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ABOUT THE COVER
Rogelio V. Tangco, MD

A huge tree is a symbol of wisdom. It is firmly rooted in the earth for centuries imbibing the nutrients of the soil much like scholars store the wisdom of the ages. It has withstood time and the calamities that came its way, much science has withstood the shifts of paradigms through the centuries. It continually spreads out its wings reaching out to where the sun is, always seeking enlightenment as scholars do. A tree stands on top of the earth, gazing forward and backward, looking east and west. It is for all to see and to share in its bounty of the fruit of knowledge. There is no better emblem for a journal than a tree, as a depository of knowledge and wisdom and its relentless quest for what is new.

Trust and Commitment

Since November of 2015, the ASEAN Federation of Endocrine Societies (AFES) in its annual meeting has entrusted JAFES to the Philippine team for another term. It is an affirmation of trust that all of us here at the editorial office, on behalf of the PSEDM, keep with the members of the Federation. We stand by our commitment to deliver a world class, high quality publication, and be the voice of endocrinology for Southeast Asia to the global community.

Trust is most important in scientific publications. There is *the trust that authors give to the editors*. That in their hands, manuscripts are dealt with in accordance with the journal's standards, with utmost conscientiousness, due process, and, more importantly, confidentiality. Precious research ideas are kept within the confines of the agreement that manuscripts never venture outside of scholarly editorial deliberations on their merits (and flaws). Manuscripts are processed always within acceptable turnaround times; although sometimes, due to conflicts in busy schedules, several rounds of searching for the appropriate and reputable reviewers and their actual reviews do take some time.

Authors must be wary of devious publications that solicit articles from researchers, promising questionable index factors, readership and reputation. And it is not impossible for unscrupulous reviewers to delay their reviews of manuscripts intentionally, bringing research ideas from such manuscripts with them, all to the disadvantage of the authors.

On the other hand, *editors trust that the authors* have abided by the journal's instructions and guidelines. Declarations that the work is original and not for simultaneous consideration elsewhere, attestations of authorship by authors who fulfill the four ICJME criteria, disclosures of any funding and conflicts of interest, are not just forms to sign. They in fact do hold, despite academic pressures and publication requirements in this "publish or perish" world. Submission of the same manuscript to multiple publications is not ethical as it "unnecessarily wastes the precious reviewer resources of one or more journals," to paraphrase a colleague editor-in-chief of another journal.

Duplication and plagiarism are serious offenses that damage trust. Before the age of the Internet, editors relied on the collective knowledge of a pool of trusted reviewers, who, because of their research and publication experience, had the ability to spot plagiarism or another form of authorial misconduct and had the mettle of letting the editors know about this. Currently, as enhancement of quality assurance, editors resort also to anti-plagiarism software solutions that compare submitted text with research databases, and flag identical content. While there are open source software options, high quality screening entails significant cost. Starting this year, JAFES is forging a partnership with CrossRef to use CrossCheck.

Institutional ethical approval of research works is essential, and we add the submission of a scanned ethics approval to our Journal's policies.

We view the final published product of JAFES as a testament to the partnership between our valued authors and our esteemed editors, symbolic of the *mutual trust* between these two parties, who both, in their unique roles, fulfill the commitment of bringing to life scientific information that touches relevant issues of health care in our region.

Elizabeth Paz-Pacheco
Editor-in-Chief

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ORIGINAL ARTICLE

JAFES

Impact of a Gluten-free Diet on Several Growth Parameters in Children with Type 1 Diabetes Mellitus and Celiac Disease in Western Uttar Pradesh, India

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Abstract

Background. Celiac disease is frequently associated with uncontrolled blood sugar and impaired linear growth in a child with type 1 diabetes mellitus.

Objective. To study the impact of a gluten-free diet on several growth parameters in children with type 1 diabetes mellitus and celiac disease.

Methodology. Two hundred and fifty six patients with Type 1 diabetes mellitus were screened (149 males and 107 females) during the study period of two years. Patients were evaluated for the clinical signs, biochemical investigations and family history of celiac disease in a tertiary care health centre in Western Uttar Pradesh, India.

Results. Twenty four (9.3%) patients were diagnosed to have celiac disease; the mean age at diagnosis of diabetes was 9.3±7 years. Only one out of twenty four patients with celiac disease had been diagnosed before the detection of diabetes mellitus. Weight standard deviation score (SDS) increased from –0.12±1.3 at the start of gluten free diet to 0.8±0.9 after 12 months ($p<0.004$). Height SDS decreased from –2.46±1.1 at the start of gluten free diet to –2.14±0.9 after 12 months later ($p=0.087$). Bone age SDS increased from 9.2±6.3 at the start of gluten free diet to 10.3±6.7 after 12 months later. Height velocity increased from 4.7±0.7 cm/year in the year before treatment to 5.1±1.2 cm/year during treatment ($p=0.05$). The increase in Haemoglobin, serum calcium, and serum iron was statistically significant ($p<0.05$).

Conclusion. Patients with celiac disease associated with type 1 diabetes mellitus frequently have poor glycemic control and impairment in several growth parameters. When these patients are put on a gluten restricted diet, they show signs of improvement in terms of weight gain, height, serum Ca, serum iron, haemoglobin, and in height velocity.

Key words: type 1 diabetes mellitus, celiac diseases, short stature

INTRODUCTION

Type 1 diabetes mellitus is a common autoimmune disorder of the pediatric population, and it is frequently associated with other autoimmune conditions, especially with autoimmune hypothyroidism and celiac disease.[1] Celiac disease, or gluten-sensitive enteropathy, is an autoimmune disorder characterized by inflammation, villous atrophy and crypt hyperplasia of the small bowel mucosa after ingestion of dietary gluten and recovers when gluten-containing cereals are withdrawn from the diet.

The prevalence of rate of celiac disease in type 1 diabetes patients varies from study to study but ranges from 1% to 11%,[2] almost 10-20 times higher than that observed in the general pediatric population.[3] It has an incidence of 1 in 96 in north India.[4]

The presentation of celiac disease in Type 1 diabetes patients is extremely variable, with about less than one third of patients presenting with gastrointestinal complaints, some patients remain asymptomatic and are diagnosed during routine screening procedures.[5] The prominent extra intestinal manifestations of celiac disease are short stature, delayed puberty, poor glycemic control, nutritional anaemia, etc.[6,7]

Patients with celiac disease frequently present with growth failure and malnutrition besides hypocalcaemia and anaemia. Suboptimal growth velocity, poor weight gain and glycemic control appears to be multifactorial. Few studies support the role of RANKL/OPG system in the pathogenesis, but the exact cause for it is still unknown.[8]

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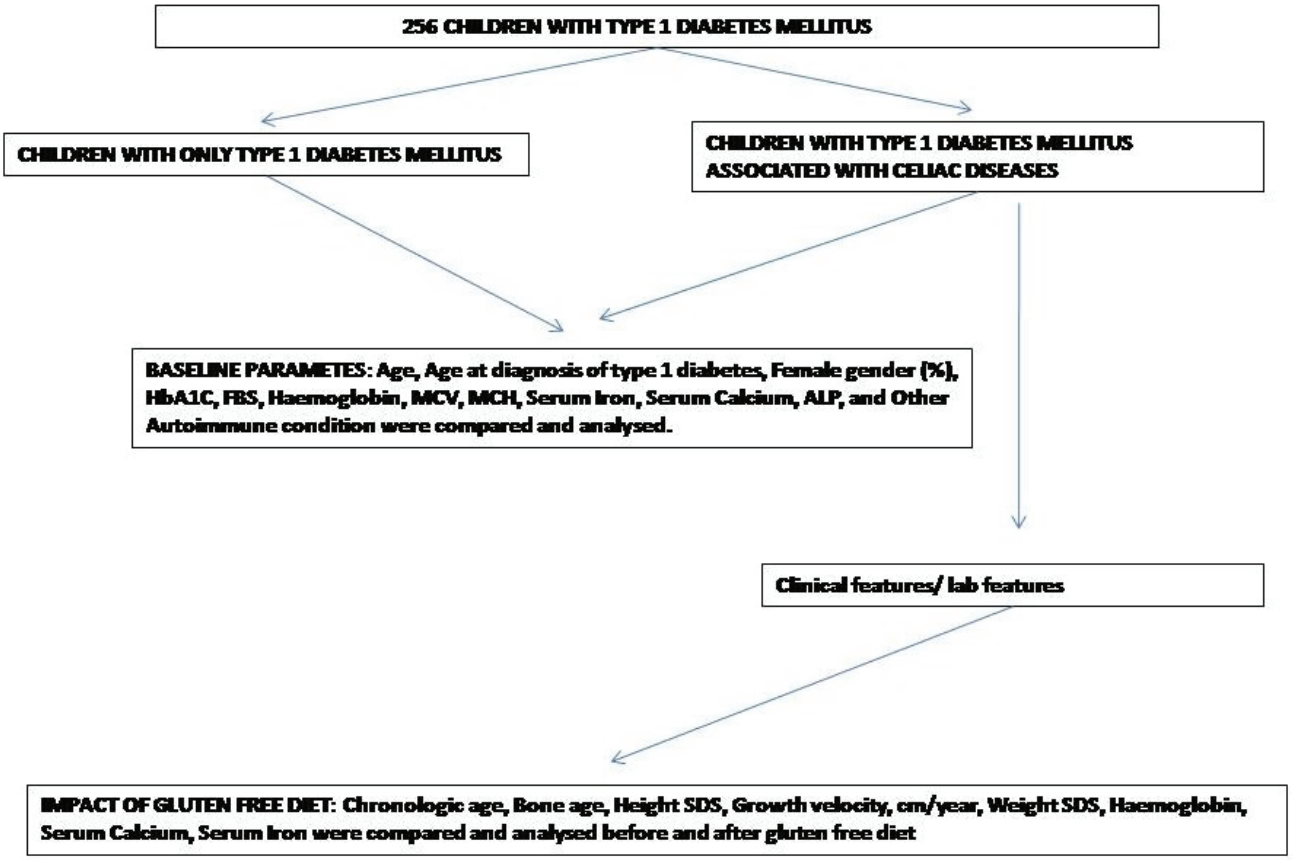

Figure 1. Study Design.

There are very few studies which show the effect of gluten free diet on weight, height, height velocity, and other biochemical parameters in celiac type 1 diabetes patients. There is very limited data from the Indian subcontinent.

The main aim of the present prospective observational study is to study the impact of a gluten-free diet on several growth parameters in children with Type 1 diabetes mellitus and celiac disease in Western Uttar Pradesh, India.

METHODOLOGY

This is a prospective cohort study carried out in the Department of Endocrinology and Metabolism during the study period of 2 years from July 2011 to June 2013.

Two hundred and fifty six children and adolescents with type 1 diabetes mellitus, aged 6 to 18 years, presenting to the endocrine OPD or admitted to the endocrinology ward were enrolled in the study (Figure 1). The study was approved by our local ethics committee.

After explaining the objectives of the study, a written informed consent was obtained from the patients or their parents. Patients were evaluated during the study period of two years from July 2011 to June 2013; inquiries were made for family history of other common autoimmune disorders, which are associated with type 1 diabetes.

Physical examination along with anthropometry and Tanner scoring was done by two endocrinologists, including one pediatric endocrinologist.

Blood samples were collected for: anti-TTG immunoglobulin subclass A (IgA) using enzyme linked immunosorbent assay (ELISA), complete blood count (CBC), iron profile, glycosylated hemoglobin (HbA1C), serum calcium, phosphorus and albumin.

Wrist and knee x-rays were done for bone age assessment in all patients with celiac disease in the hospital premises. The x-ray was reported first by experienced endocrinologists and then by radiologists, and if both agreed on a finding, it was accepted. Bone age was assessed using the Tanner Whitehouse 2 (TW2) system.

Short stature is a term used to describe a condition in which a child's or a teen's height is well below the 3rd percentile or 2 standard deviation (SD) below the mean height for age and gender and when the patient's linear growth velocity diminishes to less than 4 cm/yr (child's growth shifts to a lower channel). Delayed bone age was defined as a difference of at least 24 months between chronological age and bone age. Ethical clearance for the study was granted by the institutional ethics committee.

Vitamin D level was requested when deemed appropriate. Endoscopic duodenal biopsies were undertaken in the

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patients with signs and symptoms suspicious for celiac disease, if they were negative for anti-TTG antibody after informed consent.

Screening for other autoimmune disorders was done only when signs or symptoms were present, or if family history was suggestive of autoimmune disorders.

Statistical analysis

All categorical variables were expressed as percentages and all continuous variables were expressed as mean ± standard deviation. Student's t-test for independent samples was used to compare the mean values of continuous study variables. The 95% confidence intervals for difference of mean were used. Chi-square test and Fisher's exact tests were used to observe an association between the qualitative study and outcome variables. All p values <0.05 were taken as significant. Statistical analysis was performed by using software SPSS version 17.

RESULTS

Twenty-four (9.37%) patients were diagnosed to have celiac disease; the mean age at diagnosis of diabetes was 9.34±7.3 years. Only one patient out of twenty four (0.041%) patients with celiac disease associated with type 1 diabetes had been diagnosed before the detection of diabetes mellitus.

Table 1 shows the comparison between the patients with and those without celiac disease, the age of presentation with celiac disease was almost one year later than the age of presentation of patients without celiac disease.

Patients with celiac disease had much higher HbA1C, FBS and ALP in comparison with patients without celiac disease, which are all significant (<0.05). However, celiac disease patients had lower hemoglobin, MCV, MCH, serum iron, and serum calcium and again, all were statistically significant (<0.05). Sex ratio was found to be equal in both, while the incidence of other autoimmune conditions was found to be insignificant.

Table 2 shows the demographic profile of patients with celiac disease and the most common manifestations. Some uncommon manifestations were also present in a small number of patients, these are rickets (20.8%), recurrent hypoglycemia (16.6%), carpopedal spasm (8.3%), and night blindness (8.3%).

Table 3 shows the growth parameters and clinical characteristics of the 24 type 1 diabetes mellitus patients with celiac diseases (14 males and 10 females) less than 18 years of age enrolled in the study. Weight standard deviation score (SDS) increased from –0.12±1.3 at the start of gluten free diet to 0.8±0.9 after 12 months of study (p<0.05). Height SDS decreased from –2.46±1.1 at the start of gluten free diet to –2.14±0.9 after 12 months (p=0.087). Bone age SDS increased from 9.2±6.3 at the start of gluten

Table 1. Baseline parameters between type 1 diabetes with and without celiac diseases

Parameters	Patients with celiac diseases (24)	Patients without celiac diseases (212)	*p* value
Age (years)	12.1±4.8	11.5±6.4	0.46
Age at diagnosis of type 1 diabetes (years)	9.34 ± 7.3	9.6±6.2	0.67
Female gender (%)	10 (41.6%)	90 (42%)	0.23
HbA1C	11.2± 1.3	9.1±1.6	<0.05
FBS (mg/dl)	184± 67.4	143±26.8	<0.05
Hemoglobin (gm/dl)	9.6±1.8	10.6±1.3	<0.05
MCV (fl)	75.9±6.9	80.8±8.6	<0.05
MCH (pg)	23.8±2.1	28.2±1.6	<0.05
Serum Iron (normal 9–30.4 µmol/L)	9.2±4.3	16.8±3.7	<0.05
Serum Calcium (mg/dl)	7.4± 2.4	8.9±0.9	<0.05
ALP (IU/L)	624±164	189±56	<0.05
Other Autoimmune condition	03 (12.5%)	46 (21.5%)	0.138

T1DM = Type 1 diabetes; HbA1c = glycosylated hemoglobin, FBS = Fasting blood sugar, ALP = Alkaline phosphatase

Table 2. Clinical profile of children with type 1 diabetes associated with celiac disease, N=24, Uttar Pradesh, India

Clinical features / lab features	Number of Patients (N=24)	Percentage (%)
Short stature	14	58.3
Delayed puberty	07	29.1
Carpopedal spasm	02	8.3
Diarrhoea	15	62.5
Abdominal pain / bloating sensation	14	58.3
Sticky stools	14	58.3
Night blindness	02	8.3
Delayed bone age	18	75
Low vitamin D level	05	20.8
Rickets	05	20.8

Table 3. Evaluation of height SDS, growth velocity, weight SDS, haemoglobin, serum iron and serum calcium after gluten free diet (<18 years of age)

	At the start of treatment (24)	After 1 year of treatment (24)	p value
Chronologic age, years	12.1+4.8	13.1+4.8	----
Bone age, years (TW2)	9.2+6.3	10.3+6.7	0.145
Height SDS	-2.46+1.1	-2.14+0.9	0.087
Growth velocity, cm/year	4.7+0.7	5.1+1.2	0.067
Weight SDS	-0.12+1.3	0.8+0.9	<0.05
Hemoglobin (gm/dl)	9.6+1.8	10.8+2.4	<0.05
Serum Calcium (mg/dl)	7.4+ 2.4	9.2+1.8	<0.05
Serum Iron (normal 9–30.4 µmol/L)	9.2+4.3	15.6+3.8	<0.05

SDS: Standard deviation score

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free diet to 10.3±6.7 after 12 months. Height velocity increased from 4.7±0.7 cm/year in the year before treatment to 5.1±1.2 cm/year during treatment (p=0.05). Hemoglobin, serum calcium and serum iron all increased significantly (p<0.05).

Patients were divided into three groups: Prepubertal (7), pubertal (7 patients, either with short stature or other clinical feature of celiac disease), and postpubertal (10, seven with delayed puberty and three with age more than 14 years, normal puberty but height less than 2SD). Of 7 patients in the prepubertal age group, only 1 patient attained puberty, the rest of the patients remain prepubertal. In the postpubertal patients, 3 out of 7 patients attained the puberty; and in the rest of the cases there was improvement in height and growth velocity. Besides the gluten free diet, other confounding factors which might contribute to clinical results might be pubertal growth spurt, good nutrition, better education, motivation, and presence of other autoimmune disorders.

After 1 year of follow-up, there was a significant increase in weight SDS (p<0.05), whereas the increase in height SDS (p=0.087) did not reach statistical significance. Height velocity increased from 4.7±0.7 cm/year in the year before treatment to 5.1±1.2 cm/ year during treatment (p=0.05).

DISCUSSION

This is a prospective observation study carried out in the Department of Endocrinology and Metabolism during the 2 year study period from July 2011 to June 2013.

Celiac disease is an autoimmune-mediated enteropathy precipitated by the ingestion of gluten-containing foods (including wheat, rye and barley) in genetically susceptible persons. Celiac disease is also frequently associated with type 1 diabetes mellitus but less frequently than autoimmune thyroiditis. During the last few years, numerous screening studies conducted all over the world showed the increased celiac diseases prevalence in type 1 diabetes mellitus.[5]

However data from South Asia is very limited, especially in the Indian subcontinent.[9] Its prevalence in children and adolescents with type 1 diabetes ranges from 5 to 7%, the previous study done by Bhadada SK et al.,[10] showed the prevalence rate of 11.1% in type 1 diabetic population.

Although screening detected cases of celiac diseases in children with diabetes mellitus, the majority are reported to be asymptomatic or silent.[11-13]

Studies on the association of celiac diseases on glycemic control and growth in patients with T1D have shown conflicting results.[13–14] In the present study, patients with type 1 diabetes with celiac disease had poor glycemic control and nutritional status as judged by fasting blood sugar, HBA1C, serum Ca, serum iron and growth velocity.

While the majority of our patients with celiac diseases were found to have no gastrointestinal symptoms, an index of malabsorption with iron deficiency, and hypocalcaemia were also prominent in the celiac disease patients.[15] The potential for early reversal of abnormalities in indices of intestinal malabsorption (iron and calcium deficiencies) is one of the advantages for screening asymptomatic children for early detection of celiac diseases in T1D patients.

The predominance of male gender among celiac diseases patients in the present study has been also been observed in few studies;[17] while other studies in different races have shown female predominance.[16] The gender variation likely represents variability of genetic and environmental factors among different races.

Patients were educated on dietary modification chart, audio visual aids, continuous follow up visits, awareness about impact of nonadherence, anthropometric measurements and laboratory investigations. Poor weight gain, height and growth velocity after institution of a gluten free diet have been shown in a group of children with DM, suggesting that they struggled to eat a gluten free diet that is suitable for children with diabetes. We found that compliance with such a restricted diet was not easy in all children. However, our most important observation was a significant improvement in weight, height and growth velocity in those children who were compliant with the diet, but not in those who continued to eat gluten.

After 1 year of follow-up, there was a significant increase in weight SDS (p<0.05), whereas the increase in height SDS (p=0.087) did not reach significance. However, height velocity increased from 4.7±0.7 cm/year in the year before treatment to 5.1±1.2 cm/year during treatment (p=0.05). Haemoglobin, mean corpuscular volume, serum calcium and serum iron also increased significantly.

Numerous studies have shown the positive effect of gluten-free diet on increased weight, height and growth velocity[18] as well as on serum calcium, serum ferritin and haemoglobin.[19] Moreover improvement of bone status in patients with type 1 diabetes mellitus with adherence to gluten-free diet has been reported.[20]

CONCLUSION

Patients with celiac disease associated with type 1 diabetes mellitus frequently have poor glycemic control and impairment in several growth parameters. When these patients are put on gluten restricted diet, they show signs of improvement in the term of weight gain, height, serum Ca, serum iron, haemoglobin, and in height velocity.

Limitations

The improvement in the growth parameters may not be explained by the gluten free diet alone, but also other confounders such as pubertal growth spurt, good nutrition, better education, motivation,

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and presence of other autoimmune disorder in the patient. As a limitation of this study, the impact of these confounders and its interaction with the gluten free diet was not investigated.

Statement of Authorship

All authors have given approval to the final version submitted.

Conflict of Interest

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

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JAFES

ORIGINAL ARTICLE

Clinical Utility of Self-Reported Oral Health Measures for Predicting Periodontitis among Adult Filipinos with Type 2 Diabetes Mellitus

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Abstract

Background. The likelihood of periodontitis among type 2 diabetes is thrice the non-diabetic population and progresses rapidly when uncontrolled. An inexpensive and easy way of dental assessment via self-reported oral health questionnaire has great potential as a screening tool.

Objective.This study aims to validate self-reported oral health measures, socio-demographic and medical variables in predicting the severity of periodontitis in Filipino adults with type 2 diabetes.

Methodology. The validated self-reported oral health questionnaires created by the CDC Periodontal Disease Surveillance Project was translated into Filipino and used. A cross-sectional study of 180 participants was conducted in a single institution. Multivariable logistic regression analyses were used to determine significant predictors of serious periodontitis.

Results. Male sex [OR=2.17], low educational status [OR=2.98], poor glycemic control [OR=2.58], less frequent dental visits [OR=2.77] and teeth loss >6 [OR=5.02] were considered to be predictive of serious periodontitis. Self-reported oral health variables like gum disease –Q1 [OR=8.33], state of gum health –Q2 [OR=0.39], loose teeth –Q3 [OR=63.0], brushing of teeth –Q4 [OR=0.65], use of mouthwash –Q4 [OR=0.69] and poor tooth appearance –Q5 [OR=48.42] were also shown to be significantly predictive of serious periodontitis. A recommended set of questions and proposed scoring system based on the logistic regression analysis of each predictor's strength was then formulated.

Conclusion. The use of specific self-reported oral health questions, certain socio-demographic and medical variables appeared to be highly predictive of serious periodontitis among Filipinos with type 2 diabetes. This provides a cost-effective and rapid method of screening patients who are in need of immediate dental evaluation.

Key words: Oral Health Questionnaire, periodontitis, type 2 diabetes mellitus, dental care

INTRODUCTION

The global prevalence of type 2 diabetes mellitus is rapidly increasing as a result of population ageing, urbanization and its associated lifestyle changes. Its prevalence has more than doubled over the past three decades.[1] In 2014, the global prevalence of diabetes was estimated to be 9% among adults, where 90% were considered as having type 2 diabetes.[2] By 2030, the prevalence is expected to increase to 7.7% affecting 439 million adults. Between 2010 and 2030, there will be a 69% increase in the number of adults with type 2 diabetes in developing countries and a 20% increase in developed countries.[3] In Asia, similar epidemiologic trends are being seen as more Asians adopt a westernized lifestyle. The Philippines is a country considered to have a high prevalence of type 2 diabetes, with an estimated 7.8 million cases and is projected to be ranked 9th overall by 2030.[2] In a recent local study, the 9-year incidence of type 2 diabetes was 16.3% while its prevalence was 28.0%.[4]

Diabetes mellitus is a chronic metabolic disorder characterized by a deficiency in insulin secretion or an increased insulin resistance, resulting in hyperglycemia. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset) in particular results from the body's ineffective use of insulin and is largely the result of excess body weight and physical inactivity.[5] People with type 2 diabetes, especially when it is poorly controlled, have an increased susceptibility to chronic infections and inflammation of oral tissues, including periodontal diseases (chronic gingivitis and periodontitis), dental caries, and oral candidiasis. This contributes to substantial oral functional disability.[6] Oral complications are seen in 1/3 of people with type 2 diabetes.[7]

Type 2 diabetes is considered a risk factor for the development of periodontitis which is now considered to be the sixth complication of both type 1 and type 2 diabetes.[8-9] Severe periodontitis was more often found in

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patients with type 2 diabetes (60% vs 39%).[10] The likelihood of periodontitis among type 2 diabetics was 3 times greater than the general population, and progresses rapidly when poorly controlled.[11] Majority of well-controlled studies showed a higher prevalence and severity of periodontal disease in type 2 diabetes with similar local irritation including greater loss of attachment, greater alveolar bone loss, increased bleeding on probing, and increased tooth mobility resulting in tooth loss.[12-15] Similar trends were found in a local study where prevalence of periodontitis was noted to be at 68.23%.[16]

Furthermore, poor perception of one's oral health status among people with type 2 diabetes had a strong negative impact on health-related quality of life.[17-18] Therefore, people with type 2 diabetes must be educated about the importance of removing oral plaque daily through meticulous oral hygiene, managing mouth dryness and diet, ceasing tobacco use and obtaining regular professional dental care and cleaning.[6] The early detection and treatment of periodontal disease has led to improved glycemic control in patients with type 2 diabetes[9] and was also confirmed in a recent study from the Philippines.[16]

Adults with diabetes are less likely to consult a dentist than to seek consult with a health care provider for diabetes care.[20] A Philippine study by Ofilada among Filipinos with type 1 diabetes revealed that financial insufficiency, fear and the lack of dentists who are willing to treat diabetic patients were the common barriers to dental care.[21] Patients with type 2 diabetes were more likely to receive more recommended elements of diabetes care whereas routine dental check-ups were commonly missed. They were also more likely to have numerous follow-ups with health care providers for aggressive glycemic control.[22] This provides an opportunity for health care providers to screen and educate patients regarding the possible oral complications that might develop.

Given the importance of good oral health among type 2 diabetes patients and the current outpatient encounters with health care providers, a simplified oral health screening questionnaire might be of use in assessing oral health status of all patients diagnosed with type 2 diabetes. This would translate to earlier detection and referral to a dental specialist which would then contribute to better glycemic control when treated. Currently, the International Diabetes Federation (IDF) guidelines on oral health recommends routine clinical screening questions as the basis for further referral and management by the dentist.[23] The Philippine Dental Association and the UNITE for Diabetes Philippine clinical practice guidelines both recommend screening for clinical symptoms and early referrals to dental service for better oral care and management.[24]

As of 2007, the Center for Disease Control and Prevention (CDC) in collaboration with the American Academy of Periodontology (AAP) has been working on the creation, formulation and evaluation of a self-report questionnaire in predicting the prevalence of periodontitis among adult population. Through a rigorous systematic process of selection and evaluation, the extensive CDC–AAP effort identified a set of eight self-report oral health questions that were considered promising for predicting the prevalence of periodontitis (Table 1).[25] These eight oral health questions were previously selected and tested cognitively in United States adults where revisions were recommended (Table 2).[26] An initial field assessment of these questions done in Australia demonstrated promising results for predicting the prevalence of periodontitis in adults.[27] Similar assessment of these questions were validated in a pilot study done in the U.S. by Paul Eke and Bruce Dye.[28] In addition to the oral health variables, several demographic and medical variables (age, sex, smoking history, education, diabetes duration, glycemic control) were also considered to be predictive of prevalence and severity of periodontitis.[16, 28]

Table 1. Self-report questions created by the CDC Periodontal Disease Surveillance Project

Preamble: Gum disease is a common problem with the mouth. People with gum disease might have swollen gums, receding gums, sore or infected gums, or loose teeth.

1. Do you think you might have gum disease?
   ☐ Yes ☐ No ☐ Don't know ☐ Refused
2. Overall, how would you rate the health of your teeth and gums?
   ☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor ☐ Don't know ☐ Refused
3. Have you ever had treatment for gum disease, such as scaling and root planing, sometimes called "deep" cleaning?
   ☐ Yes ☐ No ☐ Don't know ☐ Refused
4. Have you ever had any teeth become loose on their own, without an injury?
   ☐ Yes ☐ No ☐ Don't know ☐ Refused
5. Have you ever been told by a dental professional that you lost bone around your teeth?
   ☐ Yes ☐ No ☐ Don't know ☐ Refused
6. During the past 3 months, have you noticed a tooth that doesn't look right?
   ☐ Yes ☐ No ☐ Don't know ☐ Refused
7. Aside from brushing your teeth with a toothbrush, in the last 7 days, how many times did you use dental floss or any other device to clean between your teeth?
   _____ Number
8. Aside from brushing your teeth with a toothbrush, in the last 7 days, how many times did you use mouthwash or other dental rinse product that you use to treat dental disease or dental problems?
   _____ Number

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Table 2. Recommended revised questions for periodontal disease surveillance

1. Gum disease is a common problem with the mouth. People with gum disease might have bleeding in the gums around the teeth, swollen gums, receding gums, or sore or infected gums that lasts for >2 weeks and is not caused by injury or problems with partials or dentures.
   Do you think you might have gum disease? ☐ Yes ☐ No
2. Overall, how would you rate the health of your teeth and gums?
   ☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor ☐ Don't know ☐ Refused
3. Have you ever...
   ...had surgery to clean underneath your gums? (not root canals or cleanings done at regular checkups)
   ☐ Yes ☐ No
   ...had scaling or root planing, sometimes called "deep" cleaning? (not root canals or cleanings done at regular checkups)
   ☐ Yes ☐ No
   ...had any teeth that became loose on their own, without an injury? (not baby teeth) ☐ Yes ☐ No
   ...been told by a dental professional that you lost bone around your teeth? ☐ Yes ☐ No
4. In the last 7 days, how many times did you…….
   ...brush your teeth with toothpaste? _____ Number
   ...use dental floss or dental tape? _____ Number
   ...use mouthwash or other dental rinse product? _____ Number
5. During the past 3 months, have you noticed that you have a tooth that doesn't look right? ☐ Yes ☐ No

As of now, there is still no locally validated clinical oral health screening questionnaire. Application of the validated CDC self-reported oral health questionnaire can help in predicting diabetic patients at risk for periodontitis and warrant earlier dental consults. An inexpensive and easy tool for clinical assessment would be useful especially in a developing country like the Philippines where resources for health care access are limited.

This paper aims for the following:

1. To determine the prevalence and severity of periodontitis among patients with type 2 diabetes categorized according to tooth loss, medical and socio-demographic variables;
2. To determine the response rates of patients with type 2 diabetes for each self-reported oral health questions;
3. To determine the predictors of the seriousness of periodontitis among self-reported oral health variables, clinically determined number of teeth loss and socio-demographic and medical variables;
4. To present a culturally accepted and validated self-reported oral health questionnaire and propose a scoring system that will predict severity of periodontitis among patients with type 2 diabetes.

METHODOLOGY

Self-Reported Oral Health Questionnaire

The validated self-reported oral health questionnaire created by the CDC Periodontal Disease Surveillance Project was used in this study (Table 2). The content of the questionnaire was carefully translated into the Filipino language by expert linguists. One linguist translated the English questionnaire to Filipino, while another translated the Filipino version back to English. The resulting translation was then compared to the original English version for verification until a final Filipino version of the questionnaire was created.

The translated Filipino version of the questionnaire was then incorporated with the original English version to create a questionnaire that would be expressed in two languages (English and Filipino). A pilot testing of the newly translated questionnaire was conducted with 20 Filipinos with type 2 diabetes who criticized and observed the applicability of the translated version. All suggestions, comments and criticisms were noted and resolved during the discussion thereby formulating a revised and improved version of the questionnaire.

Sample Size Calculation

Using PASS (Power Analysis and Sample Size) 2008 software, the minimum sample size requirement was computed using the parameters for logistic regression analysis: alpha (α) = 0.05, power (1-β) = 80%, X1 (percent of patients with tooth loss) = 67.6%, P0 (percent of periodontitis among patients without tooth loss) = 8.8%, P1 (percent of periodontitis among patients with tooth loss) = 30%. Except for the alpha level and power which were set by the reseachers, all other parameters were taken from the literature. The computed 136 minimum sample size was increased to 180 accounting for possible 20% non-response.

Selection of Participants

Inclusion Criteria

1. Adult (Age ≥35 years) Filipino diagnosed with type 2 diabetes for at least 1 year. Diagnosis of Type 2 diabetes will be based on the American Diabetes Association criteria[29] as follows: fasting blood sugar ≥126 mg/dl on 2 determinations; symptoms of hyperglycemia and random blood sugar ≥200 mg/dl; 2-hour plasma glucose ≥200 mg/dl after a 75 grams oral glucose tolerance test; standardized HbA1C ≥6.5%;
2. Dentulous persons with ≥6 teeth present;
3. Able to read, comprehend and respond to the series of questions;
4. Willingness to undergo a dental examination.

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Exclusion Criteria

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

Data Collection

This was a cross-sectional study conducted at the out-patient clinics of Philippine General Hospital. This study was reviewed and approved by the University of the Philippines Manila Research Ethics Board (UPMREB) Panel.

Potential study participants were provided with an overview of the study, its nature, purpose and significance. Once eligibility status was determined, recruited participants provided written informed consent (Appendix A) and contact information obtained. The interviewer then asked additional questions about gender, age, smoking status, education level, duration of diabetes and recent HbA1C level. Participants were then given the self-reported oral health questionnaire. All recruited patients were finally referred to a dentist for formal dental and periodontal evaluation. Results of the periodontal evaluation were given to the patient and subsequent intervention and follow up were advised accordingly to ensure proper treatment of periodontitis. All patient's data obtained were recorded individually using a patient data sheet while periodontal evaluation results were recorded using a separate dental sheet.

Periodontitis was determined from a full-mouth periodontal examination using the basic elements from the NHANES periodontal examination protocol. This included measuring gingival recession and probing depth (PD), to calculate loss of attachment, using a color-banded probe graduated at 2, 4, 6, 8, 10, and 12 mm. Measurements were made on six sites per tooth (mesio-buccal, buccal, distobuccal, mesio-lingual, lingual, and disto-lingual) for all teeth (excluding 3rd molars) by one examiner. Number of remaining teeth and lost teeth were also documented.[30]

Variables

From each participant, we collected socio-demographic and medical variables using a standard data collection form. Pertinent socio-demographic variables included age in years (specified as both continuous and categorical with two categories: 35-59, and ≥60), gender and educational attainment (high school graduate or lower and some college education or higher). Pertinent medical variables included cigarette smoking status (current smokers were subjects who had smoked ≥100 cigarettes in their lifetime and were currently smoking; former smokers were subjects who had smoked ≥100 cigarettes in their lifetime and not currently smoking; non-smokers were subjects who had not smoked ≥100 cigarettes in their lifetime),[31] duration of diabetes (grouped into ≤10 years and >10 years), frequency of dental visits within a year and recent HbA1C level (within the last 3 months). Number of teeth remaining and number of teeth lost were also recorded and determined.

In this study, 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 >3 mm probing depth and ≥3 mm periodontal attachment loss at the same site. Serious periodontitis was considered for participants fulfilling the criteria for moderate or severe periodontitis. Participants were classified according to severity of periodontitis using the following criteria (NHANES III protocol, 1988-1994).[32]

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 with ≥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: persons with 6 or more teeth present who did not fulfill any of the above criteria.

Data Analysis

Data analysis was done using the software Stata SE version 12. Different socio-demographic and medical variables, number of teeth lost and responses to self-reported oral health questionnaire were tabulated and recorded using descriptive statistics (mean, percentage). Multivariable logistic regression analyses were used to determine significant predictors that predicted the prevalence of serious periodontitis (created as moderate and severe disease versus mild and no disease combined). The predictive power of each variable was calculated and expressed using odds ratio, 95% confidence interval and p-value. The multivariate logistic regression analysis was then used to create a scoring system.

RESULTS

In total, 93.9% of the study participants had clinically defined periodontitis: 29.4% had mild periodontitis, 64.5% had serious periodontitis (moderate and severe periodontitis). Serious periodontitis was significantly higher among males, persons with low educational background, persons with current and smoking history, long diabetes duration, less frequent dental visits, poorly controlled glycemic state (Hba1c ≥7%) and persons who lost ≥6 teeth.

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Table 3 summarizes the response rates to each self-reported oral health questions by periodontitis status. In general, understanding and responses to all oral health questions were very high and consistent. The states of gum health in question number 2 were converted to numerical equivalents upon recording ranging from 0 to 5. As observed, a bigger percentage of participants with serious periodontitis answered yes for gum disease (Q1), loose teeth (Q3), bone loss (Q3) and tooth appearance (Q5) while no for gum surgery (Q3) and scaling or root planing (Q3). Surprisingly, almost (>98.3%) all participants reported brushing their teeth regularly regardless of their eventual periodontitis state. On the other hand, most (>70%) did not report regular dental flossing and mouthwashing regardless of their final periodontal state. Majority of participants with serious periodontitis were also observed to report poor state of their gum health in response to question 2.

Table 3. Prevalence and severity of periodontitis by responses to self-reported oral health variables

Question	Response	Total Sample N	Total Periodontitis N (%)	Mild Periodontitis N (%)	Serious Periodontitis N (%)
N		180 (100)	169 (93.9)	53 (29.4)	116 (64.5)
Gum Disease (Q1)	Yes	53 (29.4)	53 (31.4)	5 (9.4)	48 (41.4)
Health of Gums (Q2)	Excellent (5)	14 (7.8)	11 (6.5)	8 (15.1)	3 (2.6)
	Very Good (4)	16 (8.9)	13 (7.7)	11 (20.8)	2 (1.7)
	Good (3)	37 (20.6)	34 (20.1)	11 (20.8)	23 (19.8)
	Fair (2)	40 (22.2)	40 (23.7)	19 (35.8)	21 (18.1)
	Poor (1)	58 (32.2)	57 (33.7)	3 (5.6)	54 (46.6)
	Don't Know (0)	15 (8.3)	14 (8.3)	1 (1.9)	13 (11.2)
Gum Surgery (Q3)	No	170 (94.4)	159 (94.1)	49 (92.4)	110 (94.8)
Scaling or Root Planing (Q3)	No	163 (90.6)	154 (91.1)	49 (92.4)	105 (90.5)
Loose Teeth (Q3)	Yes	59 (32.8)	59 (34.9)	1 (1.9)	58 (50)
Bone Loss (Q3)	Yes	10 (5.6)	10 (5.9)	0 (0)	10 (8.6)
Toothbrush (Q4)	0	3 (1.7)	3 (1.8)	0 (0)	3 (2.6)
	1	20 (11.1)	19 (11.2)	4 (7.5)	15 (12.9)
	2	65 (36.1)	64 (37.9)	18 (34)	46 (39.7)
	3	88 (48.9)	79 (46.8)	31 (58.5)	48 (41.4)
	4	4 (2.2)	4 (2.3)	0 (0)	4 (3.4)
Dental Floss (Q4)	0	156 (86.7)	148 (87.5)	44 (83)	104 (89.7)
	1	13 (7.2)	11 (6.5)	6 (11.3)	5 (4.3)
	2	6 (3.3)	5 (3)	1 (1.9)	4 (3.4)
	3	5 (2.8)	5 (3)	2 (3.8)	3 (2.6)
Mouthwash (Q4)	0	128 (71.1)	121 (71.6)	32 (60.4)	89 (76.8)
	1	31 (17.2)	28 (16.6)	12 (22.6)	16 (13.8)
	2	9 (5)	9 (5.3)	3 (5.7)	6 (5.2)
	3	12 (6.7)	11 (6.5)	6 (11.3)	5 (4.3)
Tooth Appearance (Q5)	Yes	112 (62.2)	111 (65.7)	8 (15.1)	103 (88.8)

Table 4. Predictive value of number of tooth loss, socio-demographic, medical variables and self-reported oral health measures for serious periodontitis (moderate + severe)

Variables	Categories / Responses	Non-serious Periodontitis	Variables	Categories / Responses	Non-serious Periodontitis
SOCIO-DEMOGRAPHIC AND MEDICAL VARIABLES					
Age	Age ≥60	17 (26.6)	33 (28.5)	1.10	0.787
	Age 35-59	47 (73.4)	83 (71.5)		
Sex	Male	17 (26.6)	51 (44.0)	2.17	0.020
	Female	47 (73.4)	65 (56.0)		
Education	Elementary to High School	30 (46.9)	84 (72.4)	2.98	0.001
	College	34 (53.1)	32 (27.6)		
Smoking Status	Never	46 (71.9)	76 (65.5)	1.48	0.200
	Former	18 (28.1)	35 (30.2)		
	Current	0 (0)	5 (4.3)		
Diabetes Duration	≥10 years	27 (42.2)	63 (54.3)	1.63	0.121
	<10 years	37 (57.8)	53 (45.7)		
Glycemic Control	HbA1C ≥7%	33 (51.6)	85 (73.3)	2.58	0.004
	HbA1C <7%	31 (48.4)	31 (26.7)		
Dental Visits	Almost none per year	38 (59.4)	93 (80.2)	2.77	0.003
	At least once per year	26 (40.6)	23 (19.8)		
Tooth Loss	≥6	45 (70.3)	107 (92.2)	5.02	0.001
	<6	19 (29.7)	9 (7.8)		
ORAL HEALTH MEASURES					
Gum Disease (Q1)	Yes	5 (7.8)	48 (41.4)	8.33	0.001
Health of Gums (Q2)	1=Poor; 2=Fair; 3=Good; 4=Very good; 5=Excellent	3 (2-4)	1 (1-3)	0.39	0.001
Gum Surgery (Q3)	Yes	4 (6.3)	6 (5.2)	0.82	0.763
Scaling or Root Planing (Q3)	Yes	6 (9.4)	11 (9.5)	1.01	0.981
Loose Teeth (Q3)	Yes	1 (1.6)	58 (50.0)	63.0	0.001
Bone Loss (Q3)	Yes	0	10 (8.6)	-	-
Toothbrush (Q4)	Number of times per day	2.5 ± 0.6	2.3 ± 0.8	0.65	0.045
Dental Floss (Q4)	Number of times per day	0.3 ± 0.7	0.2 ± 0.6	0.81	0.361
Mouthwash (Q4)	Number of times per day	0.7 ± 1.0	0.4 ± 0.8	0.69	0.038
Tooth Appearance (Q5)	Yes	9 (14.1)	103 (88.8)	48.42	0.001

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Table 5. Multivariate logistic regression analysis and proposed scoring of significant oral health predictors for serious periodontitis

Predictors	Odds Ratio [95%CI]	p-Value	Proposed Score
Low Education Status	5.02 [1.47- 17.11]	0.010	+ 3
Tooth Loss >6	8.17 [1.63- 40.98]	0.011	+ 4
Health of Gums (Q2)	0.56 [0.34- 0.90]	0.017	- 1 (5)
Loose Teeth (Q3)	29.56 [2.99- 292.35]	0.004	+ 7
Tooth Appearance (Q5)	31.63 [8.87- 112.75]	0.001	+ 7

Table 6. Recommended oral health questionaire and proposed 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		

As shown in Table 4, socio-demographic and medical variables considered to be significantly predictive of serious periodontits were male sex [OR =2.17; 95%CI 1.12-4.35], low educational status [OR =2.98; 95%CI 1.57-5.63], poor glycemic control [OR =2.58; 95%CI 1.36-4.88], less frequent dental visits [OR =2.77; 95%CI 1.41-5.44] and teeth loss >6 [OR =5.02; 95%CI 2.11-11.94]. Self-reported oral health variables shown to be significantly predictive of serious periodontitis included gum disease –Q1 [OR =8.33; 95%CI 3.11-22.30], state of gum health –Q2 [OR =0.39; 95%CI 0.28-0.54], loose teeth –Q3 [OR =63.0; 95%CI 8.45-469.58], brushing of teeth –Q4 [OR =0.65; 95%CI 0.43-0.99], use of mouthwash –Q4 [OR = 0.69; 95%CI 0.49-0.98] and poor tooth appearance –Q5 [OR = 48.42; 95%CI 19.48-120.38].

DISCUSSION

Overall, the results of this study showed that the self-reported oral health questionnaire was specific and valid in predicting serious periodontitis. This is expected as the presence of type 2 diabetes is already a risk for the presence of periodontitis.[9-11,16] The higher prevalence of periodontitis (94% vs 68%) among the participants with type 2 diabetes in this study can be attributed to the socioeconomic status of patients seen in our institution that mostly caters to the indigent population of the country.[16]

Screening patients with serious periodontitis seems to be a more clinically relevant application as these patients would warrant immediate dental referral. A single model where all of the predictive factors were included and analyzed appeared to be the most predictive and useful.[28] Misclassification of periodontal disease in this study was minimized using a full mouth periodontal examination "gold standard" which resulted in reduction in errors in our validity assessments.

All predictor variables were combined in a single model using a multivariate logistic regression analysis to determine the performance of significant predictive factors in predicting periodontal state. As shown in Table 5, only low educational status [OR =5.02; 95%CI 1.47-17.11], teeth loss >6 [OR =8.17; 95%CI 1.63-40.98], state of gum health –Q2 [OR = 0.56; 95%CI 0.34-0.90], presence of loose teeth –Q3 [OR =29.56; 95%CI 2.99-292.35] and poor tooth appearance –Q5 [OR =31.63; 95%CI 8.87-112.75] were significant predictors for serious periodontitis. A recommended set of questions and proposed scoring system based on the logistic regression analysis of each predictor's strength was then formulated. Total score ranged from (-5) considered least likely to have serious periodontitis to (+20) considered most likely to have serious periodontitis (Table 6).

The state of gum health appeared to be a protective predictive factor for both the presence and seriousness of periodontitis. A score of (-) 5 for excellent gum health and (-) 1 for poor gum health was used for easier scoring. Several dental hygiene practices like brushing teeth, dental flossing and use of mouthwash did not appear to be predictive of periodontitis since other local practices like betel nut chewing and use of toothpicks were reported. Low educational status was the only demographic variable found to be a significant predictive factor for serious periodontitis. Only 3 questions (state of gum health, loose teeth, tooth appearance) were found to be useful and valid in predicting serious periodontitis for this study population. Gum surgery, scaling and root planing were less frequently reported due to inaccessibility of most of the participants to regular dental visits as most belonged to lower socio-economic status.

CONCLUSION

The use of specific self-reported oral health questionnaire, certain socio-demographic and medical variables

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appeared to be highly predictive of serious periodontitis among Filipinos with type 2 diabetes. This provided a cost-effective and rapid method of screening patients who were in need of immediate dental evaluation.

Limitations and recommendations

The performance of these variables in different racial and ethnic groups was not explored due to the small number of participants. Although Filipino language was the main medium used to state the questions in this study, several other local dialects might be more applicable for other ethnic groups and in other hospital institutions in the country. The medical institution where this study was conducted only represented the local tertiary government hospital in an urban setting acting as an end referral center for difficult cases of diabetes. Considering the different overall profile of target Filipino participants, a scoring system based on this local validation study of predictive factors would be better suited to screen candidate patients in need for immediate dental evaluation. Further studies using the recommended questions and proposed scoring will be needed to validate the questionnaire as a screening tool and to determine the cut off score that would be highly sensitive and specific in predicting presence of serious periodontitis among diabetic patients consulting a physician.

Statement of Authorship

All authors have given approval to the final version submitted.

Author Disclosure

All the authors declared no conflicts of interest.

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None.

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Appendix A

PATIENT'S INFORMED CONSENT

Validation of Self-Reported Oral Health Measures for Predicting Periodontitis among Adult Filipinos with Type 2 Diabetes Mellitus

The following have been fully explained to me and I understand them well enough before signing this consent.

1. This study is being done by Dr. Tom Edward N. Lo, who is the primary investigator for this study. It will be made up of 180 participants.
2. The objective of this study is to determine the relationship and predictive power of several measures and oral health questions in determining presence and severity of periodontitis among patients with type 2 diabetes mellitus.
3. This study will involve answering interviews on personal and medical information, answering self-administered oral health questionnaire and undergoing formal dental examination lasting for 1-2 hours. The formal dental examination will be covered by this study.
4. My participation in this study is voluntary and I am free to leave the study at any time and doing so will not in any way affect the medical care that I am receiving currently or in the future.
5. I give consent for the Ethics committee and the primary investigator to have direct access to my medical records.
6. The results of this study may be published, but my identity will remain confidential.
7. I can call the primary investigator at 554-8400 loc. 3230 at any time to ask questions regarding the study.
8. This study is approved by the UPMREB ethics review panel and can be reached at 522-2684 and asked about study participant's rights.

_____	_____	_____
Name of patient	Signature	Date
_____	_____	_____
Person who obtained informed consent	Signature	Date

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JAFES

ORIGINAL ARTICLE

Trimester-Specific Reference Interval for Thyroid Function Tests in Pregnant Filipino Women

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Abstract

Background. The interpretation of thyroid hormone function during pregnancy is difficult due to its physiologic changes. Differences in iodine status in previous studies led to different intervals; therefore the use of trimester-specific, method-specific and probably country-specific reference values is advocated.

Objective. To establish trimester-specific reference interval for thyroid function tests in pregnant Filipino women.

Methodology. Six hundred sixteen pregnant patients (5–40 weeks gestation) attending a tertiary center were recruited. Level of serum thyroid stimulating hormone (TSH) was measured using immunoradiometric assay while free thyroxine (FT4), free triiodothyronine (FT3) and thyroid peroxidase antibodies (TPOAb) were measured by radioimmunoassay method.

Main outcome measures are trimester-specific reference interval based on 2.5th and 97.5th percentiles for TSH, FT4 and FT3 among TPOAb-negative pregnant patients.

Results. The reference intervals for each trimester were as follows: TSH (0.05-4.24, 0.13-3.95, and 0.20-3.00 uIU/mL); FT4 (9.80-21.88, 9.10-18.95 and 9.16-18.64 pmol/L) and FT3 (2.40-6.20, 2.77-5.00 and 2.09-3.70 pmol/L). FT4 and FT3 are strongly and negatively correlated with age of gestation (p=<0.01and <0.01 respectively). No correlation is found with TSH and age of gestation (p=0.52).

Conclusions. Trimester-specific intervals among pregnant Filipino women are different from their non-pregnant counterparts and laboratory cutoffs. Thus, these reference values should be used in the country.

Key words: reference interval, thyroid function tests, pregnant Filipino women

INTRODUCTION

Optimal thyroid function is essential during all stages of life. This is most significant during gestation when the fetus is reliant on the transplacental supply of thyroxine which is important for normal neurological development. Studies correlate maternal hypothyroxinemia to the offsprings' delayed mental and motor function[1] and higher TSH to lower IQ scores.[2] Other adverse maternal and fetal outcomes are also significantly correlated, specifically: subclinical hypothyroidism to fetal deaths,[3] placental abruption and premature delivery;[4] and subclinical hyperthyroidism to gestational hypertension.[5]

However, interpretation of thyroid function tests in pregnancy can be difficult due to some physiologic changes, which include (1) decreased TSH during the first trimester due to stimulatory effect of human chorionic gonadotropin (hCG) which has structural similarity with TSH; (2) increased thyroid binding globulin (TBG) due to estradiol and altered hepatic glycosylation decreasing its clearance; (3) increased urinary iodide excretion which can cause impaired thyroid hormone production in areas of marginal iodine sufficiency; and (4) alterations in the immune system, leading to the onset, exacerbation, or amelioration of an underlying autoimmune thyroid disease.[6]

Studies in different parts of the world have been conducted to establish laboratory and method-specific thyroid function tests across 3 trimesters of pregnancy - in iodine-sufficient areas like the USA,[7] Switzerland,[8] Spain[9] and in iodine-insufficient areas like China[10] and Iran.[11] The Philippines is considered to no longer iodine deficient as reported by the Food and National Research Institute in 2013 with the exception of pregnant women. Data persistently showed that they are iodine deficient.[12]

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METHODOLOGY

Study Population

We recruited 616 healthy women with uncomplicated single intrauterine gestation attending the Philippine General Hospital Obstetrics and Gynecology Outpatient Department, a tertiary medical center in Manila, Philippines. History taking was done to ascertain any chronic illness, thyroid illness in the past or present, medications (current and past) and family history of thyroid illness. Obstetric history was elicited to know duration of gestation, number of pregnancies, number of pregnancies carried to term and number of abortions. Physical examination was done by the investigator who is a trained endocrinologist to ascertain absence of goiter. The age of gestation was computed from the last normal menstrual period. For those with irregular menses, transvaginal ultrasound was performed to ascertain the age of gestation.

Excluded in the study were pregnant women with goiter, history of hyperthyroid or hypothyroid disease, postpartum thyroiditis or thyroid surgery, family history of goiter, symptoms or signs suggestive of thyroid dysfunction, hyperemesis gravidarum, trophoblastic disease, preeclampsia, presence of autoimmune disease (SLE, T1DM), previous therapeutic head or neck irradiation, history of recurrent miscarriage or preterm delivery and those with thyroid antibodies when known.

This study was approved by the Ethics Review Board of the Philippine General Hospital.

Blood specimen and Hormone Analyses

Five mL of blood were extracted from each subject and the serum were assayed for anti-TPO, FT4, FT3 using radioimmunoassay (RIA) method and for TSH using immunoradiometric assay (IRMA) with the Perkin Elmer machine (2008, USA). The reference range in our laboratory is: TPO (<100 U/L), TSH (0.3-3.8 uIU/mL), FT4 (11-24 pmol/L) and FT3 (2.2-6.8 pmol/L).

Data Analysis

Reference intervals for FT4, FT3 and TSH were determined by calculating the 2.5th and 97.5th percentiles in Microsoft Excel. Median values for FT4, FT3 and TSH were likewise determined for descriptive purposes. The median, 2.5th and 97.5th percentile plots were derived using 6th-order polynomial equation in Microsoft Excel with the age of gestation on the x-axis and the thyroid function test values on the y-axis. The percentile plots are used to find the overall trend in the test parameters for increasing age of gestation.

The association between age of gestation (expressed in discrete values as weeks) and the values of FT4, FT3 and TSH variables was established using Pearson R correlation analysis. Further tests of the relationship between age of gestation and FT4, FT3 and TSH, controlling for maternal age, were performed using multiple linear regressions.

A priori wise comparisons between the median FT4, FT3, and TSH values during the first and second trimesters and during the second and third trimesters were performed using Mann-Whitney U tests.

P-values below 0.05 were considered statistically significant. All statistical tests were performed using Stata IC 13.

Results

Six hundred sixteen (616) healthy pregnant patients were recruited from the Philippine General Hospital Obstetrics and Gynecology outpatient clinic. Of these subjects, 218 were in the first trimester, 198 in the second trimester and 200 in the third trimester. Eight patients each in the first and second trimester and three patients in the third trimester were TPOAb-positive. These nineteen patients were removed from the analysis because the presence of TPOAb is predictive of subsequent thyroid dysfunction. In a nine year prospective study, women with subclinical hypothyroidism and positive TPOAb are 15.6 times more likely to convert to overt hypothyroidism.[15] The prevalence of TPOAb positivity (3.08%) in this study is lower than the worldwide prevalence of 12-23%.[9,13,14] One subject in her first trimester of pregnancy, and another subject in the second trimester were removed from the analysis due to overt hypothyroidism and hyperthyroidism respectively.

Five hundred ninety-five (595) subjects were included in final analysis. Mean age was 27and SD = 5.95 years. Primigravids represented 38% of all subjects, 32% were on their second pregnancy and the remaining 30% were on their third or more pregnancies.

Table 1 shows the trimester-specific reference intervals and median values for TSH, FT4 and FT3 based on data from 595 subjects included in the study. The median, 2.5th and 97.5th percentile plots are shown in Figure 1.

Table 1. Thyroid function tests among TPO-Ab negative patients, N=595, Manila, Philippines

	First Trimester N=209			Second Trimester N=189			Third Trimester N=197		
	2.5th percentile	Median	97.5th percentile	2.5th percentile	Median	97.5th percentile	2.5th percentile	Median	97.5th percentile
TSH 0.3-3.8 uIU/mL	0.05	1.2	4.24	0.13	1.4	3.95	0.20	1.40	3.00
FT4 11-24 pmol/L	9.80	15.2	21.88	9.10	13.0	18.95	9.16	13.40	18.64
FT3 2.2-6.8 pmol/L	2.40	3.7	6.20	2.77	3.7	5.00	2.09	2.90	3.70

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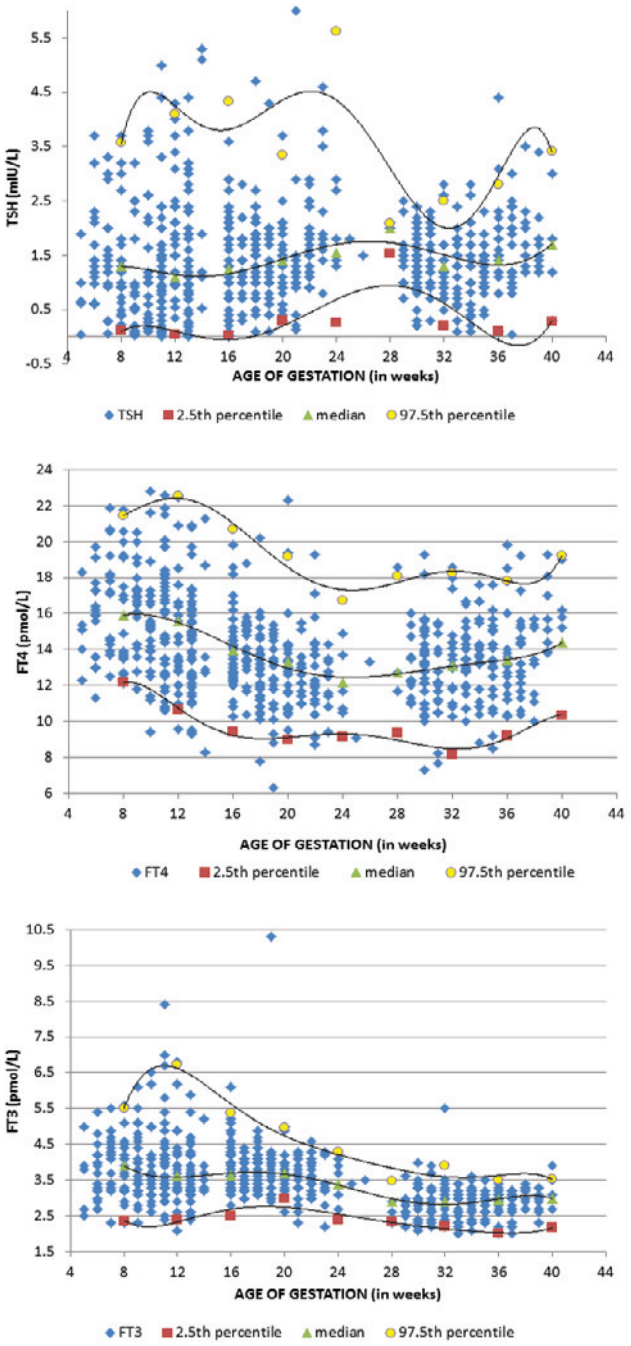

Figure 1. The scatterplot of individual results for TSH, FT3 and FT4 in pregnant women.

TSH is not correlated to age of gestation during the first trimester, (r = 0.08, p-value = 0.24) but it is positively correlated to AOG during the second and third trimester (r = 0.19, p-value = 0.01 and r = 0.16, 0.03, respectively). Specifically, TSH increases by 0.077 units for every one week increase in AOG during the second trimester (controlling for maternal age) and it increases by 0.037 units per week increase in AOG during the third trimester. However, overall, TSH is not significantly correlated to AOG (r = 0.03, p-value = 0.52). [Table 2] There is no significant difference in the median TSH values during the first and second trimesters as well as in the median TSH values during the second and third trimesters [Table 4].

Table 2. Association between thyroid function tests and age of gestation, N=595, Manila, Philippines

TSH	Pearson R	p-value	Regression Coefficient	p-value
1st trimester	0.08	0.24	0.033[a]	0.30
2nd trimester	0.19	0.01*	0.077[a]	0.01*
3rd trimester	0.16	0.03*	0.037	0.03*
OVERALL	0.03	0.52	0.002[a]	0.54
FT4				
1st trimester	-0.18	0.01*	-0.226	0.01*
2nd trimester	-0.23	0.00*	-0.217	0.00*
3rd trimester	0.19	0.01*	0.120[a]	0.03*
OVERALL	-0.26	0.00*	-0.074[a]	0.00*
FT3				
1st trimester	-0.04	0.57	-0.016	0.57
2nd trimester	-0.18	0.01*	-0.053	0.01*
3rd trimester	0.06	0.37	0.009	0.37
OVERALL	-0.47	0.00*	-0.041[a]	0.00*

** significant association (p <0.05)*
[a] controlling for maternal age (maternal age significantly associated with thyroid function test)

Table 3. Trimester-specific reference interval for serum TSH

	First Trimester	Second Trimester	Third Trimester
Soldin et al.[7]	0.98 (0.24-2.99)	1.09 (0.46-2.95)	1.20 (0.43-2.78)
Stricker et al.[8]	1.04 (0.09-2.83)	1.02 (0.20-2.79)	1.14 (0.31-2.90)
Bocos-Terras et al. [9]	0.92 (0.03-2.65)	1.12 (0.12-2.64)	1.29 (0.23-3.56)
Panesar et al.[10]	0.80 (0.03-2.30)	1.10 (0.03-3.10)	1.30 (0.13-3.50)
Mehran et al.[11]	1.50 (0.20-3.90)	1.80 (0.50-4.10)	1.80 (0.60-4.10)
Present Study	1.20 (0.05-4.24)	1.40 (0.13-3.95)	1.40 (0.20-3.00)

Median TSH in uIU/mL with 2.5th -97.5th percentile [7-10] or 5th-95th percentile[11] in parenthesis

Table 4. Pairwise comparison of median TSH, FT4, and FT3 values by trimester

	Trimester	Median	p-value
TSH	1st vs 2nd	1.2 vs 1.4	0.06
	2nd vs 3rd	1.4 vs 1.4	0.62
FT4	1st vs 2nd	15.2 vs 13	0.00*
	2nd vs 3rd	13 vs 13.4	0.04*
FT3	1st vs 2nd	3.7 vs 3.7	0.98
	2nd vs 3rd	3.7 vs 2.9	0.00*

** significant difference (p <0.05)*

Table 5. Potential for misclassification of thyroid function tests in pregnant patients if non-pregnant reference interval is used

	1st Trimester N=209	2nd Trimester N=189	3rd trimester N=197
TSH	25 (11.9%)	3 (1.58%)	4 (2%)
FT4	4 (1.91%)	28 (14.8%)	19 (9.6%)
FT3	0 (0%)	0 (0%)	2 (1.01%)

The FT4 values are negatively correlated with age of gestation from the first to second trimesters (r = -0.18, p-value = 0.01 and r = -0.23, p-value <0.01, respectively). Particularly, FT4 decreases by 0.226 units for every one week increase in AOG during the first trimester and it decreases by 0.217 units per week increase in AOG during the second trimester. However, during the third trimester, FT4 is seen to be positively correlated to AOG (r = 0.19, p-value = 0.01). Specifically, FT4 increases by 0.120 units for every one week increase in AOG during the third trimester (controlling for maternal age) [Table 2].

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Consistent with this, the median FT4 value during the first trimester was found to be significantly higher than the median FT4 value during the second trimester (15.2 pmol/L vs 13 pmol/L; p-value = <0.01) and the median FT4 value during the second trimester was found to be significantly lower than the median FT4 value during the third trimester (13 pmol/L vs 13.4 pmol/L; p-value = 0.04) [Table 4]. Overall, FT4 values are negatively correlated with age of gestation (r = -0.26, p-value = <0.01), with about 0.074 units decrease in FT4 for every week increase in AOG (controlling for maternal age) [Table 2] .

FT3 values are stable in the first and second trimesters, then declined in the third trimester with median values of 3.7, 3.7 and 2.90 pmol/L respectively with significant difference between the second and third trimester median FT3 values indicated by a p-value = <0.01 [Table 4]. During the first trimester, the FT3 values were not correlated with age of gestation (r = -0.04, p-value = 0.57). However, during the second trimester, FT3 was seen to be inversely correlated to AOG (r = -0.18, p-value = 0.01). Specifically, FT3 decreases by 0.053 units for every one week increase in AOG during the second trimester. During the third trimester, the FT3 values are again not correlated with age of gestation (r = 0.06, p-value = 0.37). Overall, FT3 values are negatively correlated with age of gestation (r = -0.47, p-value = <0.01), with about 0.041 units decrease in FT3 for every week increase in AOG (controlling for maternal age) [Table 2].

DISCUSSION

The 2.5th percentile TSH values in our study are 0.05, 0.13 and 0.20 uIU/mL respectively. These values are lower than the laboratory cut off of 0.30 uIu/mL. The lowest TSH is observed in the first trimester consistent with all studies done abroad and maybe due to high levels of β-hCG early in pregnancy. In the first trimester, there is no correlation between the TSH and the age of gestation with p value of 0.24. However, during the second and third trimester, there is a statistically significant positive correlation between TSH and the age of gestation, both with p values of 0.01 and 0.03 respectively. This implies that as the age of gestation increases, the TSH also increases. Using multiple pairwise comparison, median TSH in the first and 2nd trimester showed marginally significant rise (1.2 vs 1.4 p = 0.06) while median TSH in the 2nd and 3rd trimester did not differ (1.4 vs 1.4 p = 0.62). Our median TSH values across all trimesters are higher than in studies done in USA,[7] Switzerland,[8] Spain,[9] and China[10] and may be due to iodine-insufficient status in our pregnant women. The study in Iran[11] showed the highest median TSH values for all trimesters [Table 3].

Median FT4 is highest in the first trimester and dropped in the second trimester (15.2 vs 13 pmol/L p = <0.01) but rose again in the third trimester (13 vs 13.4 pmoL/L p=0.04) [Table 4]. FT3 values are stable in the first and second trimester (3.7 vs 3.7 pmol/L p = 0.98) but decreased significantly in the third trimester (3.7 vs 2.9 pmol/L p = <0.01) [Table 4]. Our trend is different from previous studies in Switzerland[8] and Spain[9] both showing decreasing FT4 and FT3 throughout pregnancy and in China[10] showing decreasing FT4 and FT3 in the first and second trimester and remaining unchanged from second trimester until term.

The paper entitled, "Reference Intervals in Thyroid Function Tests in the Third Trimester in Pregnant Filipino Women," by Baustista, et al[16] is part of this study. There were minor differences in the reported thyroid function tests in the first and second trimester reference intervals as we have removed overtly hyperthyroid and hypothyroid patients in the final analysis.

Trimester-specific reference interval derived from antibody-negative patients in this study is used to classify thyroid function tests as high (above 97.5th percentile), normal (within 95th central percentile) and low (below 2.5th percentile) and were compared with classification using the non-pregnant assay-specific reference interval provided by the manufacturer. If non-pregnant cut offs were used to classify our patients - 25 in the first trimester, 3 in the second trimester and 4 patients in the third trimester will be misclassified into subclinical hyperthyroidism due to low TSH. The highest difference is noted in the first trimester due to expectedly low TSH as a function of β-hCG [Table 5]. FT4 rises in the first few weeks of pregnancy and declines progressively at the end of the first trimester and in the second trimester [Figure 1] but they were all lower than laboratory cut off (9.83, 9.10, 9.16 vs 11 pmol/L). Using non-pregnant cut off – 4, 28 and 19 patients respectively will be misclassified to low FT4. Most number will be misclassified in the second trimester as FT4 is at its lowest at this time in present study.

CONCLUSION

We have established trimester-specific reference interval for thyroid function tests from TPOAb-negative pregnant Filipino women as follows: TSH (0.05-4.24, 0.13-3.95, and 0.20-3.00 uIU/mL); FT4 (9.80-21.88, 9.10-18.95 and 9.16-18.64 pmol/L) and FT3 (2.40-6.20, 2.77-5.00 and 2.09-3.70 pmol/L).

Among the 616 pregnant Filipino women recruited in the study, 595 (97%) were TPO-antibody negative. It is noted that TSH rises with age of gestation. FT4 decreases and is at its lowest in the second trimester and rises in the third trimester. FT3 is the same in the first and second trimesters and decreases in the third trimester.

Reference interval for thyroid function tests in pregnancy differs from non-pregnant patients and/or laboratory cut offs and will lead to misclassification of patients, hence pregnancy-specific reference interval should be advocated.

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Statement of Authorship

All authors have given approval to the final version submitted.

Author Disclosure

All the authors declared no conflicts of interest.

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ORIGINAL ARTICLE

JAFES

Etiology of Short Stature in Northern India

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Abstract

Objective. Short stature can be caused by a great variety of congenital and acquired conditions, some of which present with additional symptoms and signs. Overall, the number of patients seeking medical attention for short stature may be considered as the tip of the iceberg. The objective of this study was to determine the pattern and etiological factors of short stature in children.

Methodology. A cross-sectional study was carried out in the Department of Endocrinology at a tertiary care health center in north India from August 2012 to June 2015. Four hundred and fifty one children (280 boys and 171 girls), ranging from 4 to 18 years presenting with short stature were studied. Anthropometric measurements were plotted on Indian standard growth charts.

Results. In this study, the male to female ratio was found to be 1.6:1, with mean chronological age of 11.6+3.2 years, and mean bone age of 7.8+2.8 years. The common etiologic factors in the order of frequency were constitutional delay in growth and puberty (41.2%), familial short stature (15.9%), type 1 diabetes mellitus (9.9%), and hypothyroidism (8.6%) while growth hormone deficiency (2.4%) was a relatively uncommon cause. The most common pathological cause for proportionate short stature was type 1 diabetes and for disproportionate short stature was hypothyroidism. Hypothyroidism caused the maximum retardation of bone age while the least bone age retardation was noticed in familial short stature.

Conclusion. Physiological/normal variants outnumbered the pathological causes of short stature. Endocrinological causes were found in almost one fourth of children with short stature; however, growth hormone deficiency was found in only 2.4% of the children.

Key words: constitutional growth delay, familial short stature, growth hormone deficiency, short stature

INTRODUCTION

Normal growth requires adequate nutrition along with various hormonal stimuli. Hormones important for growth and development are: growth hormone (GH), insulin-like growth factor (IGF-1), thyroid hormones, sex steroids and other growth factors[1] Factors affecting growth may be due to constitutive intrinsic growth defects or any of the extrinsic factors which are required for normal growth.[1]

Short stature (SS) is defined as height below 3rd percentile or less than two standard deviations (SDs) below the median height for that age and sex according to the population standard; or even if the height is within the normal percentiles but growth velocity is consistently below 25th percentile over 6–12 months of observation.[2,3] Approximately 3% of children in any population will be short, amongst which half will be physiological (familial or constitutional) and half will be pathologic. The age of onset of puberty varies in different population and it correlates more with the bone age (BA) than chronological age (CA).[2,3]

Children with short stature have increased rate of social aversion, anxiety and attention problem.[4] Short stature may be regarded as a manifestation of many diseases rather than "a disease" itself and so, early diagnosis and treatment are imperative for the final outcome.[5] Factors implicated in the pathogenesis of short stature in developing countries are different from developed countries because of the differences in race and lifestyles along with nutritional, cultural and socio-economic factors.[6] In contrast to developed countries, the data addressing the frequencies of different causes of short stature in India are very limited, though there are a few studies focusing on the individual diseases.[20] In this perspective, the present study was contemplated with the objective to ascertain the pattern of SS, and to find out the etiological profile of SS.

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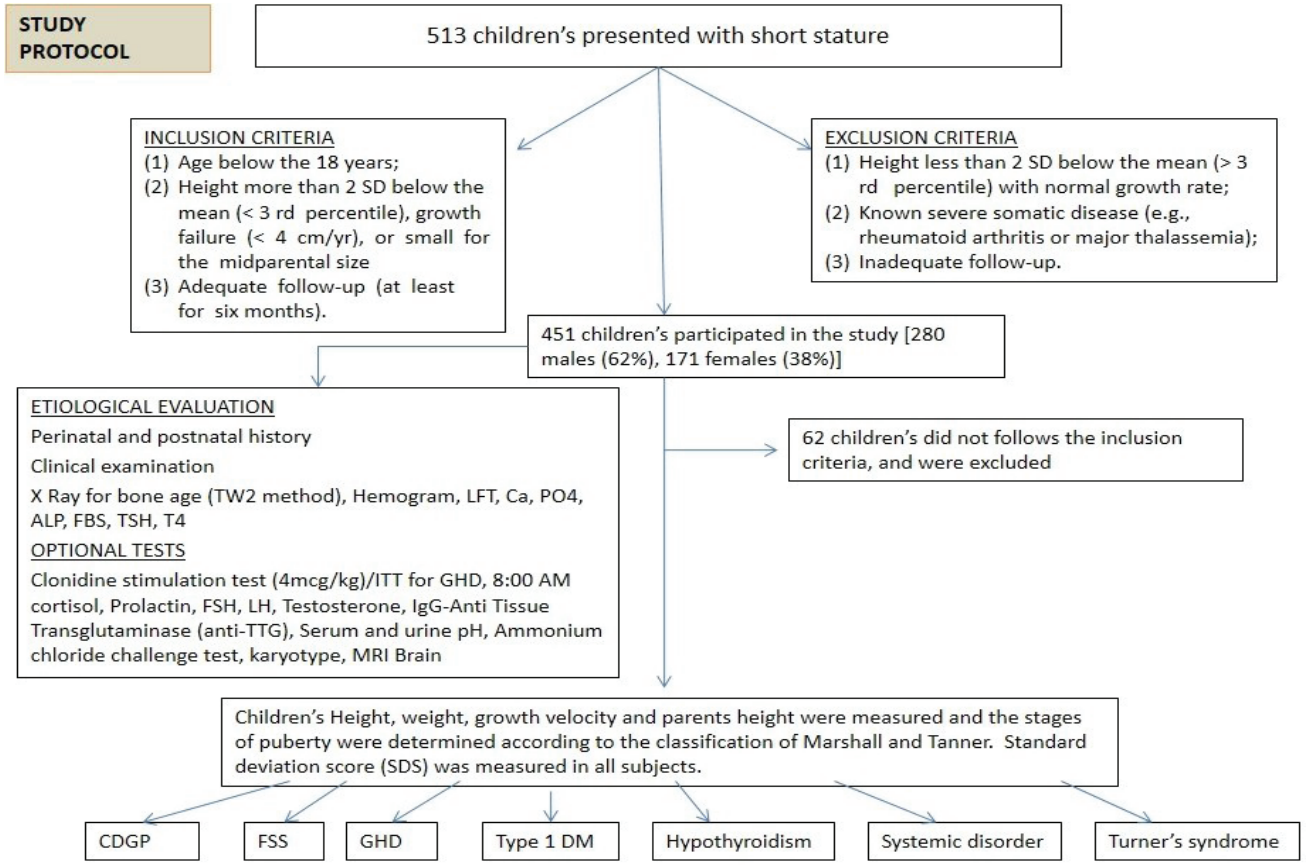

Figure 1. Summary of the study protocol and procedure for work-up and classification of subjects, N=513 (with 451 included subjects).

METHODOLOGY

Sampling and design of the study

A cross-sectional analytic study was carried out in the Department of Endocrinology at a tertiary care health center in north India from August 2012 to June 2015. The study was approved by the institutional ethics board and all patient-identifying information remains confidential. A total of 513 children with short stature were evaluated, 62 children did not follow the inclusion criteria so the remaining 451 children participated in the study. There were 280 males (62%) and 171 females (38%)] were identified as having short stature, with mean chronological age of 11.68+3.2 years. The study subjects were selected on the basis of the following inclusion criteria: (1) age below 18 years; (2) height more than 2 SD below the mean (<3rd percentile), growth velocity (<4 cm/yr), or small for the midparental size; and (3) adequate follow-up (at least for six months). The exclusion criteria were: (1) height less than 2 SD below the mean (>3rd percentile) with normal growth rate; (2) known severe somatic disease (e.g., rheumatoid arthritis or major thalassemia); and (3) inadequate follow-up. The study protocol is shown in Figure 1.

Anthropometry and body composition

All subjects were residents of North India referred to the endocrine clinic of a tertiary care health center. All patients were examined by two endocrinologists, including one pediatric endocrinologist. An extensive history was taken and physical examination was performed. Anthropometric measurements were taken and the puberty staging was done according to Marshall and Tanner classification. Standard deviation score (SDS) was calculated in all subjects. Patients were followed every 3-6 months interval for anthropometry assessment. Data were collected on age, sex, parental heights, and the age of puberty for each parent. Primary screening tests including routine and complete blood count, ESR, renal function test, Ca, P, Alk. P, T4, TSH, stool exam, urinalysis, and bone age radiographs were performed in all the subjects. Bone age was determined by Tanner and Whitehouse system 2.

Chromosomal study was performed in females with significant short stature (height more than 3 SD below the mean) and with unknown etiology, with other stigmata of Turner Syndrome. Growth aberrations were grouped as: (1) physiological/normal variants of growth and (2) pathologic short stature. The pathologic group was subdivided into proportionate and disproportionate subgroups by assessing the upper to lower segment ratio.

Physiological and pathological causes of short stature

Physiological/normal variants of short stature included constitutional delay in growth and puberty (CDGP) (i.e.,

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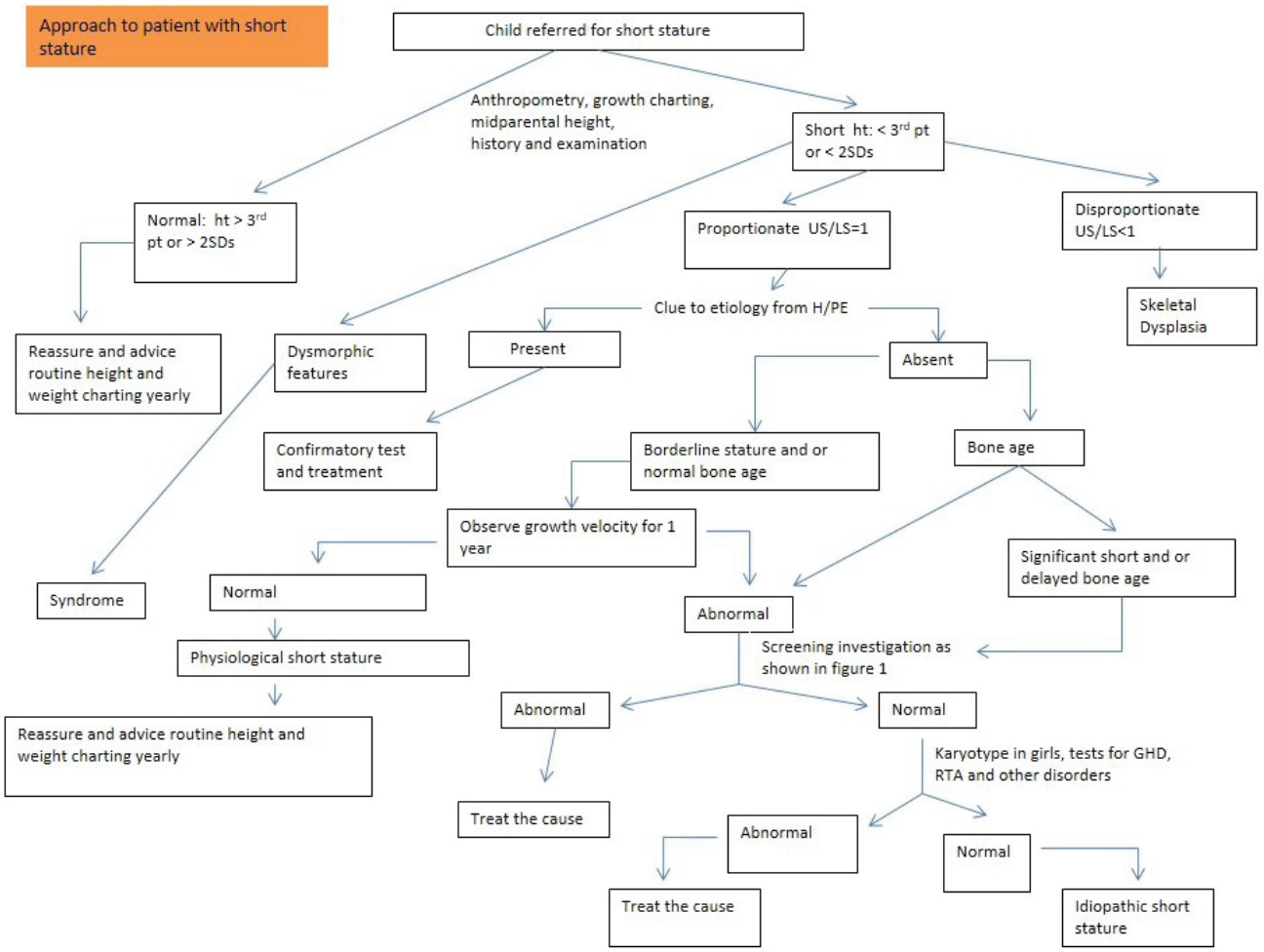

Figure 2. Approach to evaluation of short stature.

proportionate short stature with a normal growth rate, delayed skeletal maturation often with a family history of delayed pubertal development, or late adolescent growth spurt) and familial short stature (FSS) (i.e., proportionate short stature with a normal growth rate, skeletal age similar to chronologic age, absence of significant medical disorders, and short parents).

Non-endocrine systemic disorders were diagnosed by history, examination and appropriately selected laboratory tests. Primary hypothyroidism was identified by a low thyroxine level and an elevated thyrotropin level. The diagnosis of Turner syndrome was made on the basis of physical signs and confirmed by the chromosomal study.[7]

After excluding other causes of short stature, growth hormone deficiency (GHD) was considered if a child had severely short stature (height more than 3 SD below the mean), a subnormal growth rate (a 1-year height velocity more than 1 SD below the mean) or height more than 1.5 SD below the midparental height (average of mother's and father's height), delayed bone maturation, and was confirmed by the peak growth hormone concentration less than 10 ng/mL with two provocative tests done one week apart (clonidine and insulin).[8]

A diagnosis of idiopathic short stature was considered in children with short stature, a subnormal growth rate, delayed bone age, no apparent medical cause for growth failure, and normal growth hormone response to provocative testing. Skeletal dysplasia was confirmed by skeletal surveys.

Approach to evaluation of short stature is shown in Figure 2.

STATISTICAL ANALYSIS

All categorical variables were expressed as frequencies and percentages and all continuous variables were expressed as mean ± standard deviation. All p values <0.05 were taken as significant. Statistical analysis was performed by using software SPSS version 17.

RESULTS

A total of 513 children with short stature were evaluated, out of which 62 children did not meet the inclusion criteria, so the remaining 451 children participated in the study. Two hundred eighty males (62%) and 171 females (38%) were identified as having short stature, with mean chronological age of 11.68+3.2 years, mean bone age of 7.88+2.8 years, the minimum and maximum height measured was 96 cm and

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Table 1. The average of bone age, child and parent's heights and SDS scores in two sexes

Characteristics	Male (n=280)	Female (n=171)
Chronological age (yr)	11.65±3.2	11.78±3.1
Bone age (yr)	7.86±2.8	7.92±2.67
Child height (cm)	121.65±12.24	114.54±13.53
Father's height (cm)	162.43±12.43	161.87±11.78
Mother's height (cm)	156.67±12.41	156.23±11.87
SDS	-3.89±1.1	-4.1±1.2

Table 2. Diagnoses of the 451 short children and adolescents, separated by gender

Diagnosis	Boys n=280	Girls n=171	Total n=451
Normal Variants (N = 258)	N (%)	N (%)	
CDGP	127 (45.3)	59 (34.5)	186 (41.2)
FSS	43 (15.3)	29 (16.9)	72 (15.9)
Pathological variants (n=193)			
Proportionate causes of short stature			
GHD	08 (2.8)	03 (1.7)	11 (2.4)
Systemic diseases	26 (9.2)	22 (12.8)	48 (10.6)
Panhypopituitarism	06 (2.1)	02 (1.1)	08 (1.7)
Type 1 Diabetes	31 (11.07)	14 (8.1)	45 (9.9)
Tumer's syndrome	-------	06 (3.5)	06 (1.3)
ISS	11 (3.9)	01 (0.5)	12 (2.6)
Disproportionate causes of short stature			
Hypothyroidism	12 (4.2)	27 (15.7)	39 (8.6)
Skeletal dysplasia	05 (1.7)	03 (1.7)	08 (1.7)
Rickets	10 (3.5)	02 (1.1)	12 (2.6)
Pseudohypoparathyroidism	01 (0.3)	03 (1.7)	04 (0.8)
Total	280 (100)	171 (100)	451 (100)

CDGP = Constitutional delay in growth and puberty; **GHD** = Growth hormone deficiency; **FSS** = Familial short stature; **ISS** = Idiopathic short stature.

Table 3. Category wise distribution of various short stature cases

Diagnosis	Boys No. (%)	Girls No. (%)
Normal variants (n=258)		
CDGP	127 (45.3)	59 (34.5)
FSS	43 (15.3)	29 (16.9)
Pathological variants (n=193)		
Proportionate		
GHD	08 (2.8)	03 (1.7)
Systemic diseases	26 (9.2)	22 (12.8)
Panhypopituitarism	06 (2.1)	02 (1.1)
Tumer's syndrome	-------	06 (3.5)
Type 1 Diabetes	31 (11.07)	14 (8.1)
ISS	11 (3.9)	01 (0.5)
Disproportionate		
Hypothyroidism	12 (4.2)	27 (15.7)
Skeletal dysplasia	05 (1.7)	03 (1.7)
Rickets	10 (3.5)	02 (1.1)

CDGP = Constitutional delay in growth and puberty; **GHD** = Growth hormone deficiency; **FSS** = Familial short stature; **ISS** = Idiopathic short stature.

141 cm. The average height of children and their paternal and maternal heights were 119.34+12.66, 162.13+12.03, and 156.51+12.22 cm respectively. There was no significant difference in chronological age, bone age and parent's heights; however, a statistically significant difference was noticed in the children's height and standard deviation score between the two sexes (Table 1).

With consideration of children's age, height, growth curve, bone age and test results, the common causes of short stature were constitutional delay in growth and puberty (41.2%), familial short stature (15.9%), type 1 diabetes mellitus (9.9%), primary hypothyroidism (8.6%) and systemic disorders (including chronic liver disease, chronic renal disease, cardiac disorder, tuberculosis, nephrotic syndrome) (10.6%) while growth hormone deficiency (2.4%) was a relatively rare phenomenon (Table 2).

With consideration to various category wise distribution of short stature, the physiological causes for short stature (constitutional delay in growth and puberty and familial short stature) were found in 57.2% of short children and pathologic causes in 42.8% of short children. In pathologic variety of SS, majority (67.4%) belonged to proportionate category without discernable difference in gender distribution between proportionate and disproportionate varieties. Within the proportionate variety, systemic disorders (including chronic liver disease, chronic renal disease, cardiac disorder, tuberculosis, nephrotic syndrome) and type 1 diabetes mellitus were the leading causes of short stature. However, within the disproportionate category, significantly higher numbers of girls and boys were found to have hypothyroidism (Table 3).

Furthermore, comparing the mean of SDS, bone age, chronological age, height age and growth velocity in 451 short children and adolescents, the youngest patients (3-5 years) referred to endocrine clinic for short stature had rickets and skeletal dysplasia. Late referrals (15-16.5 years) were due to systemic disorders and Turner syndrome; children with CDGP and FSS presented around the age of 13.28 years and 13.34 years respectively. On comparing the bone age of children with short stature, hypothyroidism causes the maximum bone age retardation followed by growth hormone deficiency while least bone age retardation was noticed in familial short stature (Figure 3).

Table 4. The mean of SDS, bone age, chronological age, height age and growth velocity in 451 short children and adolescents

Diagnosis	Mean of chronologic age	Mean of height age	Mean of bone age	Mean of SDS	Mean of growth velocity (cm/yr)
CDGP	13.28	10.12	9.5	–2.9	4.6
FSS	13.34	11.8	13.0	–2.2	6.1
Hypothyroidism	12.8	7.9	6.2	–6.12	2.1
Type 1 Diabetes	11.5	9.2	9.4	-2.3	5.2
Tumer's syndrome	16.21	11.2	10.4	–4.6	3.2
Skeletal dysplasia	4.1	2.1	1.8	–5.9	3.7
Panhypopituitarism	12.7	9.43	8.1	–5.4	2.8
GHD	10.34	7.2	7.0	–6.1	2.4
Systemic diseases	15.64	11.34	9.8	–3.2	3.8
Rickets	5.2	2.9	2.4	–4.23	2.7

CDGP = Constitutional Delay in growth and Puberty; **GHD** = Growth hormone deficiency; **FSS** = Familial short stature; **ISS** = Idiopathic short stature; **SDS** = Standard deviation score

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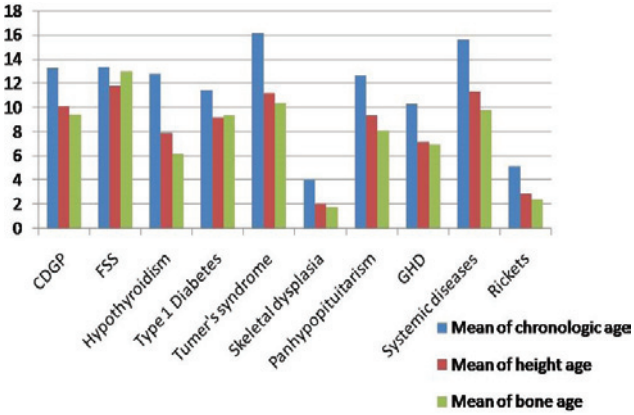

CDGP = Constitutional Delay in growth and Puberty; **GHD** = Growth hormone deficiency; **FSS** = Familial short stature; **ISS** = Idiopathic short stature.

Figure 3. The mean of SDS, bone age, chronological age, height age and growth velocity in 451 short children and adolescents.

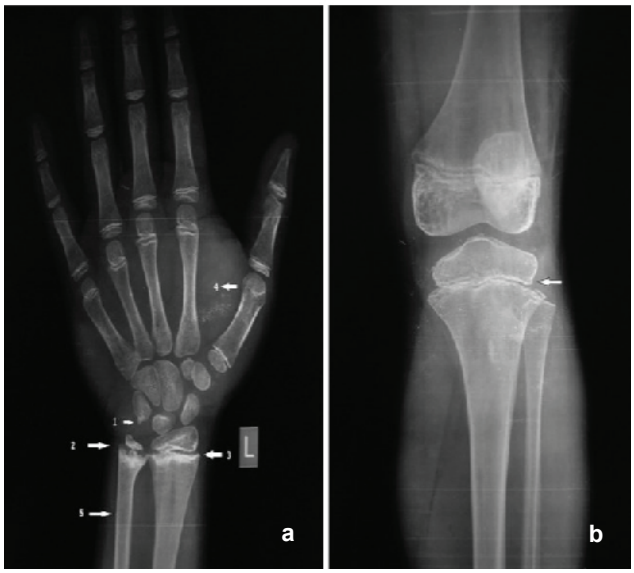

Figure 4a. X ray wrist showing bone age of 10 years (chronological age 16 years) 1. Epiphysis of pisiform just appearing 2. Irregular ossification of growth plate 3. Sclerotic band at radial metaphysis 4. Soft tissue thickening 5. Pencil thin cortex; **Figure 4b.** X ray of the knee showing heterogeneous epiphysis with irregular ossification of growth plate.

DISCUSSION

In this study, we presented characteristics and distributions of various diagnoses of short stature in children who visited a referral endocrinology clinic due to short stature over the period of 3 years. To facilitate the detection of growth disorders, growth monitoring implying regular measurements of weight and height is essential; failure to do so leads to undetected and untreated short stature in children. Short stature may be considered as the tip of the iceberg of many treatable disorders. Therefore, the early diagnosis of short stature is of paramount importance and treatment for the short stature would be effective only before epiphyseal fusion.[14,20]

The mean age of children evaluated for short stature was 11.65+3.2 years for males and 11.78+3.1 years for females, which corresponds to data reported by Song KC et al. in their studies. There was no significant difference in chronological, bone age and parental height; however, statistically significant differences were noticed in the children's height and standard deviation scores between two sexes which also correspond to the above-mentioned study.[17]

The bulk of the studies worldwide had shown that constitutional delay in growth and puberty, familial short stature, and growth hormone deficiency are the most common causes of short stature.[9,10,11] In our study the most common causes found were constitutional delay in growth and puberty (41.2%), followed by familial short stature (15.9%), systemic diseases (10.6%), type 1 diabetes mellitus (9.9%) and hypothyroidism (8.6%), while growth hormone deficiency (2.4%) was found to be a less common cause of short stature. It is worth noting that other studies from the Indian subcontinent also show lower prevalence of growth hormone deficiency.[12,13]

Fortunately, most of the children with short stature have normal growth variants[11,17] (i.e., constitutional delay in growth and puberty, and familial short stature), these normal variants of short stature need no medical treatment, reassurance and growth monitoring is usually sufficient. On the other hand, many serious and treatable diseases also cause short stature alone or with other stigmata of that particular disease. These pathological processes need immediate recognition and timely treatment, to ensure normal height gain. Short stature has been studied very extensively worldwide, but such work is scanty in Northern India. [21]

In this study, 26% of short stature children have endocrine causes (type 1 diabetes mellitus [9.9%], hypothyroidism [8.6%], rickets [2.6], growth hormone deficiency [2.4%] etc) while non-endocrine causes contributed only 16.2% (systemic diseases [10.6%], skeletal dysplasia [1.7%], Turner syndrome [1.3%], idiopathic short stature [2.6%]). Studies from the different parts of the world also showed that 20-30% of short children have endocrine causes.[9,10,13] Higher frequency of endocrine causes especially type 1 diabetes mellitus and hypothyroidism may be due to the referral nature of the endocrine center where the study was done. In our study, GHD contributed only 2.4%, in contrast to almost one third as reported by Bhadada et al. (7.4%).[12] This might be due to lower prevalence of growth hormone deficiency in the Northern Indian population. Type 1 diabetes mellitus has recently gained importance as a cause of growth retardation and short stature in the Indian subcontinent and in some studies, it constitutes about 16-20% of children with short stature.[22]

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However some studies found non-endocrine causes for growth failure to be more common, and the frequency of endocrine disorders were found to be less than 5%.[15,16]

A disproportionate body habitus may not be immediately apparent on physical examination. Therefore, anthropometric measurements such as upper/lower segment (U/L) ratio, sitting height, and arm span must be measured when evaluating a patient with short stature. Within the proportionate variety, systemic disorders (10.6%) and type 1 diabetes mellitus (9.9%) were the leading causes of short stature. However, within the disproportionate category, significantly higher number of girls and boys were found to have primary hypothyroidism (8.6%) rather than skeletal dysplasia (1.7%). The present study very well correlated with the studies done by Moayeri H et al. and Song KC et al.[9,17]

Interestingly, besides delayed bone age, characteristic x-rays were noted in about 75% of the hypothyroid patients (Figure 4).

In this study, there was a significant difference in GHD prevalence between genders, with boys outnumbering girls (2.6:1). Other independent reviews on growth retardation revealed that boys outnumbered girls by 2.5:1, and 2:1[1,10] which are compatible with the results obtained in this study. Thus, it appears that GHD may be more common in boys. The height SDS and growth rate were found to be significantly different between the two sexes; it may be because of male sex dominance in the community, early referral and better nutritional status of male children in the developing world.

CONCLUSION

Thus, from the clinical point of view, some points to remember: (1) The most common causes of short stature are physiological rather than pathologic (2) Determination of height velocity is the most critical factor in evaluating the growth of a child; therefore careful anthropometric measurements (height and weight) need to be made, recorded and plotted accurately on growth chart and decision-making should be based upon careful observations of growth and calculations of growth rate at an interval of not less than 6 months or preferably 12 months. (3) Treatment for the short stature would be effective only before epiphyseal fusion.

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This manuscript has been duly approved by the Institutional Review Board/Ethics Committee.

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

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JAFES

ORIGINAL ARTICLE

Incidence and Risk Factors for Post-thyroidectomy Hypocalcemia

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Abstract

Objectives. This study aimed to determine the incidence and risk factors for post-thyroidectomy hypocalcemia.

Methodology. This was a retrospective study of 242 patients who underwent total or completion thyroidectomy from 2011-2014 at the St. Luke's Medical Center, Quezon City, Philippines. The overall and type-specific incidences of hypocalcemia were determined. Patient and surgery-related factors were assessed and hypocalcemic events described.

Results. Overall incidence of hypocalcemia is 11.98% distributed into symptomatic (10.74%) and asymptomatic (1.24%). The following patient-related factors were not found to be significantly associated with hypocalcemia: age, gender, thyroid disease and thyroid gland weight. Among surgery-related factors, the presence of concomitant complications of thyroidectomy (hoarseness and/or hematoma) and inadvertent parathyroidectomy were significantly associated with hypocalcemia both in the univariate [p=0.046; OR 2.369 (95%CI: 0.995-5.643) and p=0.027; OR 2.426 (95%CI: 1.084-5.432), respectively] and multivariate analyses [p=0.025; OR 2.842 (95%CI: 1.142-7.069) and p=0.013; OR 2.941 (95%CI: 1.252-6.907), respectively]. Other surgery-related factors were not found to be significantly associated with hypocalcemia: extent of thyroidectomy [total vs completion]; neck dissection; surgery duration (hours); and surgeon [consultant vs. trainee].

Among those with symptomatic hypocalcemia, manifestations occurred 29.85±23.07 hours post-operatively and these were: Chvostek's (80.8%), acral paresthesia (76.9%), perioral numbness (46.1%), carpopedal spasm (15.3%), Trousseau's (7.7%) and cramps (3.8%). Those who presented with manifestations of hypocalcemia but with normal serum iCa post-operatively comprised 33.9% of the study population and the majority presented with Chvostek's sign (52%) and acral paresthesia (50%).

Conclusion. In this study, hoarseness and/or hematoma and inadvertent parathyroidectomy are risk factors for post-thyroidectomy hypocalcemia. Closer monitoring of these patients for hypocalcemia may be necessary.

Key words: hypocalcemia, thyroidectomy, incidence, risk factor

INTRODUCTION

Thyroidectomy has become a standard of care in the management of different thyroid diseases, most importantly, of thyroid malignancies. It is straightforward and associated with minimal morbidity, as the surgical technique has evolved throughout the years. And with this, hospital stay for post-thyroidectomy patients has decreased significantly. Some surgeons even advocate "short-stay thyroid surgery," defined as <24 hour hospital stay. The benefits include reduced costs, reduced in-patient waiting lists, increased availability of in-patient beds, reduced post-operative complications and the psychological benefit of avoiding prolonged hospitalization.[1] However, as with any surgical procedure, it is not without complications. And these complications are barriers to early discharge and may cause significant morbidity to the patients. The different complications related to thyroid surgery include the following: hypocalcemia, bleeding and hematoma formation, recurrent laryngeal nerve injury, superior laryngeal nerve injury, dysphagia, wound infection, poor wound healing, inability to urinate and pain.[2]

In this study, we focused on the most common complication of thyroid surgery – hypocalcemia. It can occur transiently in up to 30%, and permanently in up to 4% of patients after thyroid surgery.[3] It is a common hindrance for early discharge and may cause significant morbidity and fatality (due to cardiac arrhythmia) if not addressed promptly.

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Post-thyroidectomy hypocalcemia may be symptomatic or asymptomatic (biochemical). Manifestations of hypocalcemia include perioral numbness, paresthesia of hands/feet, Chvostek's sign, Trousseau sign, cramps, carpopedal spasms and tetany.

Several studies have enumerated factors that are associated with increased risk of hypocalcemia in patients who underwent thyroidectomy and these include: iatrogenic surgical trauma to the parathyroid glands, incidental parathyroidectomy, the number of functioning glands left behind, extent of surgery, experience of the surgeon, hyperthyroidism, retrosternal goiter, concomitant neck dissection, and thyroid carcinoma.[4,5] Even the patient's age has been found to be negatively correlated with post-operative serum calcium levels[6] in one study but protective in another.[7] On the other hand, prophylactic calcium or vitamin D supplementation has been shown to decrease the incidence of post-thyroidectomy hypocalcemia as seen in a meta-analysis,[8] although there is currently no guideline on this. The extent of thyroidectomy and the thyroid disease are also correlated with risk of hypocalcemia in one study. Patients who underwent total thyroidectomy were found to be more likely to develop hypocalcaemia than those patients who had a completion thyroidectomy. The authors surmised that the two-stage procedure (completion thyroidectomy) resulted in a lower incidence of hypocalcaemia since the parathyroid glands on the side of the previous lobectomy may have had time to recover their function prior to the completion surgery. The authors also noted that thyroidectomy of toxic goiters tend to be more bloody, requiring more diathermy to be used for hemostasis which may compromise the vasculature of the parathyroid glands leading to a higher risk of hypocalcemia post-operatively.[9]

Thyroid gland weight may also be associated with this complication as seen in 2 studies where gland weight of >100-110 grams was associated with higher rates of post-thyroidectomy hypoparathyroidism.[10, 11] In a local retrospective study by Celzo, et al in 2005 where they studied 363 patients who underwent different types of thyroidectomy, they found that bilateral operation (thyroidectomy) [p <0.05, OR 4.56 (95% CI: 2.12-9.80)] and age <40 years old [p <0.05, OR 1.04 (95% CI: 1.02-1.07)] were independent predictors of post-thyroidectomy hypocalcemia.[12]

Several laboratory tests have also been used to predict those who will develop hypocalcemia after thyroidectomy. The use of intact parathyroid hormone level (i-PTH) has been studied thoroughly, and in one study was found to be an early predictor of hypocalcemia.[13] Although there are several evidences for the use of i-PTH in predicting hypocalcemia, its availability and cost are its main limitation for widespread use. In our setting, i-PTH results cannot be made available immediately post-thyroidectomy, making it a retrospective index losing its predictive value. Other laboratory tests have also been studied as predictors of hypocalcemia and include: the relative drop in calcium level (baseline/pre-operative versus post-operative levels) defined as ≥1.1 mg/dl drop (the authors proposed a protocol of calcium replacement if this change in serum calcium is noted),[14] and the absolute level of ionized or total calcium.[4] One study was able to show that serum calcium levels measured at 6-h post-surgery and on day 1 postoperatively are useful in predicting whether the patient will develop hypocalcaemia. Day 1 postoperative calcium level and the slope may differentiate whether the patient will have a temporary or permanent hypocalcaemia.[9]

But despite all the available data, hypocalcemia is still the most common complication post-thyroidectomy. And with its attendant morbidity and possible mortality, it is a significant barrier to early discharge after thyroid surgery. Hence, there is still need to define this group of patients in order to predict those who will develop this complication post-thyroidectomy. And as one study was able to show, ethnicity may also influence the risk for this complication.[7]

METHODOLOGY

Study Objectives

The general objective of this study was to determine the incidence and risk factors of post-thyroidectomy hypocalcemia. Specifically, this study aimed:

1. To determine the overall incidence of post-thyroidectomy hypocalcemia and the incidences of the following types of hypocalcemia: symptomatic and asymptomatic;
2. To determine patient-related factors (age, gender, type of thyroid disease [toxic, non-toxic, malignant], thyroid gland weight and post-operative serum ionized calcium) and surgery-related factors (extent of thyroidectomy, performance of neck dissection, type of surgeon, duration of surgery, inadvertent parathyroidectomy, concomitant thyroidectomy complications) associated with post-thyroidectomy hypocalcemia;
3. To determine mean time of onset (hours) of symptoms and the frequencies of the different hypocalcemic symptoms among patients with symptomatic post-thyroidectomy hypocalcemia; and
4. To determine the incidence of patients with manifestations of hypocalcemia post-thyroidectomy but with normal serum ionized calcium level and the mean time of onset (hours) and frequencies of the different symptoms.

Study Design and Subjects

This was a 4-year (2011-2014) retrospective study utilizing chart review of adult Filipino patients who underwent thyroidectomy (total or completion) at St. Luke's Medical Center Quezon City, Philippines.

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Inclusion Criteria

1. Adult (≥18 years old), Filipino
2. Admitted under or referred to the Section of Endocrinology, Diabetes and Metabolism of St. Luke's Medical Center, Quezon City, Philippines
3. Underwent total or completion thyroidectomy

Exclusion Criteria

1. Known and/or with previous history of parathyroid disease
2. Abnormal serum creatinine and/or presence of medical renal disease
3. With known osteopenia/osteoporosis, any metabolic bone disease and/or active malignancy (except thyroid malignancy)
4. On any of the following medications:
   a. Calcium
   b. Vitamin D
   c. Anti-resorptive (bone) drugs
   d. Menopausal hormone replacement therapy
   e. Thiazide diuretic
   f. Anti-epileptic agents
   g. Patients not monitored with calcium assay

Sample Size Calculation

Assuming that the incidence of post-thyroidectomy hypocalcemia is 30% (Mcleod IK, et al, 2006)[3] with maximum allowable error of 5% and reliability of 90%, sample size required was 226 patients.

Data Collection

The annual "Thyroid Cases" censuses from 2011-2014 of the Section of Endocrinology, Diabetes and Metabolism of St. Luke's Medical Center Quezon City were retrieved. The hospital personal identification numbers (PIN) who underwent total and completion thyroidectomy were submitted to the Medical Records Section of St. Luke's Medical Center for chart retrieval. Data were gathered through chart review and use of St. Luke's Medical Center Health Care System Version 1.8.1, using a data sheet. Data collected included the following: age, gender, type of thyroid disease (toxic goiter, non-toxic goiter, malignancy), thyroid gland weight by final histopathology report (grams), post-operative serum ionized calcium level (mmol/L), presence of hoarseness and/or hematoma post-operatively, extent of thyroidectomy (total or completion), performance of any neck dissection, duration of surgery (hours), type of surgeon (trainee or consultant), inadvertent parathyroidectomy based on presence of parathyroid tissue on final histopathology report, onset of hypocalcemia post-operatively (hours) and presence of hypocalcemic symptoms (perioral numbness, acral paresthesia, Chvostek's sign, Trousseau's sign, cramps, carpopedal spasms, tetany). Other pertinent data that were reviewed included the following: patient's present and past medical history that may affect calcium balance, medication history and serum creatinine.

Definition of Terms

- Hypocalcemic – serum ionized calcium of: <1.00 mmol/L with or without any of the following: perioral numbness, acral paresthesia, Chvostek's sign (new-onset), Trousseau's sign, cramps, carpopedal spasms, tetany.
  - Types:
    1. Symptomatic hypocalcemia – serum ionized calcium of <1.00 mmol/L with any of the following: perioral numbness, acral paresthesia, Chvostek's sign, Trousseau sign, cramps, carpopedal spasms, tetany (onset should be post-thyroidectomy)
    2. Asymptomatic hypocalcemia – serum ionized calcium of <1.00 mmol/L without any hypocalcemic symptom/sign as enumerated above
- Normocalcemic – serum ionized calcium of 1.00-1.30 mmol/L and no symptom/sign of hypocalcemia
- Total Thyroidectomy – removal of the entire thyroid gland; also includes "near-total thyroidectomy" which means a small amount of thyroid tissue is left behind around important structures that may otherwise be injured
- Completion Thyroidectomy – removal of the remaining thyroid tissue after a previous partial thyroidectomy (i.e. lobectomy)

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics Program Version 20. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percentage. Factors associated with post-thyroidectomy hypocalcemia were determined using multiple logistic regression analysis. The level of significance was set at 5%.

Ethical Considerations

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

RESULTS

Among the 344 patients who underwent either total or completion thyroidectomy at St. Luke's Medical Center,

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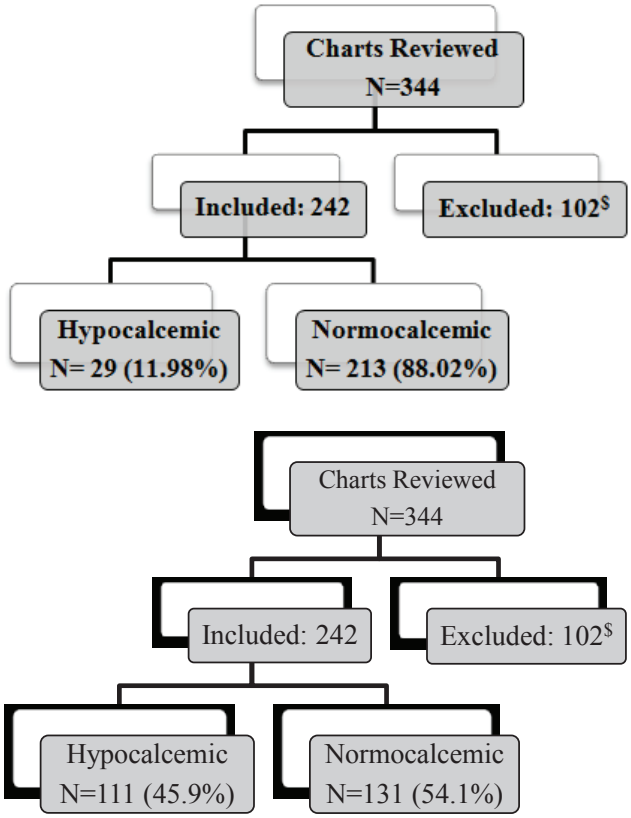
Quezon City, Philippines during the study period, 242 were included in the study (Figure 1).



$ Reasons for exclusion:
Calcium and/or Vit. D. intake – 36; No post-operative iCa result – 27; Thiazide intake – 16; Abnormal serum creatinine – 7; With bone disease/active malignancy – 5; On menopausal hormone-replacement therapy – 4; No histopathology report – 3; Anti-resorptive drug intake – 2; Anti-epileptic drug intake – 2

Figure 1. Study population.

Hypocalcemia developed in 29 patients with an overall incidence of post-thyroidectomy hypocalcemia of 11.98% (95%CI: 0.08-0.17). Among the hypocalcemic patients, 26 were symptomatic (10.74%) while the remaining 3 were asymptomatic (1.24%) (Table 1).

In the univariate analysis, the other patient-related factors were not significantly associated with hypocalcemia (age, gender, thyroid disease and thyroid gland weight). However, we can see that hypocalcemia occurred more often among females (12.5%) than males (7.7%) and that the mean thyroid gland weight is heavier in absolute terms in the hypocalcemic group (79.78 vs 66.07 grams).

Table 1. Distribution of subjects according to incidence of hypocalcemia N=242

Calcium Status	Incidence	95% Confidence Interval
Normocalcemia (n=213)	88.02%	0.83-0.92
Hypocalcemia (Overall) (n=29)	11.98%	0.08-0.17
1. Normocalcemia (n=213)	10.74%	0.07-0.15
2. Hypocalcemia (Overall) (n=29)	1.24%	0.004-0.04

As for the surgery-related factors, the presence of concomitant complication of thyroidectomy (hoarseness and/or hematoma) and inadvertent parathyroidectomy were found to be significantly associated with the outcome [p=0.046, OR 2.369 (95% CI: 0.995-5.643)] and p=0.027, OR 2.426 (95% CI: 1.084-5.432), respectively]. Extent of thyroidectomy and performance of neck dissection were not significantly associated with hypocalcemia; there was longer duration of surgery in the hypocalcemic group but this did not reach statistical significance. The status of the surgeon, as consultant or as trainee, was not significantly associated with hypocalcemia (Table 2).

When all the factors were entered into multiple logistic regression analysis, we can see that in both the initial and final models, the presence of concomitant complication of thyroidectomy and inadvertent parathyroidectomy were significantly associated with hypocalcemia with p values of <0.05 and odds ratio of 2.842 (95%CI: 1.142-7.069) and 2.941 (95%CI: 1.252-6.907) respectively (Table 3).

The onset of manifestations of post-thyroidectomy hypocalcemia for this study was 29.85±23.07 hours post-operatively. The most common manifestations of hypocalcemia were Chvostek's sign and acral paresthesia present in 80.8% and 76.9% of patients, respectively. Other manifestations noted were perioral numbness (46.1%), carpopedal spasm (15.3%), Trousseau's sign (7.7%) and cramps (3.8%) (Table 4).

Eighty-two (82) subjects or 33.9% of the population studied, presented with clinical manifestations seen in patients with hypocalcemia but were noted to have normal serum ionized calcium level on testing. These patients presented with the symptoms at 17.18±16.17 hours post-operatively. Majority of these patients presented with positive Chvostek's sign (52%) and acral paresthesia (50%) (Table 5).

DISCUSSION

The overall incidence of post-thyroidectomy hypocalcemia in this study was 11.98%. This is lower than reported in the study of Mcleod, et al., in 2006.[3] This incidence falls within the general rates reported in literature which varies widely depending on the population studied (i.e., extent of thyroidectomy, definition of hypocalcemia) and can reach up to >50%.[15] The majority of hypocalcemic subjects in our study were symptomatic (10.74%). In a previous local retrospective study,[12] the overall prevalence rate of post-thyroidectomy hypocalcemia was 21%. The type-specific rates were: 31% symptomatic (with or without low calcium levels), 16% true hypocalcemia, 26% asymptomatic hypocalcemia. However, direct comparison with the findings of this present study is not possible since the patients in the previous local study included subjects who underwent any extent of thyroidectomy, whereas the

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Table 2. Distribution of subjects according to demographic and clinical risk factors for hypocalcemia N=242

PATIENT-related factors				
Factor	**Hypocalcemic (n=29)**	**Normocalcemic (n=213)**	**p value**	**OR (95%CI)**
Age in years (mean±SD)	48.59±12.91	45.75±11.96	0.236	1.020 (0.987-1.054)
Gender			0.476	0.583 0.130-2.609
• Male (%)	2 (7.7)	24 (92.3)		
• Female (%)	27 (12.5)	189 (87.5%)		
Thyroid Disease			0.334	1.505 (0.654-3.461)
1. Toxic (%)	3 (10.3)	27 (12.7)		
2. Nontoxic (%)	6 (20.7)	57 (26.8)		
3. Malignant (%)	19 (65.5)	125 (58.9)		
4. Toxic & Malignant	1 (3.4)	4 (1.9)		
Thyroid gland weight in grams (mean±SD)	79.78±116.41	66.07±112.70	0.566	1.001 (0.998-1.004)
Post-operative serum ionized calcium in mmol/L (mean±SD)	0.95±0.04	1.10±0.06	<0.001	
SURGERY-related Factors				
Factor	**Hypocalcemic (n=111)**	**Normocalcemic (n=131)**	**p value**	**OR (95%CI)**
Presence of concomitant complication of thyroidectomy [hoarseness and/or hematoma] (%)			0.046	2.369 (0.995-5.643)
1. Yes	9 (20.9)	34 (79.1)		
2. No	20 (10.1)	179 (89.9)		
Extent of thyroidectomy			0.402	1.877 (0.421-8.360)
1. Total (%)	27 (12.6)	187 (87.4)		
2. Completion (%)	2 (7.1)	26 (92.9)		
Neck dissection (%)			0.703	1.223 (0.434-3.447)
1. Yes	5 (13.9)	31 (86.1)		
2. No	24 (11.7)	182 (88.3)		
Duration of Surgery in hours (mean±SD)	4.59±3.59	3.76±1.82	0.062	1.150 (0.993-1.331)
Inadvertent parathyroidectomy (%)			0.027	2.426 (1.084-5.432)
1. Yes	12 (20.0)	48 (80.0)		
2. No	17 (9.3)	165 (90.7)		
Type of surgeon			0.550	0.786 (0.357-1.732)
1. Consultant	17 (11.0)	137 (89.0)		
2. Trainee	12 (13.6)	76 (86.4)		

Table 3. Results of logistic regression analysis N=242

Factor	**Initial Model**		**Final Model**	
	p value	**Odds Ratio (95% CI)**	**p value**	**Odds Ratio (95% CI)**
Age in years	0.337	1.018 (0.982-1.055)		
Gender	0.396	0.396 (0.046-3.372)		
Thyroid disease (toxic, nontoxic or malignant)	0.355	1.570 (0.604-4.080)		
Thyroid gland weight in grams	0.629	1.001 (0.997-1.005)		
Presence concomitant complication of thyroidectomy [hoarseness and/or hematoma]	0.066	2.526 (0.941-6.785)	0.025	2.842 (1.142-7.069)
Type of surgery (completion vs. total thyroidectomy)	0.717	1.344 (0.272-6.629)		
Neck dissection	0.359	0.522 (0.130-2.094)		
Duration of surgery in hours	0.387	1.113 (0.873-1.418)		
Inadvertent parathyroidectomy	0.020	3.006 (1.191-7.583)	0.013	2.941 (1.252-6.907)
Type of surgeon (consultant vs. trainee)	0.958	0.975 (0.374-2.537)		

Table 4. Hypocalcemic manifestations

Manifestation	**Frequency (%)**
Chvostek's sign	21 (80.8)
Acral paresthesia	20 (76.9)
Perioral numbness	12 (46.1)
Carpopedal spasm	4 (15.3)
Trousseau's sign	2 (7.7)
Cramps	1 (3.8)
Symptom onset in hours post-operatively: 29.85±23.07	

Table 5. Incidence characteristics of subjects with reported clinical manifestation(s) of hypocalcemia but normal serum ionized calcium

Incidence (%) [95%CI]	33.9 (0.28-0.40)
Symptom onset in hours post-operatively	17.18±16.17
Manifestations	Frequency (%)
Chvostek's sign	52 (63.4)
Acral paresthesia	50 (61.0)
Perioral numbness	28 (34.1)
Carpopedal spasm	11 (13.4)
Trousseau's sign	1 (1.2)

study focused only on those who underwent total or completion thyroidectomy.

Most of the typical risk factors noted to be predictors of post-thyroidectomy hypocalcemia in literature were not found to be significantly associated with post-thyroidectomy hypocalcemia in the present study. These included the following: age, type of thyroid disease, thyroid gland weight, extent of thyroidectomy, performance of neck dissection and duration of surgery. Being a surgical procedure, success of thyroidectomy has been attributed to the experience of the surgeon. As such, complications may therefore be minimized under hands of an expert. However, for this study, there was no significant association noted in the post-thyroidectomy hypocalcemia between procedures done by consultants and trainees in our institution. This is consistent with one study where a review of 232 records of total thyroidectomies was done. Thyroidectomies done by endocrine surgery consultants were compared with those

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done by trainees. Safety, which was defined as postoperative hypoparathyroidism, recurrent laryngeal nerve palsy, and hemorrhage and efficacy defined as postoperative radioactive iodine uptake in the two groups were compared. Their results showed that the rates of occurrence of permanent hypoparathyroidism and recurrent laryngeal nerve palsy were comparable in the two groups and that postoperative radioactive iodine uptake was not significantly different.[16]

The finding in this study of a greater number of females who developed post-thyroidectomy hypocalcemia, though not statistically significant, may be attributed to females being more prone to calcium and vitamin D deficiency than males[17] and considering the age group of this cohort, the female subjects would probably be perimenopausal as well. In one large study, female gender had an odds ratio of 1.62 (95%CI 1.45–1.80) (p<.001) in developing post-thyroidectomy hypocalcemia.[7]

The most significant finding in this study is the correlation of post-thyroidectomy hypocalcemia with the presence of hoarseness and/or hematoma (both of which are also post-thyroidectomy complications) and inadvertent parathyroidectomy. In one study, the incidence of transient hoarseness was noted to be at 6.86%,[18] which is far less common than hypocalcemia. In this study, the presence of hoarseness and/or hematoma is strongly associated with the development of post-thyroidectomy hypocalcemia [OR 2.842 (95%CI: 1.142-7.069)]. Hoarseness depicts injury to the recurrent laryngeal nerve and is most often a result of extensive neck surgery, as in cases of large goiters or those who undergo neck dissection. Hematoma formation may also be attributed to extensive neck surgery. Both these complications may signify extensive neck tissue manipulation and injury with subsequent tissue swelling that can compromise the vascular supply of the parathyroid glands and cause hypocalcemia.

Inadvertent parathyroidectomy on the other hand is clearly associated with post-thyroidectomy hypocalcemia as shown in our study [OR 2.941 (95%CI: 1.252-6.907)]. Removal of the parathyroid glands can lead to transient or even permanent decrease in parathyroid hormone levels and lead to hypocalcemia.

The onset of hypocalcemia manifestations in the present study was noted to be 29.85±23.07 hours post-operatively, which means that hypocalcemia may occur as early as 6 hours up to >24 hours post-operatively. This is because the greatest decline in post-operative serum calcium levels, compared to pre-operative levels, can occur on the morning of the first post-operative day (12-18 hours after the operation) as seen in one study.[14] Furthermore, the same researchers noted that a maximum of 36 hours was needed to observe a decrease in serum calcium levels close to those expected to cause symptoms.[14] As for the manifestations, majority of the patients with hypocalcemia presented with a positive Chvostek's sign (80.8%) and acral paresthesia (76.9%). But we are unable to validate these clinical findings due to the study design.

It is interesting that a significant number of subjects in our study (33.9%) presented with clinical manifestations of hypocalcemia, but had normal serum ionized calcium level on testing. This condition has been termed "symptomatic hypocalcemia" in several studies. The finding in our study contrasts with findings in 2 other studies. The study of Kim et al., in 2011 showed that among the 62 hypocalcemic patients in their study, only 9 patients (14.5%) met the criteria for symptomatic hypocalcemia. The other 45 patients (72.5%) experienced both symptomatic and biochemical abnormalities while the remaining 8 patients (12.9%) showed only biochemical hypocalcemia.[15] In the study of Tolone et al., in 2013, they found that symptomatic hypocalcemia developed only in 9.5%, while laboratory hypocalcemia developed in 18%.[6] This "mismatch" between the manifestations of hypocalcemia and biochemical evidence is also evident in one study where only 24 out of 45 patients (53.3%) presented with symptomatic and biochemical abnormalities on the same day. The mismatch was seen in the other 21 patients (46.6%). There was a 1-day gap between the initial occurrence of hypocalcemic symptoms/signs and biochemical evidence in 11 patients (17.7%), a 2-day gap in 8 patients (12.9%), and a 3-day gap in 2 patients (3.2%).[15] This "mismatch" occurs because symptoms may be affected by the velocity of the drop in calcium and not merely by calcium level itself.[15] This explanation is difficult to substantiate in our study since pre-operative calcium levels were not determined, hence the degree of drop (or delta change) in serum calcium cannot be known. Furthermore, the manifestations of hypocalcemia are fairly non-specific and may be seen in other post-surgical patients as a result of anesthesia or other electrolyte abnormalities.

CONCLUSION

Analyzing post-thyroidectomy hypocalcemia may aid decisions on post-operative monitoring as well as prevention. This study showed 11.98% incidence of post-thyroidectomy hypocalcemia in our institution. Against this baseline the effects of reductions in morbidity may be measured in the future.

In the clinical prediction of patients who may develop post-thyroidectomy hypocalcemia, those who present with hoarseness and/or hematoma post-operatively should also be closely monitored for hypocalcemia, as these concomitant complications are strong risk factors for hypocalcemia. Patients who had inadvertent parathyroidectomy must also be monitored thoroughly during the immediate post-operative period and perhaps longer, since these patients are at greater risk for developing permanent hypoparathyroidism which may require lifetime supplementation with calcium and active vitamin D.

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The mean time of onset of hypocalcemic manifestation shown in this study emphasizes the key role of vigilance in monitoring patients for hypocalcemia post-thyroidectomy even beyond the first post-operative day.

This study has several limitations. The retrospective nature of this study did not give the researchers the opportunity to validate the hypocalcemic manifestations reported in the charts. Also, it was not routine practice in our institution to request for calcium or vitamin D assays pre-operatively particularly in asymptomatic patients. Hence, the researchers cannot ascertain the calcium or vitamin D status of the patients pre-operatively but using the exclusion criteria of this study, most of the conditions that can affect these values were eliminated. To circumvent the above limitations, a prospective study is necessary. Most of the typical risk factors mentioned in literature were not significant in this study, but perhaps an extension and/or addition of more patients may either yield the same results or may show a difference.

The presence of hoarseness and/or hematoma were found to be strong risk factors. The exact mechanism is not clear, and we recommend further studies regarding this risk factor.

Also, a significant percentage of the study population presented with symptoms of hypocalcemia despite normal calcium levels. This "mismatch" may need further studies that are designed to eliminate confounding factors if possible, to elucidate the characteristics of such patients. Future researchers may also consider following-up these patients as to who developed or will develop permanent hypocalcemia.

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

Author Disclosure
All the authors declared no conflict of interest.

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ORIGINAL ARTICLE

JAFES

Footwear Appropriateness, Preferences and Foot Ulcer Risk Among Adult Diabetics at Makati Medical Center Outpatient Department

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Abstract

Objective. To determine general and clinical characteristics associated with the use of inappropriate footwear among Filipino patients with diabetes.

Methodology. Adult patients with diabetes were recruited. Comprehensive foot examination was done checking on foot deformities, neuropathies and peripheral arterial disease. Footwear was then examined as to length and width. Appropriateness of footwear to patient's foot was measured using International Working Group on the Diabetic Foot (IWGDF) criteria.

Results. We classified 170 adults with diabetes based on foot ulcer risk classification of IWGDF. In this population, 62% of respondents were at risk for foot ulcer. Flipflops are the primary choice of footwear among 82% and 47% of the respondents for indoor and outdoor footwear respectively. Inappropriate footwear was seen in 91% of the patients. Binary logistic regression showed insufficient evidence to determine an association between the use of inappropriate footwear and patient sex, educational attainment, foot care evaluation and examination. Foot ulcer risk classification showed a trend for higher group levels to wear inappropriate footwear.

Conclusion. Flipflops and sandals are the primary preferences of the participants. Majority (91%) of the participants wear inappropriate footwear. This finding were due to multifactorial causes: preference, climate, economic reasons, and foot ulcer risk category. Educational attainment and foot care education did not improve the statistics of footwear appropriateness.

Key words: Footwear, Diabetes Mellitus, Foot ulcer

INTRODUCTION

Foot complications are a major cause of morbidity and disability in persons with diabetes mellitus.[1] The lifetime risk of a patient with diabetes for foot ulcer is 25%, with an annual incidence of 2%. A diabetic foot ulcer starts with a triad of problems. First, neuropathy leading to the loss of protective sensation; second is foot deformity due to modulation at the neuromuscular junction where muscles are deprived of innervation leading to foot deformities; and lastly, trauma to the foot.[2]

The International Working Group on the Diabetic Foot (IWGDF)[2] has classified the risk of developing foot ulcer (Table 1), in spite of this, screening to prevent diabetic foot is often overlooked. The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab)[3] noted that in the past twelve months, 77% of their patients had an eye screening for retinopathy and only 49% subjected themselves to foot screening. Both eye and foot complications are manifestations of the microvascular complications of diabetes.

Table 1. Diabetes foot ulcer risk classification IWGDF[2]

Criteria	Description
Group 0	no neuropathy, no deformity, no peripheral vascular disease(PVD)
Group 1	With neuropathy, without deformity or PVD
Group 2	With neuropathy, with deformity or PVD
Group 3	History of foot ulceration or lower extremity amputation

The IWGDF set the correct length of footwear at 1-2 cm longer than the foot. The internal width of the shoe should be equal to the width of the foot at the site of metatarsophalangeal joints.[4]

Flipflops are one of the most commonly used footwear among developing countries.[5] Flipflops are described as an open-toed footwear with a flat sole held by a Y-shaped rubber strap that passes between the first and second toes and around both sides of the foot. They usually do not have a strap around the heels.

Despite the guidelines, 35-54% of foot ulcers are due to trauma from ill-fitting footwear.[6-7] Half of the patients with diabetes and peripheral sensory neuropathy had

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footwear-related injury.[8] Patients with diabetic foot ulceration were 5.1 times more likely to have poorly-fitting shoes. Foot-shoe size mismatches can disrupt the biomechanics of the foot and ankle, predisposing to pain and falls.[9]

Significance of the Study

Preference and knowledge on footwear for patients with diabetes influence the choice of shoes that patients buy, regardless whether the shoe can fulfill or defeat its purpose as a protective device.

In the Philippines, information on knowledge of and compliance to appropriate footwear is minimal. This study aims to investigate the footwear preferences and practices among Filipino patients with diabetes. Clinical factors that contribute to or influence the use of inappropriate footwear will also be investigated.

The results of this research can provide clinicians and diabetes educators with information on foot and footwear practices and provide information for module formation.

OBJECTIVES

General Objectives

To determine general and clinical characteristics associated with the use of inappropriate footwear among Filipino patients with diabetes.

Specific Objectives

1. To investigate the footwear preferences of diabetic patients;
2. To determine the proportion of patients belonging to IWGDF diabetic foot ulcer risk groups 0, 1, 2, and 3;
3. To determine the proportion of patients with diabetes who use footwear with improper lengths and widths; and
4. To compare the proportion of patients who use inappropriate footwear across the ulcer risk classification groups.

METHODOLOGY

Study subjects

Patients included in the study were patients who consulted at Makati Medical Center Outpatient Department.

Inclusion criteria

Patients with Type 1 or Type 2 Diabetes, age 18 years old and above. Patients must be able to read, comprehend and understand Filipino or English and must consent to join the study.

The diagnosis of diabetes mellitus is based on the Unite for Diabetes Philippines Clinical Practice Guidelines:[10] Fasting Blood sugar ≥126 mg/dL; 2-hour plasma glucose ≥200 mg/dL after an oral glucose tolerance test; random blood sugar ≥200 mg/dL with signs or symptoms of diabetes.

Exclusion criteria

Impaired fasting glucose, impaired glucose tolerance, gestational diabetes, with foot dressings that may interfere with toe measurement (ulcer dressing), rheumatoid arthritis, limb prosthesis, cerebrovascular disease with residuals, hypothyroidism, currently treated for PTB, unable to maintain standing position, already included in this study from previous consultation, socioeconomic status.

Study Setting

The research was conducted at the Outpatient Department of Makati Medical Center, a tertiary hospital in Makati City, Philippines. The study subjects were all recruited from the Health Service Program of the hospital.

Study Design

Cross-sectional analytic

Sample size

The minimum sample size was computed to be 169 based on the proportion of patients wearing inappropriate footwear= 46%[11] with confidence level= 5%, margin of error= 5%, and estimated number of patients with diabetes during the sampling time= 300.

Recruitment and sampling

All patients who meet the inclusion criteria over a 9-week period were included in the analysis. The subjects were consecutively recruited (Figure 1).

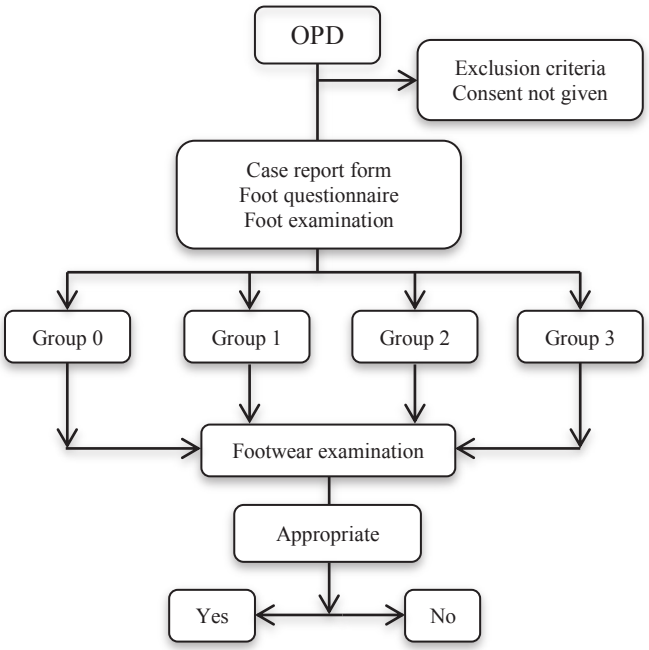

Figure 1. Flow Chart.

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Study Procedure

Recruitment started after approval of the MMC Institutional Review Board (IRB). Patients were evaluated based on the inclusion/exclusion criteria.

Recruitment

Patients who qualified were invited to join the research. The principal investigator performed the recruitment process. The following were fully explained to the patient: purpose of the study, its risks and benefits, the personal information needed, the procedures to be performed, the materials to be used for foot examination. Patients who gave consent were recruited.

Case report form

An investigator administered a questionnaire regarding previous illnesses, demographics, diabetes history, diabetes control and cigarette smoking. Latest laboratory test results were noted. Diabetes control was determined using level of HbA1c. This research used <7% as cut-off for good diabetes control, based on the UNITE for Diabetes Philippine Guidelines.[10]

Foot questionnaire

Participants were given a questionnaire regarding foot history, knowledge and preferences. Pictures of different types and styles of men's and women's footwear were shown to the patient during the interview for easier identification of the types of footwear owned.

Foot examination[12]

A nurse educator who has specialized on foot care was hired as a research assistant of the principal investigator. The comprehensive foot examination is composed of the following:

<u>Dermatologic</u>

Visual inspection of both feet as to presence of the following:

Dryness	Swelling	Calluses
Fungal infection	Erythema	Corns
Inflammation	Fissures	
Nail dystrophy	Discharge	

<u>Musculoskeletal</u>

Visual inspection of both feet as to presence of the following:

Hammer toes	Overlapping digits
Claw toes	Charcot arthropathy
Bunion	Amputation of toes or foot

Interpretation:
Deformity: when any of the aforementioned items is present.

<u>Neurologic</u>

Neurologic examination is composed of the following:

10-g Semmes-Weinstein monofilament test

Instruction: Apply the monofilament on the patient's hands (or elbow or forehead) so that he or she knows what to expect. Ask patient to close his/her eyes. The monofilament is placed perpendicular to the skin on the 1st, 3rd, 5th metatarsal heads and plantar surface of hallux, with pressure applied until the monofilament buckles. It should be held for ~1 second then released.

Press the filament to the skin and ask the patient whether he feels the pressure applied by answering: YES or NO and where they feel the pressure by answering LEFT FOOT or RIGHT FOOT. Repeat this application twice at the same site but alternate this with at least one "mock" application in which no filament is applied (total of three questions per site).

Protective sensation is present at each site if the patient correctly answers two out of three applications. Protective sensation is absent when two out of the three answers are incorrect.

Vibration test using the 128-Hz tuning fork

Instruction: Apply the tuning fork on the patient's wrists (elbow or clavicle) so that he or she knows what to expect. The patient must not be able to see where the examiner applies the tuning fork. The tuning fork is applied on a bony part on the dorsal side of the distal phalanx of the first toe. It should be applied perpendicularly with constant pressure. The patient will be asked if he or she felt the vibration by answering YES or NO and where he or she felt it by answering LEFT FOOT or RIGHT FOOT. The test is normal if the patient was able to feel the vibration.

Pinprick sensation

Instruction: A hair filament is applied proximal to the toenail on the dorsal surface of the hallux. Use just enough pressure to deform the skin. Ask the patient if he or she perceives the sensation by answering YES or NO and where he/she felt it by answering LEFT FOOT or RIGHT FOOT. An abnormal response is when there is inability to perceive it on either hallux.

Interpretation:
LOSS OF PROTECTIVE SENSATION (LOPS) was diagnosed when the patient has one or more abnormal results in section D.4C. We ruled out LOPS when the patient has at least two normal tests and no abnormal test.

<u>Vascular</u>

Vascular examination involved palpation of the posterior tibial artery, dorsalis pedis artery and computation of the ankle brachial index (ABI).

Instruction: Place the blood pressure cuff above the dorsalis pedis then place the doppler probe over the dorsalis pedis artery.

$$\text{ABI calculation} = \frac{\text{Ankle systolic blood pressure}}{\text{Brachial systolic blood pressure}}$$

Interpretation: Normal: 0.9-1.3

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Foot Examination Assessment

Patients will then be classified into four categories based on the foot ulcer risks[2] in Table 1.

Foot and shoe measurement

Both length and width were measured for foot, using Brannock's device. The patient was asked to stand, the foot being measured was lifted and placed onto the base of the Brannock's device[13] with the heel firmly located against the back of the heel cup with the researcher firmly holding the subject's ankle and heel cup together. Foot length was measured from the ankle to the longest toe. Foot width was measured at the level of the metatarsophalangeal joint.

The footwear to be assessed was what the patient was wearing during the clinic visit. It was assumed that the patient wears this shoe regularly. Shoe length was checked using plus12med shoe fitting device. Shoe width was measured using a sliding caliper in centimeters. Flipflops, sandals and open-type of footwear were recorded as inappropriate footwear, and their dimensions were not measured.

Appropriate footwear for this paper was defined as a closed-type of shoe, with length 1-2 cm longer than the foot and internal width equal to the width of the foot at the site of metatarsophalangeal joints.

Statistical Analysis

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and proportion were used for nominal variables, median and IQR for ordinal variables, and mean and SD for interval/ratio variables. Binary logistic regression was used to determine the risk factor associated with appropriateness of footwear. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α-level of significance. STATA 12.0 was used for data analysis.

Ethical Considerations

This study was conducted in accordance to the ethical principles based on the Declaration of Helsinki and the National Guidelines for Biomedical Research of the National Ethics Committee (NEC) of the Philippines. The research protocol underwent approval from the Institutional Review Board (IRB).

All observations will be preceded by a written documentation of informed consent. Participation in the study was purely voluntary and without financial compensation. The interventions and data were recorded only in writing, and was not recorded via video nor audio. The results and patient information were kept strictly confidential by the primary investigator. A unique alphanumeric code was issued to each research subject and the subjects' names did not appear in any of the data collection tools. The data were stored in the primary investigator's database, password-protected, and the projected duration of storage would be at least ten years.

Psychosocial Support

Results of the foot examination and assessment of the footwear were fully disclosed and explained to the patient. The investigator enumerated ways of preventing the progression of areas at risk to foot ulcer or amputation. A pamphlet on proper foot care and footwear were given after the patient participated in the study. Follow-up care and further management of the results obtained from the study were endorsed to the patients' attending physicians.

RESULTS

The total number of participants was 170, with a mean age of 64 years old, mostly females (72.94%), majority (88.82%) residing in Metro Manila. Nearly half (47%) were able to obtain college level education. Half the patients (50.59%) were obese based on the Body Mass Index Asia Pacific Classification. The duration of diabetes in 37.06% of the population was less than 5 years. Majority (81%) used oral hypoglycemic agents with half (51.76%) of them having good control of disease.

Hypertension was the most common co-morbidity; 7% of the population were smokers. Peripheral vascular disease was already diagnosed in 4% while 7% of the participants were currently treated for peripheral neuropathy (Table 2).

For the foot history, 9% were reported to have foot ulcer, while 1% had undergone toe amputation. Numbness and burning/shooting pain were the most common symptoms experienced by these patients.

Regarding knowledge and education on foot care (Table 3), 87% reported they have not received foot care education. Of those who did receive foot care education, 59% were taught by a physician, 36% were instructed by a nurse.

Sandals were the most common footwear used upon consultation. Flipflops were the preferred footwear both at home and outside. Further analysis on indoor footwear showed more than half of the population (53%) preferred to walk barefoot, however, but only inside the house.

Comfort was the primary consideration in their choice for indoor and outdoor wear in 95% of the female and 86% of the male respondents. Only 6.5% of the males and 1.61% of the females considered foot safety as a reason for their preference (Tables 4 and 5).

Upon foot examination, the most common dermatologic finding was dryness, seen in 51% of the population, followed by calluses at 13%. Of the 31% assessed to have a foot deformity, the majority was from bunions (17.06%). More than half (57%) had loss of protective sensation; about 19% had peripheral vascular disease.

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Table 2. Demographic and clinical characteristics of adult patients with diabetes seen at a tertiary hospital (n=170)

Demographic data	Mean ± SD, Frequency (%)
Age	63.88 ± 9.42
Sex	
Female	124 (72.94)
Male	46 (27.06)
Educational attainment	
Elementary	19 (11.18)
High School	64 (37.65)
College/Post-graduate	77 (47.64)
BMI	
Underweight	2 (1.18)
Normal	40 (23.53)
Overweight	42 (24.7)
Obese	86 (50.59)
Diabetes Duration	
Less than 5 years	63 (37.06)
5-10 years	47 (27.65)
>10 years	60 (35.29)
Diabetes Control	
Controlled	88 (51.76)
Uncontrolled	82 (48.24)
Past medical history	
Chronic kidney disease	45 (26.47)
Peripheral neuropathy	12 (7.06)
Peripheral vascular disease	6 (3.53)
Smoking history	
Yes	12 (7.06)
No	158 (92.94)

Table 3. Foot care education, risk classification, and footwear appropriateness of 170 Filipino adults with diabetes

Foot care knowledge and education	Frequency (%)
Received foot care education	22 (12.94)
Foot care education given by	
Doctor	13 (7.64)
Nurse	8 (4.71)
Others	1 (0.58)
Read any educational handout for foot care	15 (8.82)
Foot examined by a doctor	
Within last 12 months	4 (2.35)
Over a year ago	13 (7.64)
Never	153 (90)
Foot ulcer risk classification	
Group 0	63 (37.05)
Group 1	29 (17.06)
Group 2	62 (36.47)
Group 3	16 (9.41)
Appropriateness of footwear	
Appropriate	15 (8.82)
Inappropriate	155 (91.18)

Based on the foot ulcer risk classification, the majority of the patients belonged to Groups 0 and 2 (37% and 36% respectively), followed by Group 1 at 17%, and lastly Group 3 at 9%. Combining the groups at risk (Groups 1-3), 62% of the population analyzed were at risk for foot ulcer (Table 3).

Of the 170 subjects, foot to shoe length and width measurements were performed in 78 of the participants; the rest of the participants were excluded because their footwear was inappropriate for patients with diabetes. Of the patients whose shoes were measured, 15 had appropriate and 63 had inappropriate footwear (Table 3).

Of the 63 patients who had inappropriate shoes, 13 participants had disparity in foot to shoe length, while 10 participants had disparity in foot to shoe width. Of the female participants, 21 had inappropriate foot to shoe length and 19 had inappropriate foot to shoe width. Overall, 91% of the respondents wore inappropriate footwear.

Table 4. Footwear characteristics and preferences among 46 adult Filipino male patients with diabetes

	Frequency (%)
Most preferred footwear inside the house: Flipflops	38 (22.35)
Reasons for preference	
Comfortable	41 (24.12)
Convenient	4 (2.35)
Free	1 (0.59)
Most preferred footwear outside the house: Flipflops	19 (11.18)
Reasons for preference	
Comfortable	40 (23.53)
Safety	3 (6.5)
Convenient	1 (0.59)
Free	1 (0.59)
Required for work	1 (0.59)
Type of footwear during consultation	
Sandals	16(34.78)
Flipflops	10(21.73)
Slip-ons	9(19.56)
Rubber shoes	6(13.04)
Boat shoes	5(10.86)

Table 5. Footwear characteristics and preferences among 124 adult Filipino female patients with diabetes

	Frequency (%)
Most preferred footwear inside the house: Flipflops	102 (60)
Reasons for preference	
Comfortable	118 (69.82)
Convenient	4 (2.35)
Others	2 (1.61)
Most preferred footwear outside the house: Flipflops	61 (35.88)
Reasons for preference	
Comfortable	118 (69.82)
Safety	2 (1.61)
Others	4 (3.23)
Type of footwear during consultation	
Sandals	50
Flipflops	38
Slip-ons	12
Ballet flats	11
Rubber shoes/sneakers	11
Pointed-toe shoes	1
Platform shoes	1

In Table 6, binary logistic regression was conducted with select patient characteristics in the model. It showed insufficient evidence to determine an association between the use of inappropriate footwear and patient sex, educational attainment, foot care evaluation and examination. Among the foot ulcer risk classification groups, results suggest that patients in the ulcer risk classification Group 2, compared to Group 0, were more likely to use inappropriate footwear (OR 4.33, 95% CI 1.04 to 18.07, p = 0.044). For foot ulcer risk Group 3, we had insufficient evidence to demonstrate a significant difference between this foot ulcer risk group versus Group 0.

DISCUSSION

This study evaluated the general characteristics associated with inappropriate footwear. Results showed only 8.82% of the population wore appropriate footwear. This result is lower compared to the studies of Nixon et al.[9] among US veterans with diabetes and Harrison et al.[15] which showed 25.5% and 24% of the subjects, respectively, wore appropriate footwear.

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Table 6. Characteristics associated with footwear appropriateness

	Inappropriate footwear (n=155)	Appropriate footwear (n=15)	OR (95% CI)	P-Value
	Frequency (%); Mean + SD			
Female	114 (73.55)	10 (66.67)	1.23 (0.35 to 4.28)	0.745
Educational attainment				
Nonformal education	5 (3.23)	1 (6.67)	(reference)	-
Elementary	18 (11.61)	1 (6.67)	2.07 (0.10 to 44.09)	0.642
High School	58 (37.42)	6 (40)	1.05 (0.09 to 12.47)	0.972
College	70 (45.16)	7 (46.67)	1.46 (0.13 to 16.30)	0.760
Post-graduate	4 (2.58)	0	-	-
Received foot care education	19 (12.26)	3 (20)	0.23 (0.02 to 3.34)	0.284
With foot evaluation	16 (10.32)	1 (6.67)	5.85 (0.35 to 98.14)	0.219
Read any educational handout for foot care	13 (8.55)	2 (13.33)	0.90 (0.06 to 14.36)	0.940
Foot ulcer risk classification				
Group 0	53 (34.19)	10 (66.67)	(reference)	-
Group 1	29 (18.71)	0	-	-
Group 2	59 (38.06)	3 (20)	4.33 (1.04 to 18.07)	0.044
Group 3	14 (9.03)	2 (13.33)	2.12 (0.31 to 14.46)	0.442

The IWGDF[16] described an appropriate shoe as one that is well-fitted, comfortable and can protect the foot from injury. In this study, our poor results can be attributed to several factors, but at the top of the list was the patient's predilection to wear flipflops or open-type sandals. It was the primary choice of footwear among 82% of the respondents for indoors and 47% for outdoors. These data were higher compared to the study done by Chandalia et al.[14] in India, where flipflops were the primary choice in 48% of the respondents. This was also validated in a study by Morbach et al.[5] who concluded that flipflops were preferred in developing countries such as India (65%) and Tanzania (88%). Flipflops are inappropriate because these are open-type footwear which fail to protect the foot from injuries.

The tendency to develop foot ulcers is compounded because 53% of the respondents said "walking barefoot" was their secondary preference for indoors. The IWGDF[16] recommends avoiding walking barefoot because this is a common source of foot injuries. This finding is also evident in a study done in India[14] where 45% of the participants also walked barefoot indoors.

Comfort was the foremost consideration for footwear preference, the Philippines is a tropical country with humid temperatures most days of the year and flipflops, which are open-type sandals, are the most comfortable type of footwear for our climate.

This is a dilemma for clinicians and diabetes educators who must reconcile what footwear is comfortable versus what is protective for the patient's feet. The description of protective footwear in the guidelines[4,16] is made for countries with cooler climates and good podiatry services.

Prescriptive footwear is advised for patients with foot ulcer risk in categories 1-3.[4,16] These types of footwear are manufactured by a pedorthist who can custom-made a shoe to compensate for a foot deformity or LOPS. However, the majority of patients with diabetes in developing countries do not have access to a podiatrist or a pedorthist who can tailor-fit a shoe to become an "appropriate footwear." Therefore, it is not logistically feasible in our setting to follow the recommendations of our Western counterparts. Second, if a customized shoe is not an option, there is no local or international guideline, even from major societies, which can assist clinicians from developing countries on how to advice patients with diabetes belonging to categories 1-3 in their choice for off-the-shelf footwear that can be a good alternative for a customized shoe. The challenge for diabetes educators and clinicians is to make guidelines on how to choose "appropriate footwear" for patients with diabetes with foot ulcer risk in developing countries.

This sentiment was also reflected in the most recent IWGDF 2015 guideline[16] on footwear and offloading. The article highlighted the controversy on how to apply the guideline to developing countries, noting that the current research on footwear and foot care mostly originate from economically developed regions. It emphasized that specific recommendations are needed for developing countries, because of the differences in climate, resources, adherence and efficacy.

People with diabetic neuropathy often wear shoes that are too small in order to increase the sensation of fit.[17] These findings were not demonstrated in this study.

Binary logistic regression was used to determine association between appropriateness of shoe size in relation to associated factors. Of particular interest are the patients who received foot care education and those with higher levels of educational attainment who are expected to have appropriate footwear. However, there was no difference among educational levels and those who received foot care education. This finding is similar to a Cochrane metaanalysis[18] where education had a short-term influence on foot care knowledge and patient behavior. One RCT[19] concluded that the difference in foot care knowledge between intervention and control group disappeared after seven years. Lastly, Lincoln et al. [20] concluded that limited education did not reduce the incidence of foot ulcer and amputation. Hence, one-time foot care education is not

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sufficient to protect patients from lower extremity complications. This highlights the need for physicians to continually remind patients on proper foot care and footwear to prevent foot ulcers and amputation.

For foot ulcer risk classification, Group 2 patients were more likely to wear inappropriate footwear compared to Group 0. Group 3 did not reach statistical significance probably because of the small sample size of the group. Nevertheless, there is a trend for higher group levels to wear inappropriate footwear.

CONCLUSION

Majority (91%) of the participants wear inappropriate footwear. This finding is due to multifactorial causes: preference, climate, economic reasons and foot ulcer risk category. Educational attainment and foot care education did not improve the statistics of footwear appropriateness. Flipflops and sandals are the primary preferences of the participants. This study has shown that there is benefit to developing local guidelines on proper footwear for patients with diabetes because of the difference in demographics among countries.

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All authors have given approval to the final version submitted.

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

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CASE REPORT

JAFES

Torsion of the Wandering Spleen and Pancreatic Tail Precipitating Diabetic Ketoacidosis in a Patient with Prader Willi Syndrome: A Case Report

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Abstract

Prader Willi Syndrome (PWS) includes complex endocrinological issues because of the hypothalamic and pituitary dysfunction which include obesity and diabetes, as well as behavioural issues. Other important aspects of PWS, such as hepatosplenomegaly are sometimes neglected. We present a case of diabetic ketoacidosis precipitated by torsion of a wandering spleen in a 22-year-old woman with PWS and type 2 diabetes mellitus. The pancreatic tail was involved in the torsion leading to hyperamylasaemia and pancreatitis. The splenic torsion and pancreatitis were initially treated conservatively with resolution of symptoms. A year later, she had another 2 episodes of severe abdominal pain due to worsening splenic torsion which subsided with conservative management. She subsequently underwent an elective splenectomy which revealed an enlarged and wandering spleen, with 720 degrees torsion of the long splenic pedicle.

Key words: Prader-Willi syndrome, spleen torsion, wandering spleen and diabetic ketoacidosis

INTRODUCTION

Prader-Willi syndrome (PWS) is a genetic disorder due to lack of expression of genes on the paternally inherited chromosome 15q11.2-q13. The prevalence of PWS is about 1 in 25,000 live births.[1] The endocrine issues associated with PWS are extensive because of the hypothalamic and pituitary dysfunction which includes obesity, diabetes, adrenal insufficiency, growth hormone deficiency and hypothyroidism. Type 2 diabetes mellitus (T2DM) occurs in 25% of adults with PWS with mean onset age of 20 years, and a mean BMI of 27 kg/m^2.[2,3]

In the early stages of diabetic ketoacidosis (DKA), the cause of abdominal pain can be difficult to establish. Routine computed tomography (CT) scan for every DKA would lead to over-investigation. This is because diffuse abdominal pain occurs in more than 50% of patients with DKA[4] and resolves with appropriate DKA treatment. However, a persistent abdominal pain warrants further investigation. Wandering spleen is a rare disorder due to absence or weakness of the ligaments holding the spleen in the normal position. We present an interesting case of torsion of wandering spleen in a PWS patient. A search of PUBMED and other search engines were done and to our knowledge, this has not been reported in literature before.

CASE

A 22-year-old Chinese female, with a known history of PWS and T2DM presented to the emergency room with fever (Tmax 40.2^{o}C), and 3-day history of sore throat, dry cough and coryza. She also had diffuse abdominal pain, diarrhea and decreased appetite for 3 days. During this period, her father noticed she had increased thirst with polyuria. On the day of admission, she was weak and breathless. There was no dysuria, weight loss or chest pain. Further history revealed that she was not compliant with her oral diabetic medications since her mother passed away a year ago.

At birth, she was cyanotic and hypotonic. In her infancy, she had difficulty feeding and required temporary nasogastric tube feeding. Around the age of 4-5 years old, she had increased appetite. This progressed to hyperphagia and obesity a few years later. She had delayed language, milestones, delayed motor development and reduced intellectual abilities. At age 18, she had impaired fasting glucose and was started on metformin. A year later, she was diagnosed with mild T2DM that was well-controlled with HbA1c of 5.9-6.3% on metformin. Her mother passed away from cancer a year ago and she became non-compliant with her food intake

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and reduced her exercise. Eight months ago, her HbA1c deteriorated to 12.4% and she gained 5 kg. Her diabetic medications were changed to extended-release Metformin 1500 mg daily and Gliclazide modified-release 60 mg daily. Her other medical issues included dyslipidaemia and primary hypothyroidism from Hashimoto's thyroiditis, non-alcoholic fatty liver disease and irregular menses since puberty at 13 years old.

There was no significant family history of diabetes or PWS. Her father and paternal grandmother had hyperlipidaemia. This hospital admission was 10 months after her mother's death. Her height was 1.46 m and weight 64 kg, BMI 30 kg/m^2. She had typical facial features of Prader-Willi syndrome with rounded faces, narrow bifrontal diameter, almond-shaped eyes, small mouth with thin upper lip, small hands and feet.

On admission, she was hypotensive (BP of 85/41 mm Hg), tachycardic (heart rate 140 bpm), tachypneic (respiratory rate 34 breaths per min) with a pulse oxygen saturation (SpO2) of 99% at 2L O2/min and febrile at 38.6◦C. She was lethargic but was able to recognise her family members. She was severely dehydrated with dry mucous membrane and haemodynamic instability. She had generalised abdominal pain and a large palpable mass in the left upper quadrant (splenomegaly). Her lungs were clear on auscultation.

Capillary blood glucose was "High." Urine dipstick was positive with glucose and 3+ ketones. Venous blood gas confirmed metabolic acidosis (Table 1). She was diagnosed with DKA and treated with prompt hydration and intravenous insulin infusion. She received 3 litres of normal saline within the first 2 hours which resulted in normalisation of her blood pressure and heart rate. She received another 3 litres of intravenous fluids over the next 24 hours. She was given an initial intravenous bolus dose of 0.1unit/kg of regular insulin followed by 0.1 unit/kg/hour of insulin. The insulin rate was subsequently titrated according to the capillary glucose. Antibiotics were initiated for suspected sepsis but further tests showed that there was no evidence of sepsis. Insulin autoantibodies of anti-islet cell and GAD were negative.

At the point of examination, her abdominal pain had improved and therefore the decision was to monitor her symptoms. Overnight, the ketonaemia resolved and capillary glucose was subsequently maintained at 6.3-11.3 mmol/L the following day (Figure 1).

Despite resolution of DKA, she continued to have intermittent diffuse abdominal pain. Her abdomen was soft on examination. Although abdominal pain is common in DKA, the recurrence of her pain was suspicious for underlying abdominal pathology. Serum amylase and lipase were elevated at 358 U/L (38-149) and >600 units respectively. Her haemoglobin and platelets dropped. An urgent CT scan of the abdomen and pelvis was performed

Table 1. The initial blood and urine tests done on admission

Test	Patient's Result	Reference Range
Full blood count		
Haemoglobin	13.5	12-16 g/dl
Total white cell count	12.15	4-10 x 10(9)/L
Neutrophil count	9.24 with left shift	2-7.5 x 10(9)/L
Platelet count	208	140-440 x 10 (9)/L
Biochemistry		
Sodium	148	136-146mmol/L
Potassium	5	3.6-5 mmol/L
Chloride	107	100-107 mmol/L
Bicarbonate	7.6	19.0-29.0mmol/L
Glucose	51.6	3.9 – 11 mmolL
Urea	23.6	2.7 – 6.9 mmol/l
Creatinine	118	37-75 umol/l
Corrected Calcium	2.18	2.09 – 2.46mmol/l
Phosphate	0.72	0.94 – 1.5 mmol/l
Serum ketones	**>6**	0.0-0.6mmol/L
Liver function		
Total protein	56	68-86 g/L
Albumin	30	40-51 g/L
Bilirubin	5	7-32 umol/L
Alkaline Phosphatase	105	39 – 99 U/L
ALT	36	6 – 66 U/L
AST	137	1 – 42 U/L
Thyroid function test		
Free T4	10.3	8.8 – 14.4 pmol/L
TSH	1.19	0.65 – 3.7 mU/L
Venous Blood Gas		
pH	7.305	
Base Excess	-13.4	mmol/l
pCO2	32	mmHg

and showed torsion of the enlarged spleen involving the pancreatic tail with moderate amount of free fluid in the abdomen. The splenic torsion caused the anaemia, thrombocytopenia[5] and pancreatitis. The underlying reason for the spontaneous splenic torsion was a wandering spleen.

The wandering spleen is due to absence of ligaments to hold the spleen in its normal anatomical position and thus at high risk of splenic torsion, infarction and rupture.[6] An urgent surgical opinion was requested as splenic torsion usually requires splenectomy. Serial abdominal examination found that her abdominal pain was improving, and she was haemodynamically stable and thus, the decision was made for conservative management.

The major cause of DKA in this patient with PWS was precipitated by splenic torsion with acute pancreatitis. Her lifestyle changes and poor compliance to medication also contributed to her worsening diabetic control. Her HbA1c this admission was 13.1% which reflected a poor glucose control for the past 3 months. This was not surprising as her mother's absence caused emotional breakdown leading to uncontrolled hyperphagia and excessive weight gain. She was discharged well.

Outcome and Follow up

A year later, she had another 2 episodes of severe abdominal pain due to worsening splenic torsion which subsided with conservative management. Initially the patient's father was not agreeable for an elective

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splenectomy; however he subsequently changed his mind in view of the repeated abdominal pain attacks. She underwent an elective splenectomy which found a wandering enlarged spleen with long splenic pedicle that had torsion of 720 degrees. Prior to the splenectomy, she received Haemophilus type B, Pneumococcal and Meningococcal vaccinations. She was given aspirin for post-splenectomy thrombocytosis.

DISCUSSION

Patients with PWS have increased mortality rate which is mainly due to obesity-related diseases.[7] Thus, a review by Emerick and Vogt recommended that screening for diabetes, hyperlipidaemia and hepatic steatosis in PWS be done in similar way as for an obese patient.[2] Diabetic ketoacidosis (DKA) in T2DM is increasingly seen, with about 30% in United States[8] whereas 50-64% of DKA patients are made up of T2DM in China.[9-10] DKA can occur in T2DM with PWS,[11] but is rarely reported in literature.

The pathophysiology of DKA is the same in PWS and non-PWS. It occurs in absolute or relative deficiency of insulin with excess counter-regulatory hormones causing hyperglycaemia and exaggerated lipolysis with ketone production. Glucotoxicity from chronic hyperglycaemia and lipotoxicity from chronically raised plasma free fatty acids in obesity impair insulin action and secretion.[12] The recovery phase of the beta cell function requires resolution of glucotoxicity and lipotoxicity, with possibility of weaning off insulin. Treatment of the factors that precipitated the DKA is important, and in this case, a splenic torsion from a wandering spleen.

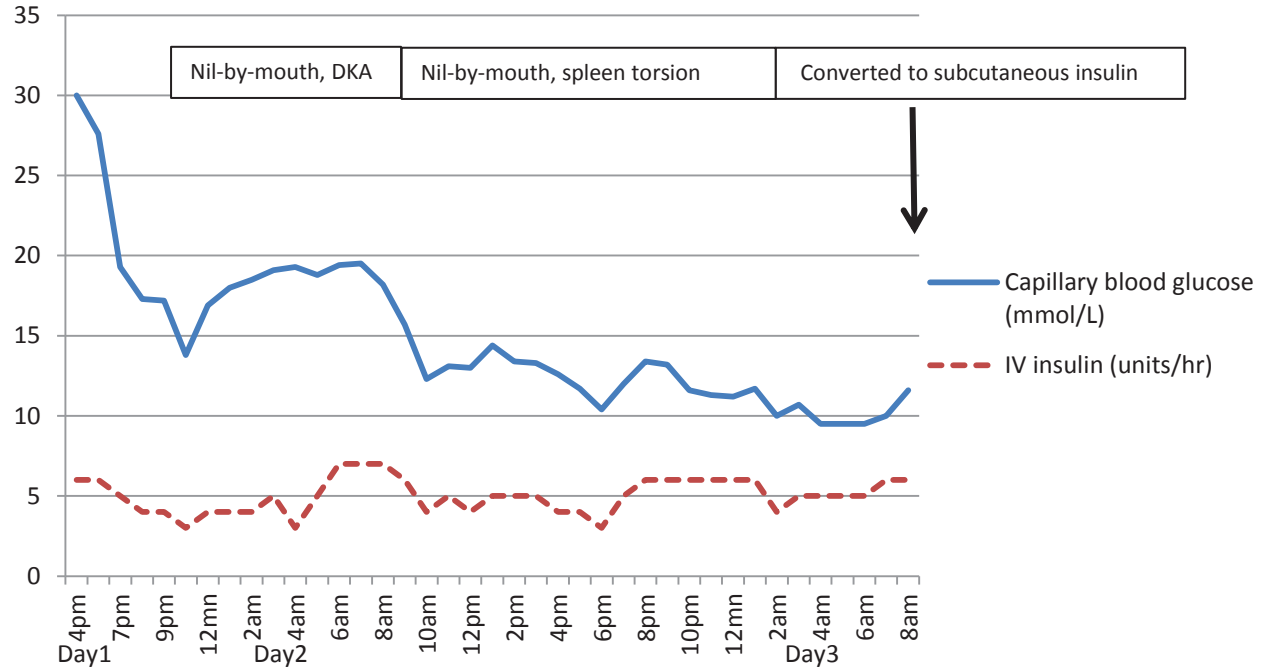

Figure 1. Capillary glucose trend with intravenous insulin therapy over 1st 40 hours.

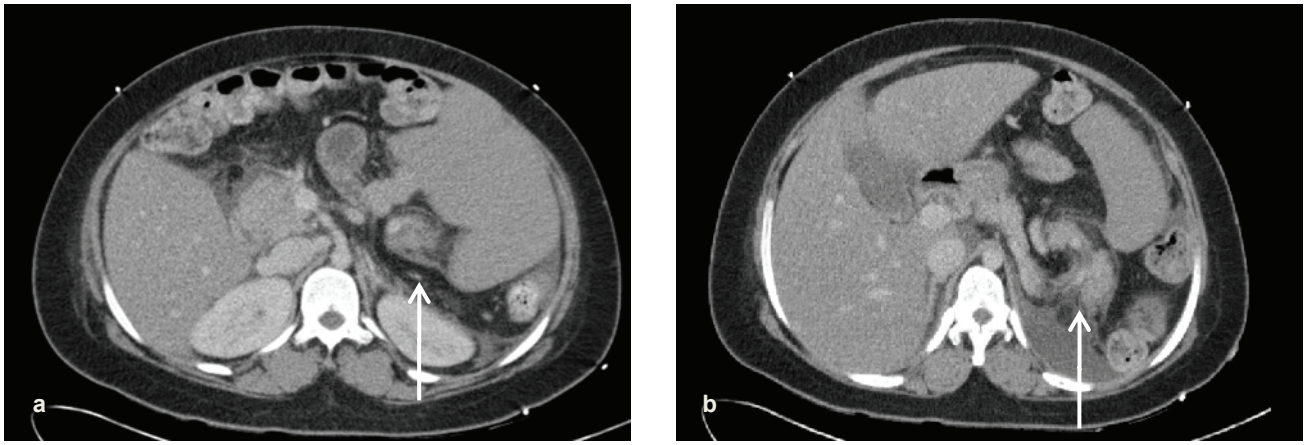

Figure 2. Torsion of patient's wandering enlarged spleen, with "whirling' of spleen (*white arrow* in picture a) and involving the pancreatic tail (*white arrow* in picture b).

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A wandering spleen is a rare disorder with the incidence in a general population of less than 0.2%.[13] A wandering spleen can be congenital or acquired. The congenital cause is due to absence or weakness of ligaments holding the spleen. In these cases, the spleen is held by a vascular pedicle instead of ligaments. The blood vessels in the vascular pedicle can be blocked leading to ischaemia and infarction of the spleen. Acquired wandering spleen is due to weakness of the ligaments such as in pregnancy[14] and abdominal wall laxity. Usually, this is found in males under 10 years old, or females at 20-40 years old when they present with splenic torsion.[6,15] A wandering spleen presents in a variety of manner from asymptomatic to an acute abdomen.[16] The complications associated with a wandering spleen include gastric obstruction, spleen infarction and recurrent pancreatitis.[17] A wandering spleen is associated with splenomegaly. The classic "whirl" appearance represents the twisted splenic pedicle signifying a torted spleen.[18] In this case, the pancreatic tail was involved because it was entrapped in the twisted splenorenal ligament during spleen torsion. This led to acute pancreatitis possibly because of pancreatic ischaemia or folding of the main pancreatic duct.[19,20]

Despite increased risk of hepatosplenomegaly in Prader-Willi syndrome, a wandering spleen was not previously reported. It is not clear in this case whether the wandering spleen was congenital or acquired. Our patient with PWS has ligament laxity[21] which may have contributed to her wandering spleen. Splenectomy is performed in most cases especially in the setting of torsion, infarction or acute abdomen.[13,16] Splenopexy can be considered if there is no evidence of infarction, thrombosis or hypersplenism.[16]

Hyperamylasemia is also seen commonly in DKA but is non-specific.[22] Lipase levels may be more helpful. A retrospective review showed that patients with DKA and abdominal pain with lipase levels >400 units were at increased risk of underlying abdominal pathology.[23] In this case, her amylase was raised at >600 units. Therefore, significantly raised levels of lipase and amylase are helpful pointers to do further abdominal imaging in a patient with DKA.

Conclusion

Splenic torsion should be considered as a differential diagnosis in a patient with PWS presenting with abdominal pain. In this case, the torsion of the wandering spleen and accompanying pancreatitis precipitated the DKA.

Ethical Consideration

Written informed consent was obtained from the parent of the patient for publication of this case report and accompanying images.

Statement of Authorship

All authors have given approval to the final version submitted.

Author Disclosure

All the authors declared no conflicts of interest.

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JAFES

CASE REPORT

Glucagonoma Syndrome: A Case Report

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Abstract

A 58-year-old Malay female with underlying diabetes mellitus, presented with chronic skin lesions, associated with weight loss and anemia. There were erosive, scaling skin lesions over the extremities, gluteal region and perioral area. Skin biopsy histopathological examination revealed Necrolytic Migratory Erythema (NME). A CT scan of the abdomen revealed a pancreatic neck and body tumor with possible liver metastases. She was successfully treated with subcutaneous somatostatin and underwent distal pancreatectomy with wedge resection of liver nodule.

Key words: Glucagonoma syndromes, necrolytic migratory erythema (NME), glucagon, somatostatin

INTRODUCTION

Neuroendocrine tumors (NET) are also known as Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs). They arise from cells of diffuse neuroendocrine systems such as enterochromaffin cells which possess secretory granules and release neurohormones.[1] Pancreatic NETs present with typical syndromes which include insulinoma, gastrinoma, glucagonoma, VIPomas, somatostatinomas and non-syndromic pancreatic NETs.[1]

A glucagonoma is a rare pancreatic NET with an estimated incidence of 1 in 20 million people per year.[2] Glucagonomas arises from islet alpha cells commonly at the tail of the pancreas.[3] The World Health Organization (WHO) classification of endocrine tumors[4] recommended that glucagonomas should be differentiated from non-functioning pancreatic alpha cell tumors and thus, is defined by its clinical syndromes. Glucagonomas may arise sporadically or in patients with Multiple Endocrine Neoplasia (MEN) type 1[5] which is rare (<3%). As depicted in our patient's case, patients with glucagonoma usually presents in the middle age group with median age of 53.5 years.[6]

CASE

A 58-year-old Malay female, with a background history of diabetes mellitus and hypertension for 2 years, presented with chronic, on-and-off skin lesions over the lower limbs and abdomen for the past 2 years. It usually starts with a skin blister which later ruptures and ulcerates with a necrotic patch. Other symptoms included lethargy and profound weight loss (20 kg in a year). The patient also had a history of anemia, abdominal pain and dyspepsia. Upper gastrointestinal endoscopy done previously only revealed mild gastritis. There was no history of chronic diarrhea, anorexia, history of mood changes or any history to suggest venous thrombosis.

Physical examination revealed a pale, cachectic lady with erythematous, erosive scaling with crusted skin patches over the upper and lower extremities, gluteal region and perioral region (Figure 1a-d). Exudates covered certain erosive areas indicative of secondary infection. There was no angular stomatitis.

Investigations revealed normochromic normocytic anemia (hemoglobin of 11.3 g/dl), normal ionized serum calcium of 1.152 mmol/L (0.80-1.29) and serum phosphate (0.90 mmol/L) with FBS of 15 mmol/L. Hepatitis screening was negative.

The patient was referred to the dermatology service and skin biopsy was done which revealed mild acanthosis with marked spongiosis. There was hyperkeratosis and parakeratosis as well as plasma, neutrophils and bacterial colonies on the keratin layers. The dermis shows perivascular and interstitial infiltration by lymphocytes, neutrophils and eosinophils. This findings are suggestive of infection and features are compatible with NME. Subsequently, CT scan of the abdomen was done which revealed a pancreatic neck and body tumor most likely representing glucagonoma (5.5 x 2 x 3 cm) with possible liver metastases. (Figure 2a-c). Further investigations revealed raised serum Chromogranin A >770 ng/ml (27-94) and serum glucagon of 1068 pg/ml (50-150).

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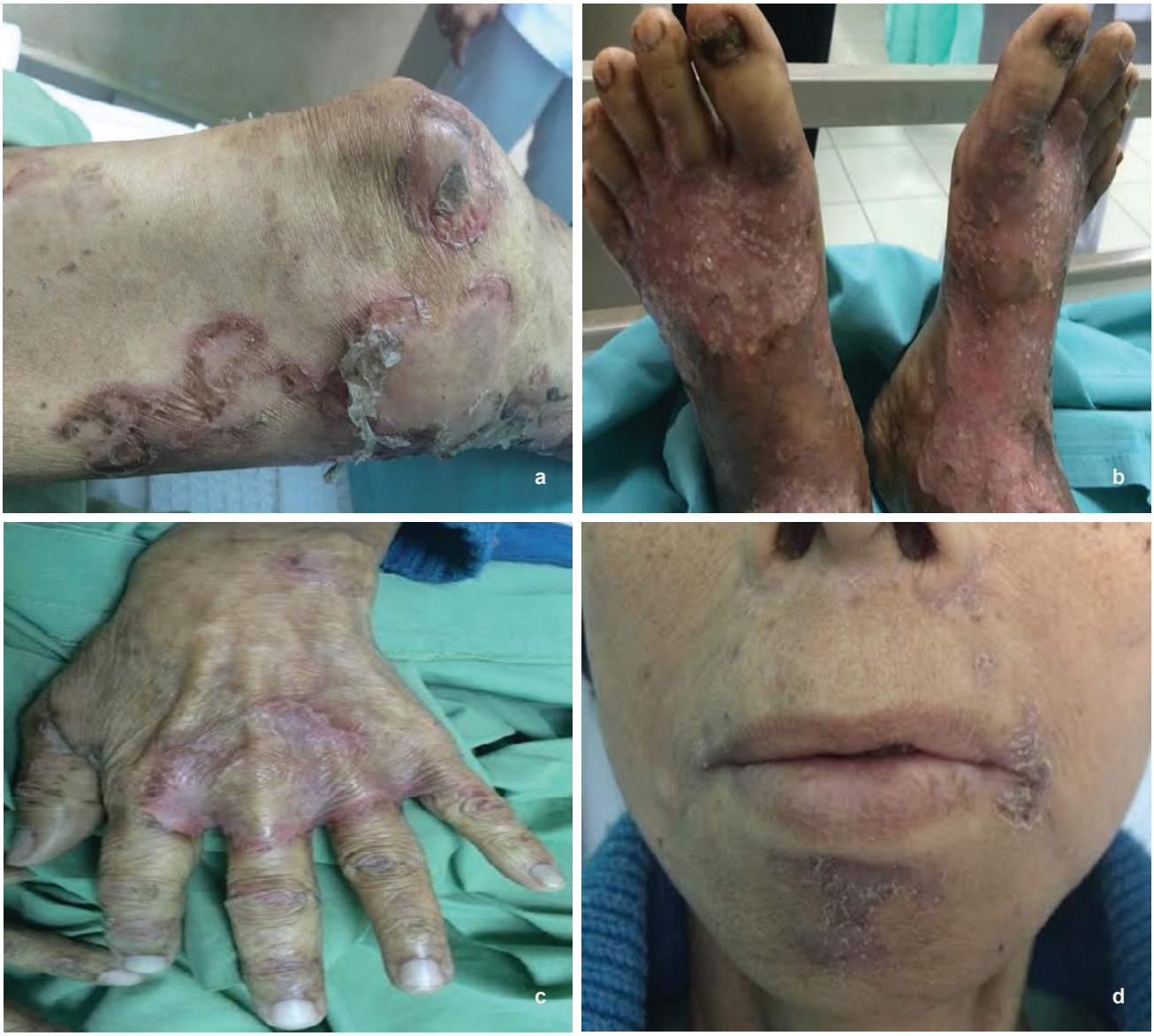

Figure 1. Erosive scaling and crusted skin patches over the (a) thigh, (b) with exudates over both feet, (c) hand and (d) perioral area.

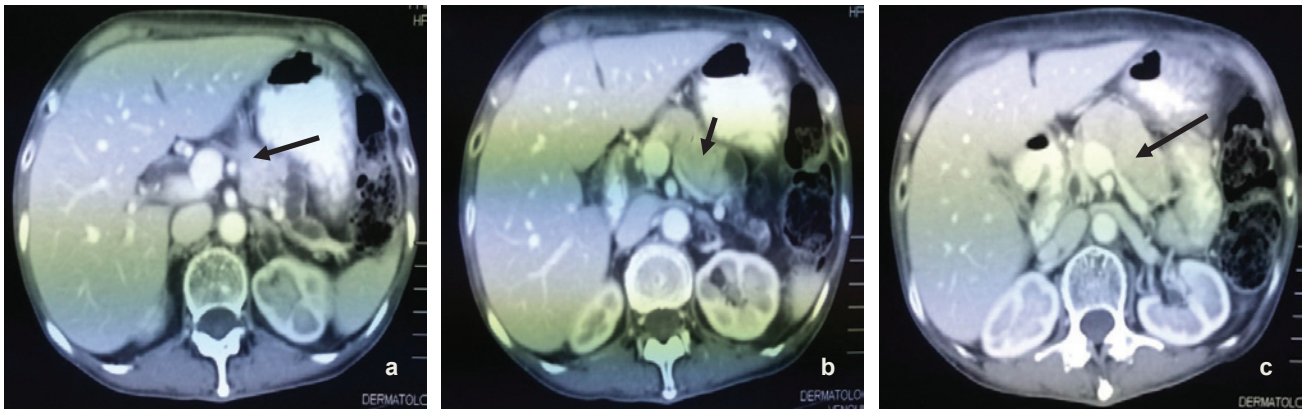

Figure 2 (a-c). Radiologic findings – (serial axial view) showing tumor at the neck and body of the pancreas measuring 5.5 x 2 x 3 cm.

She was started on subcutaneous somatostatin for 2 weeks then shifted to intramuscular Sandostatin LAR 20 mcg every 4 weeks. She tolerated the medication well without any complications. Skin lesions completely resolved by 2 months with improved general well-being and weight gain. She then underwent distal pancreatectomy with

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wedge resection of liver nodules. Histopathological examination of the tumor revealed NET of the pancreas with liver metastases, histological grade 2. Immunohistochemical staining was strong and diffusely positive for synaptophysin and focally positive for Chromogranin A. There were no postoperative complications and patient was scheduled for surveillance CT scan of the abdomen 6 month post-operation.

DISCUSSION

Glucagonoma Syndromes (GS) are paraneoplastic syndromes consisting of a clinical triad which includes glucagon-secreting pancreatic tumor, diabetes mellitus (DM) and NME.[7] Stacpoole suggested a set of diagnostic criteria for glucagonoma in which all criteria should be fulfilled.[8] The diagnostic criteria consist of demonstration of the tumor by direct visualisation or radiographically, proof that the tumor shows a preponderance of glucagon-containing cells on appropriate staining and/or proof of increased tissue levels of immunoreactive glucagon; elevation of basal circulating immunoreactive glucagon; and at least one of the following coincidental findings; (a) skin rash, (b) glucose intolerance, or (c) hypoaminoacidemia. Other clinical syndromes associated with glucagonoma are stomatitis, anaemia,[9] venous thromboembolism[10] neuropsychiatric disturbances (most often depression and/or psychosis),[11] diarrhoea and, rarely, dilated cardiomyopathy. GS can be further classified into 3 clinical types i.e., glucagonoma with skin syndrome (NME), glucagonoma with mild diabetes and glucagonoma with multiple syndromes.[12] Our patient fulfilled all the diagnostic criteria for glucagonoma and belongs to the last group with presence of diabetes and NME.

NME is present in almost 70% of patients.[13,14] NME is characterised by irregular annular eruptions (central healing area) with serpiginous advancing borders, erosion, and crusting, resulting in a scalded appearance.[15] It is suggestive of glucagonoma but is not pathognomonic for the syndrome. NME was also reported to be found in other disorders such as hepatic dysfunction and cirrhosis,[16] jejunal and rectal adenocarcinoma, villous atrophy of the small intestines and myelodysplastic syndromes.[6] The skin eruption usually involves the inguinal canal, perineum, buttocks and lower extremities.[7] It is characterized by cyclical pattern of spontaneous remission and exacerbation.[7] The underlying cause for NME skin changes is still unclear. Increased glucagon *per se* does not cause NME since it was also reported in other disorders not related to high glucagon level as mentioned above. However, normalisation of glucagon level by means of surgery or somatostatin analogues invariably results in rapid resolution of NME.[15] Hyperglucagonemia probably provokes the metabolic deficiency of zinc, essential fatty acids and amino acids and has been considered as a possible cause of NME. However, not all patients with NME present with these metabolic changes, and not all patients with NME and metabolic deficiency achieve complete resolution of the skin lesion with supplementation.[17] Early recognition of NME is essential as it will prevent catabolic clinical features and reduce the risk of metastasis.[18]

Impaired fasting glycaemia or diabetes mellitus is present in 80% of patients with GS.[19] The tumor secretes high levels of glucagon which in turn promotes glycogenolysis, gluconeogenesis, ketogenesis and lipidioresis by activating phosphorylase in the liver, stimulating secretion of insulin and inhibiting external secretion of the pancreas, thus resulting in hyperglycaemia.[18] Hyperglucagonemia reduces plasma amino acid concentration and stimulates amino acid catabolism.[18]

The diagnosis of glucagonoma in this case was confirmed by elevated plasma glucagon levels in keeping with similar findings in all patients in a case series in which the glucagon level ranged from 200 to >10,000 pmol.[6] Plasma glucagon levels are usually elevated 10 to 20-fold in patients with glucagonoma (normal <50 pg/mL). Concentrations above 1000 pg/mL are virtually diagnostic of glucagonoma.[20] Chromogranin A (Cg A) level was elevated in our case and in half of subjects in the case series.[6] Cg A is a NETs biomarker and is expressed in almost 90% of NETs independent of its site of origin.[21] It can aid in the diagnosis of NETs and can also be used as prognosis and as a biomarker to monitor disease progression.[21]

Another biochemical result noted was anemia. Plurihormonal secretion of the tumor (serum glucagon, gastrin and chromogranin A) confers a guarded prognosis with short survival possibly due to the less-differentiated nature of the plurihormonal subtype.[6] Somatostatin receptor scan (SRS) was positive in most of the patients in a case series.[6] It is frequently used as a complementary method to conventional imaging like CT scan and MRI for supervision of somatostatin expression and dissemination of tumor metastases.[22,23]

As illustrated in our patient case, the pancreatic tumor was readily visualised by CT scan imaging and the size was comparable with the average size of 6 cm reported in a case series.[24] However, the position of the tumor at the neck and body of the pancreas was not classic for glucagonoma, which is more commonly found at the tail of the pancreas (45-75%).[12] CT scan is usually the initial non-invasive radiographic test. Other imaging techniques that can be used to detect the tumor are abdominal ultrasound, MRI and selective visceral angiography.[7] Selective angiography of the celiac and superior mesenteric[15] arteries is the gold standard in the diagnosis and localisation of glucagonoma as this tumor shows significant hypervascularity.[7] In addition, this technique is able to demonstrate hepatic metastases even in a patient with a negative liver scan.[7] The role of pancreatic venous sampling for glucagon levels in the diagnosis of small

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tumor has been reported.[8] As a result of subtle and non-specific manifestations, glucagonoma is usually diagnosed late with metastatic spread on diagnosis[6] and in this patient's case, liver metastases. The liver is the most common site for metastasis. Most of the time, the metastases are multiple, involving many hepatic segments and are variable in size.[6] Other common sites for metastases are regional lymph nodes, bone, adrenal gland, kidney and lung.[25,26]

The prognosis of glucagonoma varies depending on the stage in which the tumor was diagnosed. The tumor is resistant to chemotherapy as discussed later. This tumor however is slow-growing, and prolonged survival is possible (>20 years).[15] In a case with metastasis, the cause of death is unrelated to the tumor.[27]

Our patient was given a multimodal treatment combining medical and surgical therapy. Surgery rendered 2 patients with prolonged progression-free survival (4-6 years) and 1 patient with free disease with additional hepatic metastasectomy in a case series.[6] Surgical resection can lead to prolonged disease-free remission.[28-30] As for the liver metastases, control by metastasectomy, cryoablation, radiofrequency ablation, or chemoembolization has been reported.[19,22]

Our patient was also treated with somatostatin analogue (SSA), a potent inhibitor of glucagon secretion preoperatively and she responded well in terms of weight gain, general well-being and resolution of paraneoplastic manifestation i.e., NME. She was treated with long-acting octreotide (Sandostatin LAR), with a half-life of 3-4 weeks. As shown by the PROMID study, Octreotide LAR offers symptomatic control as well as reduction of tumor growth progression.[31] However, we did not assess biochemical and imaging response of this SSA. In a case series, some response was noted following SSA therapy – 4/6 patients showed improvement of cutaneous symptoms, weight loss and general well-being, 50% reduction of plasma glucagon level in 2/6 patients but no objective tumor response on imaging.[6] Other alternatives available are lanreotide autogel injection and interferon-alpha alone or in combination with SSA. New targeted therapies include antiangiogenic agents, peptide receptor radiotherapy (PRRT), mTOR inhibitors and VEGF inhibitors.[1] Another available treatment modality utilised in a case series is an amino acid infusion which induced rapid long term resolution of NME rash & glossitis in 2/4 patients and local therapy to the liver (symptomatic response for external radiation to the liver and no response for trans-arterial chemoembolization or TACE).[6] Intermittent infusions of amino acids and fatty acids have been associated with long-term resolution of necrolytic migratory erythema (NME).[32] However, the evidence to support their use is limited to observational studies. In addition, amino acid infusions do not cause regression of tumor growth or other symptoms.[32]

The following are recommendations for follow-up after treatment of a pancreatic neuroendocrine tumor:[33]

- Three and six months postresection – history and physical examination, serum glucagon, and computed tomography/magnetic resonance imaging.
- Long-term – history and physical examination with tumor markers every 6 to 12 months for years 1 to 3, and as clinically indicated thereafter. Imaging studies are recommended only as clinically indicated.

CONCLUSION

Glucagonoma is a rare NET with a subtle, variable presentation leading to late diagnosis. Therefore increased awareness and recognition of Glucagonoma Syndrome is vital in order for early diagnosis before development of metastases.

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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.

Conflict of Interest

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

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CASE REPORT

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Post-Gastrectomy Osteomalacia Mimicking Rheumatologic Disorders: A Case Report

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Abstract

Osteomalacia is one of the post-gastrectomy complications resulting from the impaired absorption of vitamin D and calcium.[1] Vitamin D deficiency or osteomalacia can be diagnosed by clinical, biochemical and radiographic parameters, and bone biopsy. The radiologic findings of "Looser zones" or pseudofractures aid in the diagnosis. Severe generalized pain, mimicking rheumatologic disorders is one of the features that maybe a presenting complaint of osteomalacia. We report a case of osteomalacia as a consequence of gastric by-pass surgery.

Key words: osteomalacia, post-gastrectomy, malabsorption, Looser zones

INTRODUCTION

Osteomalacia is a condition of defective skeletal mineralization in adults. Generalized aches and pain may be one of the presenting features in osteomalacia and it can be overlooked and misdiagnosed as a rheumatological disorder. Vitamin D deficiency is a recognized complication of gastric by-pass surgery due to malabsorption of vitamin D and calcium.

CASE

A 33-year-old Indian woman presented with the complaint of generalized body pain. Previously she had been treated as a case of rheumatoid arthritis by her primary care doctor. She had been frequently taking various analgesics for the pain, which she had felt for many years. The pain was non-specific and not well-localized but more noticeable in the four extremities, shoulders and chest. Severe pain was experienced even with light touch. She also complained of difficulty in getting up from a sitting position.

She had a gastric bypass surgery at the age of 14 for complicated peptic ulcer. Since then, she had been having frequent loose bowel movement, with no apparent blood, mucus or steatorrhoea. Other than worsening with intake of coffee, tea or milk, there were no other specific identified aggravating factors for the diarrhea. During this time, she experienced repeated attacks of epigastric pain and vomiting of gastric contents and occasional bile-stained fluid. She became fastidious with her diet and only ate rice, beans and dried fish. She also felt weak and breathless on exertion.

On physical examination, the patient appeared pale and thin, with a body weight of 41.8 kg, height of 1.63 m, and body mass index of 15.8 kg/m^2. Her blood pressure was 90/60 mmHg and pulse rate was 88/min. Respiratory and cardiovascular examinations were normal. Abdominal examination was unremarkable apart from a surgical scar. On examination of the musculoskeletal system, there was neither joint swelling nor deformity. Tenderness was elicited on pressure over her chest and limbs. On neurological examination, there was no significant neurologic deficit.

Initial laboratory tests revealed a hemoglobin level of 8.6 g/dL, with a mean corpuscular volume of 63 fL/cell (Table 1). The white cell count, platelet, ESR, blood urea and electrolytes were within normal range (Table 2). Biochemical analysis for malabsorption revealed iron deficiency anemia, with low serum iron (5.14 μmol/L), low serum ferritin (7.14 ng/mL) and normal total iron-binding capacity (59 μmol/L). Corrected calcium level was also low (2.1 mmol/L). Vitamin B12, serum folate and serum albumin levels were within normal limits. To exclude other causes of malabsorption like celiac disease, anti-gliadin antibodies and anti-endomysium IgA was done and were negative. Viral and bacterial causes of enteritis, such as antibodies to HIV, hepatitis B, hepatitis C and mycobacterium, were all negative. Fecal studies showed absence of reducing sugar, glucose, occult blood and fat globules. Other endocrine disorders were excluded by normal serum cortisol and thyroid function tests (Table 3). Tests for rheumatologic disorders such as rheumatoid factor, anti-nuclear antibody and antibody to extracted nuclear antigen profile were negative (Table 4).

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Table 1. Hematologic assays

Variable	Result	Reference range
Haemoglobin, g/dL	8.6	11.5-16.5
Red blood cell count, x 10^{12} /L	4.7	3.9 -5.6
Mean corpuscular volume, fL	63	76-96
Platelet count, x 10^9/L	316	150-400
White blood cell count, x 10^9/L	5.4	4-11
Neutrophil, %	40%	40-75
Lymphocyte, %	50%	20-45
Monocyte, %	7%	2-10
Eosinophil, %	3%	0-6
Basophil, %	0%	0-2
ESR, mm/1st hour	15	6-12
Vitamin B12, pg/mL	421	200-900
Serum folate, ng/mL	10.1	4.6-16
Serum iron, µmol/L	5.14	6.6-26
Total iron-binding capacity, µmol/L	59	49-69
Serum ferritin, ng/mL	7.14	13-150

Table 2. Biochemical assays

Variable	Result	Reference range
Fasting glucose, mg/dL	85.4	59-115
HbA1C, %	4.6	4-6.5
Urea, mg/dL	5	7-18
Sodium, mmol/L	140	137-150
Potassium, mmol/L	3.8	3.5-5.3
Chloride, mmol/L	106	96-108
Bicarbonate, mmol/L	26	22-29
Creatinine, µmol/L	40	45-84
Magnesium, mg/dL	2.3	1.3-2.1
Total protein, g/dL	6	6-7.8
Albumin, g/dL	3.5	3.5-5.5
Stool reducing substance	Absent	
Stool for glucose	Negative	
Stool for fat globules	Negative	
Stool for occult blood	Negative	

Table 3. Hormonal assays

Variable	Result	Reference range
Thyroid stimulating hormone, mIU/L	1.08	0.27-4.2
Free thyroxine, ng/dL	1.3	0.932-1.71
Cortisol, µg/dL	12.34	2.3-11.9
Parathyroid hormone, pg/mL	248.8	15-65

Table 4. Screening test results for rheumatologic and connective tissue disorders

Variable	Result	Reference range
Rheumatoid factor, IU/mL	7	0-14
Anti-nuclear antibody	Negative	
Anti-extracted nuclear antigen profile		
Antibodies to nRNP/Sm		
Antibodies to Sm		
Antibodies to SS-A		
Antibodies to SS-B		
Antibodies to Rib.P-Protein		
Antibodies to Ro-52		
Antibodies to Scl-70		
Antibodies to Jo-1		
Antibodies to CENP B		
Antibodies to dsDNA		
Antibodies to nucleosomes		
Antibodies to histones		

Table 5. Bone profile

Variable	Result	Reference range
Calcium, mmol/L	2.07	2.12-2.52
Corrected calcium, mmol/L	2.1	2.12-2.52
Inorganic phosphate, mmol/L	0.6	0.78- 1.65
25-OH vitamin D, mmol/L	17.6	75-100
Alkaline phosphatase, IU/L	109	39-117
Parathyroid hormone, pg/mL	248.8	15-65

Bone profile evaluation showed low inorganic phosphate, normal alkaline phosphatase, increased parathyroid hormone and reduced 25-OH vitamin D level (Table 5).

With symptoms and biochemical findings correlated with osteomalacia, the patient underwent further radiological assessment. Radiographs showed small cortical breaks at the proximal part of the left femur and the right scapula (Figures 1 and 2).

To assess dyspepsia and frequent vomiting, upper GI endoscopy was planned but not done, as the patient did not give consent.

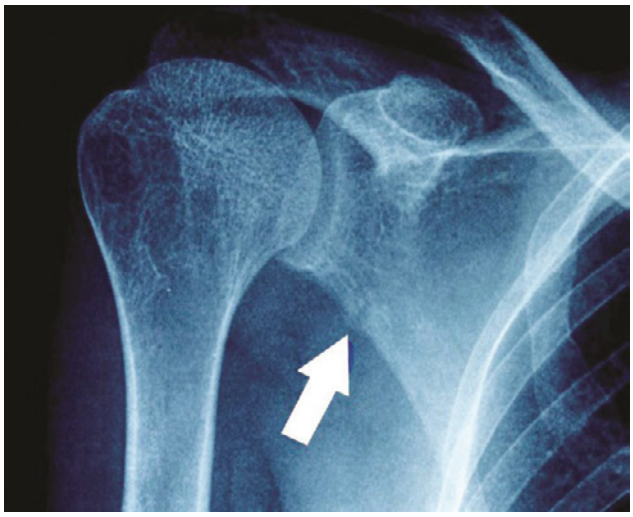

Figure 1. X-ray of the right shoulder showing a Looser zone (pseudofracture) at the outer surface of the scapula.

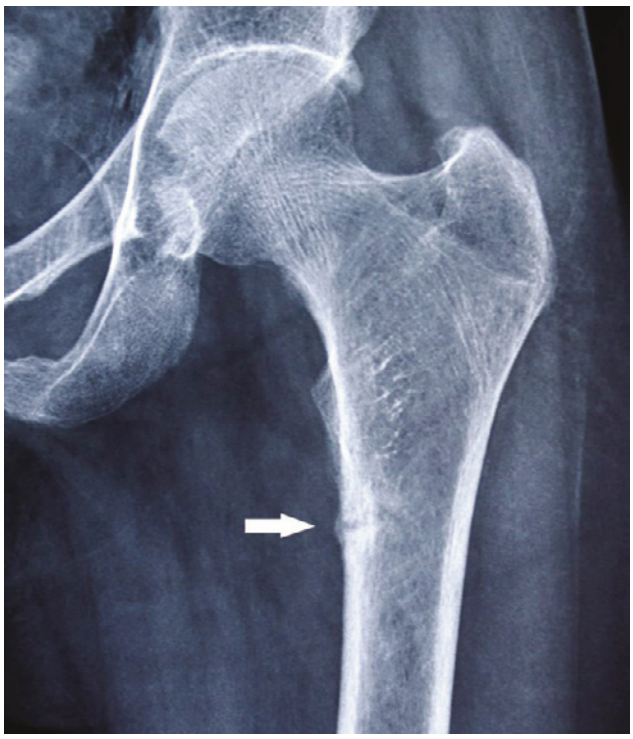

Figure 2. X-ray of the pelvis showing a Looser zone (pseudofracture) at the left femur.

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DISCUSSION

We evaluated a case of osteomalacia due to vitamin D deficiency as a consequence of previous gastric bypass operation, presenting with long standing, undiagnosed generalized aches and pain. While clinical and radiologic findings (pseudofractures or Looser zones over the periosteal surface of the femur and the outer border of scapula, Figures 1 and 2) favor the diagnosis of osteomalacia, we also encountered some dilemmas in her biochemical findings. Low levels of serum 25-OH vitamin D, calcium and phosphate were accompanied by high parathyroid hormone and upper normal alkaline phosphatase. Although increased serum alkaline phosphatase activity is a typical association of osteomalacia, some may have normal or borderline levels.[2]

A cohort study on 80 Asians and 4 Europeans with osteomalacia revealed that some patients had normal levels of calcium (66%), phosphate (81%) and alkaline phosphatase (29%).[3] A study in India also found that serum vitamin D levels may not be correlated with serum alkaline phosphatase levels.[4] Our case also supported their findings.

Our patient had a significantly elevated PTH, which has been found to be a better determinant of histological osteomalacia than 25-OH vitamin D in Asian populations.[3,5,6] Although the definitive diagnosis for osteomalacia is established by bone biopsy with double tetracycline labelling, the history of gastrectomy together with radiologic and biochemical findings are sufficient for the diagnosis in this case.[1]

Osteomalacia is not an uncommon metabolic bone disease in the Southeast Asian region.[7] It may be found in up to 18% of patients who underwent gastrectomy for peptic ulcer disease, and 30% of patients with gastric surgery or bypass for obesity.[2,8] It has been reported that gastric bypass operation predisposes the patients to severe vitamin D deficiency and osteomalacia in the absence of pharmacologic doses of vitamin D therapy.[9] The severity depends on the duration and extent of the surgery. Apart from vitamin D, calcium absorption is also impaired due to exclusion of the duodenum.[1,8,10] The possible mechanism of vitamin D deficiency/osteomalacia is the short duration of interaction of gastric acid and ingested food affecting the activation of pancreatic enzymes. This subsequently leads to impaired absorption of fat, causing deficiency in fat-soluble vitamins A, D, E and K.[11] Another mechanism is the reduction in gastric volume, causing the patient to consume small quantities and affecting dietary choices.[1] There is a higher risk of development of metabolic bone disease in those who have undergone Billroth II operation compared to Billroth I, where the duodenum is excluded.[1] In this case, apart from her previous gastric bypass surgery, the patient also had decreased intake because of her dyspepsia and vomiting. The pigmented skin and reduced sun exposure may also have contributed to osteomalacia.

CONCLUSION AND LEARNING POINTS

Osteomalacia can present with non-specific aches and pain. It should be highly suspected especially in patients who have undergone gastric bypass operation. The typical findings of both laboratory and radiologic investigations, with the exception of a normal alkaline phosphatase level, were presented in this case report. It is essential to monitor for nutritional deficiencies, especially vitamin D, in these patients.

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 declared no conflicts of interest.

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CASE REPORT

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Acute Adrenal Insufficiency as the Primary Manifestation of Extrapulmonary Tuberculosis: A Case Report

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Abstract

Acute adrenal insufficiency (AI) is a life-threatening condition. While Addison's disease (AD) is rare, in developing countries, tuberculosis (TB) still remains as the primary cause in 7 to 20% of cases. Urinary TB is also the third most common form of extrapulmonary disease. We report a case of 37-year-old male who presented with weakness, anorexia, weight loss, dysuria, flank pain and low grade fever. Examination revealed hypotension, hyperpigmentation, hyponatremia, hypoglycemia and low serum cortisol. He was diagnosed to have adrenal crisis due to Addison's disease and extrapulmonary TB manifesting as urinary tract infection (UTI). He was treated with corticosteroids and anti-TB medications. Urologic reconstructive surgery was subsequently planned..

Key words: Addison's disease, acute adrenal insufficiency, serum cortisol, urinary symptoms, tuberculosis

INTRODUCTION

Addison's disease (AD), or primary adrenocortical failure, was first described by Thomas Addison in 1855 following his observations in 6 patients with adrenal tuberculosis.[1-3] Since then, the most commonly identified cause of adrenal failure has been bilateral adrenal destruction due to Mycobacterium tuberculosis infection. Recent studies also indicate that urinary TB is the third most common form of extrapulmonary disease, after peripheral lymphadenopathy.[4-7]

Tuberculosis continues to be a public health problem, as it is the most common worldwide cause of mortality from infectious disease, with an estimated global incidence of 8 to 10 million per year. Failure to treat initial pulmonary tuberculosis itself may lead to catastrophic outcomes such as peritonitis, lymphadenitis, orchitis and other urogenital disease and adrenal insufficiency, among other manifestations of extrapulmonary tuberculosis. Diagnosing extrapulmonary tuberculosis can also be challenging due to poor access to disseminated lesions, low rates of bacteriological positivity accounting only for a quarter of overall cases, paucibacillary lesions often resulting to negative smear results, and the absence of pathognomonic histopathologic findings. As such, the diagnostic approach to AD and urinary TB is difficult, especially in a resource-limited area.[8-10]

Studies on Addison's disease and genitourinary TB in non-HIV patients are scarce, as these conditions are rare and probably underdiagnosed. We report the case of a 37-year-old male with chronic fever, weight loss, skin hyperpigmentation, hypoglycemia and hyponatremia due to Addison's Disease secondary to tuberculosis in Malang, Indonesia.

CASE

A 37-year-old male presented with a chief complaint of generalized weakness for 4 months, progressing to inability to stand independently on the day prior to admission. In the last 6 months, he noted dry cough, urinary urgency, dysuria, hematuria, right flank pain, decrease in appetite and hyperpigmentation of the skin. Two months prior to admission, he experienced low grade fever, more often observed at night. During the previous week, he began having nausea and started vomiting residual food 2 to 3 times a day, amounting to 50 to 100 mL each episode. He also noted passage of 100 to 200 mL of watery, non-bloody and non-mucoid stool once to twice a day, accompanied by loss of appetite and cold sweats. He noted weight loss of approximately 16 kg in the last 4 months.

He was diagnosed with a lung infection necessitating thoracentesis 20 years ago. He was declared as "cured" and

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never received anti-TB medications. In the ensuing years, he often experienced weakness and needed hospitalization for sudden episodes of unconciousness. He denied any contact with TB patients, and had no other chronic or congenital diseases. He smoked 12 cigarettes per day for 20 years, but stopped 1 year ago when he felt unwell.

On examination, the patient looked ill and agitated, with a Glasgow Coma Scale of 15. He was hypotensive (blood pressure 70/50), tachycardic (pulse rate 106 beats/minute), tachypneic (respiratory rate 26 cycles/minute) and afebrile (axillary temperature 37oC), with a body mass index of 15 kg/m2 (body weight 39 kg, height 163 cm). We found hyperpigmentation of the skin and mucous membranes, pale palpebral conjunctivae, multiple left lateral cervical lymphadenopathy, and suprapubic and right flank tenderness (Figure 1). The other findings were within normal limits.

Figure 1. Comparison of the patient's appearance before his illness in 2013 (a) and during the time of examination in 2015 (b), showing marked skin hyperpigmentation.

Laboratory results showed anemia (hemoglobin 7.80 g/dL, hematocrit 21.40%), normal leucocyte count (6,000/μL, differential counting 3/0/48/30/19, normal range: 0-4, 0-1, 51-67, 25-33, 2-5) and normal platelet count (339,000/μL). Further workup of anemia revealed hypochromic cells with anysocytosis on peripheral blood smear, serum iron 20 μg/dL, total iron binding capacity 108 μg/dL and iron saturation 22%. He had hypoglycemia which improved after correction (random blood sugar 45 mg/dL to 104 mg/dL), azotemia (serum creatinine 1.25 mg/dL), hypoalbuminemia (2.3 g/dL) and hyponatremia (119 mmol/L). Serum cortisol serum at 0800H was low at 0.23 μg/dL (Table 1). Human immunodeficiency virus- ELISA was negative. Fecal analysis showed no abnormal result. Electrocardiogram revealed sinus tachycardia (heart rate 106 beats/minute).

Ultrasonography of the neck revealed left perijugular lymphadenopathy. Plain chest and apicolordotic radiographs revealed moderate pulmonary TB (Figure 2). Urinalysis revealed albuminuria, pyuria, hematuria and bacteriuria (Table 1). Staining for acid-fast bacilli (AFB) was negative in sputum samples, and positive (+) for urine specimen. Urine culture showed no bacterial growth. Abdominal ultrasound revealed bilateral grade

Table 1. Laboratory results on initial evaluation

Variable	Result	Reference range
Haemoglobin, g/dL	7.8	11.4-15.1
Platelet count, x 10^9/L	339	142-424
White blood cell count, x 10^9/L	6.0	4.7-11.3
Neutrophil, %	48	51-67
Lymphocyte, %	30	25-33
Monocyte, %	19	2-5
Eosinophil, %	3	0-4
Basophil, %	0	0-1
Serum iron, μg/dL	20	49-151
Total iron-binding capacity, μg/dL	108	250-350
Iron saturation, %	22	16-45
Random blood sugar, mg/dL	45	<200
Blood urea nitrogen, mg/dL	24.8	16.6-48.5
Creatinine, mg/dL	1.25	<1.2
Albumin, g/dL	2.3	3.5-5.5
Aspartate transaminase, U/L	43	0-32
Alanine transaminase, U/L	22	0-33
Sodium, mmol/L	119	136-145
Potassium, mmol/L	3.88	3.5-5
Chloride, mmol/L	98	98-106
Arterial blood gas[a]		
pH	7.47	7.32-7.45
pCO_2, mmHg	20.1	35-45
pO_2, mmHg	116.5	80-100
HCO_3, mmol/L	14.9	21-28
Base excess, mmol/L	-9.1	(-3) – (+3)
Oxygen saturation, %	99	95-100
Urinalysis		
Albumin	+1	Negative
Leucocyte, cells/high power field	+3 (533 cell/hpf)	Negative (≤ 5 cell/hpf)
Erythrocyte, cells/high power field	+2 (217 cell/hpf)	Negative (≤ 3 cell/hpf)
Bacteria, x10^3/mL	160 x 10^3	<93 x 10^3
Serum cortisol, 0800H (μg/dL)	0.23	3.09 - 16.66

[a]O_2 supplementation at 2 liters per minute

II to III hydronephrosis and chronic cystitis. This was consistent with subsequent findings in the intravenous urogram, which showed bilateral grade III hydroureteronephrosis due to obstruction at the distal ureters and contracted urinary bladder. However, histopathology result of urine cytology showed non specific chronic inflammation. Computerized tomography (CT) of the abdomen showed left adrenal gland hypoplasia, multiple cysts on the right adrenal gland, grade III to IV right hydronephrosis, grade II left hydronephrosis, chronic ureteritis and cystitis (Figure 3).

The patient was assessed to have adrenal crisis, Addison's disease secondary to tuberculosis infection, urinary TB with bilateral hydroureteronephrosis, pulmonary TB with moderate lesion, anemia of chronic disease, and hypoalbuminemia. In the acute setting, he was treated with dexamethasone 5 mg intravenously four times daily, and maintained on two intravenous peripheral lines containing maintenance IVF D10% on one, and IVF NaCl 3% on the other. D40% was given with each episode of hypoglycemia, and fluid challenge with NaCl 0.9% following hypotension. Other treatments included ranitidine 50 mg intravenously two times daily, metoclopramide 10 mg intravenously three times daily and ceftriaxone 1 g intravenously two times daily. Packed red blood cells and albumin 20% transfusions were also given. Fludrocortisone was not available in our hospital.

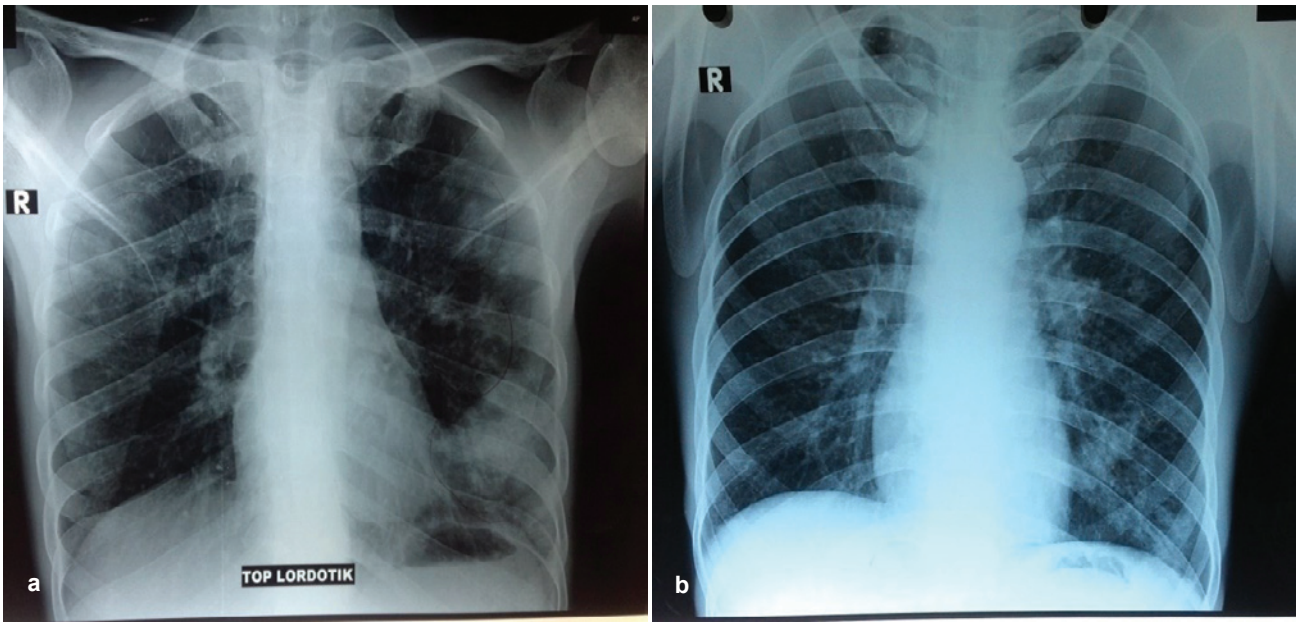

Figure 2. Chest radiographs (a) apicolordotic view revealed fibrotic infiltrates and calcifications on the upper right and lower left lung fields. (b) improvement after 2 weeks of antituberculosis treatment.

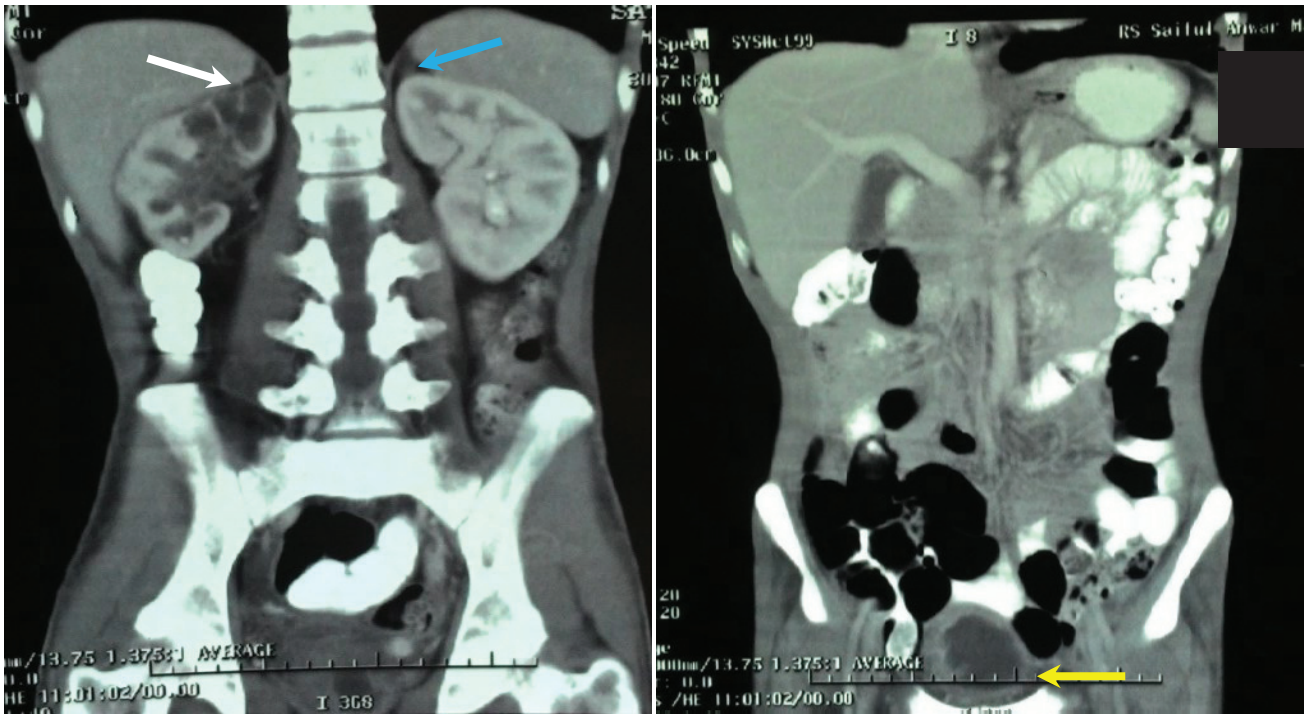

Figure 3. CT scan of the abdomen on coronal view showed a right adrenal gland measuring 3.3 cm x 2.6 cm with multiple cysts *(white arrow)*, a hypoplastic left adrenal gland measuring 1.4 cm x 0.9 cm (normal value 4 cm x 2 cm) *(blue arrow)*, right hydronephrosis grade III to IV, left hydronephrosis grade II, chronic ureterithis and cystitis *(yellow arrow)*.

After serum cortisol data became available, intravenous steroid was continued and later tapered to low dose oral dexamethasone 1 mg once daily with the resolution of acute adrenal insufficiency. With chest X-ray, urine AFB and adrenal CT scan results supporting tuberculosis as the cause of the chronic lung infection, complicated UTI and Addison's disease, first category anti-TB medications (2 months of rifampicin, isoniazid, pyrazinamide, ethambutol followed by 7 months of rifampicin and isoniazid, or 2RHZE + 7RH) were given. The patient was discharged with instructions to maintain prednisone 5 mg once daily, calcium lactate and vitamin D supplementation, anti-TB medications and vitamin B6, and to plan urologic surgery to release the urinary tract obstruction to prevent progression of chronic kidney disease. Subsequently, he never had any recurrence of weakness. Chest radiographs, electrolytes and glucose also improved.

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DISCUSSION

Addison's disease is a rare disorder with an estimated prevalence of approximately 120 individuals in one million.[11] Tuberculosis is a common cause, accounting for 7 to 20% of cases. In developing countries, tuberculosis still remains the main cause of Addison's disease.[3,11,12] Infection, including TB, should always be considered in males and in the elderly.[3] Lam and Lo found that the five most common locations of extrapulmonary TB were the liver, spleen, kidneys, adrenal glands and bones.[6] They reported that adrenal tuberculosis is found in 6% of patients with active tuberculosis. The adrenal glands were the only organs involved in active TB in 25% of cases, and bilateral involvement was seen in 69%. Nomura and colleagues observed that 93% of the patients with adrenal tuberculosis had previously suffered from extra-adrenal TB, mostly of the lung and pleura.[10] As a young adult male living in a developing country with a history of lung infection, our patient matched the profile described in the epidemology of extrapulmonary tuberculosis.

Depending on the acuteness of the hormonal deficit and the presence of concurrent illness, symptoms may present acutely in adrenal crisis, or insidiously. Our patient developed nonspecific but progressive symptoms of fatigue, weakness, weight loss, anorexia, nausea and vomiting and diarrhea, which may have delayed consult and subsequent diagnosis. He finally presented with hypotension leading to shock accompanied by hypoglycemia, which were classic signs of adrenal crisis.[9,12,15,16] Physical examination revealed cutaneous and mucosal hyperpigmentation, emaciation and hypotension. Routine laboratory findings revealed hyponatremia, azotemia and hypoglycemia.[17-21]

The diagnosis is usually made based on typical symptoms, and by documenting low serum cortisol, low concentration of urinary cortisol and its metabolites in the presence of elevated plasma ACTH. Biochemical findings are confirmed by a poor cortisol response to synthetic ACTH (tetracosactrin, 250 μg intramuscularly or intravenously) given at 0900H, with serum cortisol determinations measured at 0, 30 and 60 minutes after administration.[3] Plasma ACTH, rapid ACTH stimulation test and serum aldosterone were not available in our hospital. The diagnosis of primary adrenocortical insufficiency was based on clinical signs, symptoms, low serum cortisol, and the CT scan findings of hypoplasia and multiple cysts on the adrenal glands. The presence of hyperpigmentation suggested that adrenocortical insufficiency was due to a primary adrenal gland abnormality, in contrast to secondary causes (pituitary and hypothalamus), as low serum cortisol induces pituitary secretion of melanocyte-stimulating hormone (MSH) and ACTH. Abdominal CT scan findings on the adrenals, along with evidence of pulmonary and extrapulmonary tuberculosis, supported TB infection as the cause of Addison's disease.[16]

TB of the adrenal glands may be seen on CT scan imaging as bilateral enlargement on active infection, followed by atrophy and calcification on remote infection. We think our patient had remote infection in both adrenal glands, despite the absence of calcification. Calcification is observed in longstanding TB infection, with incidence on CT imaging varying from 40 to 59%. Adrenal cysts have been reported to be caused by *Echinococcus* species. However, since *Echinococcus* infection is rare in Indonesia, and the patient's clinical appearance and fecal analysis did not support the evidence of infection, we concluded that TB was the main cause of adrenal insufficiency in our patient.[3,12,16-18]

Tuberculosis of the adrenal glands leads to inflammation, necrosis and destruction of adrenal cortical tissue.[10] Adrenal tuberculosis results from hematogenous or lymphatic spread of primary tubercle bacilli infection elsewhere in the body.[15] This is the reason for the more common finding of bilateral rather than unilateral involvement in TB infection.[7,9,12] To date, the distinct tropism of tubercle bacilli with respect to the adrenal glands remains unknown.

In most cases, extra-adrenal TB is usually evident, but may be clinically latent.[15] Nomura and colleagues described that in patients with tuberculous Addison's disease, the ensuing period from the precedent nonadrenal TB to the onset of AD ranges from 0 to 50 years, with a mean of 31.9 ± 14.9 years.[10] Adrenal autoantibodies are usually absent in adrenal TB.[15] It was found that only 7.1% patients with tuberculous AD had positive adrenal autoantibodies.[15]

The aims of treatment are to replace the deficient hormones and treat any reversible causes of adrenal disease.[13] Despite the considerable capacity for regeneration of the adrenal cortex, AD due to tuberculosis is generally regarded as irreversible.[6] Although recovery is sometimes possible after appropriate anti-TB therapy, only a few patients with adrenal TB have been shown to have recovered adrenal function.[3] This recovery may be dependent upon the amount of residual viable adrenal tissue at the time of diagnosis, and on the adequacy of anti-TB therapy. However, patients usually have to maintain hormone replacement.[11,15] Kelestimur suggested that recovery from adrenal insufficiency is not possible in patients with AD due to remote tuberculosis in which the adrenal glands are atrophic and calcified.[19] Anti-TB medications may not be required if there is adrenal atrophy. However, if the adrenal glands are enlarged, anti-TB medications may be needed.[19]

Glucocorticoid replacement in chronic adrenal insufficiency involves the use of hydrocortisone 15 to 30

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mg/day orally or its equivalent (oral prednisone 5.0 to 7.5 mg/day or dexamethasone 0.75 to 1.25 mg/day). In the acute setting, hydrocortisone 50 to 100 mg or dexamethasone 4 mg intravenously every 4 to 8 hours can be given until stabilization of the patient's condition.[3] The aim of treatment with fludrocortisone in chronic adrenal insufficiency is to achieve normal sodium homeostasis and normal blood pressure. Over-treatment may result in hypertension and edema.[3] Additional adrenal androgen replacement can be added, particularly if the patient has poor quality of life. DHEA may improve self-esteem, mood, fatigue scores, and libido, particularly in women.[3] We did not have fludrocortisone or hydrocortisone in our hospital, thus the use of dexamethasone 5 mg intravenously at the nearest converted dose once daily in the morning to mimic the physiologic peak. Correction of hyponatremia and hypoglycemia was stopped right after steroid coverage was given, with note of clinical and biochemical improvement. Dexamethasone was then tapered to 1 mg orally, and then shifted to prednisone 5 mg once daily along with anti-TB medications.

Following anti-TB therapy, worsening of the patient's condition was anticipated due to the effect of rifampicin on cortisol metabolism. Many reports also describe the occurrence of adrenal insufficiency after the administration of rifampicin. Rifampicin facilitates the clearance of many drugs from the blood, including various glucocorticoids, via the induction of cytochrome CYP3A4, which metabolizes glucocorticoids in the liver.[5] We monitored the patient closely during antituberculosis drug administration because of these effects.

Our patient was also had upper and lower urinary tract infections, based on history, physical findings and urinalysis. He received ceftriaxone as empirical treatment. Following urine tests indicating negative bacterial culture and positive AFB smear, urinary TB infection was considered as the cause of complicated UTI. Treatment of urinary tuberculosis includes antituberculosis treatment with rifampicin, isoniazid, pyrazinamide and ethambutol for 9 months; corticosteroid to reduce mucosal inflammation and relieve symptoms; and surgical intervention. About 55% of genitourinary TB cases require surgery. Since the imaging findings revealed bilateral hydroureteronephrosis and chronic cystitis, urologic surgery was planned for obstruction release, drainage of pus, evacuation of calculi, augmentation of the urinary bladder and reconstruction of the upper and lower urinary tracts to prevent the progression of CKD.[18,20]

CONCLUSION

We reported a 37-year-old male with acute adrenal insufficiency and complicated UTI caused by tuberculosis. This report highlights the importance of prompt, adequate and complete treatment of pulmonary tuberculosis, as the likelihood of progression to extrapulmonary infection is very high. In this case, involvement of the adrenal glands and the kidneys led to a life-threatening condition of adrenal crisis and chronic kidney disease. Because of its significant impact on healthcare resources, our case underscores the importance of adequate provision of resources needed to conduct full implementation of programs for the treatment and eradication of of tuberculosis.

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.

Conflict of Interest

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

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CASE REPORT

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A Case Report on Severe Hypothyroidism Associated with Complete Bilateral Ptosis: A Rare Presentation

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Abstract

Thyroid hormones exert a major control over many vital functions of the human body and thus have an important role in maintaining homeostasis. Therefore, the hypothyroid state is associated with a wide spectrum of symptoms affecting almost all bodily functions. Among the major organs affected, nervous system and body metabolism are severely affected. Facial appearance, including ocular changes, is a characteristic of the hypothyroid state. The most prominent ocular features of hypothyroidism include loss of eyelashes and eyebrows, especially on the temporal side, puffiness of the eyelids, ocular irritation and ocular protrusion. Mild drooping of the eyelids is also seen in some patients due to loss of sympathetic tone; however the occurrence of complete bilateral ptosis is rare in the setting of hypothyroidism. Our patient, who presented with sudden onset bilateral ptosis, had no manifestations of diseases involving the ocular structure, cranial nerves or central nervous system primarily; the cause may be attributed to severe hypothyroidism considering the dramatic response to thyroxine replacement therapy.

Key words: hypothyroidism, thyroxine, ptosis, myokymia

INTRODUCTION

Thyroid hormones are major regulators of a number of vital organ systems. Therefore, it is obvious that in a state of depressed hormone production, all the body's major organs are affected. As signs and symptoms develop gradually, many patients seek medical attention many months or years after the disease onset. Hypothyroidism has a higher prevalence in the female population because of its frequent association with autoimmunity. Initial symptoms of disease may be subtle, such as dry coarse skin and cold intolerance that may be ignored before the appearance of symptoms of major system involvement.

Among its varied presentations, involvement of the central nervous system is commonly encountered in hypothyroidism. It can affect both central and peripheral nervous systems at multiple levels along with severe muscular disorders.[1] Patients may present with fatigue, psychomotor slowing and sometimes with severe intellectual disturbances such as dementia. Proximal myopathy is seen in around 25% of patients.[2] Weakness is usually mild and is slowly progressive over months to years. Myxedema is present in around one third of hypothyroid patients. Although ocular symptoms are also present in many patients, manifesting as periorbital puffiness and drooping of eyelids, presenting exclusively as complete ptosis is rare. We report the case of a female who presented with long standing features of hypothyroidism with proximal myopathy with sudden onset changes in consciousness levels and bilateral ptosis.

CASE REPORT

A 55-year-old housewife presented to the emergency department with complaints of excessive drowsiness, decreased oral intake and complete inability to open her eyes for 3 days. In the last three years, she also had difficulty getting up from the squatting position, combing her hair and dressing. These difficulties were gradually progressive with no diurnal variations or periodic fluctuations. She complained of increased sensitivity to cold, dryness of skin, increased hair loss, hoarseness of voice and easy fatigability. She had no history of intake of any prescribed or over-the-counter medications. She also had no history or family history of any major illnesses.

Her detailed physical examination revealed periorbital puffiness and dry, coarse skin with a lemon-yellow tinge. She suffered from extreme psychomotor retardation and only responded to simple motor commands. Complete bilateral ptosis was present although cranial nerve function examination was normal with no facial abnormality. External ocular movements were normal in all directions. No tremors or fasciculations were elicited. Pupillary reaction and pupil size were normal bilaterally. Muscle bulk of the upper and lower limbs was normal. Power in the proximal muscle groups in both upper and

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lower limbs was decreased (3/5), however it was normal in the distal group of muscles (5/5). Deep tendon reflexes although present, showed delay in relaxation phase. There was no sensory deficit in any limb. Examination of the pulmonary, cardiovascular and abdominal systems was unremarkable and did not reveal any abnormality.

Her baseline investigations revealed hemoglobin level of 11 g/dl with normocytic, normochromic picture on peripheral blood smear with normal serum levels of ferritin, vitamin B12 and folic acid. Renal and liver function analyses along with serum electrolytes were within normal limits. Blood sugar levels and HbA1c were also normal. Lipid profile was deranged with increased serum triglyceride and cholesterol levels. Further investigations revealed a state of primary hypothyroidism (Table 1). Her CPK levels were raised to 410 U/L (60-174 U/L). Serum cortisol and Serum ACTH levels were normal.

Table 1. Biochemical parameters of the case

Laboratory parameter	Value	Normal range
Free T3	1.43 pg/ml	2.3-4.2 pg/ml
Free T4	0.046ng/ml	0.8-1.8 ng/L
TSH	>100µlU/ml	0.5-5 µlU/ml
Anti TPO Antibodies	1160 U/ml	<60 U/ml
Total CPK	410 U/L	60-174 U/L
Serum Cortisol (7 a.m.)	12µg/dl	7-28 µg/dl
Serum ACTH	8 pg/ml	5-27 pg/ml

Electromyographic study revealed myopathic pattern of weakness in the proximal muscle groups of both upper and lower limbs. Repeated nerve stimulation for ocular muscles was negative for myasthenia gravis. Acetylcholine receptor and anti-skeletal antibody levels were not elevated. Cranial MRI and abdominal ultrasound were normal. Contrast-enhanced computed tomography of the chest ruled out any evidence of thymoma. Ultrasound of the thyroid gland revealed small lobes and isthmus with normal blood flow on color doppler. Echocardiography showed grade I diastolic dysfunction with normal left ventricular ejection fraction. Detailed ophthalmic examination ruled out any local, infectious, inflammatory or aponeurotic causes of ptosis.

The patient was started on 100 µg (1.6 µg/Kg body weight) of thyroxine daily. After one week of treatment, the patient dramatically improved, with complete recovery of ptosis and significant improvement in her consciousness level. Her muscle power also improved, although some residual weakness was still persistent. The patient was discharged after 2 weeks of hospitalization on the same treatment, and was advised regular monthly follow up. Her thyroid function tests were repeated every 2 months with necessary titration of the dose until her free T4 and TSH levels were restored to normal range. Her sense of well-being improved gradually, with definitive improvement in muscle power. After 6 months of follow-up, all her symptoms pertaining to hypothyroidism had resolved and she had no active complaint.

DISCUSSION

Hypothyroidism is one of the most common endocrine disorders, more frequently affecting females. About 42 million people in India suffer from thyroid disease and iodine deficiency has largely been implicated as the leading cause of hypothyroidism.[3] Among these patients, autoimmune thyroiditis was demonstrable in 7.5% of subjects.[4] Hashimoto's thyroiditis is the most common form of autoimmune thyroid disease in areas of iodine deficiency, caused by T-cell mediated disease with a strong genetic component.[5] It is usually diagnosed by demonstration of anti-thyroid antibodies and findings of thyroiditis on ultrasonography. Secondary hypothyroidism from pituitary or hypothalamic dysfunction is usually rare.

Thyroid hormones exert control over basic metabolic functions of the body, therefore its deficiency is expected to produce a wide array of symptoms. It covers a wide spectrum of clinical and biochemical diseases, from clinically inapparent disease to myxoedema coma.[6] Hypothyroidism emerges insidiously and is nonspecific. The clinical features may be atypical, and the diagnosis may be missed easily particularly in the elderly.[7]

Without regard to the cause of hypothyroidism, neuromuscular and musculoskeletal manifestations are present in many of these patients.[8] The hypothyroid state severely impairs protein and carbohydrate metabolism affecting many organ systems, especially the muscles manifesting as pain with muscle exertion. A shift in distribution of muscle fiber types is also observed as shift from fast twitch fibers to slow twitch fibers which causes slowed muscle contraction and relaxation known as "hypothyroid myopathy." A reduction in muscle mitochondrial oxidative capacity and beta-adrenergic receptors, as well as the induction of an insulin-resistant state, may result in these changes. Hypothyroid myopathy typically manifests as polymyositis-like myopathy with proximal muscle weakness and an increased creatine kinase level.[9] Typical facial features and ocular changes

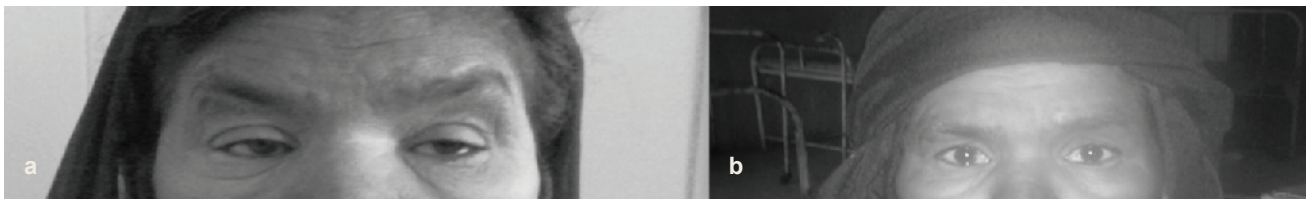

Figure 1a. Showing ptosis in patient on day 4 of admission. **Figure 1b.** Showing complete recovery on day 7 of admission.

are characteristic of hypothyroid state manifesting with loss of eyelashes and eyebrows especially on the temporal side, puffiness of eyelids, ocular irritation and ocular protrusion. These are largely attributed to accumulation of glycosaminoglycans and cross reactivity of autoantibodies with orbital and dermal fibroblasts.

The occurrence of complete bilateral ptosis is very rare in the setting of hypothyroidism, although mild drooping of eyelids may be present in some patients due to loss of sympathetic tone. Since our patient, who presented with sudden onset bilateral ptosis had no manifestations of disease involving the eye, cranial nerves or central nervous system primarily; the cause may be attributed to severe hypothyroidism, particularly the ptosis responded dramatically to thyroxine replacement therapy. Various mechanisms may be postulated, although the exact cause is still unknown.

Myokymic discharges may be the etiology behind this rare manifestation.[10] An autoimmune basis due to antibody interference with the function of potassium channels, leading to increased nerve terminal excitability, is a documented cause of myokymia.[11] Another hypothesized mechanism is focal demyelination involving isolated terminal branches to the orbicularis oculi followed by multiple grouped discharges on demyelinated axon terminals leading to myokymia and persistent ptosis. Lee et al. reported a similar case of ptosis due to hypothyroidism which was secondary to Sheehan's syndrome.[12] Cho et al. described a case of pituitary apoplexy with Sheehan's syndrome and isolated third cranial nerve palsy. In their case, direct mechanical compression of the third cranial nerve or the vascular supply to the nerve resulted in a sudden onset of isolated third cranial nerve palsy. The patient's ptosis was improved by surgical decompression.[13] Proximal myopathy and severe bilateral ptosis due to hypothyroidism were also reported by Green PH in a 28 year-old female.[14] Apart from these, there have been few case reports of patients of myasthenic syndromes who responded completely with thyroxine treatment alone.[15]

CONCLUSION

In this paper, we intend to highlight the unusual presentation of hypothyroid state in the form of sudden onset bilateral ptosis with features of proximal myopathy and no other identifiable etiology for this presentation. This is further supported by the fact that the patient completely recovered with thyroxine replacement therapy alone.

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.

Conflict of Interest

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

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For Case Reports, Images in Endocrinology and Clinical Case Seminars, authors are required to submit scanned soft copy of signed informed consent for publication from the involved subject/s ("Patient Consent Form"). In case signed informed consent cannot be obtained (e.g., retrospective studies), the author should state so in his declaration.

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

Title Page

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

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

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

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

References
1. References in the text should be identified by Arabic Numerals in superscript on the same line as the preceding sentence.
2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
3. All references should provide inclusive page numbers.
4. Journal abbreviations should conform to those used in PubMed.
5. A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
6. The style/punctuation approved by JAFES conforms to that recommended by the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org. Follow the format of the examples shown below:

Journal Article
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One to Six Authors (Commentary, Online)
Krause RM. The origin of plagues: old and new. Science. 1992;257:1073-1078.

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

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

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

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

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

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

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

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

Illustrations and Photographs
1. Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as .jpeg or .gif files).
2. For photomicrographs, the stain used (e.g. H&E) and magnification (e.g. X400) should be included in the description.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn or printed on good quality laser printers. Photocopies are not acceptable.
4. All letterings for illustration should be done professionally and should be of adequate size to retain even after size reduction.

5. Figure legends should be numbered sequentially, typed double-spaced on a separate sheet of paper. Give the meaning of all symbols and abbreviations used in the figure.
6. Up to a maximum of five (5) illustrations/photographs are allowed.

N.B.: For tables, figures, graphs, illustrations and photographs that have been previously published in another journal or book, a note must be placed under the specific item stating that such has been adapted or lifted from the original publication. This should also be referenced in the **References** portion.

PROCESS

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

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ARTICLE TYPES

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

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

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

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

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

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

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

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

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

Checklist Guide for Submission of Manuscripts to JAFES	
Instructions to Authors	☐ Review manuscript submission guidelines
Cover Letter	☐ Include cover letter as an attachment ☐ Indicate in the letter the title of the work ☐ Indicate all the authors (complete names and affiliations) ☐ Indicate in the letter the corresponding author and provide complete contact information (post address, telephone, fax number, e-mail address)
EQUATOR Network Guidelines	☐ Review manuscript if compliant with appropriate EQUATOR Network Guidelines (e.g., CONSORT for clinical trials, CARE for case reports, et cetera)
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Patient Consent Form (if applicable)	☐ For Case Reports, Images in Endocrinology and Clinical Case Seminars, submit a scanned copy of the fully accomplished form ☐ If all attempts have been made and consent form is not signed, state so in the Cover Letter
Title Page	☐ Full names of the authors directly affiliated with the work (First name and Last name), highest educational attainment ☐ Name and location of 1 institutional affiliation per author ☐ If presented in a scientific forum or conference, provide a footnote should be provided indicating the name, location and date of presentation
Abstract	☐ Provide an abstract conforming with the format ☐ Structured for Original Articles: Objective/s, Methodology, Results, Conclusion ☐ Unstructured for Case Reports and Feature Articles
Keywords	☐ Provide 3-5 keywords (listed in MeSH)
Content	☐ Provide text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion) ☐ Make sure all abbreviations are spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses; the same abbreviation may then be used subsequently ☐ Make sure all measurements and weights are in SI units ☐ If appropriate, provide information on institutional review board/ethics review committee approval ☐ Acknowledgements to individuals/groups of persons, or institution/s should be included at the end of the text just before the references; grants and subsidies from government or private institutions should also be acknowledged
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Author Form

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☐ The undersigned author(s) of the manuscript hereby certify that the submitted manuscript represents original, exclusive and unpublished material. It is not under simultaneous consideration for publication elsewhere. Furthermore, it will not be submitted for publication in another journal, until a decision is conveyed regarding its acceptability for publication in the JAFES.

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Patient Consent Form

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For a patient's consent to publication of information about them in the Journal of the ASEAN Federation of Endocrine Societies (JAFES).

Name of person described in article or shown in photograph:_____
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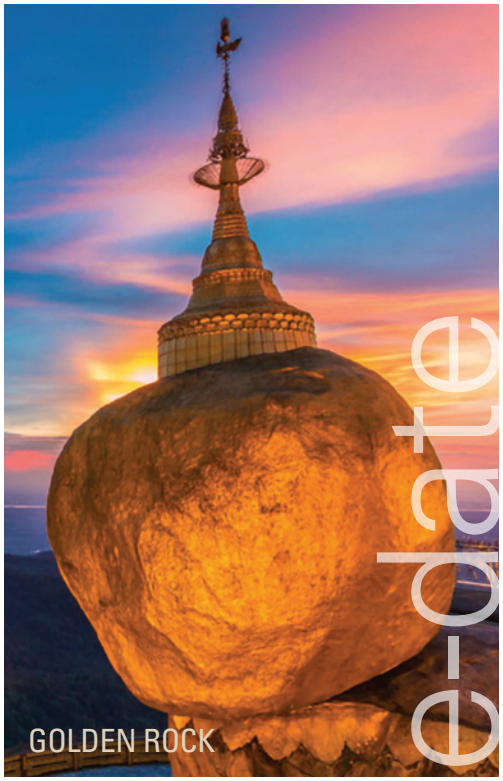

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