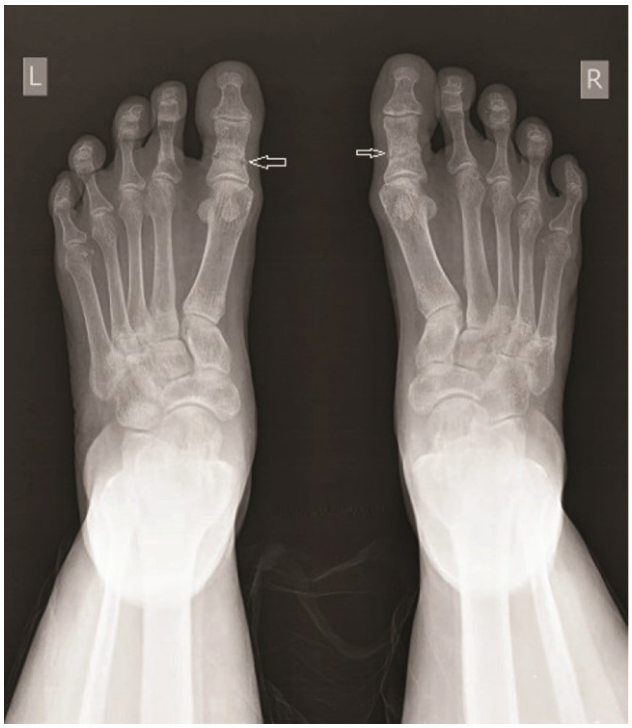

Figure 1. X-Ray showing metatarsal fracture.

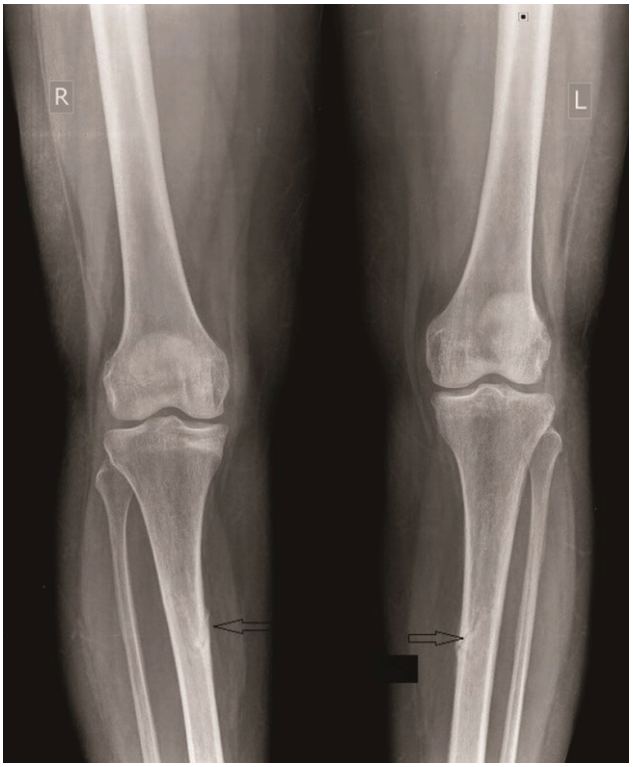

Figure 2. X- ray showing bilateral mid-shaft tibia fracture.

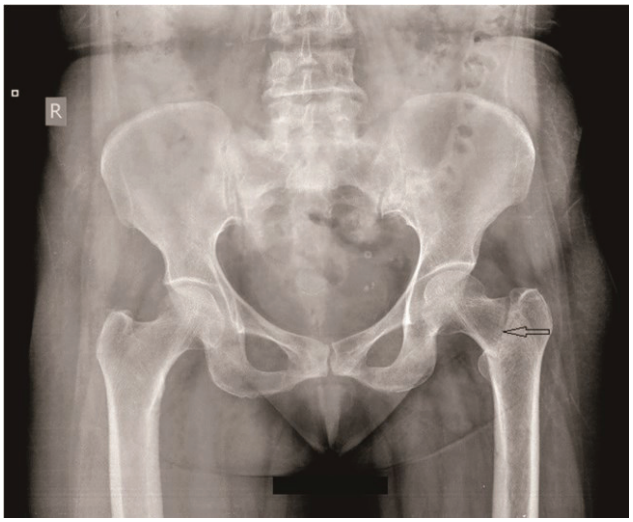

Figure 3. X- ray showing neck femur fracture on left side.

Instead of 24-hour urinary phosphorous, levels of phosphorus and creatinine were measured from a spot urine sample and tubular re-absorption of phosphorus (TRP) was calculated. Walton and Bijovet Nomogram was then used to estimate the TMP/GFR, which was 1.6, suggestive of renal phosphate wasting. The patient's FGF23 was 500 RU/ml.

Since the parotid tumour also has a mesenchymal component, it was thought to be a source producing FGF-23. ^{68}Ga-DOTATE scan was done which showed increased uptake over left parotid, SUV (Standard uptake values) max – 97.5, other areas, had normal physiological uptake (Figure 8).

ONLINE FIRST | November 8, 2016 | https://doi.org/10.15605/jafes.031.02.15

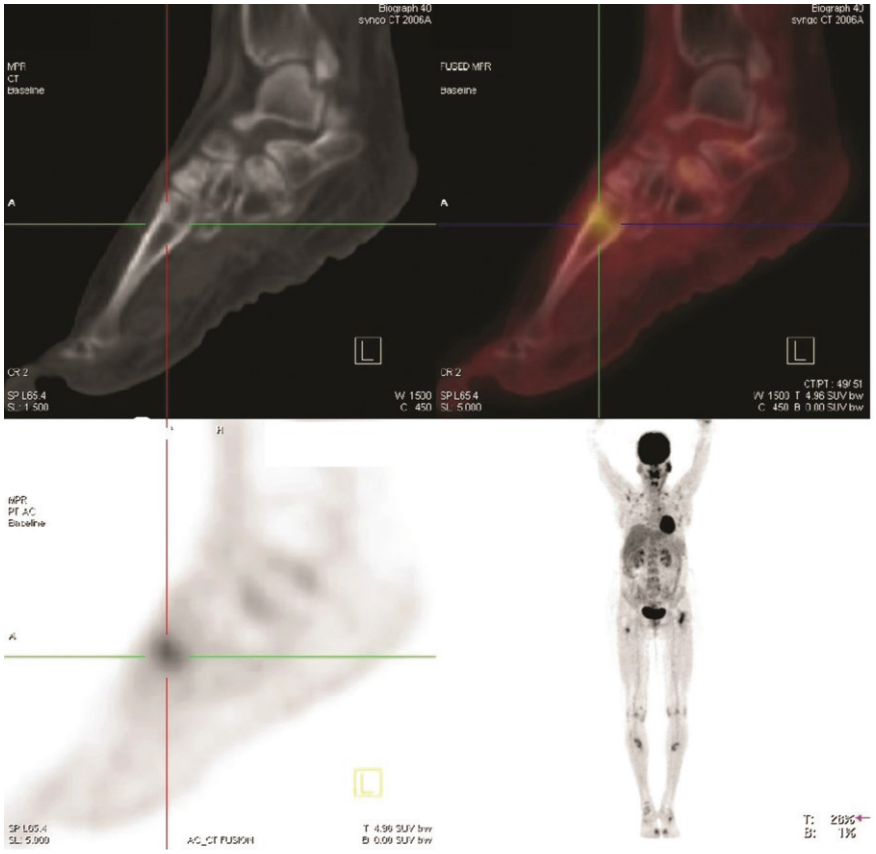

Figure 4. PET scan picture showing uptake over fracture part.

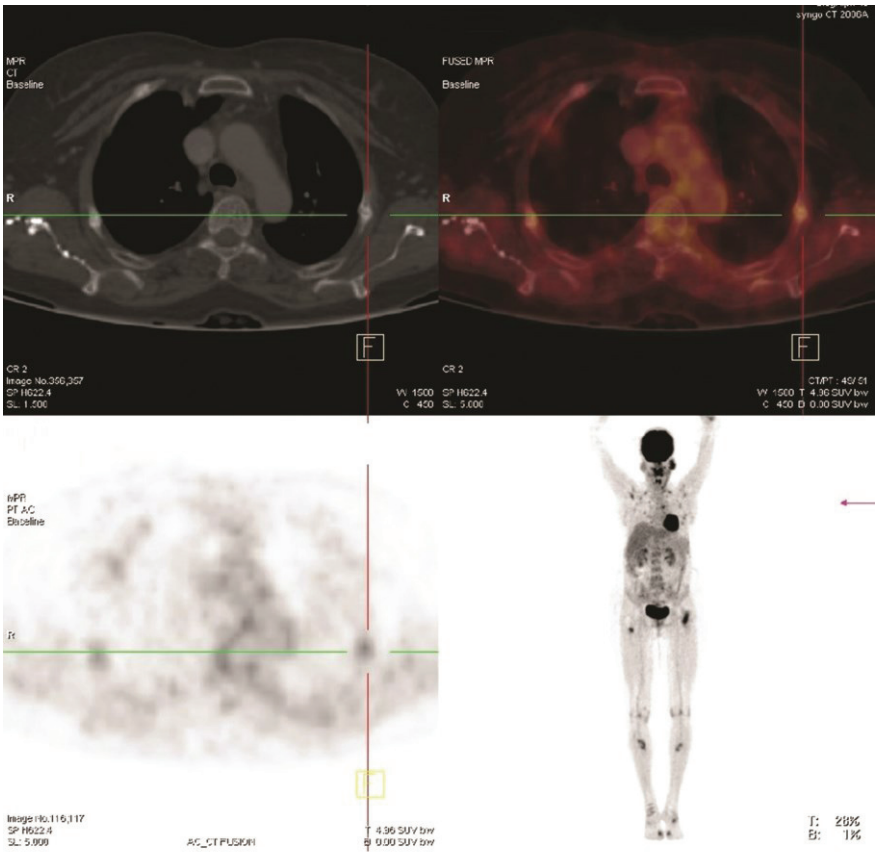

Figure 5. PET scan showing fracture of ribs.

ONLINE FIRST | November 8, 2016 | https://doi.org/10.15605/jafes.031.02.15

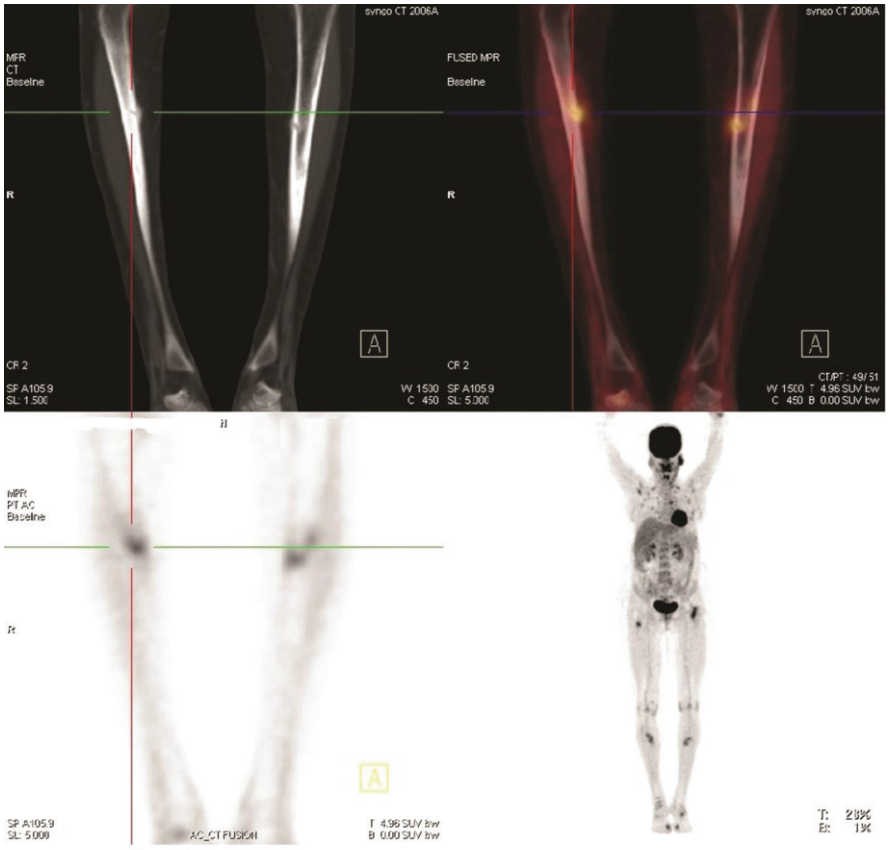

Figure 6. PET scan showing fracture of tibial shaft.

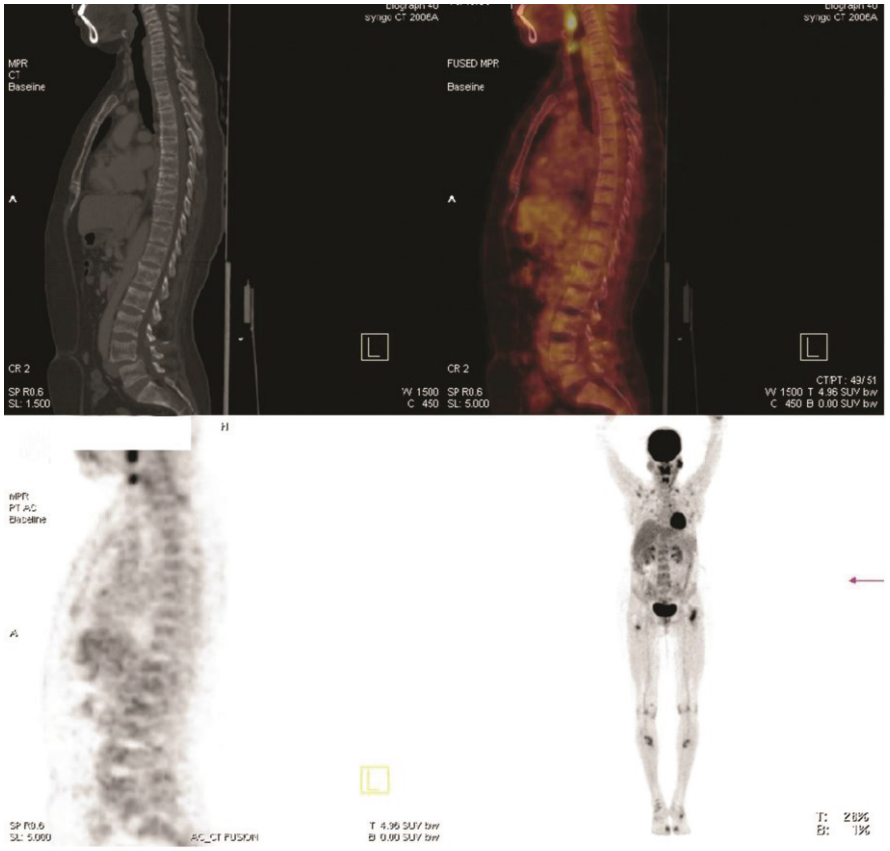

Figure 7. PET scan showing multiple fractures.

ONLINE FIRST | November 8, 2016 | https://doi.org/10.15605/jafes.031.02.15

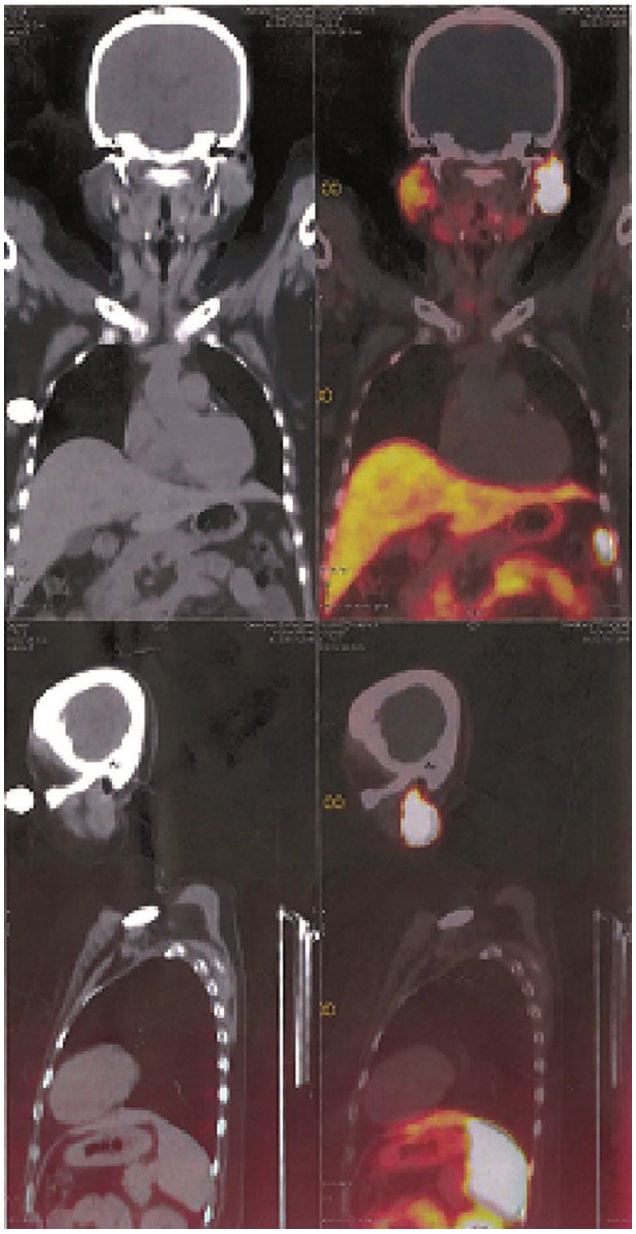

Figure 8. ^{68}Ga-DOTATE scan showing coronal and saggital view of mass in left parotid.

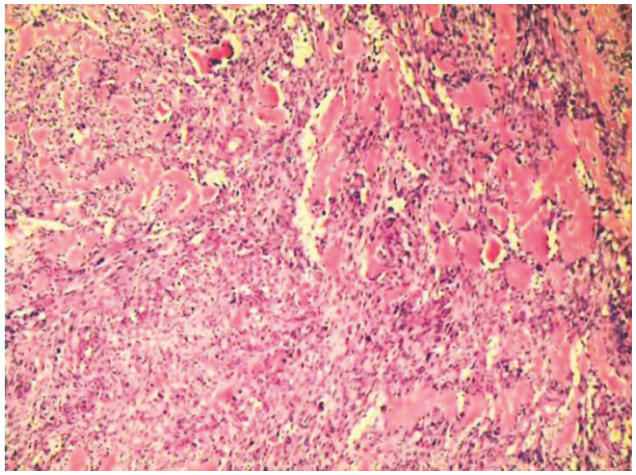

Figure 9. Cellular spindle cell tumour with deposition of basement membrane like eosinophilic material (20x).

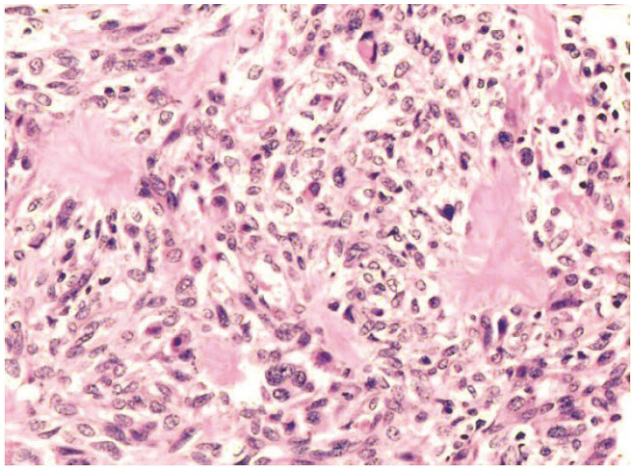

Figure 10. High power view of the tumour showing increased cellularity and mild nuclear pleomorphism. However the mitotic activity is low (40x).

The patient was started on oral phosphate supplement 2-3 gms/ day, and her symptoms improved from baseline, but serum phosphorous remained on lower side. The patient underwent left parotid resection. The excised left parotid gland measured 4 x 3 x 2.5 cm and on cut section there was a grayish white ill-defined firm and focally hard solid tumour measuring 2.8 x 2.2 x 2 cm. A similar nodule measuring 0.5 cm in diameter was found in the adjacent parotid parenchyma. The rest of the parotid was unremarkable. The histopathology showed cellular myoepithelial rich pleomorphic adenoma of the parotid gland. Focal nucleal pleomorphism was noted. Mitotic count was low (Figures 9 and 10). Immunostaining of the tumour tissue for FGF23 could not be done as this test was not available.

The patient's symptoms improved after resection, and serum phosphorous done 1 week after resection showed a normal phosphorus.

DISCUSSION

Tumour induced osteomalacia (TIO) is an acquired disorder of renal phosphorus wasting. It is associated with tumour producing phosphaturic factor leading to phosphaturia, low serum phosphorus levels and low or inappropriately normal serum calcitriol levels. Hypophosphatemia is normally a stimulus for production of calcitriol, and the level of normal vitamin D is abnormal in the context of low serum phosphorus level.[4,5,6]

Clinical symptoms include the gradual onset of muscle weakness, fatigue and bone pain especially from ankle, legs, hips and back.[3-5] Insufficiency fractures and proximal muscle weakness causes pain and inability to walk; so the patient becomes slowly bed bound. Our patient had multiple fractures of tibia, femur and metatarsals due to which she had gradually become bed bound. She was diagnosed and treated as having Rheumatoid Arthritis due to the intense pain in her legs while walking.

ONLINE FIRST | November 8, 2016 | https://doi.org/10.15605/jafes.031.02.15

The phosphaturic peptides are known as phosphatonins and FGF23 is the most extensively described. FGF23 has an important role in maintaining phosphorus homeostasis.[3,-6] In TIO, the level of FGF23 is high and results in phosphate wasting through the urine.[7] If the responsible tumour is surgically removed, the abnormalities of phosphorus wasting and vitamin D metabolism are rapidly corrected. According to White, PTH which decreases renal phosphorus reabsorption is usually within normal range in TIO patients.[8] Hence in our patient, due to increased FGF23, the serum PTH must have been low. Other studies have supported this hypothesis by showing that implantation of tumour tissue into nude mice resulted in increased urinary phosphorus excretion.[9]

When TIO tumours and several control tissue were tested by northern blot for the presence of FGF23 transcripts, it was determined that FGF23 was present in a tumour lysate and it was confirmed by western blot analysis, with an anti human FGF antibody. The mice receiving implanted transcripts from tumour also showed growth retardation, kyphosis, osteomalacia and marked decrease in renal 1α hydroxylase. Under normal circumstances, FGF23 has an important role in maintaining phosphorus homeostasis . In patients of TIO however, circulating level of FGF23 are high which leads to renal phosphate wasting.[2]

FGF23 also has a central role in the pathogenesis of autosomal dominant hypophosphatemic rickets (ADHR) which is caused by mutation in the FGF23 gene that makes peptides resistant to degradation by regulatory proteases. Some patients of TIO have normal FGF23 level. This lead to the discovery of other phosphatonins including secreted frizzled related protein 4 (SFRP-4). Matrix extracellular phosphoglycoprotein (MEPE) and fibroblast growth factor (FGF7) whose roles in TIO are under investigations.[6, 11]

TIO is a rare condition. Our case demonstrated the importance of considering the diagnosis of TIO and assessing serum phosphorus levels in patients with unusual osteomalacia and persistent musculoskeletal symptoms. Measurement of serum phosphorus is an important step for understanding phosphaturia.[11] Also with the levels of serum calcium, alkaline phosphate, PTH, 25(OH) D3, 1,25 dihydroxyvitamin D should be measured to distinguish other causes of hypophosphatemia and osteomalacia.

A spot 2 hour urine sample was collected in our patient. Calculation of TMP/ GFR and a nomogram was used to derive this from serum phosphorus and tubular reabsorption of phosphate (TRP=1- [urine phosphorus] x [serum creatinine]/[urine creatinine] x [serum phosphorus level])[11]. This is a reliable tool for evaluation of hypophosphatemia. The patient was not on any phosphorous supplement at that time. In our patient, TMP/GFR was low despite hypophosphatemia which indicated renal phosphorus wasting.[11]

FGF23 is a confirmatory test for diagnosis of TIO. In one survey, 22 patients with clinical evidence of TIO had elevated FGF23.[11] These tumours usually arise from soft tissue and bones and are benign in nature. The definitive treatment of TIO being resection of a tumour, localization of such tumour is essential.[11]

In our patient, the source of the tumour was readily visible. But tumours can occur in elusive sites and their localisation can be challenging. Careful physical examination with special attention to oral cavity and extremities is needed.

For tumour localisation, imaging modalities such as X-ray, CT and MRI can be used. Some tumours express surface somatostatin receptors. Somatostatin receptor PET scan is used as a diagnostic tool in refractory cases. In our patient Somatostatin receptor PET scan was used as nuclear imaging method. Radiolabelled octreotide was injected in a patient and whole body follow images were taken. Tumours that have surface somatostatin receptors bind to the octreotide and light up images.

Renal phosphate wasting and abnormal vitamin D metabolism can also be seen in X- linked hyphosphatemia (XLH) and ADHR (Autosomal dominant hypophosphatemic rickets) and both are caused by genetic mutations. As indicated by their names, they differ in mode of inheritance. These disorders present in childhood, although ADHR can exhibit variable and delayed onset. In all these syndromes circulating phosphatonins lead to inhibition of renal tubular phosphate reabsorption and downregulation of renal 1α hydroxylase.[1,11]

TIO is managed by complete resection of the tumour which results in decrease in bone pain and muscle pain and healing of multiple fractures within several months.[11] Until the tumour is located and resected, the patient requires 1-4 gm of phosphorus/day in divided dosage as well as calcitriol supplementation (1-3 gm/day).[11] These lead to renal and gastrointestinal phosphorus reabsorption and prevent secondary hyperparathyroidism.[11] The patient had already received calcitriol as well as alphacalcidol before coming to hospital and had no symptomatic relief and her serum vitamin D level was normal, hence calcitriol or alphacalcidol was not started. Our patient was given oral phosphorus (4.5 gm/day), until she underwent resection of the tumour. Subsequent to the resection, her serum phosphorous values improved. She was given phosphorous supplementation, which was tapered gradually. Over the next few months, bone and muscle pain subsided and she was able to walk without support.

ONLINE FIRST | November 8, 2016 | https://doi.org/10.15605/jafes.031.02.15

CONCLUSION

TIO is an acquired disorder of renal phosphate wasting that is associated with tumour. Patients with TIO present with hypophosphataemia with inappropriately suppressed 1,25 (OH)2 D concentration. Clinical symptoms include gradual onset of muscle weakness, fatigue and bone pain, especially for ankles, legs, hips and back. Insufficiency fractures are common and proximal muscles weakness can become severe enough for patients to require wheel chair or they become bedbound. This case highlights the importance of measuring serum phosphorus and phosphate clearance in patients with unusual musculo-skeletal pain and myopathic weakness. ^{68}Ga-DOTATE scan helps in localization of such a tumour and surgical resection can lead to total cure.

Ethical Consideration
Patient consent form has been procured prior to the case report study.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
All the authors have declared no conflict of interest to the work carried out in this paper.

Funding Source
None.

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ONLINE FIRST | October 19, 2016 | https://doi.org/10.15605/jafes.031.02.16

JAFES

CASE REPORT

A Case Report on Congenital Hyperinsulinism Associated with ABCC8 Nonsense Mutation: Good Response to Octreotide

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Abstract

A 2.4 kg baby boy born via Caesarian section at 35 weeks had the first onset of hypoglycemia at 2 hours of life. The infant required a glucose load of 30 mg/kg/min. Insulin level was 19.6 pmol/L (normal value 17.8-173.0) in the absence of ketosis. He was resistant to oral diazoxide but responded to octreotide infusion. The boy was found to be heterozygous for an ABCC8 nonsense mutation, p.R934*. We present our experience on the use of subcutaneous octreotide for 2 years for the treatment of diazoxide resistant congenital hyperinsulinism (CHI)

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Key words: congenital hyperinsulinism, PHHI, ABCC8 mutation, diazoxide, octreotide, K_{ATP} channel

INTRODUCTION

Congenital hyperinsulinism, also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI), is a group of genetic diseases characterized by inappropriate insulin release during hypoglycemia due to a mutation in the β cells of the pancreas.[1] Involving at least 8 genes with more than 100 mutations, it is genetically and clinically heterogenous. The most common mutation affects the adenosine triphosphate-sensitive potassium channel (K_{ATP}). The molecular diagnosis in CHI could only be found in about 45% of all cases.[2] There are many other genes that have yet to be discovered. Mutations of the β cells of the pancreas are basically divided into channelopathies, affecting the K_{ATP} channel, or metabolopathies, affecting other metabolites and transcription factors.[3]

CASE

The proband is the only child in the family. There was no history of parental consanguinity. He was born at 35 weeks via emergency low segment Caesarian section due to bleeding placenta previa. He had an Apgar score of 9 at 1 minute and 10 at 5 minutes. His anthropometric measurements were below the 3rd percentile (birth weight 2.4 kg, length 44 cm, head circumference 32 cm). Midline defects, such as cleft lip and cleft palate, were absent. There were no neurocutaneous stigmata. He had normal male external genitalia, with a normal-sized penis and descended testes. He had no phenotypic features to suggest Beckwith-Wiedemann syndrome. Other systemic examinations were unremarkable.

The first onset of hypoglycemia was seen at 2 hours of life. Despite regular breastfeeding, he continued to have multiple episodes of hypoglycemia manifesting as jitteriness. His capillary blood sugar ranged from low reading to 2.5 mmol/L. At the Neonatal Intensive Care Unit, he received boluses of intravenous dextrose 10% in water (D10W), followed by maintenance dextrose solution of increasing strength. Additionally, intravenous glucagon and hydrocortisone were started for persistent hypoglycemia. His blood sugar could only be maintained more than 3.0 mmol/L after a glucose load of 30 mg/kg/min and a glucagon infusion of 50 μg/kg/hr. Oral diazoxide was started at 5.0 mg/kg/day in divided doses, combined with chlorothiazide at 7.0 mg/kg/day. As he had poor response to oral diazoxide, it was titrated up to 20 mg/kg/day. Oral nifedipine 2.5 mg/kg/day was also added to the combination therapy. Octreotide was initially started as a continuous infusion after diazoxide dose was maximized. Within an hour after starting octreotide infusion, his blood sugar began to improve. Subsequently, subcutaneous octreotide was administered every 4 to 6 hours. We then decided to put him on a portable subcutaneous pump for the purpose of convenience, reducing the number of injections per day and making glucose regulation more physiologic.

The parents were educated on the identification and treatment of hypoglycemia. They were advised to perform home monitoring and recording of capillary blood sugar 3 to 4 times a day. During episodes of hypoglycemia, the boy was observed to be pale and inactive. His mother would then treat him with milk. In the first 1 year of life, he had hypoglycemia about 3 to 4 times a week,

eISSN 2308-118x
Printed in the Philippines

Received: May 23, 2016. Accepted: August 2, 2016.
https://doi.org/10.15605/jafes.031.02.16

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ONLINE FIRST | October 19, 2016 | https://doi.org/10.15605/jafes.031.02.16

particularly if he took very little milk or refused to eat. The episodes of hypoglycemia occurred less as he grew older, with a frequency of 2 to 3 episodes in a month.

Currently 1 year and 9 months old, the boy has fairly normal neuro-developmental milestones. He was diagnosed very early and received the appropriate treatment within the neonatal period. He started to walk at the age of 1 year. At almost 2 years, he is able to talk in two-word sentences, help in dressing and scribble spontaneously. A formal IQ test is being planned before school entry. He is seen regularly every 3 months.

DISCUSSION

There are many causes of recurrent and persistent hypoglycemia in the neonatal period. Hyperinsulinism is the most common cause of recurrent and persistent hypoglycemia.[4] Hyperinsulinism could be primary, due to a defect in the pancreatic β cells, or secondary.[5] Mutation of the genes that regulate insulin secretion is a rare condition. It is estimated to occur in 1 in 50,000 live births worldwide. The prevalence is higher, about 1 in 2000, in isolated populations with high rates of consanguinity, such as in Saudi Arabia and central Finland.[6] The most common genetic mutation is in the ABCC8 gene that encodes for the subunit of sulfonylurea receptor 1 (SUR1). Eighty percent of diazoxide-resistant cases of CHI is due to K_{ATP} channel mutation. Other mutations that cause dysregulated insulin secretion by the β cells include KCNJ11, GLUD1, GCK, HADH, HNF1A, HNF4A, SLC16A1 and UCP2 genes.[7] Secondary hyperinsulinism is a more common condition observed in large for gestational age, macrosomic and syndromic babies; and perinatal asphyxia. The triggers of excessive insulin release in these babies are unknown.[8]

Clues for hyperinsulinism in our patient include persistent hypoglycemia; the need for a very high glucose load, more than 2 to 3 times the usual requirement; the presence of inappropriate levels of insulin during hypoglycemia (19.6 pmol/L, normal value 17.8-173.0) and the absence of ketones during hypoglycemia (Table 1). The significant response to glucagon demonstrated that persistent hypoglycemia was less likely caused by metabolic causes, such as glycogen storage disease and gluconeogenic enzyme deficiencies.[9] Persistent hypoglycemia associated with the absence of ketones may be caused by congenital hyperinsulinism and defects in β-oxidation of fatty acids. As insulin was present during hypoglycemia, congenital hyperinsulinism was the more likely cause. The clinical parameters that may suggest K_{ATP} channel mutation in the boy are the very early onset of hypoglycemia at the second hour of life and severe hypoglycemia and diazoxide resistance.[10]

Comparing the findings of a large cohort of diazoxide resistant CHI treated with octreotide (n=28), our patient had lower birth weight (2.4 kg, as against 4.0±0.8 kg with a range of 2.5-6.0) at 35 week period of gestation (versus 37.5±2.4 weeks with a range of 33-40). The boy had unrecordable or low blood sugar on presentation, compared to 1.9±0.8 mmol/L with a range of 0.1-3.0 mmol/L. Our patient's measured insulin during hypoglycemia was 2.82 mU/L, while the levels documented in the cohort ranged from 31.4±39.1 mU/L.[11] However, there is no single physical finding or biochemical parameter that is able to predict diazoxide resistance or sensitivity in CHI, as the condition is clinically and genetically heterogenous.

There is a limited choice of drugs to treat persistent hypoglycemia from hyperinsulinism. First line therapy is oral diazoxide at 5 to 20 mg/kg/day in divided doses, which acts by opening K_{ATP} channels to inhibit insulin production. It works synergistically with chlorothiazide to reduce fluid retention. Nifedipine works by blocking voltage-gated calcium channels, as calcium is required for insulin exocytosis, but the experience for this indication is limited. Octreotide, a somatostatin analog, suppresses insulin release by acting on K_{ATP} channels and binding to somatostatin receptors.[12] The boy was treated with a combination of glucagon, diazoxide, nifedipine and hydrocortisone to treat persistent and refractory hypoglycemia, following the protocol suggested by the European Network for Research Into Hyperinsulinism of Infancy.[12] The mean dose of octreotide infusion from the largest cohort of patient with CHI was 17.8±7.5 μg/kg/day (range 7.5-30).[11] Our patient's dose of 10 μg/kg/day was comparatively lower but still within the range of that

Table 1. Laboratory results on initial investigation and on follow-up

Parameter	Age							
	5 days	1 month	2 months	5 months	13 months	19 months	22 months	26 months
Insulin, pmol/L	19.6	-	-	-	-	-	-	-
Cortisol, nmol/L	185.8	-	-	-	-	-	-	-
FT4, pmol/L	27.0	-	-	17.8	-	-	-	-
TSH, mIU/L	3.3	-	-	3.4	-	-	-	-
IGF-1, μg/L	36.6	-	-	-	-	-	-	-
17-OHP, nmol/L	11.0	-	-	-	-	-	-	-
PRA, ng/ml	20.4	-	-	-	-	-	-	-
Ammonia, μmol/L	93.0	-	-	-	-	-	-	-
HbA1c (%)	-	-	-	4.8	5.9	5.3	-	5.2
AST (U/L)	-	35	48	43	56	45	47	51
ALP (U/L)	-	320	422	339	394	345	342	317
ALT (U/L)	-	45	38	20	26	15	14	17

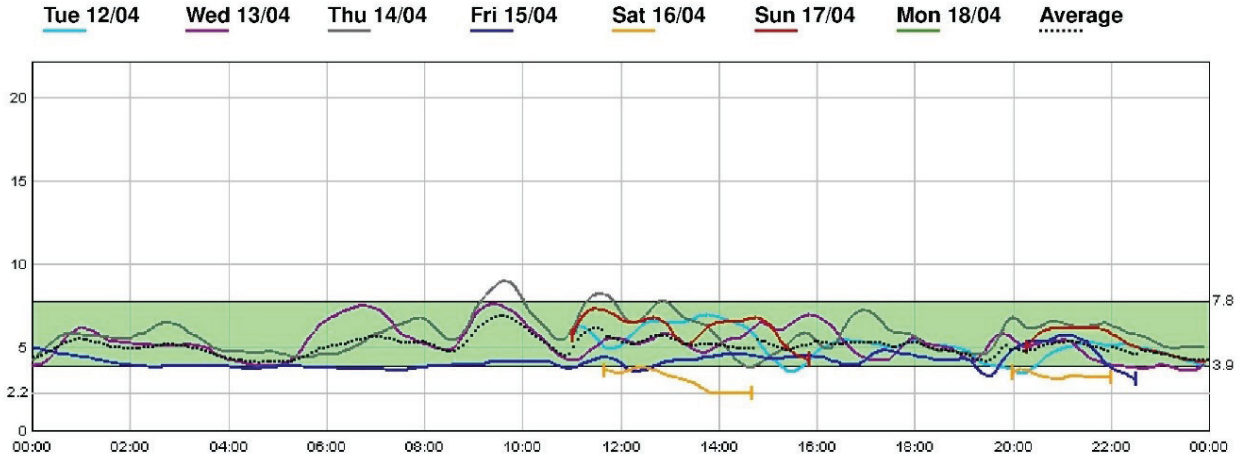
ONLINE FIRST | October 19, 2016 | https://doi.org/10.15605/jafes.031.02.16

study. The primary aim of starting octreotide is to turn off excessive insulin production, which has detrimental effects on brain development. Glycated hemoglobin increased from 4.8 to 5.2%, and 80% of his seven-day continuous glucose monitoring system readings fell within the targeted blood sugar range (Figure 1). These indicated that insulin production was suppressed to some extent, with fewer incidences of hypoglycemia .

Octreotide is known to cause gastrointestinal tract dysmotility, elevation of liver enzymes, gallbladder stones and growth and thyroid axis suppression. Use of octreotide for a mean follow up of 52.4±33.8 months (range of 6 months to 9.5 years) was associated with transient elevation of liver enzymes in 46.4% as early as one month after initiation, and resolution within 4 to 8 weeks despite continuation of treatment (n=13). Octreotide dose did not seems to be correlated with elevation of liver enzymes. In contrast, median age was found to be significantly lower in those with high liver enzymes (0.25 versus 1.5 months).[11] Due to very early onset hypoglycemia, regular octreotide has been maintained for about 2 years, starting as early as 2 weeks of life, with acceptable levels of transaminases (Table 1).

(7 days) Medtronic iPro2 Recorder #3059178

Sensor Data (mmol/L)



	Tue 12/04	Wed 13/04	Thu 14/04	Fri 15/04	Sat 16/04	Sun 17/04	Mon 18/04	Average / Total
# Sensor Values	155	288	288	271	62	104	0	1,168
Highest	7.0	7.6	9.0	5.7	3.8	7.3	N/A	9.0
Lowest	3.4	3.6	3.8	3.1	2.2	4.1	N/A	2.2
Average	5.1	5.3	5.9	4.2	3.1	5.8	N/A	5.1
Standard Dev.	0.9	1.0	1.1	0.5	0.5	0.9	N/A	1.2
MAD %	23.4	24.0	20.4	13.2	0.5	5.5	N/A	18.7
Correlation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
# Valid Calibrations	3	4	4	2	1	1	0	15
Designation	X	X	X	X	X	X	S	

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

Excursion Summary (mmol/L/day)

	Tue 12/04	Wed 13/04	Thu 14/04	Fri 15/04	Sat 16/04	Sun 17/04	Mon 18/04	Average / Total
# Excursions	3	3	4	5	1	0	0	16
# High Excursions	0	0	3	0	0	0	0	3
# Low Excursions	3	3	1	5	1	0	0	13
AUC Above Limit	0.00	0.00	0.03	0.00	0.00	0.00	N/A	0.01
AUC Below Limit	0.02	0.01	0.00	0.05	0.77	0.00	N/A	0.06

Duration Distribution (hh:mm)

Above 7.8	0:00	0%	0:00	0%	1:35	7%	0:00	0%	0:00	0%	0:00	0%	N/A		1:35	2%		
Within (3.9 - 7.8)	11:25	88%	21:45	91%	22:15	92%	13:55	62%	0:00	0%	8:40	100%	N/A		78:00	80%		
Below 3.9	1:30	12%	2:15	9%	0:10	1%	8:40	38%	5:10	100%	0:00	0%	N/A		17:45	18%		

Figure 1. Results of seven days on continuous glucose monitoring system.

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Gallbladder pathology was detected in 32.1%: 6 presented with gallstones and another 3 with bile sludge. There was no difference in the dose of octreotide between those with and without gallbladder pathology. The mean duration of treatment before the development of gallbladder pathology was 4.3±4.6 months in 9 patients. The 19 patients remained free of the complication after a follow up of 53.6±32.9 months on octeotide. The age at initiation of octeotide and development of gallbladder pathology was not found to be significant.[11] As there is a small risk of gallbladder pathology from literature, we plan to do regular hepato-biliary ultrasonography for the boy.

The birth weights of patients with the primary form of CHI or those with genetic mutations varied from low to large for gestational age.[11,13,20] In contrast, secondary hyperinsulinism may be seen in some newborns large for gestation, macrosomic, infant of diabetic mothers and asphyxia. What really triggers hyperinsulinism in the transient/secondary form of CHI is unknown.[8]

Secondary hyperinsulinism is a more common condition observed in large for gestational age, macrosomic and syndromic babies; and perinatal asphyxia.

Three out of 28 patients (10.7%) had height measurements less than -2 standard deviations (SD) for height-for-age. However, as their projected height was still within the target height, it was concluded that the patients had familial short stature. From the cohort, there was no significant difference in the levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 (IGFBP-3) before and after octreotide treatment.[11] Our patient had a height less than -2 SDs or 3rd percentile. With his mother's height at 146.0 cm and father's height at 160.0 cm, the target/mid-parental height is 159.5 cm. The boy's projected height is not more than 10 cm from the target height, indicating that he has familial short stature.

Looking at the boy's growth curve, his weight was also less than the 3rd percentile for weight-for-age, and the magnitude of his serial weight decrement was more abnormal than his height deficit. There are a number of reasons for failure to thrive. Nutritional intake is the predominant factor that affects the size of the child during the first 2 years of life, while growth hormone mainly exerts its influence later. Being a very picky eater with very little solid intake contributed to the boy's poor nutrition. Other factors were low birth weight, small for gestational age and small-built biological parents. The boy had no history of recurrent vomiting and diarrhea.

Congenital hyperinsulinism is most often sporadic.[14] While uncommon, familial disease connotes different genetic changes. Homozygous mutation is usually associated with severe disease, diazoxide resistance and KATP channel mutation. In contrast, autosomal dominant disease is milder, diazoxide-responsive and involves a non-KATP mutation.[13] Genetic or molecular studies can guide treatment, especially in the case of diazoxide resistance as it is highly suggestive of KATP channel mutation.[15] Interestingly, CHI is also characterized by a unique genetic feature. There is loss of normal maternal chromosome during embryonic development, indicating a loss of heterozygosity via a non-Mendelian mechanism. The patient would then have only a copy of mutant SUR1 genes from the unaffected father. The presence of growth-stimulating genes together with the absence of growth suppressing genes, the affected area would grow into a discrete focal lesion.[16]

Histologically, congenital hyperinsulinism is classified into focal (40% of cases) or diffuse forms.[17] Eighty percent of diazoxide resistance cases is due to the focal form, which is cured by surgical treatment. As such, diazoxide resistance warrants further workup to determine if surgery may be indicated.[18]

For the proband, analysis of coding and flanking intronic regions of the KCNJ11 gene, all coding regions and exon/intron boundaries of the ABCC8 gene (U63421 and L78208), P2 promoter and all coding regions and exon/intron boundaries of the HNF4A gene were performed by Sanger sequencing. The boy had heterozygous nonsense mutation, p.Arg934Ter (p.R934*) involving the amino acids c.2800C>T. This mutation resides in exon 23 of ABCC8 gene. He inherited this from his unaffected father who had the same mutation. No mutation was detected upon screening his mother. It is highly likely that he had loss of heterozygosity, and that his CHI is focal in nature. The only way to confirm this is by extracting DNA from the focal site during surgery. 18F-fluorodihydroxyphenylalanine (18-FDOPA) positron emission tomography scan is required to localize the focal lesion before surgery.[19] Arrangements are being made to fund and eventually refer this boy to the CHI Centre in Europe for 18F-DOPA scan and definitive surgery of the focal lesion.

This is the first case of diazoxide resistant CHI in our hospital since the Paediatric Endocrine Services opened to serve the East Coast of Malaysia 5 years ago. The uniqueness of this case is due to the boy's response to treatment with octreotide and the high possibility of a having focal form of CHI based on the genetic analysis. If he did not respond to the specified medical treatment, pancreatic surgery may have been the only option. However, this entails long term morbidities such as diabetes, pancreatic exocrine dysfunction and neurobehavioural deficits.[21]

As there is a likelihood of focal CHI based on the genetic study, this short review and follow-up of a confirmed case of diazoxide resistant congenital hyperinsulinism was able to demonstrate the efficacy of octreotide in turning off excessive insulin production, and the safety of long term use while awaiting definitive treatment.

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CONCLUSION

Diazoxide resistant congenital hyperinsulinism may respond to octreotide. The latter proved to be safe and effective for this patient.

Ethical Consideration
Patient consent form has been procured prior to the case report study.

Statement of Authorship
All authors have given approval to the final version submitted.

Author Disclosure
The authors declare that the abstract has been published in the International Journal of Paediatric Endocrinology entitled, "Diazoxide-unresponsive congenital hyperinsulinism associated with ABCC8 nonsense mutation with the following link: Int J Pediatr Endocrinol. 2015(Suppl1):86 and online on 28 April 2015 [doi: 10.1186/1687-9856-2015-S1-P86].

Funding Source
None.

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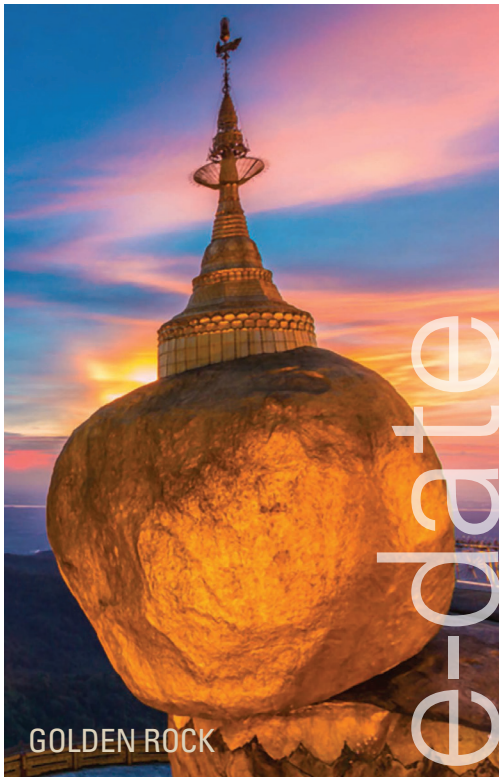

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