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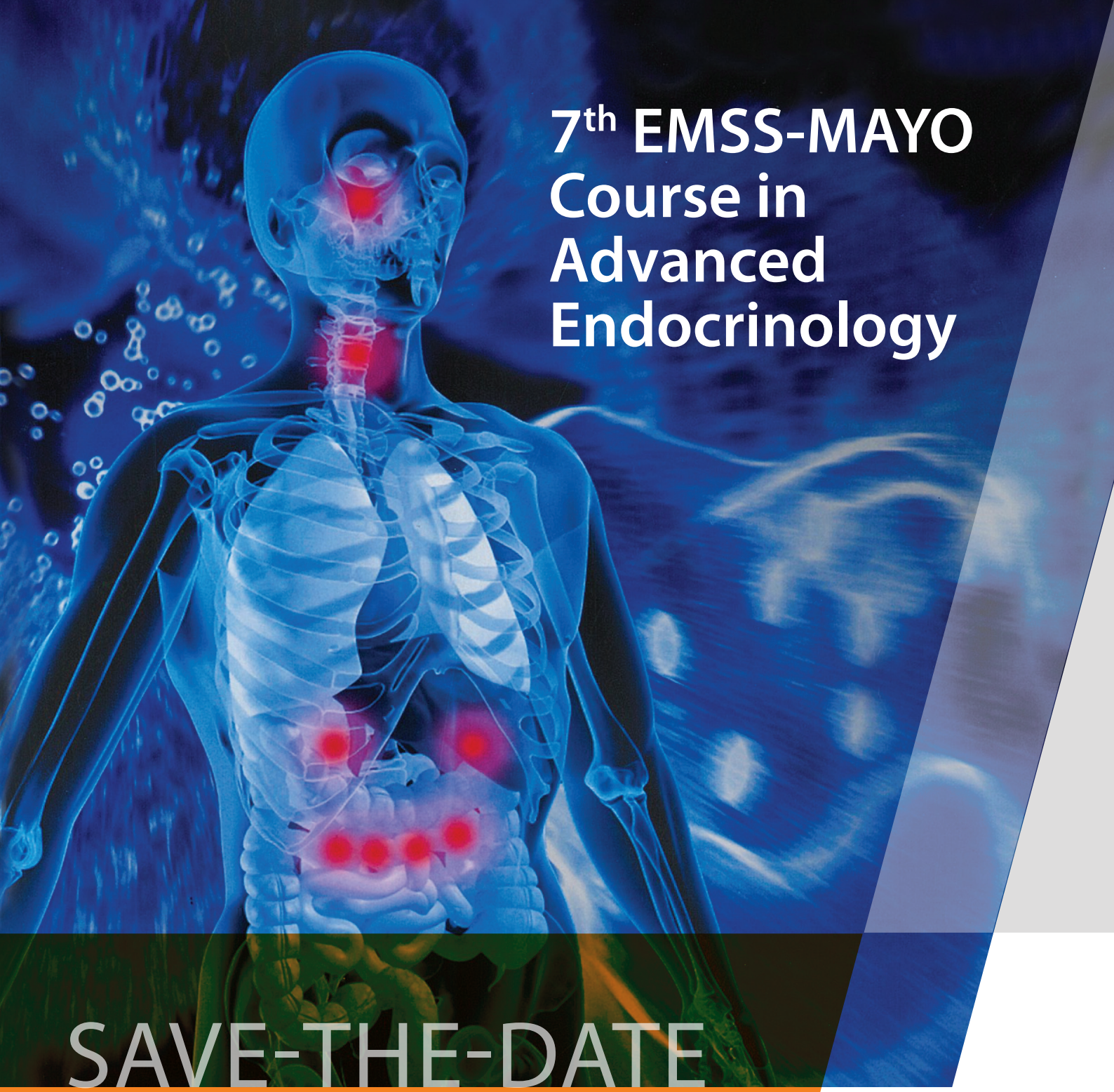

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Editorial

Change and Our Commitment to Continual Improvement

After six years of continuous, regular and timely publication of high quality endocrinology articles from the Southeast Asian region, we are pleased to announce that JAFES is now indexed in Scopus, one of the largest abstract and citation databases of peer-reviewed literature. Along with our efforts of adopting international standards, shifting to 100% open access, and utilization of technologies such as our Open Journal Systems-based website, CrossRef digital object identifiers for all published articles, and Similarity Check for plagiarism detection, our being indexed is aligned with our goal to make scientific output from the region global and accessible to a wider audience.

In addition to DOAJ, WPRIM, APAMED and Scopus, it is also our aim to be included in other indexing services, such as PubMed and Thomson Reuters.

Indexing in recognized and established databases increases journal visibility and searchability. The metrics embedded in these databases allow for the journal to analyze its performance and identify not only gaps but also opportunities for improvement. Inclusion is, also, a stamp of quality, as journals pass through rigorous screening, review and content selection.

As we continue our efforts of enhancing JAFES, we get to encounter not only technical but also editorial policy issues. The ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals serves as our general guideline for operations. We have registered in the World Association of Medical Editors (WAME) online forum, reading through questions and answers, posting our own questions and getting constructive feedback from peers from all over the globe. The Committee on Publication Ethics (COPE) flowcharts serve as a valuable resource when we are faced with suspected misconduct, such as duplicate publications, plagiarism, and authorship issues. We have also acknowledged the fact that even our own journal's editors publish in JAFES, but protecting the journal's objectivity by strictly inhibiting them from the deliberation, peer review process, and final decision.

We appreciate the importance of formally providing third party permissions for articles published in the JAFES when contacted several times by a copyright clearance center. Though all articles in the journal are open access to all, they are governed by a Creative Commons License BY-NC, that allows free use of the information provided there is proper attribution and strictly for non-commercial purposes only. Protecting the scientific output of our regional researchers from misuse, we shall keep all of you updated on this matter.

Finally, in the last Asia Pacific Association of Medical Editors' Conference in Thailand, we were introduced to the 2015 version of the GPP3 Guidelines, an update to the original Good Publication Practice (GPP) guidelines, and which we are adopting to strengthen the JAFES' stand on integrity and transparency for industry-sponsored medical publication. We are now realizing that the process of improvement of editorial policies and operations is a dynamic and continuous one, and our receptivity to change as we learn more from colleague editors from this region and the world, underscores our commitment to our readers..

Our official logo, the proverbial tree, continuously growing, spreading, tested by inclement weather and harsh seasons, getting only stronger with time, reminds us all that much have been accomplished, much remain to be done.

Elizabeth Paz-Pacheco
Editor-in-Chief

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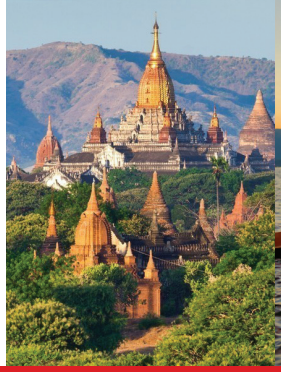

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FEATURE ARTICLE

A Consensus of Key Opinion Leaders on the Management of Pre-diabetes in the Asia-Pacific Region

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Abstract

The Asia-Pacific region carries a high disease burden, with over half of the global diabetic population residing in this region. Increasing evidence shows that without targeted intervention, the progression from impaired glucose tolerance (IGT) to type 2 diabetes occurs more frequently in Asians compared with Caucasians. Furthermore, IGT is independently associated with an increased risk of cardiovascular disease, and should be managed as early as possible. Because diabetes is now a major public health issue, strategies aimed at prevention and treatment are urgently required. Lifestyle modification, including weight loss, dietary changes and increased physical activity, play a major role in controlling the disease. Significant evidence also supports the effectiveness of a combination of lifestyle modification and pharmacologic therapy, such as metformin, in delaying the onset of diabetes. Although the importance of lifestyle interventions is well recognized throughout Asia, many countries do not have formal recommendations to guide the diagnosis and management of individuals at risk of progression to diabetes. At a recent regional meeting, experts from the Asian region convened to develop consensus recommendations to guide clinicians in the management of Asian patients with pre-diabetes. These consensus recommendations provide a clear and concise approach to the management of individuals with IGT based on the available evidence and current best clinical practice.

Key words: impaired glucose tolerance, pre-diabetes, Asia

INTRODUCTION

Globally, there are 387 million individuals living with type 2 diabetes, 46.3% of whom are undiagnosed.[1] A disproportionate diabetes burden is carried by the South East Asian and Western Pacific nations, as it affects 75 million people in South East Asia (8.3% of the adult population) and 138 million in the Western Pacific (8.5% of the adult population).[1] With this rising trend, it is estimated that Asia will contribute to more than 60% of the world's diabetic population.[2] Furthermore, Asians have a strong ethnic and genetic predisposition for diabetes and lower thresholds for environmental risk factors.[2] Within the Asian region, diabetes and pre-diabetes are more prevalent among Indians (37.9 and 18.9%, respectively) and Malays (23.8 and 22.6%, respectively). Pre-diabetes is more prevalent in women (21.9%) and urban dwellers (21.5%).[3]

Of particular concern is the evidence indicating that a significant proportion of individuals with diabetes or pre-diabetes are unaware of their condition. Consequently, adoption of risk reduction behavior is suboptimal. An evaluation of the United States National Health and

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Nutrition Examination Survey (NHANES 2005-2006) data revealed that almost 30% of the adult population had pre-diabetes but only 7.3% were aware of their condition.[4] Further, estimates for the prevalence of undiagnosed diabetes in South East Asia and the Western Pacific region were high (52.8 and 53.6%, respectively).[1] A cross-sectional survey of Malaysians found that the prevalence of newly diagnosed type 2 diabetes reached 12.6% adults, with an increasing prevalence of undiagnosed diabetes observed with age.[5] This high prevalence of undiagnosed diabetes poses a serious problem for public health, warranting an escalated effort to address and improve the burden of diabetes.[5]

METHODOLOGY

The consensus working group consisted of an assembly of 13 regional experts working as academics, researchers, clinicians, and policy makers from national and international organizations. The experts have substantial knowledge in relevant disciplines, including endocrinology and metabolism.

The expert group used a qualitative approach involving a question-and-answer format to shape and direct the flow of the discussions. This was followed by a comprehensive literature review of published academic articles for identifying the research evidence to guide recommendations. The research findings were subsequently triangulated and circulated electronically among all consensus group members.

The recommendations were formulated by the chairperson and members of the advisory board committee, after the initial group discussion and multiple e-mail communications. The diagnostic cut-off fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), and oral glucose tolerance test (OGTT) values for pre-diabetes are based on the consensus-based outcomes of that meeting and the subsequent literature review.

Consensus was *a priori* defined as agreement of a large majority of advisory group members, without strong disagreements. If consensus was not reached, the working group would take a vote, where at least a simple majority vote would be required for the recommendation to pass. Any dissenting opinion would be captured and presented in the report. Every effort was made to achieve consensus among the committee members, and consensus was reached on every recommendation.

A preliminary review of the literature showed that several consensus statements exist, including the official position of the American Association of Clinical Endocrinologists and American College of Endocrinology, and another by the working group of the Spanish Diabetes Society.[6,7] However, this consensus statement was written to reflect the various aspects of pre-diabetes management from an Asian perspective. Majority of the consensus statements were crafted based on studies conducted in Western populations without consideration of the cultural nuances that are sensitive and specific to Asian populations.

Recommendations for Pre-diabetes Management in Asian Patients

At a regional consensus meeting held in Manila, Philippines on June 6, 2014 sponsored by Merck, experts from the Asia-Pacific region convened to develop consensus recommendations to guide clinicians in the management of Asian patients with pre-diabetes. The following are their recommendations:

Recommendation 1: Screening and Diagnosis of Pre-diabetes

Screening and treatment of IGT can delay or prevent the development of type 2 diabetes, providing a window of opportunity for primary prevention of diabetes and CVD. The authors recommend targeted screening for patients aged ≥35 years and/or high risk individuals, followed by laboratory tests (i.e., FPG, HbA1c and/or 75-gram OGTT). High risk individuals include overweight or obese patients (country-specific), family history of diabetes, high blood pressure, dyslipidemia, history of large babies or gestational diabetes.

Pre-diabetes is diagnosed if the FPG ≥100 mg/dL (5.5 mmol/L), 2-hour OGTT is 140-199 mg/dL (7.8-11.0 mmol/L), and HbA1C of >5.7%. If initial screening of pre-diabetes is negative, patients should be rescreened every 1 to 3 years, depending on risk factors (based on clinical judgment) and local resource availability. The optimal cut-offs for diagnosing pre-diabetes in Chinese patients are HbA1c of 5.6% (38 mmol/mol) in the young and middle-aged and 5.7% (39 mmol/mol) in the elderly.[8]

The bases for the cut-off of 35 years and older for routine screening were reports from Bangladesh and Eastern Uganda that these individuals could have abnormal glucose regulation with a normal body mass index (BMI).[9,10] Together with majority consensus voting, these formed the rationale for periodic screening of all persons older than 35 years for pre-diabetes. The HbA1c threshold set at 5.7% when screening for pre-diabetes was based on a previously published cost-effectiveness strategy.[11] Therefore, the authors recommend age-specific cut-offs for detecting pre-diabetes or diabetes in populations where such differences have been observed.

Recommendation 2: Treatment of Pre-diabetes

Current guidelines on diabetes prevention recommend intensive lifestyle intervention as the cornerstone of pre-diabetes management.[12-17] The authors strongly recommend lifestyle intervention, preferably with a dietician referral specifically encompassing the following:

- Reduced intake of simple sugars
- Reduced fat intake, specifically saturated fats and oils
- Reduced *trans* fatty acid intake

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- 5 to 10% weight loss from baseline
- Total calorie intake deficit based on target weight loss
- 30 minutes of exercise 5 to 7 times per week

Patients should ideally undergo a review after a period of 3 to 6 months.

Recommendation 3: Pharmacologic Therapy

Pharmacologic intervention is recommended if there is inadequate response to lifestyle intervention after 3 to 6 months. Metformin should be initiated at a starting dose of 500 mg/day titrated up to a maximum of 2,000 mg/day as required. Alternative treatment should be considered if the patient is nonresponsive or intolerant to metformin (e.g., acarbose), or when it is contraindicated. Follow up is recommended at 3 to 6 months. These recommendations are in line with international and local guidelines and reflect current practice within the region.[12-15,17] However, important considerations concerning pharmacotherapy with metformin for high-risk individuals should be emphasized, because the impact of duration of therapy with metformin, and long term cost-effectiveness of such early intervention, remain unclear.[18]

Burden Attributable to Pre-diabetes in Asia

Individuals with impaired fasting glucose (IFG) and/or IGT are considered to have pre-diabetes, indicating a relatively high risk for future development of diabetes.[19] IFG and IGT should not be viewed as clinical entities in their own right but rather as risk factors for diabetes as well as cardiovascular disease (CVD).[19] Both IFG and IGT are associated with obesity or adiposity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low high density lipoprotein (HDL) cholesterol, and hypertension.

Increasing evidence shows that without targeted intervention, the progression from IGT to type 2 diabetes occurs more frequently in Asians compared with Caucasians.[20-23] The population-based controlled Da Qing study (n=110,660, aged 25 to 74 years), which explored the incidence of progression to diabetes among 577 IGT subjects, reported an incidence rate of 15.7% per 100 person-years in Chinese individuals with IGT.[20] In Indians, the progression rate of pre-diabetes to diabetes was found to be as high as 18.3% per year.[21] These data are in stark contrast to Finnish (with an average progression rate of 6% per year) and American (11% per 100 person-years) individuals with pre-diabetes.[22,23]

The prevalence of overweight/obesity (BMI ≥25 kg/m$^{2)}$ is increasing rapidly in the Asia Pacific region. It is important to note that a significant proportion of adults have undiagnosed diabetes, suggesting that the prevalence within the region is likely to be higher than is currently reported (Table 1).[1,24] An IGT comparative prevalence in excess of 10% has been reported in Malaysia (15.19%), Hong Kong (13.30%), Japan (12.64%), Singapore (12.40%) and Taiwan (11.19%).[24]

Table 1. Estimated prevalence of DM[a] and IGT[b] in Asia compared with the US[c] and the UK[d] [1,24]

Country	DM comparative prevalence, 2014 (%)[1]	Adults with undiagnosed DM, 2014 (in 1000s)[1]	IGT comparative prevalence, 2013 (%)[24]
Hong Kong	7.66	307	13.30
Indonesia	6.03	4,854	9.38
Japan	5.12	3,891	12.64
Malaysia	17.64	1,717	15.19
Mainland China	8.64	51,273	5.16
Philippines	6.71	1,743	6.61
Republic of Korea	5.97	1,493	8.75[e] to 8.45[f]
Singapore	10.79	288	12.40
Taiwan	8.3	948	11.19
Thailand	7.36	2,223	7.88
Vietnam	5.71	1,776	1.0
United Kingdom	3.9	834	6.63
United States	9.39	7,143	12.37

[a]DM, diabetes mellitus
[b]IGT, impaired glucose tolerance
[c]US, United States
[d]UK, United Kingdom
[e]North Korea
[f]South Korea

In Thailand, it is estimated that 4.1 million adults have IGT.[24] India is estimated to have 21.5 million adults with IGT, making it the country with the highest number of persons with diabetes in the South East Asian region.[24,25] Almost one-third of adults with IGT are younger than 40 years of age. It is projected that by 2035, one in 8 adults will have IGT, while one in 10 will have diabetes. Therefore, prompt and effective IGT management is essential.[24] A similar pattern is emerging in the Philippines where the prevalence of pre-diabetes (i.e., combined IFG and IGT) was 31.3%, while it was 17.5% for IFG and 23.9% for IGT.[26]

Of note, the high prevalence of IGT throughout the region indicates that the incidence of diabetes is likely to increase over the coming decade. The alarming prevalence of pre-diabetes (IFG and/or IGT) and diabetes in the Asian region warrants urgent strategies aimed at preventing the conversion from pre-diabetes to diabetes.[27]

Current Management of Patients with Pre-diabetes

Not everyone with IGT will subsequently develop type 2 diabetes. A large body of evidence supports the effectiveness of lifestyle interventions, specifically healthy diet and physical exercise, to prevent progression to diabetes.[20,22,23] The primary aim of lifestyle interventions is to prevent or delay the development of type 2 diabetes and its complications by targeting obesity and physical inactivity, which are the two most important modifiable risk factors of diabetes development.

The beneficial effect of lifestyle interventions has been confirmed in Asian populations. Among 577 Chinese individuals with IGT, long-term lifestyle interventions involving diet and/or exercise have been shown to significantly decrease the incidence of diabetes.[20] Over a 6-year period, there was a reduction in the incidence of

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Table 2. Overview of lifestyle and pharmacologic interventions in individuals with IGT[a] or IFG[b]

Intervention	Study	Patient Characteristics	N	Duration Main Study and Follow-up (years)	Risk Reduction Main Study and Follow-up (%)
Lifestyle					
	Da Qing[20]	IGT	577	6 20	31 - 46 43
	Finnish DPS[c 22,28]	IGT	522	3.2 7	58 43
	DPP/DPPOS[23,34]	IGT and/or IFG	3324	2.8 10	58 34
Pharmacologic					
Metformin	DPP/DPPOS[23,34]	IGT and/or IFG	3234	2.8 10	31 18
Acarbose	STOP-NIDDM[31]	IGT	14	3.3	25

[a]IGT, impaired glucose tolerance
[b]IFG, impaired fasting glucose
[c]DPS, Diabetes Prevention Study
[d]DPP, Diabetes Prevention Program
[e]DPPOS, Diabetes Prevention Program Outcomes Study
[f]STOP-NIDDM, The Study to Prevent Non-insulin Dependent Diabetes Mellitus

diabetes in individuals practicing lifestyle interventions. Compared with the control group, both diet and exercise resulted to reductions in the risk of developing diabetes (31% and 46%, respectively).[20] These findings were replicated in the Finnish Diabetes Prevention Study (DPS) in 522 overweight (mean BMI ≥31 kg/m^2) adults aged 40 to 65 years with IGT.[22,28] At 4 years, the cumulative incidence of diabetes was 11% in the intervention group compared with 23% in the control group.[22] From these results the authors concluded that one case of diabetes could be prevented by treating 22 IGT patients with lifestyle intervention for one year, or 5 patients for a period of 5 years.[22] The Diabetes Prevention Program (DPP) in the US, one of the largest randomized controlled clinical trials to date, found similar results. In a population of 3234 adults with IGT and/or IFG (with a mean BMI of 34.0 kg/m^2 and a mean age of 51 years), the incidence of diabetes for the lifestyle intervention group was lower than in the placebo group (4.8 and 11.0 cases per 100 person-years, respectively).[23] The authors concluded that one case of diabetes could be prevented by treating 7 patients with intensive lifestyle modification for 3 years.[23] These studies found that type 2 diabetes can be prevented by lifestyle changes in those deemed to be at high-risk, such as those with IGT (Table 2).[20,22,23]

The DPP study also showed that treatment with metformin could also delay or prevent type 2 diabetes. Compared with placebo, metformin reduced the incidence of type 2 diabetes by 31% (Table 2).[23] A subsequent washout study showed that approximately one-quarter of this effect could be accounted for by the pharmacologic effect of metformin that disappeared following discontinuation of the therapy.[29] Notably, even after the washout period, a significant 25% reduction in the incidence of diabetes persisted.[29] Although the DPP study was not powered to demonstrate statistical significance for between subgroup effects, analysis revealed that metformin was more effective in patients with higher fasting plasma glucose (FPG) levels (≥110 mg/dL), in those younger than 60 years of age, and in individuals with a BMI ≥35 kg/m^2.[23]

Despite the benefits of delaying or preventing the onset of diabetes, it has been shown that metformin is rarely prescribed as preventive therapy in working-age adults with pre-diabetes. Over a period of 3 years, only a minority of US adults with pre-diabetes (3.7%, or one in 27) were prescribed metformin, and only 7.8% (fewer than one in 12) of high-risk patients as identified by the national guidelines received metformin in a retrospective cohort study.[30] These findings highlight the need for intensive lifestyle modification programs. Patients should, at a minimum, be educated on the benefits of metformin and should ideally also be offered this option as preventive treatment for diabetes.

Acarbose has also been shown to effectively reduce the risk of progression to diabetes in individuals with IGT (Table 2).[31] The STOP-NIDDM trial reported a decrease in progression to diabetes by 25% of patients with IGT.[31] Patients on acarbose additionally improved in their tolerance to glucose as the probability of reversing to normal glucose tolerance was significantly higher in these patients than in those on placebo ($p<0.0001$).[31]

Positions on Specific Questions Addressed to Guide Recommendations

1. Do prevention interventions have sustained effects?

A 20-year follow-up of the Da Qing study determined that combined lifestyle intervention resulted in a 51% reduction in the incidence of diabetes during active intervention and a 43% reduction over 20 years (Table 2).[32] The benefits of the active lifestyle intervention translated to an average delay of diabetes onset of 3.6 years.[32] The Da Qing study found that the 20-year cumulative diabetes incidence was 93% in the controls versus 80% among those who received the combined lifestyle intervention.[32] The 20-year follow-up did not detect significant differences in the incidence of first CVD events, CVD mortality, or all-cause mortality between the combined lifestyle intervention and control group, as it was not powered to detect statistical differences in these outcomes.[32] Nevertheless, the follow-up study showed that lifestyle interventions over 6 years

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were able to delay or prevent diabetes onset for up to 14 years after active intervention ceased.[32]

The most recent 23-year follow-up of the Da Qing study confirmed that active lifestyle intervention significantly reduced the risk of CVD and all-cause mortality. The cumulative incidence of CVD mortality was 11.9% for patients in the lifestyle intervention group and 19.6% in the control group. In terms of all-cause mortality, the cumulative incidence was 28.1% in the lifestyle intervention and 38.4% in the control group.[33] The significant differences in the incidence of diabetes between the two groups persisted during the 23-year follow-up: the cumulative incidence was 72.6% in the intervention group and 89.9% in the control group.[33] These findings justify the adoption of lifestyle interventions in patients with IGT.

2. Are we preventing type 2 diabetes or delaying it?

Interventions that may prevent or delay IGT, which is associated with cardiovascular disease and conversion to type 2 diabetes, are clinically important. The 10-year follow-up of the DPP, the Diabetes Prevention Program Outcomes Study (DPPOS), found that patients who were on intensive lifestyle had a 34% reduction in the incidence rate of diabetes, with an average delay of diabetes progression by about 4 years versus placebo (Table 2).[34] Those treated with metformin had an 18% reduction in diabetes incidence rate, with the onset of diabetes delayed by an average of 2 years.[34]

It is clear that high risk patients must be identified and lifestyle changes should be implemented and sustained over the long term. Delaying or preventing type 2 diabetes is cost-effective and will help turn the tide in the diabetes epidemic.[35]

3. What is the current management of pre-diabetes in countries of the Asia-Pacific region?

Most countries within the region do not have country-specific guidelines and therefore follow the American Diabetes Association (ADA) or the International Diabetes Federation (IDF) recommendations.[12,13] The IDF consensus guidelines on the prevention of type 2 diabetes recommend the following three steps for the prevention of diabetes development: (1) identification of individuals at high risk of developing diabetes, (2) assessment of risk levels by measuring plasma glucose levels, and (3) initiation of lifestyle interventions with or without pharmacologic therapy.[36] Once individuals with pre-diabetes have been identified, they are advised to undergo structured lifestyle modifications, with the aim of achieving gradual and sustained weight loss and maintaining a healthy body composition through physical activity and change of dietary habits.[36] The World Health Organization (WHO) and IDF also recommend to address other risk factors, including smoking.[13,37] In addition, the WHO highlights the need for a global approach to reduce the growing global burden of diabetes.[37]

The ADA recommends the referral of patients with IGT, IFG or HbA1c of 5.7 to 6.4% to an ongoing support program targeting weight loss of 7% of body weight and moderate exercise of ≥150 minutes per week.[12] The ADA states that metformin therapy for prevention of type 2 diabetes may be considered in individuals with IGT, IFG or an HbA1c of 5.7 to 6.4%, especially for those with BMI >35 kg/m^2, individuals aged <60 years, and women with prior gestational diabetes.[12] In addition, the ADA guidelines encompass recommendations for follow-up counselling for successful lifestyle interventions, annual monitoring of individuals with pre-diabetes for development of diabetes, as well as screening for and treating of modifiable risk factors for CVD.[12]

In Asia-Pacific countries, lifestyle modifications remain the mainstay of recommended first-line interventions for patients with pre-diabetes. In Malaysia, lifestyle interventions, such as diet and physical therapy, are the pillars for pre-diabetes therapy.[14] In addition, the 2015 Ministry of Health (MOH) guidelines state that metformin (as the preferred first-line oral anti-diabetic agent) should be considered for patients at very high risk of progressing to diabetes (combined IFG and IGT, IGT plus other risk factors, or failed lifestyle intervention after 6 months).[14] Off-label metformin may be initiated at the discretion of the prescribing physician.

In Thailand, there are no available guidelines for the management of pre-diabetes. Majority of physicians follow the IDF recommendations, ADA guidelines or findings from randomized controlled trials on pre-diabetes prevention.[12,13,20,22,23,34] Likewise, given a lack of guidelines in the Philippines, physicians generally follow the ADA recommendations. However, in the Philippines, metformin is approved for the treatment of pre-diabetes after failed lifestyle intervention.

Guidelines in Singapore indicate that lifestyle modification should be the first-line treatment of choice.[15] Metformin may be considered for individuals with a very high risk of progressing to diabetes, particularly patients with IFG, IGT, less than 60 years of age, or BMI ≥35 kg/m^2.[15] Hong Kong has pre-diabetes management guidelines aimed at the primary care sector.[16] The emphasis is mainly on lifestyle modifications using dietary or behavioral interventions to reduce and maintain body weight and practice healthy lifestyle. Pharmacologic therapy is not routinely recommended at present.[16]

The Indonesian guidebook on the management of pre-diabetes and prevention of type 2 diabetes 2009 [*Buku Panduan - Pengurus Besar Persatuan Diabetes Indonesia* (*PB Persadia*)] states that the diabetes prevention strategy should encompass a three-step process that includes identification of high-risk individuals (step 1), risk calculation, (step 2) and intervention (step 3).[17] Step 3 involves lifestyle changes, body weight management

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(reduction by 5 to 7% of baseline body weight, 0.5 to 1 kg/week), physical activity and pharmacologic intervention. The latter involves either metformin given 250 to 850 mg twice daily in individuals 60 years or younger, with BMI >25 kg/m^2 and FBS >110 mg/dL (6.1 mmol/L) if no contraindications are present; or acarbose 50 to 100 mg thrice daily.[17]

Within the region, despite the lack of formal recommendations, metformin is often used off-label for certain patient populations. For example, there are no pre-diabetes guidelines in India, but metformin is used off-label by physicians if pre-diabetes patients require pharmacotherapy. Pakistan also has no formal guidelines for pre-diabetes treatment. In view of long-standing safety information about metformin, this drug is prescribed to individuals who are noncompliant with lifestyle interventions. For other potential drugs, further long-term studies are needed on safety and vascular outcomes before lifelong treatment can be safely recommended.

CONCLUSIONS

Pre-diabetes represents a window of opportunity to prevent or delay the progression to diabetes and its associated complications, underscoring the critical need for screening at the primary care level. Lifestyle modification including weight loss, dietary changes and increased physical activity play a major role in controlling the disease. Furthermore, significant evidence support the effectiveness of combining lifestyle modification and pharmacologic therapy on certain patient populations in delaying the onset of diabetes. A cost-effectiveness analysis of lifestyle intervention and metformin therapy for the prevention of diabetes in Singapore concluded that both lifestyle modification and metformin are likely to be cost-effective and worth implementing in Singapore to prevent or delay the onset of type 2 diabetes.[35] Although the importance of lifestyle interventions is well recognized throughout Asia, many countries do not have formal recommendations to guide the diagnosis and management of individuals at risk of progression to diabetes.

Overall, these consensus recommendations provide a clear and concise approach to the management of individuals with IGT based on the available evidence and current best clinical practice. Furthermore, local applicability of these recommendations will be far-reaching, particularly in guiding action and policy for pre-diabetes and other related endocrine and metabolic disorders at the regional, national and local levels.

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ORIGINAL ARTICLE

Indicators of Accurate Health Information on the Internet on the Use of *Momordica Charantia* in Diabetes Mellitus*

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Abstract

Objectives. The increasing use of the Internet as a source of health information makes the accuracy of such information crucial. An example is the use of the widely advertised bitter melon (*Momordica charantia)* in treating diabetes despite its unproven efficacy. This study aims to assess the accuracy of websites containing information on bitter melon's role in diabetes, to search for the presence of the proposed quality indicators, and to determine their correlation with accuracy.

Methodology. An Internet search was used to generate a list of websites. The accuracy of each website was determined by comparing its content with that of a tool that was developed from authoritative sources. The presence of the proposed quality indicators, taken from published guidelines, was then correlated with accuracy.

Results. Of the 158 websites identified, 10 (6.33%) were characterized as "most accurate" and 21 (13.3%) as "somewhat accurate." The identified indicators of accuracy were the HONcode logo (OR 12.1, p=0.011); the author, identified as a healthcare professional (OR=6.11, p=0.008); and a citation from a peer-reviewed medical literature (OR 2.92, p=0.029).

Conclusion. These findings suggest that most of the Internet-based information on bitter melon's role in diabetes is inaccurate. The public can use several indicators of accurate information on the use of bitter melon in diabetes to improve health care.

Key words: internet, accuracy, diabetes, Momordica charantia

INTRODUCTION

Millions of people now use the Internet to gather medical information.[1] This can be seen as both an advantage and a concern. It is an advantage because it has become a rather easy tool for healthcare professionals and patients to acquire and share medical information. However, according to Silberg,[2] it is also a cause for concern, as when it comes to medical information, the Internet too often resembles a hodgepodge of information than a tool for effective health care communication and decision-making. The problem is not because of limited information, but rather, because it is too much, and that most of it may be inaccurate, misleading, and dangerous.[3] It has become increasingly difficult to discern which information is accurate and appropriate for users. This could potentially result in detrimental effects on those who do not use it appropriately.

There are several studies that have shown that some of the consumer health information on the Internet is inaccurate. Impicciatore and colleagues[4] looked at the accuracy of information on the treatment of fever in children and concluded that only a few of their reviewed web pages provided complete and accurate information for such a common and widely discussed condition.

Several published guidelines for evaluating the quality of health information on the Internet are available, which can help Internet users to avoid inaccurate information. [2,3-5] These guidelines usually include a list of markers, indicators or criteria that are intended to help Internet users evaluate the overall quality, and, in effect, assume the accuracy of the content of the websites. Some of the more common indicators are the following:

1. Authorship. Authors and contributors, their affiliations, and relevant credentials should be provided.
2. Attribution. References and sources for all content should be listed clearly and all relevant copyright information noted.
3. Disclosure. Website "ownership" should be prominent and disclosed, as should any sponsorship, advertising, commercial funding arrangements or support or potential conflict of interest.

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4. Currency. Dates that content was posted and updated should be indicated.
5. Contact address or feedback mechanism. Contact information or address should be provided.
6. Links. The links to other sources should be included.
7. Design, aesthetics, grammar. It should characterize quality layout, interactivity, presentation, appeal, graphics, and use of media.

In a study by Fallis et al.,[6] they tried to find out if the proposed indicators of quality from the guidelines were indeed correlated with accuracy. Using the same topic by Impicciatore and colleagues[4] on the treatment of fever in children, they found that only some of the proposed indicators were correlated with accuracy, and that many of them were not. The presence of the HONcode logo (Health on the Net code), for example, turns out to be a fairly good indicator of accurate information about the treatment of fever in children. Several proposed indicators from prior published guidelines, such as *authority* and *currency*, do not appear to be good indicators of accurate health information.

One of the crucial health information readily available on the Internet pertains to diabetes mellitus. This particular health condition continues to be an important public concern, causing substantial morbidity and mortality and long-term complications. With the increasing rates of childhood and adult obesity, diabetes is expected to become even more prevalent in the coming decades. Despite advances in diagnosis and therapy, many people with diabetes are using complementary and alternative medicine (CAM).

In the United States, CAM is frequently used by adults, with 40% reporting use in the past 12 months[7] and an estimated 34% of adults with diabetes use some type of CAM therapy[8] despite the fact that most of them have not been proven to be beneficial. In the Philippines, a study done by Dahilig and Salenga[9] showed that 68.4% of the respondents in the rural area and 51.5% in the urban areas they surveyed in selected communities in Batangas, Caloocan, and Paranaque admitted to the use of CAM for the treatment of various diseases, including diabetes. Also from that study, it was observed that bitter melon (*Momordica charantia*), or *ampalaya* in the vernacular, was one of the more commonly used herbs, amounting to up to 43.5% usage by the respondents.

Bitter melon (*Momordica charantia*), also known as bitter gourd, has been traditionally used for diabetes. Several preparations of this plant are locally available and are widely advertised. However, the clinical efficacy of bitter melon is unproven. According to the American Diabetes Association guideline,[10] there is insufficient evidence to support the use of herbs or supplements for the treatment of diabetes. Safety issues are also a concern, as adverse effects are not well documented in some studies. Because patients with diabetes often take multiple prescription medications, there exists the potential for herb-drug and herb-dietary supplement interactions, leading to adverse events.[11-12] This is particularly troublesome for the majority (63%) of the general population does not disclose the use of CAM therapies to their physicians.[13]

It is, therefore, important for the health and well-being of the consumers of health information on the Internet, and for the societies to which they belong, that they are able to distinguish accurate from inaccurate information. Reliable quality indicators can be of help in evaluating data on the Internet. In this study, the objectives were to assess the accuracy of websites that contain information on the use of bitter melon in diabetes mellitus by comparing it to an accuracy tool that was developed, to seek the presence of the proposed quality indicators, and to determine whether these indicators indeed correlate with accuracy.

METHODOLOGY

Ethical Consideration

The study was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) Panel for ethics review and approval. The study was conducted only upon approval from UPMREB Panel. There are no conflicts of interest for the conduct of this study.

I. Internet Search Protocol

Websites containing information on the use and role of bitter melon in diabetes mellitus were searched and noted. Popular internet search engines, specifically, the local versions of Google (google.com.ph) and Yahoo (ph.search.yahoo.com) were used, using the keywords "*ampalaya*" or "bitter gourd" or "bitter melon" and "diabetes." The goal was to search for health information on the Internet in a manner that might be used by a layperson who needed information on bitter melon use in diabetes.

Included websites were those that specifically provided information on the role of bitter melon in diabetes mellitus. Websites that were simply selling bitter melon products in any form and not detailing information on its role in diabetes were not included. Websites with information found in peer-reviewed medical articles or electronic article databases were excluded. Websites were limited to English and Filipino languages. An attempt was made to find as many websites on this topic as possible, but, as there can be more than 400,000 results in a single search, only the first 20 search pages of Google and Yahoo, with each search page containing 10 websites, were included. The Internet search was done on a pre-specified time period, specifically, December 22-29, 2014.

II. Measure of Accuracy

In order to determine the accuracy of the content of the websites, the information contained on the websites was compared with the recommendations of authoritative

ONLINE FIRST | April 11, 2017 | https://doi.org/10.15605/jafes.032.01.03

sources, mainly published guidelines, and review articles. In particular, the following resources were used:

1. Nutrition Therapy Recommendations for the Management of Adults With Diabetes: A Position Statement of the American Diabetes Association.[14]
2. Complementary and Alternative Medicine Therapies for Diabetes: A Clinical Review by Birdee and Yeh.[15]
3. Standards of Medical Care in Diabetes (2014) by the American Diabetes Association.[10]
4. Systematic Review of Herbs and Dietary Supplements for Glycemic Control in Diabetes, Yeh.[16]
5. Anti-diabetic and hypoglycaemic effects of Momordica charantia (bitter melon): a mini review by Leung et al.[17]

An **accuracy measure tool** was developed which consisted of several statements covering the following topics:

1. The insufficiency of evidence to support the use *Momordica charantia* in the treatment of diabetes **OR** that it has not been approved for therapeutic use for patients with diabetes
2. Potential adverse effect/s and contraindication/s to use (short and long term effects)
3. The potential for drug interactions

Among the 3 topics, the first or the statement on the evidence of bitter melon and its recommendation for use in diabetics is deemed the most important.

Two observers (DPH, RJH) independently applied this accuracy measure tool to each website and recorded the results in a spreadsheet. For each of the topics, a website received 1 point for a completely correct statement, 0.5 points if it did not mention that specific topic and 0 points for an incorrect statement on the topic. In cases of disagreement, the two observers reassessed the information on the website to reach a consensus.

An overall accuracy score (between 0 and 3) was computed for each website by adding the scores on the individual statements or questions. This overall accuracy score takes into account both the correctness and the completeness of the information. Websites with the perfect score of 3 are deemed the "most accurate." As mentioned above, the topic on the evidence/recommendation for use of bitter melon in diabetes is deemed the most important among the three topics, and as such, those websites that have at least a correct statement on that specific topic even though they did not get all three statements correct are deemed "somewhat accurate." Those websites that did not give a correct statement on the first topic were deemed "least accurate."

Accuracy, which is commonly used in diagnostics testing, is defined as the extent to which a measurement reflects the true value. For this study, this particular technique for assigning an overall accuracy score to a website was based on a previous study by Fallis et al.,[6] and was modified to reflect the importance of the recommendation for use of bitter melon in diabetes over the other topics.

III. Measure of the Proposed Indicators of Quality

In addition to measuring the accuracy of the websites, the presence of the proposed quality indicators was determined. Several proposed indicators of quality were taken from published guidelines for evaluating the quality of health information on the internet.[2-3,5] For each website, each proposed indicator below would be determined if it is present or absent.

- Whether the website had a commercial domain (e.g., webmd.com), an organization domain (e.g., bitter-gourd.org), an education domain (e.g., med.nyu.edu), and a government or country domain (e.g., ampalaya.ph)
- Whether the website was up to date
- Whether the website displayed the HON code logo – a code of ethical conduct for medical and health-related information available on the internet established by the Health On the Net (HON) Foundation
- Whether the website carried any advertising
- Whether the author was identified (and if so, whether the author was identified as a healthcare professional – a licensed physician, nurse, or a dietitian)
- Whether copyright was claimed or acknowledged
- Whether contact information or contact page was given
- Whether spelling errors appeared on the page (and, if so, how many)
- Whether peer-reviewed medical literature was cited

IV. Data Analysis: Correlation of the Proposed Indicators and Accuracy

Data analysis was done using Stata SE Version 13. Quantitative variables were summarized and presented as the mean and standard deviation, while qualitative variables were tabulated and presented as frequency and percent distribution. Indicators associated with the "most accurate," "somewhat accurate," and "least accurate" websites were determined using logistic regression analysis. The level of significance was set at 5%.

RESULTS

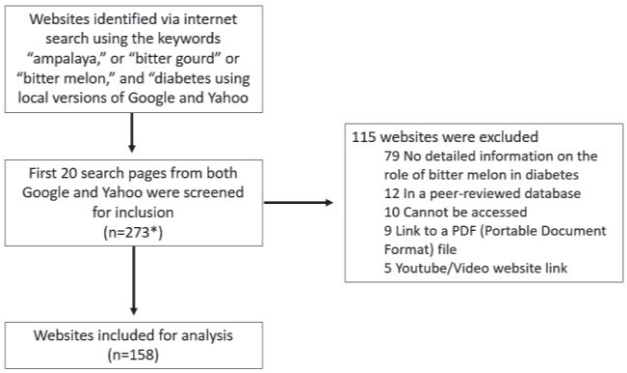
Out of the first 20 search pages for both Google and Yahoo search, 158 websites were included in the study (see Figure 1). Table 1 describes the profile of the websites based on the presence of the proposed quality indicators.

Most of the current internet-based information on bitter melon's role in diabetes is inaccurate as only 10 websites (6.33%) got an overall perfect score of 3, and thus, were deemed the "most accurate" and complete (Table 2). Logistic regression analysis showed that only the indicator *HONcode logo* (OR 12.1, p=0.01) was significantly correlated with having a perfect score of 3.

Out of the 158 websites, only 21 (13.3%) at least gave a correct statement on the evidence/recommendation for use of bitter melon, (the most important among the 3

ONLINE FIRST | April 11, 2017 | https://doi.org/10.15605/jafes.032.01.03

topics) and were deemed the "somewhat accurate" websites. Indicators, namely the *author identified as a healthcare professional* (OR 6.11, p=0.008) and the *cited peer-reviewed medical literature* (OR 2.92, p=0.029), were significantly correlated with at least giving the correct statement on the evidence/recommendation for use of bitter melon (Table 3). In contrast, the indicator *no date given* (OR 0.28, p 0.031) had a low probability of being accurate with regard to the above statement (Table 3).



*Websites found in both Google and Yahoo searches were counted as one website.

Figure 1. Diagram showing how the websites were identified and screened for inclusion.

Table 1. Profile of websites based on the presence of the proposed quality indicators

Characteristic (n=158)		n (%)
A.	Domain	
	Commercial	139 (87.97)
	Organization	12 (7.59)
	Education	3 (1.90)
	Government or Country	4 (2.53)
B.	Currency	
	More than 3 yr. old	28 (17.72)
	3 yr. old or less	48 (30.38)
	No date given	82 (51.90)
C.	HONcode logo displayed	5 (3.16)
D.	Advertising displayed	111 (70.25)
E.	Authorship	
	Author identified as a healthcare professional	12 (7.59)
	Author not identified as a healthcare professional	60 (37.97)
	No author identified	86 (54.43)
F.	Copyright claimed or acknowledged	119 (75.32)
G.	Contact information or with contact page provided	115 (72.78)
H.	With spelling errors	40 (25.32)
I.	Peer-reviewed medical literature cited	37 (23.42)

Out of the 158 websites, 103 (65.2%) gave an incorrect statement on the evidence/recommendation for use of bitter melon and were deemed the "least accurate" websites. No indicator was noted to have the likelihood that the website would give an incorrect statement on the evidence/recommendation for use of bitter melon (Table 4).

DISCUSSION

Most of the information on bitter melon use in diabetes mellitus in the internet appeared to be inaccurate based on the accuracy measure that was developed, as only 21 (13.3%) websites stated the correct evidence or recommendation for its use, and fewer still, only 10 (6.33%) gave a more complete and accurate information. This was consistent with the findings of Molassiotis and Xu[18] about the quality of web-based information about herbal medicines, but this time, in the treatment of cancer, which showed that most sites were of low quality in several factors, including the accuracy of information.

The only indicator that was identified which correlated with the "most accurate" and complete websites was the presence of the HONcode logo (Table 2). It seemed that the quality-control checks required for certification by the **H**ealth **O**n the **N**et (HON) Foundation's Code of Conduct tend to result in giving out more accurate and complete health information. This is in accord with the conclusion of a study done by Fallis[6] using a different health topic. In a study on the health information on hip resurfacing, it was noted that websites with the HONcode logo scored twice the total scores of those websites without it. The authors advocated that the patients should look for the presence of an "independent credibility check" such as the HONcode when searching for information on hip resurfacing.[19] Thus, the presence of the HONcode logo seemed to be a proven indicator of accurate health information. The Health on the Net (HON) Foundation has also made it easier for the public to look for HON-accredited websites by creating a search engine, the HONcodeHunt (http://www.hon.ch/HONsearch/Patients/hunt.html) to search for HONcode-accredited websites, and the HON toolbar that users can install in their internet browsers (IE and Firefox) to

Table 2. Indicators of websites that were deemed as "most accurate" (Score of 3/3)

Proposed Quality Indicator		Perfect score (n=10)	Score <3 (n=148)	Odds Ratio	p value
A.	Domain				
	Commercial	8 (80.00)	131 (88.51)	-	
	Organization	1 (10.00)	11 (7.35)	1.49	0.71
	Education	1 (10.00)	2 (1.35)	8.19	0.10
	Government or Country	0 (0)	4 (2.70)	1	
B.	Currency				
	More than 3 yr. old	2 (20.00)	26 (17.57)	-	
	3 yr. old or less	4 (40.00)	44 (29.73)	1.18	0.85
	No date given	4 (40.00)	78 (52.70)	0.67	0.65
C.	***HONcode logo displayed***	2 (20.00)	3 (2.03)	***12.08***	***0.011***
D.	Advertising displayed	7 (70.00)	104 (70.27)	0.99	0.99
E.	Authorship				
	Author identified as a healthcare professional	2 (20.00)	10 (6.76)	2.67	0.27
	Author not identified as a healthcare professional	2 (20.00)	58 (39.19)	0.46	0.35
	No author identified	6 (60.00)	80 (54.05)	-	
F.	Copyright claimed or acknowledged	10 (100.00)	109 (73.65)	1	
G.	Contact information provided or with contact page	10 (100.00)	105 (70.95)	1	
H.	With spelling errors	1 (10.00)	39 (26.35)	0.31	0.28
I.	Peer-reviewed medical literature cited	5 (50.00)	32 (21.62)	3.62	0.05

ONLINE FIRST | April 11, 2017 | https://doi.org/10.15605/jafes.032.01.03

Table 3. Indicators of websites that has at least an accurate statement on the evidence/recommendation for use of bitter melon ("somewhat accurate" websites)

Proposed Quality Indicator		Correct in Topic 1 (n=21)	Incorrect or has no mention of it (n=137)	Odds Ratio	p value
A.	Domain				
	Commercial	18 (85.71)	121 (88.32)	-	
	Organization	2 (9.52)	10 (7.30)	1.34	0.72
	Education	1 (4.76)	2 (1.46)	3.36	0.33
	Government or Country	0 (0.00)	4 (2.92)	1	
B.	Currency				
	More than 3 yr. old	7 (33.33)	21 (15.33)	-	
	3 yr. old or less	7 (33.33)	41 (29.93)	0.51	0.26
	No date given	7 (36.33)	75 (54.74)	***0.28***	***0.031***
C.	HONcode logo displayed	2 (9.52)	3 (2.19)	4.70	0.10
D.	Advertising displayed	14 (66.67)	97 (70.80)	0.82	0.70
E.	Authorship				
	Author identified as a healthcare professional	5 (23.81)	7 (5.11)	***6.11***	***0.008***
	Author not identified as healthcare professional	7 (33.33)	53 (38.69)	1.13	0.82
	No author identified	9 (42.86)	77 (56.20)	-	
F.	Copyright claimed or acknowledged	16 (76.19)	103 (75.18)	1.06	0.92
G.	Contact information or with contact page provided	17 (80.95)	98 (71.53)	1.69	0.37
H.	With spelling errors	5 (23.81)	35 (25.55)	0.91	0.87
I.	Peer-reviewed medical literature cited	9 (42.86)	28 (20.44)	***2.92***	***0.029***

Table 4. Indicators of websites that had an *inaccurate* statement on evidence/recommendation for use of bitter melon ("least accurate" websites)

Proposed Quality Indicator		Incorrect in topic 1 (n=103)	Correct or has no mention of it in topic 1 (n=55)	Odds Ratio	p value
A.	Domain				
	Commercial	94 (91.26)	45 (81.82)	-	
	Organization	5 (4.85)	7 (12.73)	0.34	0.08
	Education	1 (0.97)	2 (3.64)	0.29	0.25
	Government or Country	3 (2.91)	1 (1.82)	1.43	0.76
B.	Currency				
	More than 3 yr. old	18 (17.48)	10 (18.18)	-	
	3 yr. old or less	31 (30.10)	17 (30.91)	1.01	0.98
	No date given	54 (52.43)	28 (50.91)	1.07	0.88
C.	HONcode logo displayed	0 (0)	5 (9.09)	1	
D.	Advertising displayed	70 (67.69)	41 (74.55)	0.72	0.39
E.	Authorship				
	Author identified as a healthcare professional	2 (1.94)	10 (18.18)	0.08	0.003
	Author not identified as healthcare professional	41 (39.81)	19 (34.55)	0.93	0.85
	No author identified	60 (58.25)	26 (47.27)	-	
F.	Copyright claimed or acknowledged	78 (75.73)	41 (74.55)	1.06	0.87
G.	Contact information provided or with contact page	71 (68.93)	44 (80.00)	0.55	0.14
H.	With spelling errors	27 (26.21)	13 (23.64)	1.15	0.72
I.	Peer-reviewed medical literature cited	16 (15.53)	21 (38.18)	0.30	0.002

automatically check the certification of the website being viewed. One foremost limitation of the HONcode is that it is not commonly seen in the websites that were included in this study, as it is only present in 5 (3.2%) of the 158 websites. Also, only about 5% of consumers would recognize the HONcode logo and know what it means,[20], which may greatly limit its value.

Focusing only on the websites that at least gave the correct statement on the recommendation for use of bitter melon in diabetes and that were deemed "somewhat accurate," two indicators – the *author identified as a healthcare professional*, and the *presence of citation of a peer-reviewed medical literature* – were correlated with being accurate (Table 3). Because the HONcode logo is infrequently seen, these two indicators may be the next best option for the public to use. It should be noted these two indicators were not seen to be consistent predictors of accuracy in a previous study[6] unlike the HONcode logo, which was correlated with accuracy in previous studies, and thus, may be seen as a less robust indicator of accuracy. It seems that some indicators that were previously not correlated with accuracy do not guarantee that it will always remain that way. Also, identifying that a citation correctly comes from a peer-reviewed medical literature database may be challenging for the general public to do so to be truly useful.

The above-mentioned indicators of accuracy can be helpful in evaluating health information about bitter melon's role in diabetes on the Internet, especially for the lay people. However, it should be noted that the presence of these indicators on a website does not guarantee that it contains accurate information because the relationship between these indicators and accuracy is probabilistic. Although the HONcode logo was significantly correlated with the "most accurate" websites, its presence on a website does not guarantee that it would have accurate information all the time, as was explicitly mentioned on its homepage[21] – it just would have a higher probability that its content would be accurate.

A major limitation of this study is that only the websites from the first 20 search pages from both Yahoo and Google were included out of the possible hundreds of thousands of websites. An automated Internet tool is ideal and should be developed to facilitate reviewing this large number of websites faster.

ONLINE FIRST | April 11, 2017 | https://doi.org/10.15605/jafes.032.01.03

CONCLUSION

With increased use of the Internet for health information nowadays, it is important that lay people be able to distinguish accurate information from inaccurate ones. Most of the information on the use of bitter melon in diabetes mellitus on the Internet is inaccurate and misleading. This can be potentially hazardous to the general public. Reliable indicators of accuracy can be of help to them. This study has identified that the presence of the HONcode logo is a good indicator of the "most accurate" websites. Other indicators that can be used, at least to predict the accurate statement on the evidence or recommendation for use of bitter melon, include that the author is identified as a healthcare professional and that there is the presence of citation of a peer-reviewed medical literature. The absence of the date when the article was posted or updated seems to give a low probability of being accurate.

Future research can be done to include a wider range of health topics to see if these indicators of accuracy hold true to them and not just on this specific topic on bitter melon use on diabetics. It will also serve to monitor if a specific indicator continues to be correlated with accuracy and thus a relevant tool that the public can use.

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ORIGINAL ARTICLE

Efficacy of Heparinoid Supplementation on Mortality and Disease Progression in Adults with Diabetic Kidney Disease*

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Abstract

Objective. To evaluate the safety and efficacy of heparinoid supplementation on all-cause mortality and disease progression in diabetic kidney disease (DKD).

Methodology. Trials evaluating heparinoid supplementation in DKD were included. Two authors performed a literature search with eligible studies undergoing validity screen, data extraction, and statistical analysis. Results were calculated using the Mantel-Haenszel odds ratio for dichotomous variables and the inverse variance method for continuous variables, and pooled using a random or fixed effects model depending on heterogeneity.

Results. Twelve trials were included in the analysis. Eight involved sulodexide while two each involved low molecular weight heparin and danaparoid. We found no statistically significant difference between the heparinoid and placebo groups for all-cause mortality (95% CI, HR 0.79 [0.41, 1.53], p=0.49), number of patients reaching therapeutic success (95% CI, OR 0.97 [0.71, 1.33], p=0.87), serum creatinine (95% CI, MD 2.55 umol/L [-0.54, 5.65], p=0.11), and creatinine clearance (95% CI, MD -8.55 mg/min [-18.28, 1.18], p=0.09). We also found no statistically significant difference in urinary albumin excretion rate (UAER) between Type 2 heparinoid-treated DKD patients compared to placebo (95% CI, log transformed MD 0.13 mg/24h [-0.42, 0.68], p=0.65); however, a statistically significant UAER reduction was seen in Type 1 heparinoid-treated DKD patients compared to placebo (95% CI, log-transformed MD -1.5 mg/24h [-2.79, -0.21], p=0.02). This subgroup analysis was performed due to initial heterogeneity (I^2=57%).

Conclusion. Heparinoid supplementation was not associated with statistically significant changes in Type 2 DM patients. However, it may be associated with a statistically significant UAER reduction of approximately 31.62 mg/24 h as compared to placebo in Type 1 DM patients. Due to sparse data on hard clinical outcomes, larger studies are recommended.

Key words: diabetes mellitus, diabetic nephropathy, heparinoid, meta-analysis

INTRODUCTION

Diabetic kidney disease (DKD), or diabetic nephropathy (DN), is a major microvascular complication of diabetes mellitus (DM) and is now the leading cause of end-stage renal disease (ESRD) worldwide.[1] It affects 30-40% of Type 1 DM patients, usually 20-25 years after disease onset, as well as an approximate number of Type 2 DM patients after a variable number of years.[2] The pathogenesis and clinical stages of DKD appear to be similar for both types of DM.[3] Kidney damage initially manifests with renal hypertrophy and hyperfiltration, eventually progressing to microalbuminuria with increased urinary albumin excretion rates (UAER) of 30-300 mg/day. Microalbuminuria is the earliest clinically detectable stage of DKD at which appropriate intervention can delay or reverse the disease process.[4] Without proper intervention, 20-40% of microalbuminuric patients progress to macroalbuminuria with UAER exceeding 300 mg/day; of these, 20% eventually reach ESRD in their lifetime.[1] As both micro- and macroalbuminuria are powerful risk factors for cardiovascular disease – another leading cause of mortality and morbidity in DM – the importance of intensive efforts to prevent and treat DKD is justified.[5]

Primary prevention of DKD is attained in patients with normal kidney function through strict glycemic and blood pressure (BP) control, preferably employing renin-angiotensin-aldosterone system (RAAS) modulating drugs such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB). Secondary prevention, on the other hand, aims to retard the progression from micro- to macroalbuminuria and likewise requires ACEI or ARB to achieve BP targets.[6] However, with worsening DKD, the efficacy of these interventions becomes less than optimal, often necessitating additional therapies to delay the progression of renal disease.[7]

The typical pathological changes in DKD involve glomerular basement membrane (GBM) thickening and

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mesangial expansion and proliferation, leading to nodular glomerulosclerosis and the formation of Kimmelstiel-Wilson lesions. Glycosaminoglycan (GAG) moieties – of which heparan sulfate is the most abundant – are also decreased in the diabetic GBM in proportion to the degree of proteinuria, mainly due to abnormalities in synthesis, sulfation, composition, and matrix interactions.[8] This explains the potential use of heparin derivatives, or heparinoids, as potentially useful anti-proteinuric drugs that could supplement RAAS modulating-treatment. They include sulodexide, an oral heparinoid with high concentrations in the renal parenchyma; conventional and low molecular weight heparin (LMWH); factor Xa-inhibitors such as danaparoid and fondaparinux; and animal-derived sources such as chondroitin, keratan, and dermatan sulfate.[9] Proposed mechanisms include restoration of GBM ionic permselectivity, prevention of GAG degradation, suppression of albuminuria-induced and endothelin-mediated inflammation, and inhibition of apoptosis in glomerular cells.[10,11]

In streptozotocin-induced diabetic rats, sulodexide effectively lowered UAER, improved renal ultrastructure, and prevented GBM thickening, in addition to exerting direct endothelial protective effects.[12] In humans, the results were more equivocal. Some trials demonstrated reductions in UAER and serum creatinine (SCr) levels in sulodexide-treated groups, as well as improvements in HbA1c, BP, and lipid profile.[13-17] Other studies, however, failed to demonstrate renoprotective benefits, particularly in terms of the patient number achieving significant reduction or normalization of the urine albumin-creatinine ratio (ACR).[18,19] Similarly, for other heparinoids, small trials showed conflicting data. Reductions in UAER were seen with enoxaparin but not with tinzaparin; for danaparoid, reductions occurred with Type 1 but not with Type 2 DM patients.[8,20-22] Thus, the exact role of heparinoid supplementation in DKD remains unknown and these substances are not part of treatment recommendations. This study attempts to consolidate available information and evaluate their safety and efficacy in DKD patients.

METHODOLOGY

Search Strategy

Electronic databases including MEDLINE, Embase, Scopus, Herdin, ClinicalTrials.gov, Google Scholar, and the Cochrane Central Register of Controlled Trials were systematically searched by two independent investigators for eligible articles. For the intervention of interest, the following terms were used individually and in combination: "sulodexide," "Vessel Due-F," mucopolysaccharide,* proteoglycan,* syndecan,* galactosaminoglycan,* glycosaminoglycan,* glycoamin,* chondroitin,* keratin,* dermatan,* heparinoid,* heparin,* heparin,* hyaluron,* "low molecular weight heparin," "LMWH," ardeparin,* "Normiflo," bemiparin,* "Hibor," certoparin,* Sandoparin,* dalteparin,* enoxaparin,* "Clexane," nadroparin,* Fraxiparin,* Seleparin,* parnaparin,* "Fluxum," reviparin,* tedegliparin,* tedelparin,* tinzaparin,* "Innohep," "danaparoid," "fondaparinux," "Arixtra," "idraparinux". For the disease of interest, the following search terms were used: diabetes,* diabetic,* "DM," "IDDM," "NIDDM," kidney,* renal,* nephro,* nephriti,* glomerulo.* These key terms were utilized as text words, Medical Subject Headings (MeSH), and Clinical Queries. Cross-references of original publications, books of abstracts, and conference proceedings from the WHO Network of Collaborating Clinical Trial Registers, US FDA registry, and International Committee of Medical Journal Editors (ICMJE) were searched as well. Manufacturers were also contacted for possible unpublished studies.

Study Selection

Trials involving heparinoid supplementation to delay or prevent the progression of DKD were included. We included patients ≥18 years old, diagnosed with either Type 1 or Type 2 DM according to the American Diabetes Association 1997 criteria [fasting plasma glucose (FBS) ≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL after an oral glucose tolerance test], having either microalbuminuria (UAER 30-300 mg/day) or macroalbuminuria (UAER >300 mg/day). Those diagnosed with other forms of DM (i.e. gestational DM) and having contraindications to heparinoid use (i.e., pregnancy, deranged clotting parameters, bleeding diathesis, or thrombocytopenia) were excluded. There were no restrictions on ethnicity, language, or gender. Studies must utilize a heparinoid as the primary intervention, regardless of dosage, mode of administration, or duration of treatment, and on top of standard DKD therapy in terms of glycemic control and use of either an ACEI or ARB. The primary outcome measure is all-cause mortality rate. Secondary outcomes include parameters of disease progression such as changes in UAER, ACR, SCr, or creatinine clearance (CrCl), changes in patient number with reductions in the above parameters, rates of hospitalization or dialysis, time to ESRD, and changes in health-related quality of life.

Data Extraction and Management

Two authors independently screened the eligibility of studies. Studies agreed upon for exclusion by both reviewers were excluded at this stage, with the reason for exclusion documented. Eligible studies then underwent methodological quality assessment based on the Cochrane Collaboration's tool for assessing risk of bias. Any disagreements were resolved by a third author. Studies that passed all screenings underwent data extraction using a customized data extraction form. The following data were extracted from each of the included trials: author, year of publication, location of study, duration of study, intervention, comparator, sample size and type of population, and study outcomes.

ONLINE FIRST | April 11, 2017 | https://doi.org/10.15605/jafes.032.01.04

Table 1. Characteristics of the studies included in the review

Study	Duration	Sample Size	Population	Outcome of Interest	Intervention	Comparator
Dedov 1997[14]	6 weeks	36	T1DM with micro- or macroalbuminuria	UAER, CrCl	Sulodexide 60mg/d, 5 days/wk	Placebo
Solini 1997[17]	4 months	12	T2DM with micro- or macroalbuminuria	UAER, SCr	Sulodexide 100mg/d	Placebo
Gambaro 2002[15]	4 months	223	T1 or T2DM with micro- or macroalbuminuria	UAER	Sulodexide 50,100,200 mg/d	Placebo
Achour 2005[13]	12 months	60	T1 or T2DM with micro- or macroalbuminuria	UAER, SCr	Sulodexide 50mg/d	Placebo
Sulikowska 2006[16]	120 days	45	T1DM with micro- or macroalbuminuria	UAER, SCr	Sulodexide 100mg/d	Placebo
Heerspink 2008[23]	24 weeks	130	T1 or T2DM with microalbuminuria	Proportion who achieved ACR <20 mg/g and 25% drop from baseline OR 50% drop from baseline	Sulodexide 200,400 mg/d	Placebo
Lewis 2011[18]	34 weeks	1056	T2DM with microalbuminuria	Proportion who achieved ACR <20 mg/g and 25% drop from baseline OR 50% drop from baseline; % change in ACR from baseline; % patients who progress to overt DKD	Sulodexide 200 mg/d	Placebo
Packham 2012[19]	18 months	1248	T2DM with macroalbuminuria	All-cause mortality; first CV fatal or non-fatal event; Time to composite end point of doubling SCr, development of ESRD, or SCr≥ 6mg/dl	Sulodexide 200 mg/d	Placebo
Tamsma 1996[21]	1 month	6	T1DM with macroalbuminuria	UAER, CrCl	Enoxaparin 4000 U/d	Placebo
Nielsen 1999[22]	3 weeks	44	T2DM with microalbuminuria	SCr	Tinzaparin 50 IU/kg/d	Placebo
Van der Pijl 1997[8]	6 weeks	9	T1DM with macroalbuminuria	UAER, CrCl	Danaparoid 750 IU/d	Placebo
Van der Pijl 1999[20]	8 weeks	23	T2DM with macroalbuminuria	UAER, CrCl	Danaparoid 750 IU/d	Placebo

Table 2. List of excluded studies and reasons for exclusion

Study	Reason for exclusion
Perusicova 1997; Poplawska 1997; Shestakova 1997; Skrha 1997 and 1998; Sorrenti 1997; Szelachowska 1997; Rasovskii 1998; Zalevskaia 1998; Oksa 1999; Blouza 2010; Zilisteanu 2015	No active comparator
Myrup 1997; Velussi 1997	No data on outcomes of interest
Weiss 1997; Gambaro 2000; Gaddi 2010	Review article
Leu 1998; Li 2010; Satirapoj 2015	Different disease population
Benck 2007	Different intervention
House 2011	Editorial

Statistical Analysis

The study was analyzed using Review Manager, version 5.1. Results were presented as mean differences (MD) and standard deviations (SD) with 95% confidence intervals, and graphically presented as forest plots. Estimates were calculated using the Mantel-Haenszel odds ratio for dichotomous variables and the inverse variance method for continuous variables. These were pooled using either the fixed or random effects model depending on heterogeneity (defined as I^2>50%). Heterogeneity, if present, was further explored using both sensitivity and subgroup analysis. For studies with multiple follow-up periods, data at the end of treatment or at maximum follow-up period were used. Unit of analysis issues were resolved by looking for uniformity among the analyses of the individual studies.

RESULTS

Search Results

Thirty-four potentially relevant articles were retrieved. On initial deliberation, only thirty were eligible for inclusion; the other four were excluded because they were either editorials or review articles. Of the thirty screened-in articles, eighteen were further excluded because they either had no active comparator or had different interventions, disease populations or outcome measures. Twelve studies ultimately satisfied the selection criteria. Figure 1 shows the study selection flowchart, while Tables 1 and 2 show the list of included and excluded studies, respectively.

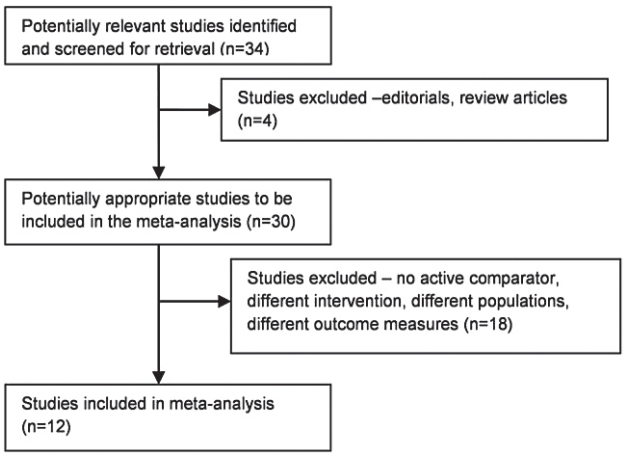

Figure 1. Flowchart of the process of retrieval and selection of studies for the meta-analysis.

Study Characteristics

The twelve included studies were all published from 1996-2012 and totaled 2,892 patients. Most were conducted in Europe, with only three studies having participants outside of the region (Australia, New Zealand, Canada, USA, and

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Table 3. Risk of bias assessment

Study/Year	Randomization	Allocation Concealment	Baseline Characteristics	Blinding	Adequacy of Follow-up
Dedov 1997	Yes	Unclear	Yes	No	Yes
Solini 1997	Yes	Unclear	Yes	Yes	Yes
Gambaro 2002	Yes	Yes	Yes	Yes	Yes
Achour 2005	Yes	Unclear	Yes	No	Yes
Sulikowska 2006	Yes	Unclear	Yes	No	Yes
Heerspink 2008	Yes	Yes	Yes	Yes	Yes
Lewis 2011	Yes	Unclear	Yes	Yes	Yes
Packham 2012	Yes	Unclear	Yes	Yes	Yes
Tamsma 1996	Yes	Unclear	Yes	Yes	Yes
Van der Pijl 1997	Yes	Unclear	Yes	Yes	Yes
Van der Pijl 1999	Yes	Unclear	Yes	Yes	Yes
Nielsen 1999	Yes	Unclear	Yes	Yes	Yes

Israel). Four studies dealt with Type 1 DM while five dealt with Type 2 DM; the remaining three included both types of patients. In terms of albuminuria, three studies involved microalbuminuria while four involved macroalbuminuria; the remaining five studies involved both stages of DKD. Eight had sulodexide as the main intervention with doses ranging from 50-400 mg/day (Gambaro et al., used three different doses while Heerspink et al., used two different doses) while two each had LMWH (enoxaparin and tinzaparin) and danaparoid as primary therapies. Treatment duration ranged from three weeks to 18 months and all studies had placebo as the comparator. Only one study evaluated all-cause mortality rate; the rest mostly evaluated changes in UAER and either SCr or CrCl, with additional endpoints being HbA1c, BP, and lipid levels, as well as titers of clotting parameters such as fibrinogen, von Willebrand factor, and antithrombin III. With regards to methodological quality, all studies were sufficiently randomized with adequate follow up rates. The baseline characteristics of the groups being compared also yielded no significant differences. Three studies were open-label while the rest were double-blind. However, allocation concealment was unclear in most of the studies; hence the overall methodological quality of the trials is at most moderate. Table 3 summarizes the risk of bias assessment for the included studies.

Data Synthesis

Effects of Heparinoid Supplementation on All-Cause Mortality

Only the study by Packham et al., evaluated all-cause mortality rate, which was not statistically significant between the sulodexide and placebo groups (95% CI, HR 0.79 [0.41, 1.53], p=0.49). The same study also found no statistically significant difference in the first cardiovascular fatal or non-fatal event between the two groups (95% CI, HR 1.12 [0.82, 1.54], p=0.48).[19]

Effects of Heparinoid Supplementation on Albuminuria

Five studies reported changes in UAER.[13,15-17,21] One used enoxaparin while the remaining four involved sulodexide. Gambaro et al., utilized three different sulodexide doses and was treated as three separate treatment arms (a, b, c). The analysis was carried out using the inverse variance method on log-transformed UAER values due to the skewed distribution of the sample. On initial analysis, no statistically significant difference (95% CI, log-transformed MD -0.78 mg/24h [-1.76, 0.21], p=0.12) was found between the heparinoid and placebo groups (Figure 2). Significant heterogeneity (I^2=57%) was present, hence the random effects model was used. To investigate the source of heterogeneity, sensitivity analysis was first performed

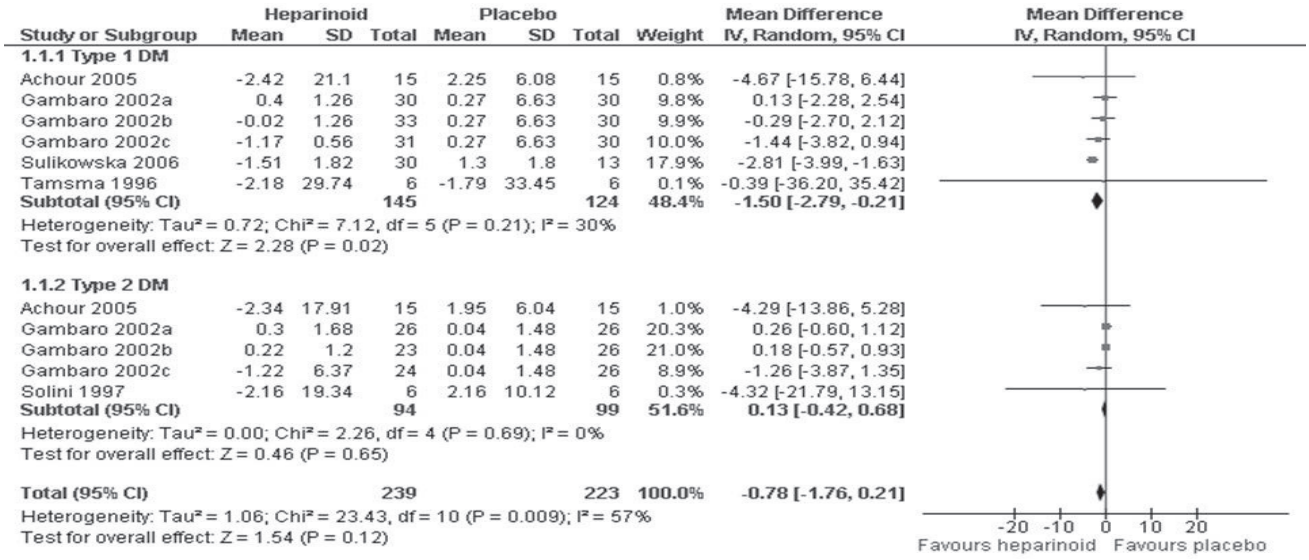

Figure 2. Log-transformed mean difference in urinary albumin excretion rates (mg/24 hours) between the heparinoid and placebo groups according to DM type.

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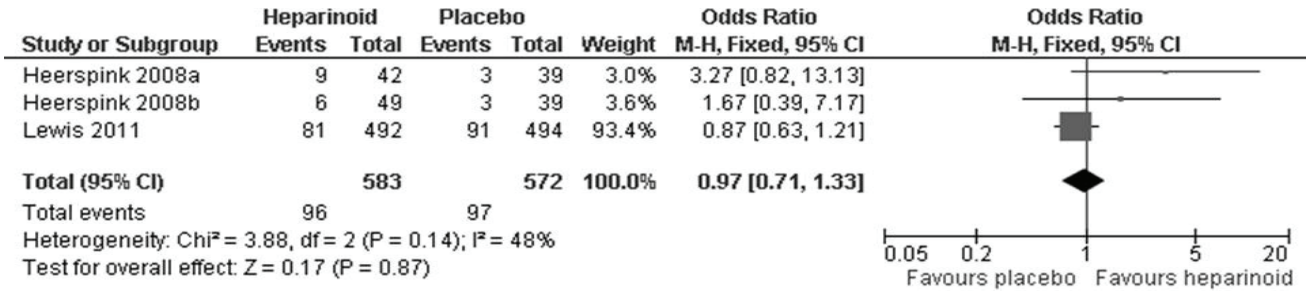

Figure 3. Mean difference in the proportion of patients attaining therapeutic success between the heparinoid and placebo groups.

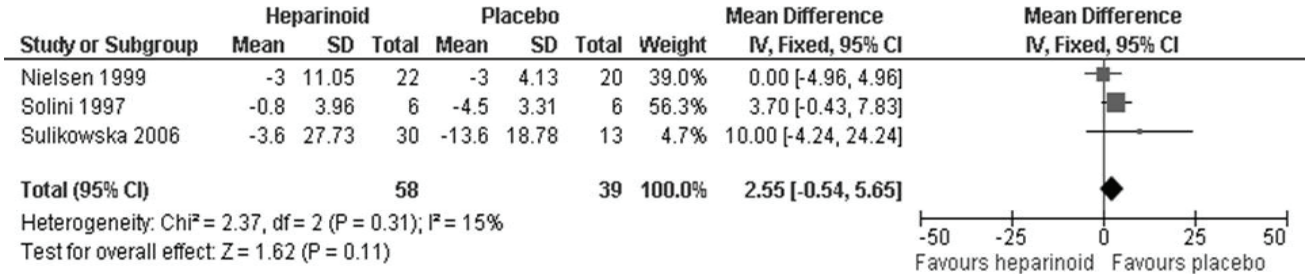

Figure 4. Mean difference in serum creatinine (umol/L) between the heparinoid and placebo groups.

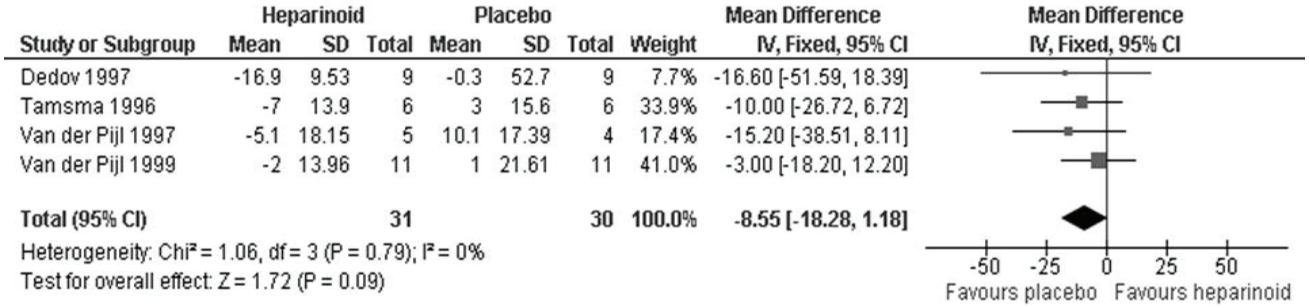

Figure 5. Mean difference in creatinine clearance (mg/min) between the heparinoid and placebo groups.

by removing one study at a time, starting with the studies that had the highest potential risk for bias. We subsequently found no significant changes in the values of the pooled log-transformed MD, indicating the quality of the studies to be satisfactory. Post-hoc subgroup analysis was then performed according to type of DM. This time, acceptable homogeneity was seen for both subgroups (I^2=30% and I^2=0% for Type 1 and Type 2 DM, respectively). Moreover, a statistically significant decrease in UAER was found in the heparinoid group for Type 1 (95% CI, log-transformed MD -1.5 mg/24h [-2.79, -0.21], p=0.02) but not Type 2 DM (95% CI, log-transformed MD 0.13 mg/24h [-0.42, 0.68], p=0.65).

Two trials also looked at the number of patients reaching therapeutic success, which we defined as either (1) an ACR <20 mg/g and at least a 25% drop from baseline; or (2) at least a 50% drop from baseline. This was similar to the criteria set in previous studies.[18,23] Heerspink et al., utilized two different sulodexide doses and was treated as two separate treatment arms (a, b). For this analysis, the Mantel-Haenszel odds ratio was used since the variable was dichotomous. We found no statistically significant difference (95% CI, OR 0.97 [0.71, 1.33], p=0.87) in the patient number achieving therapeutic success between the heparinoid and placebo groups (Figure 3). We used the fixed-effects model since I^2 <50%.

Effect of Heparinoid Supplementation on Azotemia

Eight studies evaluated heparinoid effects on azotemia.[8,14-17,19-22] Three expressed the results in terms of SCr (Figure 4) while four expressed the results in terms of CrCl (Figure 5). The inverse variance method was used since the variables were continuous. We found no statistically significant difference in both SCr (95% CI, MD 2.55 umol/L [-0.54, 5.65], p=0.11) and CrCl (95% CI, MD -8.55 mg/min [-18.28, 1.18], p=0.09) between the heparinoid and placebo groups. The fixed effects model was used as no significant heterogeneity was seen for both SCr (I^2=15%) and CrCl (I^2=0%) analyses. The study by Packham et al., meanwhile, looked at a composite endpoint of SCr doubling, development of ESRD, or SCr ≥6 mg/dL and also did not find a statistically significant difference between the two groups (95% CI, HR 0.85 [0.50, 1.44], p=0.54).[19]

Adverse Effects

Nine studies briefly reported adverse events.[8,13,15,18,19-23] The incidence of likely study-related side effects was similar

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between the heparinoid (10.9% to 13%) and placebo (12.2% to 17.58%) groups. For the sulodexide studies, these included skin rash, nonspecific muscle aches, epigastric pain, diarrhea and a slight increase in liver function tests. For the LMWH and danaparoid studies, the most common complaint was a small, transient hematoma at the injection site. There were no significant changes in the levels of hemostatic variables and clotting parameters. Likewise, on ophthalmic evaluation, no progression of retinopathy or new onset hemorrhages were seen. Most importantly, no serious adverse event (SAE) was reported by any of the investigators as being possibly related to the study drug.

DISCUSSION

This review summarized the current available data on the efficacy of heparinoid supplementation in DKD patients. Compared to placebo, heparinoid-treated Type 1 DM patients experienced a statistically significant log-transformed MD of 1.5 mg/24h (or a raw MD of 31.62 mg/24h, p=0.02) in UAER. Given that the threshold of albuminuria is >30 mg/24h, this may be clinically significant. However, it is equally important to remember that the log-transformed lower limit of 0.21 mg/24h translates to a raw MD of only 1.62 mg/24h, which is clinically insignificant.

For heparinoid-treated Type 2 DM patients, we found a negligible log-transformed MD of 0.13 mg/24h (or a raw MD of 1.35 mg/24h, p=0.65) compared to placebo. While the result for Type 1 DM may affirm the renoprotective mechanisms of heparinoids, the lack of response for Type 2 DM supports the view of some articles that the nephropathy for both DM types may not be totally similar as was previously assumed. Micro- or macroalbuminuria may already be present when Type 2 DM is diagnosed, reflecting its long asymptomatic period; furthermore, hypertension more commonly accompanies DKD in Type 2 DM. Studies have also shown that glomerular changes are less pronounced in Type 2 DM, hence microalbuminuria may be less predictive of macroalbuminuria and progression to ESRD in these patients. Finally, it should be noted that the albuminuria in Type 2 DM may be secondary to other comorbidities including congestive heart failure, prostate disease, or concurrent infections. These different factors result in a heterogeneous pattern of renal disease and may explain the lesser predictability of response to therapy in Type 2 DM.[24]

For the number of patients reaching therapeutic success, the Mantel-Haenszel OR of 0.97 (p=0.87) implied no statistically significant difference between the two arms of the study, although this analysis was limited only to two studies on sulodexide. The reasons cited by these studies include the complex manufacturing requirements for sulodexide and the fact that having patients on preexisting maximal doses of an ACEI or ARB left little room for a significant superimposed heparinoid effect.[18,23]

Also, we did not find statistically significant differences in all-cause mortality (HR 0.79, p=0.49) as well as in both SCr (MD 2.55 umol/L, p=0.11) and CrCl (MD -8.55 mg/min, p=0.09) between the heparinoid and placebo groups. This is consistent with data showing that the hypoalbuminuric effect of heparinoids appeared to be independent of any detectable variation in renal hemodynamics as reflected by SCr and CrCl.[15] The rate of adverse events did not also differ significantly between the heparinoid and placebo groups, supporting the safety profile of the intervention.

This meta-analysis was limited by the generally small sample sizes of the trials (with two exceptions) and their intermediate methodological quality. The duration of treatment may have not also been long enough to sufficiently effect observable clinical changes. Moreover, there was a relative lack of data on other heparinoids, with two-thirds of the studies dealing with sulodexide alone. Data on hard endpoints was also scarce, with only one study evaluating all-cause mortality and only two studies evaluating achievement of therapeutic success.[18,19,23] Similarly, no study evaluated other outcomes such as rates of dialysis and hospitalization and health-related quality of life. As the included trials were mostly conducted in Western countries, it may be important to see how heparinoid supplementation fares in DKD patients from other parts of the world. In Asia, for instance, DM patients have higher rates of microalbuminuria and faster progression to ESRD compared to their Western counterparts.[25]

Another important factor to consider is the baseline chronic kidney disease (CKD) stage of the subjects in the different studies. Save for the Packham study, whose subjects had a moderately decreased mean baseline estimated glomerular filtration rate (eGFR) of 31.4 ml/min (categorized as CKD Stage III), the rest of the trials included patients with relatively mild CKD (Stages I-II), regardless of DM type. This may have explained the lack of efficacy seen in the Packham study – resulting to its early termination – and somehow defeats the intended purpose of the intervention as an add-on drug for advanced CKD. Additional sensitivity analyses were not warranted as the Packham study was not included in any of the forest plots.

Since no outcome contained more than ten studies, we agreed not to do a funnel plot as it can be misleading.[26] An attempt to minimize publication bias was done instead by extensively searching for unpublished data, while minimization of selection bias was done via pre-specified inclusion and exclusion criteria, performance of a systematic search, and independent evaluation of trial quality by two reviewers. Although the results of this study suggest a beneficial hypoalbuminuric effect of heparinoids in Type 1 DM patients, data remains limited to warrant routine clinical use. Larger trials are needed to further evaluate their application in DKD.

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CONCLUSION AND RECOMMENDATIONS

Heparinoid supplementation was not associated with statistically significant changes in all-cause mortality, SCr, CrCl, and achievement of therapeutic success for both Type 1 and Type 2 DM patients. However, it may be associated with a statistically significant UAER reduction of approximately 31.62 mg/24h as compared to placebo in Type 1 DM patients. Due to lack of data on hard endpoints as well as optimal dosing and duration of therapy, we cannot yet recommend its routine use for DKD patients. More studies involving larger populations are recommended.

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

Author Disclosure
The authors have declared no conflict of interest.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

A Comparison of Pregnancy Outcomes Using Two Diagnostic Criteria for Gestational Diabetes Mellitus-Carpenter Coustan Criteria and International Association of the Diabetes and Pregnancy Study Groups (IADPSG) Criteria*

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Abstract

Objective. To compare the maternal and perinatal outcomes in women with GDM diagnosed by Carpenter & Coustan (CC) criteria and by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria.

Methodology. A cross-sectional comparative study was conducted using data of women who were screened and diagnosed with GDM between April 2006-March 2007 using the CC criteria and April 2013-March 2014 using IADPSG criteria. Maternal and perinatal outcomes were noted. Means and proportions were calculated for continuous and categorical variables respectively. Data were analyzed using t-test for normally distributed data and Mann-Whitney U test for those that were not normally distributed. Pearson Chi-square test was used to find an association between the various outcomes between the two groups.

Results. Among 500 pregnant women screened, 36 were diagnosed GDM in the CC group. In the IADPSG group, 733 women were screened and 167 were diagnosed GDM. Prevalence of GDM was 7.2% in CC group and 22.78% in IADPSG group (p=0.000). There was a statistically significant difference in the number of women who developed hypertension and polyhydramnios among the two groups. Women who had an operative vaginal delivery (16.67% vs. 6.6%, p=0.085) and mean birth weight (3.10 ± 0.55 kg vs. 2.97 ± 0.48 kg, p=0.165) were higher in CC group than the IADPSG group. Among the perinatal outcomes, a statistically significant improvement was found in the number of neonates developing respiratory distress syndrome (p=0.000) and hyperbilirubinemia (p=0.000), when the IADPSG criteria were used.

Conclusions. There is a statistically significant difference between the maternal and neonatal outcomes when the newer IADPSG criteria were used for diagnosis of GDM.

Key words. gestational diabetes mellitus, prevalence, Carpenter-Coustan criteria, IADPSG criteria

INTRODUCTION

The World Health Organisation (WHO) has estimated a rise in the prevalence of diabetes from 4.7% to 8.5% in the adult population worldwide between 1980 and 2016. This rise in prevalence has been faster in low- and middle-income countries than in high-income countries.[1] Diabetes mellitus is a common medical complication of pregnancy. Gestational diabetes mellitus (GDM) is defined as any glucose intolerance with onset or first recognition during pregnancy.[2] One in 25 pregnancies is affected worldwide and about 4 million women have GDM in India.[3] The variation in the prevalence is due to the difference in race, ethnicity, age, body composition and screening and diagnostic criteria used in that particular population.

The increasing trend of prevalence of diabetes and GDM is due to the rising incidence of obesity and changing lifestyle patterns. Women with GDM are at a higher risk of both maternal complications like gestational hypertension, pre-eclampsia, operative delivery and fetal complications like macrosomia, birth injuries, stillbirths, neonatal hypoglycemia and hyperbilirubinemia. In addition, these women and their offsprings are known to develop type 2 diabetes mellitus later in life.[1]

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The screening and diagnosis of GDM has been a matter of considerable debate. The first diagnostic criteria of GDM was proposed by O'Sullivan using 100 g, 3-hour oral glucose tolerance tests (OGTT) which were modified by Carpenter and Coustan in 1982.[4,5] The International Association of Diabetes and Pregnancy Study Group Consensus Panel (IADPSG) recommended a one-step 75 g OGTT based on results of the Hyperglycemia and Adverse Perinatal Outcomes (HAPO) study.[6,7] The WHO has also recommended this strategy since 2013.[8] The American Diabetes Association (ADA) adopted the IADPSG recommendation since 2010, but emphasised in 2014 that a one-step 75 g OGTT or two-step approach with a 50 g oral glucose challenge test (OCT) followed by a 3-hour 100 g OGTT at 24-28 weeks of gestation for those who screen positive, are both equally efficacious in diagnosing GDM, pending long-term outcome studies.[9] However, American College of Obstetricians and Gynecologists (ACOG) continues to recommend the two-step strategy for diagnosis of GDM.[2]

This study was undertaken to compare the prevalence of GDM and feto-maternal outcomes between CC and IADPSG groups.

METHODOLOGY

A cross-sectional comparative analysis of women who were screened and diagnosed GDM at a tertiary care teaching hospital was performed. The protocol for screening and diagnosis of GDM at our hospital was changed from that of a two-step approach using Carpenter & Coustan criteria to a one-step approach using the IADPSG criteria in 2011. Data of women screened and diagnosed as GDM between April 2006-March 2007 (using Carpenter & Coustan criteria) and April 2013-March 2014 (using the IADPSG criteria) were included in the study. The study protocol was approved by the Institute's Ethics Committee. Waiver of consent was granted as it was a retrospective study and patient confidentiality was maintained.

In the CC group, women who screened positive at 24–28 weeks of gestation (plasma glucose of ≥ 140 mg/dL after 1 hr of a 50 g GCT), underwent a 3-hour 100 g oral glucose tolerance test (OGTT) and were diagnosed GDM when at least two values were more than or equal to the following threshold values: Fasting plasma glucose-5.3 mmol/L; 1 hr-10.0 mmol/L; 2 hr-8.6 mmol/L; 3 hr-7.8 mmol/L. In the IADPSG group, women underwent a single-step 75 g OGTT and were diagnosed GDM when one or more of the following threshold values were exceeded: Fasting plasma glucose 5.1 mmol/L; 1 hr-10 mmol/L; 2 hr-8.5 mmol/L.

The antenatal care protocol followed remained the same for both the cohorts. Women with GDM were initially treated with diabetic diet for 1-2 weeks and plasma glucose was measured in the fasting and post-meal states. When the target plasma glucose values (fasting 5.0 mmol/L and post-meals 6.7 mmol/L) were exceeded even with diabetic diet, insulin was started and dose titrated to achieve the target plasma glucose values.

Maternal and perinatal outcomes in both these groups were noted from the case files of these women. The maternal outcomes studied were polyhydramnios, hypertensive disorders in pregnancy, mode of delivery and shoulder dystocia. Neonatal outcomes studied were birth weight, respiratory distress syndrome and hyperbilirubinemia. These outcomes were compared between the two groups.

Table 1. Patient characteristics and pregnancy outcomes

Characteristics	CC group (n=36)	IADPSG group (n=167)	P value
Age			
≤20 years	5 (13.9%)	10 (5.9%)	
21-30 years	25 (69.4%)	123 (73.7%)	0.352
31-40 years	6 (16.7%)	33 (19.8%)	
>40 years	0 (0%)	1 (0.6%)	
Parity			
0	19 (52.8%)	73 (43.7%)	0.322
≥1	17 (47.2%)	94 (56.3%)	
Gestational age at delivery			
Preterm (less than 37weeks)	5 (13.9%)	27 (16.2%)	
early term (37-39weeks)	29 (80.6%)	82 (49.1%)	**0.150**
full term (39-41weeks)	2 (5.6%)	58 (34.7%)	
Maternal complications			
Hypertension in pregnancy	9 (25%)	13 (7.8%)	**0.003**
Polyhydramnios	4 (11.1%)	2 (1.2%)	**0.025**
Shoulder dystocia	2 (5.6%)	0 (0%)	**0.002**
Mode of delivery			
Spontaneous vaginal delivery	16 (44.4%)	99 (59.3%)	
Operative vaginal delivery	6 (16.7%)	11 (6.6%)	0.085
Lower segment caesarean section	14 (38.9%)	57 (34.1%)	
Neonatal outcomes			
Large for gestational age	1 (2.8%)	4 (2.4%)	**0.831**
Respiratory Distress Syndrome	7 (19.4%)	0 (0.0%)	**0.000**
Hyperbilirubinemia	11 (30.6%)	8 (4.8%)	**0.000**

*CC – Carpenter Coustan criteria
**IADPSG – International Association of the Diabetes and Pregnancy Study Groups.
Data are presented as n (%).
For age, parity and gestational age, Mann-Whitney U test was used to obtain the p value, as data were not normally distributed.
For all other variables, Pearson Chi-square test of association was used to obtain the P values.
P-value <0.05 was considered as statistically significant.

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Data were entered in Microsoft Office Excel spreadsheet and analysed using SPSS software version 19.0. Means and proportions were calculated for continuous and categorical variables respectively. Continuous data were tested for normality using the Shapiro-Wilk test. Normally distributed data were presented as mean ± SD and analysed using t-test. Data that were not normally distributed were presented as medians and analysed using Mann-Whitney U test. Pearson Chi-square test was used to find the association between the various outcomes between the two groups. A p-value <0.05 was considered as statistically significant.

RESULTS

Five hundred pregnant women were screened between April 2006-March 2007 and 36 were diagnosed GDM using Carpenter & Coustan criteria (CC group). After the protocol for screening and diagnosis of GDM at the hospital was changed from a two-step to a one-step approach, 733 women were screened between April 2013-March 2014. Among them, 167 women were diagnosed as GDM using the IADPSG criteria (IADPSG group). The prevalence of GDM was 7.2% in the CC group and 22.78% in the IADPSG group (p=0.000).

Majority of women in both groups were primigravidae (54% and 43.7% in CC and IADPSG groups respectively). Median age of women in the CC group was 25 years (interquartile range 23.50-27.00) and 26 years (interquartile range 23.00-30.00) in the IADPSG group. There was a statistically significant difference in the number of women who developed hypertension and polyhydramnios among the two groups (Table 1). Women who had an operative vaginal delivery (16.67% vs. 6.6%, p=0.085) were higher in the CC group than the IADPSG group and mean birth weight (3.10 ± 0.55 kg vs. 2.97 ± 0.48 kg, p=0.165) was higher in the CC group than the IADPSG group. However, both these outcomes were not found to be statistically significant. Among the perinatal outcomes, a statistically significant improvement was found in the number of neonates developing respiratory distress syndrome (p=0.00) and hyperbilirubinemia (p=0.00) in the IADPSG group.

DISCUSSION

The prevalence of GDM was found to have increased from 7.2% to 22.78% when diagnostic criteria were changed from CC criteria to the IADPSG criteria. This increase in prevalence was similar to that observed by many other authors (Table 2).[10–14] The prevalence was found to be as high as 35.5% in one study conducted among a Spanish population.[13] This is mainly due to the lower threshold values for diagnosis as per the IADPSG criteria and noted originally in the HAPO study as well.

Table 2. Prevalence of GDM in various studies

Study	Prevalence using CC criteria* (n)	Prevalence using IADPSG criteria* (n)
Present study	7.2% (36)	22.78% (167)
Wu et al.[10]	2.59% (888)	13.44% (952)
Feldman et al.[11]	17% (513)	27% (847)
Kong et al.[18]	7.9% (1838)	9.4% (2104)
Duran et al.[13]	10.6% (185)	35.5% (542)
Hung et al.[14]	4.6% (3641)	12.4% (3056)
Gopalakrishnan et al.[19]	-	41.9% (139)

*Data are presented as %; n represents the sample size in each study.

The rate of preterm deliveries was not significantly different among the two groups, like that reported among Belgian, Spanish and Taiwanese cohorts.[13–15] The rates of hypertension, polyhydramnios and mean birth weights were found to have decreased after changing the diagnostic protocol to the IADPSG criteria. However, only hypertensive disorders in pregnancy, polyhydramnios and shoulder dystocia were significantly reduced in the IADPSG group in our study (Table 1). This appears to be due to a higher number of women being treated for gestational diabetes. Similarly, Duran et al., in their study found a statistically significant decrease in maternal hypertension and large for gestational age (LGA).[13] Hung et al., also demonstrated an improvement in perinatal outcomes like LGA and caesarean delivery rates.[14] This is in contrast with the results obtained by other authors who did not find any significant changes in most other outcomes (Table 3).

A major limitation of our study is its retrospective nature and another is the small sample size. Data on the maternal weight gain during pregnancy, the pre-pregnancy BMI, high risk factors like prior GDM and blood sugar control are lacking. Further, the two criteria were applied on different groups of women and in different time periods, which could have influenced the prevalence in the IADPSG group due to a general background increase in prevalence of obesity and type 2 DM in the population.

The results of the HAPO study[6] demonstrated an increasing risk of adverse maternal, fetal and neonatal

Table 3. Comparison of selective outcomes (CC cohort vs. IADPSG cohort) in various studies

Outcomes (P value CC cohort vs. IADPSG cohort)	Present Study	Duran et al[13]	Benhalima et al[15]	Ethridge et al[20]	Hung et al[14]	Feldman et al[11]
Hypertension in pregnancy	**0.003**	**Sig.**	NS	NS	-	**Sig**
Polyhydramnios	**0.025**	-	-	-	NS	-
Shoulder dystocia	**0.002**	-	NS	NS	-	NS
Spontaneous vaginal delivery	0.587	-	-	NS	NS	-
Operative vaginal delivery	0.085	-	-	-	NS	-
Caesarean section rate	0.587	-	NS	NS	NS	**Sig.**
Preterm delivery rate	0.150	**Sig.**	NS	-	NS	NS
Large for gestational age	0.831	**Sig.**	NS	NS	**Sig.**	NS
Hyperbilirubinemia	**0.000**	-	-	-	-	NS

P-value <0.05 was considered as statistically significant; Sig.-significant; NS- not significant.

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outcomes with increasing maternal glycemic levels. These glycemic levels were observed to be well within the normal range as per the previously followed diagnostic cut-offs for diagnosis of GDM. Based on these findings, although the IADPSG and WHO adopted these criteria in 2010 and 2013 respectively, FIGO advocated the use of these criteria only in 2015. However, considering the limitations in medium to low resource countries, FIGO still considers alternative strategies like the one step non-fasting 75 g OGTT as recommended by the Diabetes in Pregnancy Study Group in India (DIPSI), as equally acceptable for diagnosis of GDM. In the DIPSI test, a glucose level of ≤7.8 mmol/L or ≤140 mg/dL is taken as the cut-off for diagnosis of GDM.[16,17]

Following alternative strategies like the DIPSI test makes the comparison in outcomes more complex and hence it would be more useful to evaluate outcomes using IADPSG criteria alone and comparing these with the non-diabetic population as determined by these criteria. From the results of our study, important maternal and neonatal outcomes were found to be statistically significantly better when the newer IADPSG criteria are applied for diagnosis. This may have been due to lower threshold values used for diagnosis and consequently earlier intervention and treatment in the IADPSG group. Our study is not adequately powered to determine if this change is truly significant. As most national and international organisations seem to be accepting and adopting the IADPSG criteria, large multicentre population and hospital based studies are needed to demonstrate a significant improvement in the pregnancy outcomes using these criteria.

CONCLUSION

The diagnosis of Gestational Diabetes Mellitus (GDM) is presently being made by different criteria applied to various populations and with different approaches, taking into consideration the health services, resources and prevalence of glucose intolerance in the population. FIGO now advocates universal screening of all pregnant women for GDM by the single-step 75 g OGTT using IADPSG criteria. The use of alternative strategies in some countries is still acceptable, but causes confusion and inability to draw adequate comparisons between the different outcomes. Our study demonstrated a significant improvement in important maternal and perinatal outcomes, but is limited by its small sample size. Further large prospective trials are required to validate these results.

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ORIGINAL ARTICLE

Diabetes Mellitus and Prediabetes in Patients with Hepatocellular Carcinoma in a Tertiary Philippine Hospital

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Abstract

Background. Diabetes mellitus (DM) has been shown to be associated with an increased risk for hepatocellular carcinoma (HCC). DM and obesity are coexisting conditions that can increase the risk and severity of nonalcoholic fatty liver disease (NAFLD), leading to HCC even in the absence of cirrhosis. With the rising incidence of HCC and DM worldwide, it is important to identify the clinical characteristics of individuals with DM among those with HCC in our local setting.

Objectives. To determine the prevalence of DM among Filipino patients with HCC at our institution, determine their demographic and clinical profile, and compare the characteristics of HCC patients with and without DM.

Methodology. This is a retrospective, analytical, cross-sectional study involving patients with HCC seen at The Medical City's Center for Liver Disease Management and Transplantation from January 2010 to December 2014. A chart review was conducted and patients were grouped according to the presence or absence of DM. Data on demographics, body mass index (BMI), comorbidities, social and family history, risk factors for liver disease, and laboratory test results were gathered. STATA 12.0 was used for data analysis.

Results. We included 180 patients with HCC in the analysis. The prevalence of type 2 DM and prediabetes was 52.78%. The median age of patients with DM and prediabetes was 65 years, and 58 years for patients without DM (p=0.002). The average BMI was 27.35 $\pm$ 4.68 for patients with DM, and 25.04 $\pm$ 5.11 for those without DM (p=0.002). Among the patients without DM, 50.59% had hepatitis B virus (HBV) infection compared to 24.21% of patients with DM (p=0.000). Twenty one percent of patients with DM had cryptogenic cirrhosis compared to 8.24% of patients without DM (p=0.016). Patients with DM had a higher proportion of hypertension (66.32% vs. 42.35%, p=0.001) and dyslipidemia (48.42% vs. 10.59%, p=0.000).

Conclusion. The prevalence of DM and prediabetes among HCC patients is higher in our institution compared to findings from previous studies. HCC patients with DM were older, and had increased BMI, higher proportion of hypertension and dyslipidemia, lower incidence of HBV infection, and higher incidence of cryptogenic cirrhosis.

Key words: hepatocellular carcinoma, diabetes mellitus

INTRODUCTION

In 2012, liver cancer was reported to be the fifth most common cancer in men, the ninth in women, and the second most common cause of cancer death worldwide.[1] In the Philippines, it is the fourth most common cancer, with incidence rates of 14 per 100,000 persons for males, and 4.8 per 100,000 persons for females.[2] Major risk factors for hepatocellular carcinoma (HCC) include infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD).[3] In some studies, however, none of these major etiologies were identified in cases of HCC, suggesting that there might be other less commonly known risk factors associated with HCC such as diabetes mellitus (DM).[4]

DM is now the most common cause of liver disease in the United States with the entire spectrum of liver findings being seen in these patients including abnormal liver enzymes, NAFLD, cirrhosis, and HCC.[5] NAFLD affects 10-24% of the general population and can potentially progress to cirrhosis and liver failure.[6] DM and obesity are coexisting conditions that can increase the risk and severity of NAFLD, leading to HCC even in the absence of cirrhosis.[7,8] Among Filipino patients, one study found a 12.2% prevalence of NAFLD in a single hospital.[9] They were younger in age compared to previous studies, and female sex, obesity, elevated liver enzymes, and the presence of DM were characteristic features of these patients. Other studies have likewise shown a significant association of NAFLD with DM, obesity and metabolic syndrome.[10,11]

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Several epidemiologic studies done in different geographic regions have shown an association between DM and HCC. A systematic review of 13 case-control studies and 13 cohort studies indicated that DM is associated with a 2.5-fold increase in the risk for HCC.[12] One of the studies in this review suggested a temporal relationship by showing that DM preceded the development of liver disease, and it also found that a longer history of DM significantly strengthened the association.[4] The positive association between DM and HCC may be confounded by the presence of other risk factors. While those studies that adjusted for viral hepatitis and alcohol use found no change or minimal change in the risk estimate, other potential confounders such as obesity, diet and physical activity were not addressed.[12]

In the Philippines, two studies conducted at the Philippine General Hospital have shown similar clinical characteristics of patients diagnosed with HCC. The mean age of diagnosis is 54 years, the male-to-female ratio is 3.5:1 to 4:1, and the most common risk factors are chronic hepatitis B and alcohol use.[13,14] Hepatitis B remains hyperendemic in the Philippines with an HBsAg seroprevalence of 16.7%.[15] In addition, Lucas et al., reported a 13.5% prevalence of DM among HCC patients, which was three times the national prevalence of DM at that time.[13]

With the rising incidence of HCC and DM worldwide, it is important to identify the clinical characteristics of individuals with DM among those with HCC in our local setting. At our institution, internal reports suggest a much higher prevalence of DM among patients with HCC, hence the need to confirm existing local data. The Medical City is a private tertiary hospital and while it caters mainly to residents of Metro Manila, it also receives referrals from rural areas. The Medical City's Center for Liver Disease Management and Transplantation (CLDMT) opened in 2008 and is a valuable repository of information on Filipino patients with HCC.

OBJECTIVES

1. To determine the prevalence of DM among Filipino patients with HCC at The Medical City's CLDMT
2. To determine the demographic and clinical profile of patients with HCC
3. To compare the characteristics of HCC patients with and without DM

METHODOLOGY

Study design

This is a retrospective, analytical, cross-sectional study.

Study population

This study included all Filipino adult patients aged 19 years and above seen at The Medical City's CLDMT from January 2010 to December 2014 with a diagnosis of HCC. Patients with other non-HCC liver tumor/s (e.g. metastatic liver cancer, cholangiocarcinoma) were excluded.

Sample size

The sample size was calculated[16] based on a desired width of the 95% confidence interval of 0.10, or an accuracy of $\pm$ 0.05, and an estimated prevalence of 13.5% as noted from the reference article by Lucas et al. A minimum of 180 subjects with HCC were required for this study.

Methods

Data was retrieved mainly by reviewing outpatient medical records from the CLDMT. Inpatient medical records were reviewed when available to supply missing outpatient chart data. A census of all liver cancer patients was generated from January 2010 to December 2014, and the diagnosis of HCC for each patient was verified. The diagnosis of HCC was based on histopathology or through the demonstration of typical dynamic radiologic findings on computerized tomography or magnetic resonance imaging. The hallmark of HCC is the presence of arterial enhancement, followed by washout of the tumor in the portal-venous and/or delayed phases. The diagnosis of type 2 DM was based on physician notes, use of relevant medications, and/or an HBA1c $\geq$6.5% prior to or at the time of diagnosis with HCC. Patients not known to have diabetes but who had an HBA1c of 5.7% to 6.4% prior to or at the time of diagnosis with HCC were labeled as having prediabetes.

For all subjects, demographic data included age, sex, and nationality. Body mass index (BMI) was calculated and cut-offs for Asians was used to classify subjects into the following categories: underweight (<18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2), and obese ($\geq$25 kg/m^2).

Information on the presence of co-morbidities (hypertension, dyslipidemia, obesity, CKD and others), alcohol and smoking history, and family history was collected. The month and/or year of diagnosis of HCC was based on physician notes, histopathology reports, and imaging tests. The risk factors for underlying liver disease were classified into hepatitis B, hepatitis C, NAFLD, alcoholic and cryptogenic cirrhosis.

Data on the duration of DM prior to diagnosis of HCC, the presence of diabetes-related complications, the use of relevant medications (oral drugs and insulin), and the level of control based on HBA1c results was collected.

Results of laboratory tests done such as liver function tests (ALT, AST, alkaline phosphatase, bilirubins, GGT, albumin, platelet count, INR), hepatitis profile and lipid profile were tabulated.

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Statistical analysis

Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and SD for interval/ratio variables. Independent sample T-test, Mann-Whitney U test and Chi-squared/Fisher's Exact test were used to determine the difference of mean, median and frequency between groups, respectively. Missing data was neither replaced nor estimated, as these are count variables which cannot be imputed. Patients with incomplete charts were included only in the analysis of variables for which data was available. If data on a specific variable was missing for a particular patient, the patient was not included for that variable only. STATA 12.0 was used for data analysis.

Ethical consideration

The protocol was submitted to the Institutional Review Board for approval. All patient information was kept strictly confidential. All data gathered was kept solely in the possession of the primary investigator.

RESULTS

Of the 233 patient charts retrieved with a possible diagnosis of HCC, 53 patients were excluded due to misdiagnosis. A total of 180 patients with a confirmed diagnosis of HCC were included in this study. Among these patients, 91 were found to have type 2 DM, and 4 patients were diagnosed with prediabetes. There were no cases of type 1 DM identified. The prevalence of type 2 DM and prediabetes was 52.78% among patients with HCC in our institution.

Table 1 compares the demographic and clinical profile of HCC patients with and without DM. Patients with DM were significantly older with a median age of 65 years; the median age for patients without DM was 58 years. In both groups, patients with HCC were predominantly male. The male-to-female ratio was 5.33:1 for patients with DM, and 4.4:1 for patients without DM. For the 170 patients with documented weight and height measurements, average BMI was significantly increased in the diabetic group, with 67% falling into the obese category. Information on alcohol and smoking history was inadequate. Quantity of alcohol intake and cigarette pack years were often lacking. There was a stronger family history of DM among those diagnosed with this condition that those without it.

For both groups, hepatitis B infection was the leading risk factor for underlying liver disease, but the number of cases was significantly increased in the non-diabetic group (50.59% vs. 24.21%, p=0.000). Of the 27 patients with cryptogenic cirrhosis as their underlying risk factor for liver disease, a significant number had DM (21.05% vs. 8.24%, p=0.016).

Among patients with DM who had available data on the duration of their disease, the average duration of DM prior to the diagnosis of HCC was 7 years. Majority had been diagnosed with DM at least 5 years prior to being diagnosed with HCC. 71% were on oral hypoglycemic agents only (Table 2).

Patients with DM had a higher proportion of hypertension (66.32% vs. 42.35%, p=0.001) and dyslipidemia compared to non-diabetics (48.42% vs. 10.59%, p=0.001) (Table 3).

Table 1. Demographic and clinical profile of HCC patients with and without DM

	Diabetic (n=95)	Non-diabetic (n=85)	P-Value
	Frequency (%); Mean ± SD; Median (Range)		
Age (years), median (range)	65 (42 to 90)	58 (21 to 82)	*0.002*§
Sex, frequency (%)			0.590ǂ
Male	80 (84.21)	70 (81.18)	
Female	15 (15.79)	16 (18.82)	
Weight (kg), mean ± SD	73.89 ± 14.82	68.15 ± 17.32	*0.021**
Height (cm), mean ± SD	164.09 ± 7.41	164.56 ± 9.42	0.724*
BMI (kg/m^2), mean ± SD	27.35 ± 4.68	25.04 ± 5.11	*0.002**
BMI categories, frequency (%)			
Underweight	0	5 (6.10)	*0.001*ǂ
Normal	13 (14.77)	22 (26.83)	
Overweight	16 (18.18)	22 (26.83)	
Obese	59 (67.05)	33 (40.24)	
Alcohol history, frequency (%)			0.066ǂ
Never	39 (45.35)	26 (34.67)	
Previous	31 (36.05)	26 (34.67)	
Current	16 (18.60)	23 (30.67)	
Smoking history, frequency (%)			0.727ǂ
Never	44 (52.38)	37 (50.68)	
Previous	28 (33.33)	28 (38.36)	
Current	12 (14.29)	8 (10.96)	
Family history, frequency (%)			
HCC	14 (14.74)	6 (7.06)	0.102ǂ
DM	49 (51.58)	21 (24.71)	*0.000*ǂ
Risk factors for underlying liver disease, frequency (%)			
HBV	23 (24.21)	43 (50.59)	*0.000*ǂ
HCV	2 (2.11)	6 (7.06)	0.151ǂ
NAFLD/NASH	16 (16.84)	8 (9.41)	0.188ǂ
Alcohol	8 (8.42)	4 (4.71)	0.318ǂ
Cryptogenic	20 (21.05)	7 (8.24)	*0.016*ǂ
Unknown	29 (30.53)	21 (24.71)	0.384ǂ
With Cirrhosis, frequency (%)	45 (47.37)	37 (43.53)	0.606ǂ

Statistical tests used: * - Independent Sample T-test; ǂ - Chi-squared test; § - Mann-Whitney U test; ǂ - Fisher's Exact test

Table 2. Duration of diabetes and medications used by HCC patients with diabetes (n=95)

	Frequency (%)
Diabetes duration (years)	
Less than 5 years	19 (32.20)
5 years to 10 years	14 (23.73)
More than 10 years	26 (44.07)
Undocumented	36 (37.89)
Diabetes medication	
OHAs only	59 (71.08)
Insulin only	21 (25.30)
OHA and Insulin	3 (3.61)
Undocumented	12 (12.63)

Table 3. Co-morbidities of HCC patients with and without DM

	Diabetic (n=95)	Non-diabetic (n=85)	P-Value
Hypertension	63 (66.32)	36 (42.35)	***0.001***
Dyslipidemia	46 (48.42)	9 (10.59)	***0.000***
CKD	7 (7.37)	4 (4.71)	0.457
Others	33 (34.74)	17 (20.00)	***0.028***

Statistical tests used: Chi-squared test
Data are presented as frequency (%)

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Table 4 provides a summary of the clinical chemistries done in all patients with HCC. There is insufficient evidence to demonstrate a difference in blood test results between patients with and without DM.

Table 4. Clinical chemistries of HCC patients with and without DM

	Diabetic	Non-diabetic	P-Value
Platelet count (n=155)			0.701
Decreased	17 (20.73)	17 (23.29)	
Normal	65 (79.27)	56 (76.71)	
INR (n=149)			0.404ǂ
Increased	2 (2.38)	4 (6.15)	
Normal	82 (97.62)	61 (93.85)	
FBS (n=100)			***0.000***
Increased	50 (89.29)	10 (22.73)	
Normal	6 (10.71)	34 (77.27)	
HbA1c (n=61)			***0.042***ǂ
Increased	22 (40.74)	0	
Normal	32 (59.26)	7 (100)	
ALT (n=155)			0.915
Increased	27 (32.53)	24 (33.33)	
Normal	56 (67.47)	48 (66.67)	
AST (n=147)			0.916
Increased	61 (77.72)	53 (77.94)	
Normal	18 (22.78)	15 (22.06)	
Alkaline phosphate (n=130)			0.357
Increased	34 (50.00)	26 (41.94)	
Normal	34 (50.00)	36 (58.06)	
GGT (n=55)			0.660
Increased	21 (80.77)	22 (75.86)	
Normal	5 (19.23)	7 (24.14)	
Undocumented	69 (72.63)	56 (65.88)	
Albumin (n=149)			0.541
Decreased	41 (50.62)	31 (45.59)	
Normal	40 (49.38)	37 (54.41)	
AFP (n=151)			0.093
Increased	55 (67.90)	56 (80.00)	
Normal	26 (32.1)	14 (20.00)	

Statistical tests used: Chi-squared test; ǂ - Fisher's Exact test
Data are presented as frequency (%)

DISCUSSION

The prevalence of DM among patients with HCC varies from region to region. In the United States, Hassan et al., reported a prevalence of 33.3%,[17] while Taura et al., reported 25% among Japanese patients.[18] In the Philippines, Lucas et al., reported a 13.5% prevalence of DM among HCC patients at one hospital.[13] In our study, the prevalence of type 2 DM and prediabetes was 52.78%, which is much higher compared to the findings of the previously mentioned international and local studies.

The study by Lucas et al., was conducted at a government hospital in Manila that caters mostly to indigent patients, and included only those patients that had been hospitalized, thus it is possible that the diagnosis of DM was underestimated in its study population. The higher prevalence of DM among HCC patients at our center may also be reflective of an increasing prevalence of DM in our country's general population. From 2003 to 2008, the estimated national prevalence of DM increased from 4.6% to 7.2%.[19] The subjects in our study also came from a single center, therefore, we cannot claim that they are representative of the entire population. Nonetheless, it is important to note that our institution is a referral center for patients coming from all over the Philippines, both urban and rural areas, and with diverse socioeconomic backgrounds.

In our study, we found that, regardless of the presence or absence of DM, patients at our center were diagnosed with HCC at a later age compared to patients in two other local studies done at the Philippine General Hospital. Lucas et al., reported a mean age of 54 years at the time of diagnosis with HCC, and Daez et al., had a similar mean age of 54.42 years. Furthermore, HCC patients with DM were significantly older compared to those without DM. Although not statistically significant, there was a greater proportion of male patients among those with DM (5.3:1 vs. 4.3:1). The higher median age and higher male-to-female ratio of patients without DM in our study is in agreement with previous findings that patients who develop HCC in the background of metabolic syndrome are more predominantly males, and are older at the time of diagnosis as compared to patients with HCC due to other causes.[20]

The older age at diagnosis of HCC among patients without DM may also be linked to their underlying risk factors for liver disease. While we found that HBV infection remains to be the leading cause of HCC, there is a significantly lower incidence of HBV among those patients with DM. This has also been previously observed among Japanese and Chinese patients.[18,21] Compared to other countries in the Asia Pacific region where the prevalence of HBV infection has already fallen, the Philippines remains hyperendemic for HBV perhaps because the universal HBV vaccination program, although first introduced in 1992, was only fully implemented in 2007.[15]

It is estimated that 5-30% of HCC cases do not have readily identifiable risk factors for HCC such as viral hepatitis and alcohol.[20] Many cases of cryptogenic cirrhosis are now being attributed to NAFLD, and its more severe stage, non-alcoholic steatohepatitis (NASH). Diabetes-associated NASH leading to HCC has been described.[12] In our study, we found that there were significantly more patients with DM among those with cryptogenic cirrhosis. This is similar to previous studies showing that DM is indeed prevalent in patients with HCC and cryptogenic cirrhosis.[12]

For both groups, a large proportion of HCC patients were overweight or obese, with those patients with DM having significantly increased BMI compared to those without DM. Obesity is associated with a higher incidence of many types of cancers including HCC.[22] A BMI greater than 30 kg/m^2 is an independent predictor of poor overall survival.[23] The main mechanism involved appears to be hyperinsulinemia, a positive energy balance and other hormonal abnormalities.[22] Since both obesity and DM are characterized by hyperinsulinemia and increased cancer incidence, it is difficult to identify the contribution of each individual risk factor.[22] There was a higher proportion of hypertension and dyslipidemia among patients with HCC and concurrent DM. There are few studies that examine the individual association of these conditions with HCC,

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but taken together as components of the metabolic syndrome, it is well established that this syndrome contributes to the development of HCC.[20]

For most of our patients with DM, the diagnosis of DM preceded the diagnosis of HCC by at least 5 years. Unfortunately, data on glycemic control in terms of HBA1c levels was lacking in many patients. Most charts also failed to mention if there were any diabetes-related complications present, and many did not indicate the specific type of anti-diabetic medications that patients were taking and their compliance with treatment.

In the study by Hassan et al., the adjusted odds ratio was higher with increasing duration of DM.[17] Furthermore, it was found that certain medications were implicated in the development of HCC. The risk for HCC was greater for patients on sulfonylureas and insulin, while biguanides and thiazolidinediones were associated with lower HCC risk.[17] The degree of glycemic control is another factor that can determine who among patients with DM are at higher risk of being diagnosed with HCC. Donadon et al., reported that among patients with HCC, HBA1c levels were significantly higher in those with DM compared to patients with cirrhosis and control groups of patients with DM. There was a 26-50% increase in the HCC risk for each 1% increase in HBA1c level.[24]

The Philippines has recently been recognized as a newly industrialized country, one whose economy is somewhere in between those of developing and developed nations. While infectious diseases remain to be a problem, noncommunicable diseases such as DM have become a growing concern in developing and newly industrialized countries. This shift is believed to have been brought about by lifestyle related risk factors associated with social and economic changes.[25] There is a need therefore for public health programs to widen their focus from eradication of infectious diseases and to address lifestyle related diseases that were previously thought to be just a concern of the developed world. Until then, it is likely that diseases like HCC that are multifactorial in etiology will continue to be a significant cause of morbidity and mortality. There are currently no guidelines for HCC screening aimed specifically at patients with DM. However, given that there is such a high prevalence of DM among Filipino HCC patients at our institution, it is important to raise the awareness of physicians regarding the association of these two conditions. Diabetes prevention and control should be emphasized, and liver-related symptoms in patients with DM should prompt appropriate investigations.

This study has several limitations. The retrospective nature affected the completeness of the data and we were unable to gather enough information on certain variables that we had intended to collect. There were many charts that had missing laboratory results and many physician notes were incomplete. In the future, a prospective design is recommended to improve on the quality of data collected. A multi-center recruitment of subjects would be ideal in order to have a sample population that is more representative of HCC patients in the Philippines. While our study was not designed to determine whether DM is a risk factor for the development of HCC, our preliminary findings showing a high prevalence of DM among HCC patients could generate more interest in related research areas. It would be worthwhile to investigate how DM affects HCC prognosis and if control of DM will lead to better outcomes for patients with HCC.

CONCLUSION

The prevalence of DM among patients with HCC is higher in our institution compared to findings from previous international and local studies. HCC patients with DM were older, had increased BMI, and had a higher proportion of hypertension and dyslipidemia. They also had a lower incidence of HBV infection and a higher incidence of cryptogenic cirrhosis.

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

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ORIGINAL ARTICLE

Efficacy of Magnesium Supplementation on Glycemic Control in Type 2 Diabetes Patients: A Meta-analysis

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Abstract

Objective. To evaluate if magnesium supplementation, in addition to standard therapy, improves fasting blood sugar (FBS) and/or glycosylated hemoglobin (HbA1c) in patients with type 2 diabetes mellitus (T2DM) compared to placebo or other comparator.

Methodology. We searched MEDLINE/PubMed, Cochrane Library, Acta Medica Philippina, Health Research and Development Information Network (HERDIN) and references of reviewed journals from 1966 to July 2015 using the following search terms: "magnesium" OR "magnesium supplementation" OR "magnesium replacement", AND randomized controlled trial AND diabetes OR diabetes mellitus OR non-insulin dependent diabetes mellitus OR diabetic OR diab* (with MeSH, where available). Studies were retrieved and rated independently using the standards provided by The Cochrane Collaboration. High quality trials were included in a systematic review and meta-analysis.

Results. Of the 689 records screened, 10 studies were included in the qualitative synthesis and 7 studies in the meta-analysis. Pooled data showed a non-significant trend towards improvement in glycemic control in the magnesium-treated group (mean difference -0.19, CI -0.58 to 0.21). There was a stronger but still non-significant trend in T2DM patients with hypomagnesemia (mean difference -1.16, CI -2.92 to 0.6).

Conclusion. Routine magnesium supplementation for improvement in glycemic control in T2DM patients cannot be recommended based on data from included studies in this meta-analysis.

Key words: diabetes, magnesium, supplementation, glycemic control, meta-analysis

INTRODUCTION

Diabetes is one of the leading causes of morbidity and mortality around the world. Its prevalence is rapidly increasing every year: by 2035, the International Diabetes Federation estimates that the number of diabetics will increase to 592 million from 382 million in 2013.[1] While diabetes is caused by a variety of hereditary and acquired factors, the diabetes pandemic has been attributed to an increasingly poor diet and sedentary lifestyle.[1] Magnesium deficiency, one of the nutritional factors associated with diabetes, has been attributed to urinary magnesium loss, inadequate intake or a combination of both.[2-5]

Magnesium is a major intracellular cation that acts as a co-factor in more than 300 enzymatic reactions, including those in the glycolytic pathway.[2] Several studies have shown that magnesium deficiency is associated with decreased insulin sensitivity and increased insulin resistance. Fasting plasma magnesium levels have been positively correlated with glucose disposal rate.[3,5,6] Oral supplementation or intravenous infusion of magnesium in diabetic patients increases acute insulin response and glucose disposal rate, and decreases insulin resistance.[7-10]

Because of these findings, magnesium has been suggested as a possible treatment for diabetes. Several randomized controlled trials on the effect of magnesium supplementation on glycemic control in diabetes have conflicting results. A meta-analysis done by Song et al., in 2006 found that magnesium supplementation for 4 to 16 weeks may be effective in reducing fasting blood sugar (FBS) levels in patients with type 2 diabetes mellitus.[11] However, glycemic control is better evaluated by HbA1c, which is less affected by acute or transient changes. We also wanted to see if any improvement in glycemic control was related to plasma magnesium levels, which was not studied in the previous meta-analysis. This study reviews available data on magnesium supplementation and its effect on glycemic control in patients with type 2 diabetes.

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Serum Magnesium Levels in Patients with Diabetes and Insulin Resistance

Several studies have demonstrated that magnesium levels are significantly lower in patients with diabetes and in obese people with insulin resistance, compared to normal controls.[12-14] While frank hypomagnesemia (serum level less than 0.61 mmol/L) usually occurs only in patients with uncontrolled diabetes, patients with magnesium concentrations less than 0.75 mmol/L may have preclinical disease.[15]

Recommended Daily Intake and Dietary Adequacy

The recommended daily intake (RDI) in the United States for magnesium is 420 mg for males and 320 mg for females, based on magnesium balance studies.[2,4] The National Health and Nutrition Examination Survey (NHANES) of 2005-2006 showed that 45 to 80% of Americans failed to meet these daily requirements.[5] In contrast, findings from a meta-analysis showed that higher dietary magnesium intake was associated with a lower risk for incident type 2 diabetes mellitus.[16] Note that the studies on daily magnesium intake were estimated from food questionnaires and not from supplementation using magnesium salts. The major sources of dietary magnesium from these questionnaires were green leafy vegetables and nuts, which are components of a healthy diet recommended by various endocrine and diabetes societies.

Urinary Magnesium Loss in Patients with Diabetes

Patients with poorly controlled diabetes have increased urinary magnesium excretion.[13,16-18] A study by Khan et al., compared the serum and urinary magnesium and blood glucose levels of 40 diabetic patients with 26 healthy and malnourished controls. They found significantly higher urinary magnesium (30 mmol/L versus 6.3 mmol/L, $p<0.05$) and low serum magnesium (0.66 mmol/L versus 0.73 mmol/L, $p<0.05$) in patients with diabetes mellitus from pancreatic disease compared to normal individuals.[19] A recent study by Xu et al., evaluated urinary magnesium levels in patients with prediabetes, type 1 and type 2 diabetes mellitus, with different end-organ complications of diabetes. Patients with type 1 or type 2 diabetes had significantly lower serum magnesium and higher urinary magnesium excretion compared to healthy controls.[20]

Magnesium Levels, Glycemic Control and Insulin Levels

Plasma glucose levels were found to be inversely correlated to plasma magnesium levels in patients with diabetes ($rs=-0.33$, $p<0.01$). In this group, patients who were on insulin had lower mean plasma magnesium (0.84 mmol/L) compared to those on oral hypoglycemic agents (0.89 mmol/L) and non-diabetic patients (0.95 mmol/L).[3] This finding is consistent with a cross-sectional study by Kumari, which showed that 74% of the study patients with diabetes were hypomagnesemic. Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR) was inversely correlated with serum magnesium levels (Spearman $r=-0.44$, $p<0.05$).[21]

Magnesium Intake, Risk of Diabetes and Insulin Resistance

Several studies demonstrated that diets with higher amounts of magnesium were associated with a significantly lower risk of diabetes, and a 100 mg/day increase in magnesium intake was associated with a 15% lower risk of diabetes.[16,21] Conversely, higher intake of magnesium-rich food was inversely correlated with serum insulin levels and HOMA-IR. Patients with high magnesium intake (mean 597 ± 224.1 mg/day or 7.99 ± 3.6 mg/kg/day) had significantly lower HOMA-IR and insulin levels compared to medium and low magnesium intake.[22]

Chronic magnesium supplementation was found to improve insulin response to glucose load and glucose disposal rate in hyperinsulinemic euglycemic clamp studies.[7,9] In a study by Wang et al., patients with T2DM who were in the upper quartile of magnesium intake (quantified through food questionnaires) had a mean HOMA-IR of 3 (a value of >3.6 interpreted as insulin resistant).[23]

Multiple prospective cohort studies have tested the efficacy of magnesium supplementation on glycemic control, with conflicting results.[10, 24-29]

METHODOLOGY

We followed the recommendations of the Cochrane Collaboration on the flow and content of conducting a systematic review/meta-analysis.

We searched the literature for relevant randomized clinical trials on oral magnesium supplementation and glycemic parameters in patients with type 2 diabetes mellitus. The authors searched MEDLINE/PubMed, Cochrane Library, Acta Medica Philippina, HERDIN and references of reviewed journals from 1966 to July 2015 using the following search terms: "magnesium" OR "magnesium supplementation" OR "magnesium replacement" AND randomized controlled trial AND diabetes OR diabetes mellitus OR non-insulin dependent diabetes mellitus OR diabetic OR diab* (with MeSH, where available)

We included only published randomized controlled studies in the English language or with English translation. The studies met the following criteria for inclusion: random assignment of treatment and control, use of placebo or alternative treatment, human subjects with non-insulin dependent diabetes mellitus/T2DM, indication of magnesium status pre- and post-treatment, and measurement of glycemic status (FBS, HbA1c) pre- and post-treatment. Each journal was evaluated for eligibility by two of the authors independently.

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Discrepancies were resolved by group discussion, with the third author assigned to adjudicate.

Data Extraction

The authors independently performed the literature search, study selection, quality assessment and data extraction. A standardized reporting form was used to independently extract data from each included study. The data collected included first author's name, year of publication, country where study was conducted, title, number of subjects, sample size, type and duration of diabetes, mean age, sex ratio, number of study groups, study design, type of magnesium supplement, equivalent dose of elemental magnesium, treatment duration, pre- and post-treatment glycemic and magnesium status (or placebo/alternative treatment phase versus magnesium phase in crossover studies). The primary outcome measures were mean reductions in FBS and HbA1c.

Data Analysis

The collected data was coded and analyzed using RevMan 5.3 software provided by the Cochrane Collaboration. The principal summary of measures used was the difference in means for the outcome measures between the magnesium-treated group versus placebo. Pre- and post-treatment (magnesium versus comparator) mean FBS and HbA1c values and standard deviations were extracted and coded into the software for incorporation into the Forrest plot. The Chi-square test was used to test for heterogeneity across studies. Subgroup analysis was done on studies with normomagnesemic and hypomagnesemic patients.

Bias Assessment

Each study was assessed for bias using the Cochrane Collaboration tool for bias risk assessment which included the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

For crossover studies, the domains for assessment were: appropriate crossover design, randomized treatment order, carry over effect, unbiased data, allocation concealment, blinding, incomplete outcome data and selective outcome reporting.

RESULTS

Following electronic and manual searches, a total of 12 full text articles were identified to have met the inclusion criteria. However, 2 of these did not include the outcome of interest. Three more studies were excluded from the quantitative analysis because of the use of different measures of glycemic control/utilization, but were included in the qualitative analysis. Subjects included in the studies were of similar age and sex ratio, and were treated with diet and/or oral hypoglycemic agents. The work flow for screening and assessment of journals are outlined in Figure 1.

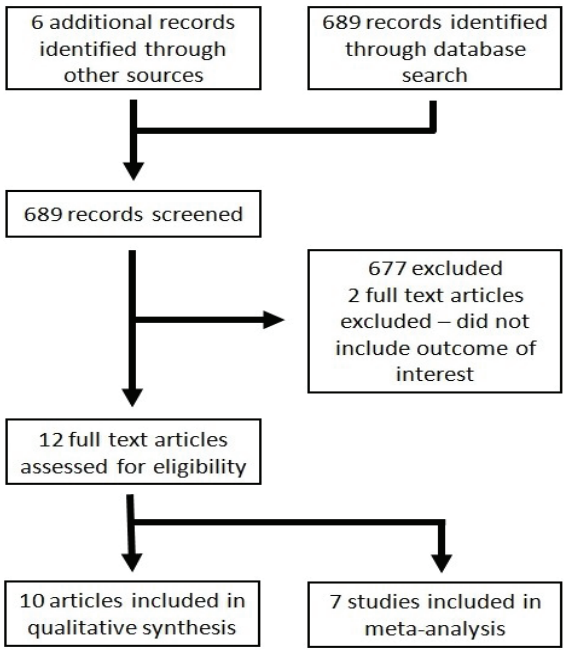

Figure 1. Flowchart for article selection for meta-analysis.

Of the 7 studies included in the meta-analysis, 2 had a crossover study design and 5 had a parallel study design. Majority of the studies included patients with normal plasma magnesium levels (>0.75 mmol/L), while 2 studies had subjects with hypomagnesemia. The studies utilized various magnesium salts with different amounts of elemental magnesium. While there is no consensus on the bioavailability of these magnesium salts, all of the studies reported an increase in plasma magnesium in the treatment arm at the end of the supplementation/ replacement period, suggesting that magnesium from the varied supplements were systemically absorbed.

The study by Eriksson et al., included patients with NIDDM and insulin-dependent diabetes mellitus (IDDM), but did not indicate if the IDDM patients had type 1 or type 2 DM.[28] Because of this, we opted to compare the data from the NIDDM group with the placebo group.

The study by de Lordes Lima compared placebo, low dose magnesium and high dose magnesium.[24] We compared the data from the high dose group with the placebo group. The studies and their respective results are described in Tables 1 and 2.

Majority of the included studies reported that they were randomized, double-blind, placebo-controlled trials. Only 2 reported the method of randomization (Rodriguez-Morán 2003[30] and Navarrete-Cortes 2014[31]), and none of them reported the method of allocation concealment and method of blinding. We were in agreement, though, that blinding was unlikely to have affected the outcomes of

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Table 1. Characteristics of populations and interventions of included studies

Author, place and year of publication	Population	Intervention, equivalent elemental magnesium	Comparator	Number of patients (Comparator/ Treatment)	Type and duration of study	Glycemic outcomes measured
Gullestad et al, Norway, 1989[35]	Elderly NIDDM[a]	Magnesium lactate, 184.5mg, No diet specified	Placebo	29/25	Parallel, 2 weeks pre-study (placebo tablets) followed by 4 months treatment	FBS[c], HbA1c[d]
Eibl et al, Austria, 1995[34]	T2DM[b] with hypomagnesemia	Magnesium citrate, 730mg, No specified diet but stated equal dietary magnesium	Placebo	20/18	Parallel, 3 months treatment	HbA1c[d]
Eriksson et al, Finland, 1995[29]	NIDDM[a]	Unspecified magnesium supplement (600mg?), No diet specified	Ascorbic Acid	27 NIDDM	Crossover, 3 months run-in period, 3 months treatment, 1 month washout, then crossover	FBS[c], HbA1c[d]
de Valk et al, Netherlands, 1998[27]	T2DM[b]	Magnesium L-aspartate HCl, 184.5mg, No diet specified	Placebo	56/56	Parallel, 1 month treatment	FBS[c], HbA1c[d]
de Lourdes Lima et al, Brazil, 1998[26]	NIDDM[a] with HbA1c >8% and hypomagnesemia	Magnesium oxide, 254mg and 508mg, No specified diet	Placebo	54/35/39	Parallel, 4 months treatment	FBS[c], HbA1c[d]
Rodriguez-Morán et al, Mexico, 2003[30]	T2DM[b] with hypomagnesemia	Magnesium chloride 50 mL 5% solution, 638g, No diet specified	Placebo	25/25	Parallel, 3 months treatment	FBS[c], HbA1c[d]
Navarrete-Cortes et al, Mexico, 2014[31]	T2DM[b]	Magnesium lactate, 360mg, No diet specified	Placebo	56	Crossover, 3 months treatment with 3 months washout, then crossover	FBS[c], HbA1c[d]

[a]NIDDM, non-insulin dependent diabetes mellitus
[b]T2DM, type 2 diabetes mellitus
[c]FBS, fasting blood sugar
[d]HbA1c, glycosylated hemoglobin

Table 2. Pre- and post-treatment glycemic control and magnesium levels in parallel studies

Author, Place and Year of Publication	Magnesium, mmol/L		HbA1c[a], %		FBS[b], mg/dL	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Gullestad et al, Norway, 1989[35]	Normal and not significantly different between groups and between pre- and post-treatment		M: 7.3 ± 1.5 P: 7.4 ± 1.6	M: 7.8 ± 1.5 P: 7.4 ± 1.6	M: 158.4 ± 41.4 P: 153 ± 48.6	M: 172.8 ± 57.6 P: 160.2 ± 54
Eibl et al, Austria, 1995[34]	M: 0.73 ± 0.8 P: 0.72 ± 0.8	M: 0.81 ± 0.1 P: 0.69 ± 0.8	M: 7.2 ± 0.7 P: 7.5 ± 0.9	M: 7.4 ± 0.9 P: 7.6 ± 1.4	No FBS[b]	
Rodriguez-Morán et al, Mexico, 2003[30]	M: 0.64 ± 0.12 P: 0.65 ± 0.09	M: 0.74 ± 0.1 P: 0.65 ± 0.07	M: 11.5 ± 4.1 P: 11.8 ± 4.4	M: 8 ± 2.4 P: 10.1 ± 3.3	M: 230.4 ± 100.8 P: 255.6 ± 70.2	M: 144 ± 43.2 P:185.4 ± 37.8
de Valk et al, Netherlands, 1998[27]	M: 0.79 ± 0.04 P: 0.77 ± 0.08	M: 0.81 ± 0.07 P: 0.77 ± 0.05	M: 8.65 ± 1.45 P: 8.72 ± 1.27	M: 9.1 ± 1.5 P: 9.1 ± 1.1	M: 212.4 ± 64.8 P: 214.2 ± 102.6	M: 196.2 ± 68.4 P: 223.2 ± 117
de Lourdes Lima et al, Brazil, 1998[26]	M: 0.73 ± 0.19 P: 0.72 ± 0.17	M: 0.80 ± 0.24 P: 0.72 ± 0.17	M: 9 ± 2.4 P: 9.3 ± 2.6	M: 9.2 ± 3 P: 9.5 ± 2.2	M: 226.8 ±75.6 P: 232.2 ± 77.4	M: 228.6 ± 75.6 P: 219.6 ± 131.4

[a]HbA1c, glycosylated hemoglobin
[b]FBS, fasting blood sugar
M, magnesium-treated group
P, placebo-treated or comparator group

Table 3. Pre- and post-treatment glycemic control and magnesium levels in crossover studies

Author, Place and Year of Publication	Magnesium, mmol/L		HbA1c[a], %		FBS[b], mg/dL	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Eriksson et al, Finland, 1995[28]	0.76 ± 0.02	M: 0.8 ± 0.01 P: 0.78 0.01	9.1 ± 0.3	M: 8.9 ± 0.3 P: 8.9 ± 0.3	169.2	M: 157.86 ± 16.2 P: 198 ± 18
Navarrete-Cortes, Mexico, 2014[31]	M: 0.9 ± 0.12 P: 0.86 ± 0.13	M: 0.95 ± 0.06 P: 0.9 ± 0.13	M: 7.9 ± 3.7 P:8 ± 3.4	M: 8.5 ± 3.7 P: 8.69 ± 4.15	M: 153.9 ± 130.8 P: 159.84 ± 97	M: 154.3 ± 140.8 P: 154.3 ± 117.1

[a]HbA1c, glycosylated hemoglobin
[b]FBS, fasting blood sugar
M, magnesium-treated group
P, placebo-treated or comparator group

FBS and HbA1c levels. All included studies provided information on missing data from attrition, including reason of attrition and group assignment (placebo or magnesium). All studies fully reported the expected glycemic outcomes. For the 2 crossover studies, there were appropriate settings and washout periods, and randomization of treatment order. Data from the different periods of the study were all reported.

The Philippine Food and Nutrition Research Institute (FNRI) recommended nutrient intake (RNI) for magnesium is 240 mg/day for males and 210 mg/day for females, or 3.5 to 5 mg/kg/day with average male weight of 60 kg and female weight of 55 kg, adapted from the World Health Organization (WHO)/Food and Agriculture Organization (FAO).[32-33] The recommendation from the WHO/FAO 2004 was based on a combination of magnesium balance studies and the absence of any evidence of magnesium deficiency at these intake levels. The report only included decreased bone density, hypocalcemia and hypokalemia as the possible consequences of magnesium deficiency.[33] We were not able to find any studies on magnesium sufficiency in the Philippines or the Southeast Asian region.

There was no significant difference in the mean post-treatment FBS and HbA1c between the magnesium supplementation groups and placebo (or other comparator) groups (Figures 2 and 3). There were wide variations in FBS and HbA1c levels of subjects since none

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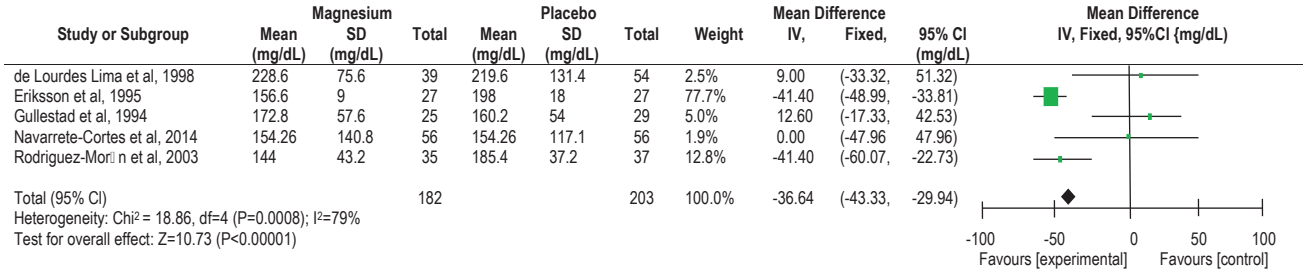

Figure 2. Weighted mean difference and forrest plot of FBS levels in magnesium-treated and placebo groups.

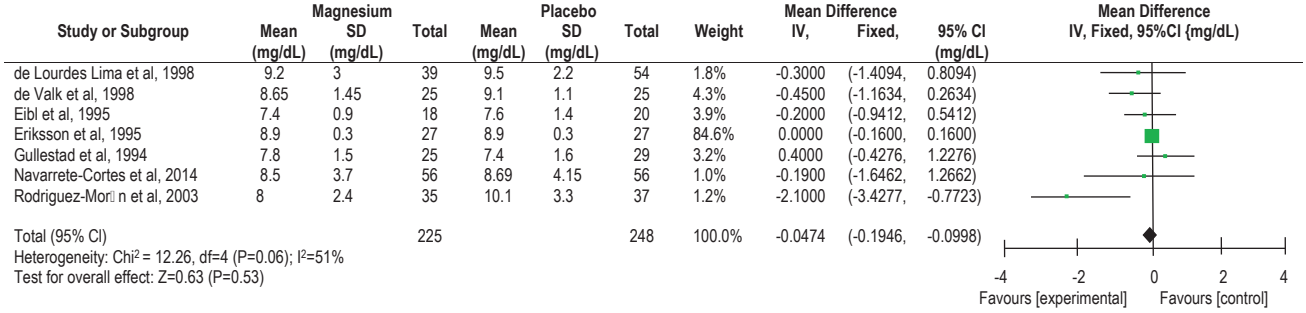

Figure 3. Weighted mean difference and forrest plot of HbA1c in magnesium-treated and placebo groups.

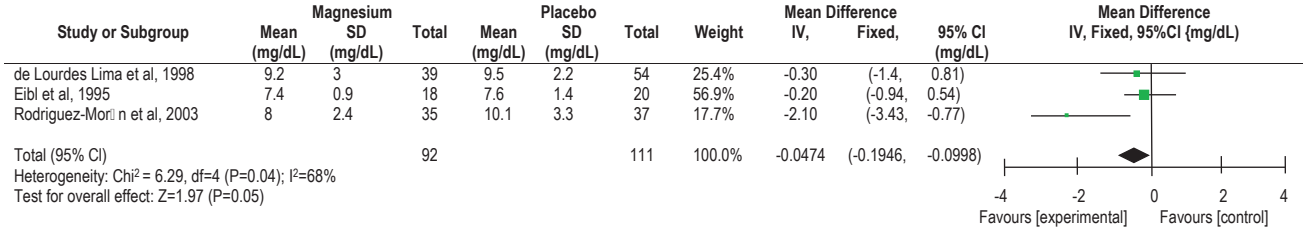

Figure 4. Weighted mean difference in HbA1c of magnesium-treated and placebo groups among subjects with hypomagnesemia (serum Mg <0.75 mmol/L).

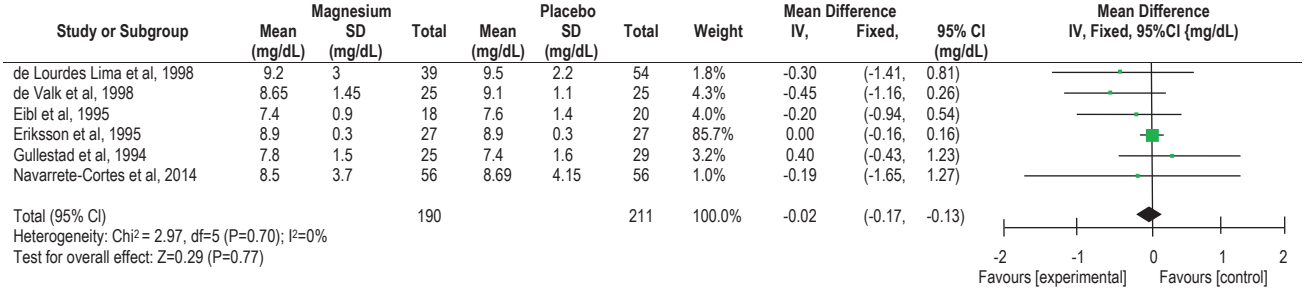

Figure 5. Weighted mean difference in HbA1c of magnesium-treated and placebo groups, analyzed without the study with severe hypomagnesemia (Rodriguez-Morán, 2003[30]).

of the studies used a glycemic range as inclusion criteria. These wide variations in FBS and HbA1c resulted to a short and broad normal distribution of values, making it difficult to conclude that there was no difference between the two groups. The differences between two groups with short and broad normal distributions may not be detected unless the magnitude of effect was very large, because of the significant overlap that will occur.

Subgroup analysis of the trials on hypomagnesemic patients showed a larger but non-significant trend toward benefit for the magnesium-treated group (Figure 4). There was moderate to substantial heterogeneity between studies, with I² of 71%, 59% and 68%, for studies with FBS as outcome, HbA1c as outcome and among hypomagnesemic patients with HbA1c as outcome, respectively (Figures 2 to 4).

DISCUSSION

In this meta-analysis of randomized controlled trials, we found no significant difference in short-term and long-term glycemic control between the two groups. There seemed to be a trend favoring magnesium supplementation,

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Table 4. Bias risk assessment for included parallel studies

Author, place and year of publication	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other bias
Gullestad et al, Norway, 1989[35]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data explained by dropout due to 2: intercurrent illness	Low risk: outcomes fully reported	None identified
Eibl et al, Austria, 1995[34]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data explained by dropout due to 1: rash, 1: GI effects	Low risk: outcomes fully reported	None identified
Rodriguez-Morán et al, Mexico, 2003[30]	Low risk: computer random number generator	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data explained by dropout due to 2: treatment failure, 2: withdrawal of consent, 5: loss to follow up	Low risk: outcomes fully reported	None identified
de Valk et al, Netherlands, 1998[27]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data due to dropout from: 4: personal circumstances, 1: difficulty swallowing, 3: non-compliance, 7: HbA1c outside 7–11%, 1: physician-instigated change in insulin regimen	Low risk: outcomes fully reported	None identified
de Lourdes Lima et al, Brazil, 1998[26]	Uncertain: method of randomization not specified	Uncertain	Double blind but method not indicated	Low risk: outcomes unlikely to be affected by blinding	Low risk: incomplete data due to dropout from: 20: did not follow instructions correctly, 9: other medical problems, 16: irregular use of Mg or placebo, 6: forgot to take the drug, 10: stopped due to side effects	Low risk: outcomes fully reported	None identified

Table 5. Bias risk assessment for included crossover studies

First author, place and date of publication	Appropriate crossover design	Randomized treatment order	Carry over effect	Unbiased data	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting
Eriksson et al, Finland, 1995[28]	Low risk: condition is chronic, intervention provides only temporary effect with appropriate washout	Low risk: method is appropriate and clearly described	Low risk: carry over effect was assessed and no persistent effect after washout period	Low risk: data for each period was reported	Uncertain: method of randomization not specified	Uncertain	Low risk: no missing data	Low risk: outcomes fully reported
Navarrete-Cortes et al, Mexico, 2014[31]	Low risk: condition is chronic, intervention provides only temporary effect with appropriate washout	Low risk: method is appropriate and clearly described	Low risk: carry over effect was assessed and no persistent effect after washout period	Low risk: data for each period was reported	Low risk: computer random number generator	Uncertain	Low risk: missing data explained by attrition from poor compliance, withdrawal of consent and ADR	Low risk: outcomes fully reported

particularly in the 3 studies which included diabetic subjects with hypomagnesemia (de Lourdes Lima, Eibl,[34] and Rodriguez Morán[30]). It must be noted that while baseline characteristics of patients in the magnesium and comparator arms were not significantly different, the magnesium supplementation groups had a lower mean HbA1c values at the start of the trial. Measurement of mean HbA1c change from baseline would have been more meaningful.

Only one study (Rodriguez-Morán[30]) showed a significantly lower mean HbA1c value (with a reduction in mean HbA1c from baseline) in the magnesium treated group. While this may be due to the fact that the patients in that group had much more severe hypomagnesemia (Rodriguez-Morán et al.,[30] 0.64 mmol/L ± 0.12 mmol/L versus Eibl et al.,[34] 0.73 mmol/L ± 0.08 mmol/L; and de Lourdes Lima et al.,[26] 0.73 mmol/L ± 19 mmol/L), the true effect could not be ascertained. Excluding this study from other studies with HbA1c as an outcome yields a mean difference of -0.02 (-0.17, 0.13 at 95% CI) (Figure 5).

The trend for improved glycemic control in the magnesium-treated arm may not have been statistically significant for at least 2 reasons. The treatment effect of magnesium is likely related to blood levels of magnesium, with diminishing returns with higher magnesium values. Additionally, patients included in the studies had a large variance in FBS and HbA1c values, which may lead to a failure in detecting a significant change in glycemic parameters.

CONCLUSIONS

Available data from present studies do not support a recommendation for routine magnesium supplementation in patients with T2DM with normal serum magnesium, defined in most included studies as a plasma magnesium concentration above 0.75 mmol/L. This is consistent with the ADA recommendation that micronutrient supplementation should not be given in patients without micronutrient deficiency. Only one study (Rodriguez-Morán[30]) showed a significant benefit for magnesium

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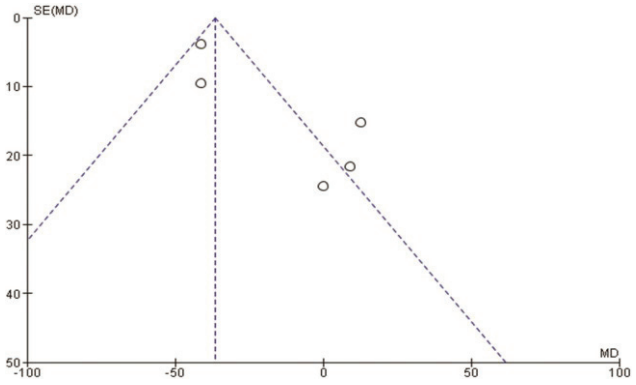

Figure 6. Funnel plot of included studies with FBS as an outcome measure.

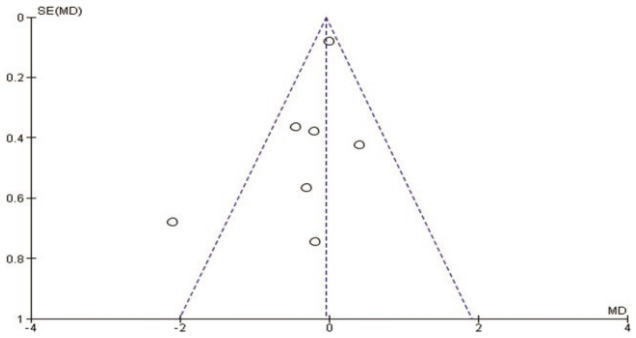

Figure 7. Funnel plot of included studies with HbA1c as an outcome measure.

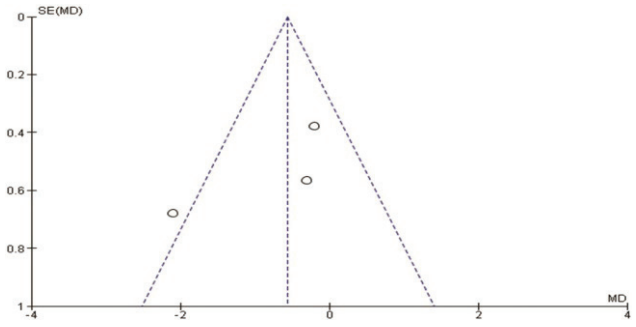

Figure 8. Funnel plot of included studies on subjects with hypomagnesemia at baseline, with HbA1c as an outcome measure.

supplementation in patients with hypomagnesemia. More studies are needed to make appropriate recommendations on magnesium supplementation for patients with type 2 diabetes.

RECOMMENDATIONS

We recommend a larger randomized controlled study of magnesium supplementation on patients with diabetes mellitus with a small HbA1c range, similar to more recent clinical trials. Investigation of other parameters, such as estimated dietary magnesium intake and use of newer anti-diabetic agents are also timely. A separate study on sufficiency of magnesium intake and serum magnesium levels will also provide better insight. A positive finding of a treatment effect in patients with suboptimal magnesium levels in future studies will be helpful in fulfilling our goal of individualized medical care by targeting specific defects in insulin secretion or action.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors have declared no conflict of interest.

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None.

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Speakers:

Silva A. Arslanian, MD
(Children's Hospital of Pittsburgh)

- Childhood Obesity Prevention and Management
- Management of Type 2 DM in Children and Adolescents

Byron J. Hoogwerf, MD
(Cleveland Clinic)

- Diabetes, Weight Loss and Heart Disease: What do the Studies Say?
- Diabesity Treatment Arsenal

Daniel L. Hurley, MD
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- Nutrition Guidelines in the Obese Hospitalized Patient
- Nutritional Issues and Care Post-Bariatric Surgery

Sethu K. Reddy, MD
(Joslin Diabetes Center & Cleveland Clinic)

- Environment & Genetics: Origins of Diabesity
- Diabesity and the Gut Microbiome

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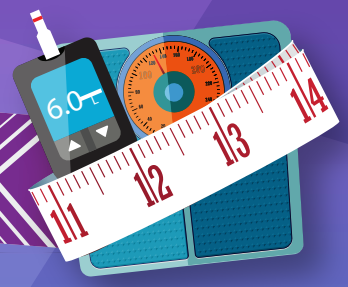

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CASE REPORT

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Macroglossia: An Uncommon Manifestation of Primary Hypothyroidism due to Hashimoto's Thyroiditis in a Teenage Child

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Abstract

Thyroid disorders are prevalent in the paediatric population and untreated hypothyroidism leads to several adverse consequences like mental retardation, neurological impairment, short stature, delayed puberty and increased morbidity. Owing to a wide range of non-specific clinical manifestations, one must have a high index of suspicion for timely diagnosis and treatment of primary hypothyroidism. We describe the case of an adolescent girl who presented with short stature, delayed puberty and feeding difficulties owing to undiagnosed and subsequently untreated hypothyroidism.

Key words: macroglossia, short stature, delayed puberty, hypothyroidism

INTRODUCTION

Primary hypothyroidism is a common paediatric entity which is frequently undiagnosed and untreated. Its protean manifestations include lethargy, hypothermia, hypotonia, constipation and mental retardation.[1] Oral manifestations causing difficulty in feeding include large-sized tongue (macroglossia), delayed dentition and crowding of teeth.[2] Long term consequences include growth retardationand pubertal delay, though isosexual precocious puberty may occur in rare cases.[3-8]

Here we describe a 16-year-old adolescent girl presenting with short stature, delayed puberty and feeding difficulties due to undiagnosed and subsequently untreated hypothyroidism.

CASE

A 16-year-old Indian girl presented to the endocrinology out-patient department with short stature and delayed pubertal development with absence of menarche. She also complained of gradually progressive difficulty in chewing food since last 2 years. There was no history suggestive of dental malocclusion, trauma or any abnormalities in jaw opening or closing. There was no family history of growth retardation or pubertal delay, neither any surgical intervention nor radiation exposure during childhood. She was born of an uneventful pregnancy at 36 weeks gestation age by normal spontaneous vaginal delivery with normal birth length and weight. There was no history of any chronic illness during childhood. She studied in 8th grade and her academic performance was average.

On examination, facial puffiness was prominent along with a dry and scaly skin. There was crowding of her incisors (Figure 1). She had a large sized tongue, more evident on protrusion (Figure 2). Her hair seemed brittle with mild alopecia noted in the frontal region. There was no madarosis of eyebrows. There were no signs of goitre while the higher mental functions and neurological examination were within normal limits with slightly sluggish deep tendon reflexes in the lower limbs (grade 1+). Anthropometric measurements revealed a standing height of 134 cm (<3rd percentile for age and sex) and an arm span of 132 cm. She weighed 28 kg (<3rd percentile for age and sex). The mid-parental height as calculated from her parents was 164 cm. Tanner scoring was B1, P1 and A1.

Her investigations revealed the following (Table 1): Hemoglobin=10.2 g/dl, and general blood picture suggestive of normocytic normochromic anemia, normal serum electrolytes, CPK and LDH. Liver functions and kidney functions were within normal limits. Thyroid function tests revealed TSH level >150 μIU/L (normal: 0.4-5) with low T4 and T3 levels, suggestive of overt hypothyroidism. Anti-thyroid peroxidase antibody (Anti TPO Ab) was >1000 IU/ml (normal: 0-50 IU/ml). Ultrasound study of the thyroid gland was mostly normal with a few hypoechoic lesions noted. Her bone age from x-ray of the left hand as calculated by Tanner-Whitehouse 2 was 8.9 years. Her gonadotropin levels (both FSH and LH) were low, implying pre-pubertal status. Thus, her short stature, delayed bone age and delayed pubertal development were attributed to hypothyroidism due to Hashimoto's thyroiditis.

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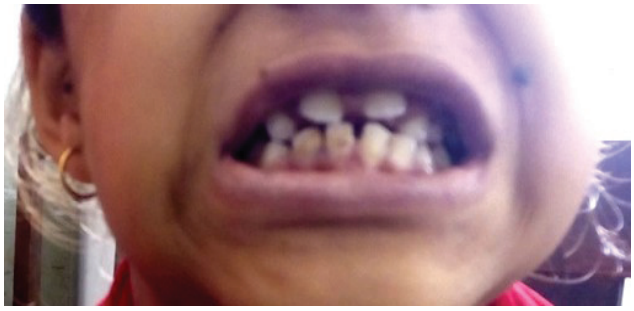

Figure 1. Dental anomalies due to large tongue.

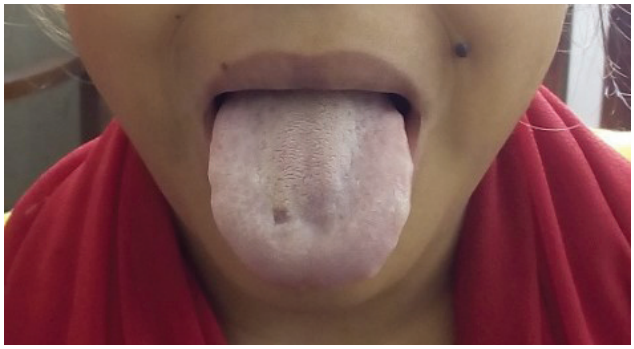

Figure 2. Macroglossia.

Table 1. Laboratory investigations

Parameter	Lab Values
Hemoglobin (Hb)	10.2 g/dl
Total Leuco. Count (TLC)	5200/cu mm
MCV	75 fl
Creatinine	08 mg/dl
Sodium (Na)	138 meq/l
Potassium (K)	3.8 meq/l
Calcium(Ca)-total	9.5 mg/dl
Creatinine Kinase (CK)	50 U/L
LDH	105 U/L
TSH	>150 µIU/L
T3	30 ng/dl
T4	2.5 µg/dl
Anti-TPO antibody	>1000 IU/ml
FSH	0.7 IU/L
LH	1.2 IU/L

She was started on levothyroxine replacement and counselled appropriately. After 6 months of therapy, she noted improvement in her chewing abilities. She is being monitored regularly for catch up growth and subsequent pubertal development.

DISCUSSION

Thyroid disorders are a fairly common occurrence in the paediatric population, and the prevalence of juvenile hypothyroidism was found to be 9.3-10.5% in the developing world.[9] The presentation ranges from asymptomatic, isolated biochemical abnormalities of thyroid function tests to overt clinical manifestations. Autoimmune thyroid disease, thyroid dysgenesis, binding protein abnormalities, TSH receptor mutations, thyroid hormone resistance, iodine deficiency, infectious thyroiditis are the common thyroid disorders observed in this age group.[1]

Overall, Hashimoto's Autoimmune Thyroiditis is the most common cause of hypothyroidism in iodine-sufficient areas of the world. The worldwide incidence is estimated to be 0.3–1.5 cases per 1000 individuals with a definite gender predilection for females (M:F =15:1).

Deficiency of thyroid hormones during intra-uterine life leads to impairment of normal fetal brain development.[1] In childhood, hypothyroidism manifests as prolonged jaundice, umbilical hernia, constipation, lethargy, hypothermia and cold or mottled skin. Feeding difficulties are seen due to various oral manifestations like delayed eruption of teeth, malocclusion, large sized tongue (macroglossia) and thick lips.[2] Macroglossia can be attributed to accumulation of glycosaminoglycans and over-development of tongue musculature. [10]

Hypothyroid children may present with short stature and delayed onset of puberty. Height deficit correlates with duration of untreated hypothyroidism and can be estimated by calculating the difference between chronological and bone age.[3] They generally have very low T4 values and highly elevated TSH. On treatment with levothyroxine, bone age advances faster in comparison to height gain, hence final height always remains short of the genetic growth potential.

Besides, thyroid hormone deficiency results in delay of onset or retardation of progress of puberty, since it interferes with gonadotropin secretion.[4] Treatment with levothyroxine normalises the gonadotropin secretion and allows further progress of puberty. In rare cases, long standing untreated hypothyroidism may result in paradoxical isosexual precocious puberty (Van-Wyk Grumbach Syndrome) due to action of high levels of TSH on the FSH receptors.[5]

Our patient had features of macroglossia, short stature and delayed puberty owing to long duration of undetected and untreated hypothyroidism. Hence, clinicians must be aware of the protean manifestations of primary hypothyroidism and treat the child timely to prevent long term adverse consequences.

CONCLUSION

Primary hypothyroidism must be diagnosed and treated early to provide opportunity for adequate gain in height and timely onset and progress of puberty before complete skeletal maturation occurs.

Ethical Consideration
Informed consent has been taken before submission of the manuscript.

Statement of Authorship
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Author Disclosure
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CASE REPORT

Autoimmune Thyroiditis as Initial Presentation of Systemic Lupus Erythematosus Complicated by Massive Ascites: A Case Report*

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ABSTRACT

Autoimmune thyroiditis in the course of other autoimmune diseases such as systemic lupus erythematosus (SLE) is common because these disorders are attributed to the production of autoantibodies against various autoantigens. Beyond this association, autoimmune thyroiditis can occur before, during or after the development of SLE. In this report, we describe a female who presented with facial puffiness, lethargy and progressive abdominal distension. She was diagnosed with autoimmune thyroiditis followed by the diagnosis of SLE complicated by a massive ascites, a rare form of lupus peritonitis, which is sterile ascites that results from severe serositis. Her presentation was complex and posed a diagnostic challenge and dilemma to the physicians involved in her care.

Key words: autoimmune thyroiditis, systemic lupus erythematosus, serositis

INTRODUCTION

Autoimmune thyroid disease, defined by the presence of antibodies directed against thyroid antigens, is associated with a number of non-organ-specific rheumatological disorders such as systemic lupus erythematosus (SLE). A number of studies have suggested that thyroid disease is more common in SLE than in the general population and the development of thyroiditis can occur before, during or after the diagnosis of SLE.[1,2] We report a female with autoimmune thyroiditis as the initial presentation of SLE which was complicated by a massive ascites. Her presentation was complex and posed a diagnostic challenge and dilemma to the physicians involved in her care. The ascites was a rare form of lupus peritonitis, with massive ascites that results from severe serositis.

CASE

A 37-year-old Malay female, presented with facial puffiness, lethargy, reduced effort tolerance and progressive abdominal distension for 3 months. Apart from that, she did not have cold intolerance, weight gain, constipation, reduced cognitive function, slowness or other symptoms of hypothyroidism. At her initial presentation, she had no symptoms to suggest she may have a connective tissue disease such as prolonged fever, arthralgia, photosensitivity, hair loss or oral ulcers. She had normal regular menstruation and there were no constitutional symptoms such as weight loss, poor appetite or night sweats. Systemic symptoms were unremarkable. She had no previous medical problems and she was not on any medications. There was no family history of autoimmune disease. She was married with 3 children who were all well. She was a non-smoker and abstained from alcohol. Her main concern was the extreme lethargy and the abdominal distension which caused significant discomfort. Her waist circumference expanded from 80 cm to 130 cm within 3 months. Clinically, she appeared hypothyroid with facial and periorbital puffiness, dry skin and dry hair with a massive ascites (Figures 1 and 2). The heart rate was 60 beats/min with slowly relaxing reflexes. She was pink, had no jaundice, good hydration status, no goitre, no lymphadenopathies, no skin rashes or photosensitivity, oral ulcers, alopecia or other features to suggest autoimmune disease. Thyroid function tests revealed overt primary autoimmune hypothyroidism with TSH >100 mU/L (0.34-5.6) and FT4 4.0 pmol/L (7.9-14.4) supported by significantly high anti-TPO antibody 468.6 U/ml (<34) and antithyroglobulin antibody 770.4 U/ml (<155). She was started on levothyroxine replacement, 300 mcg once a day before breakfast for a week in view of the severe hypothyroidism. Her weight at presentation was 60 kg and the high dose of the initial levothyroxine was administered with a prespecified plan to review her at weekly intervals with repeat thyroid function tests, and further reduction in the levothyroxine dose. The following were her baseline blood investigations (Table 1).

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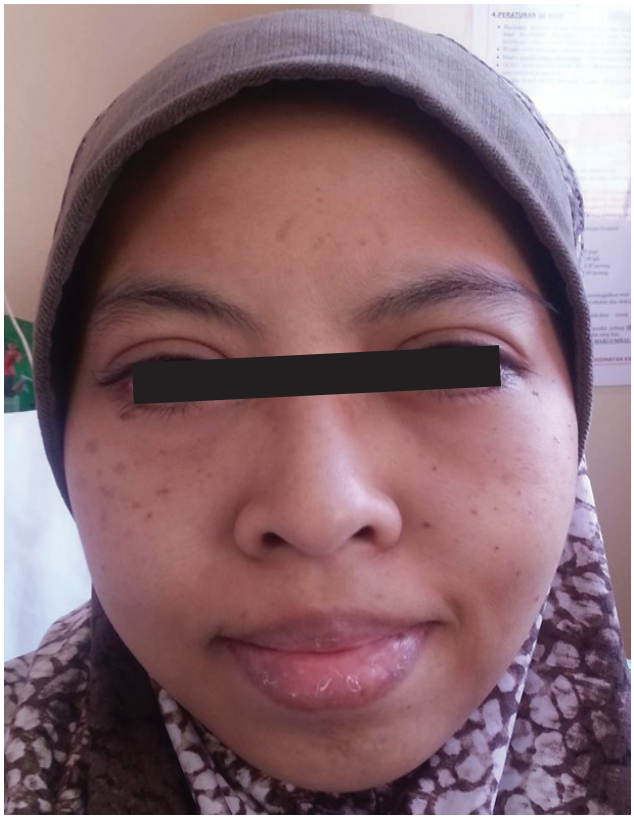

Figure 1. Hypothyroid facies with facial and periorbital puffiness.

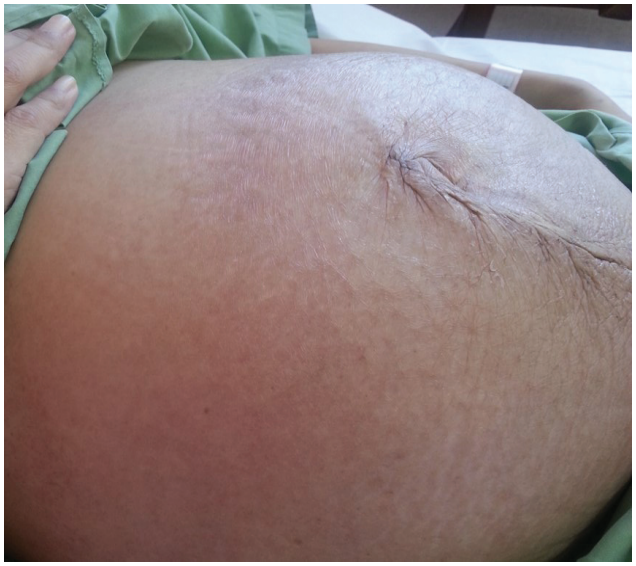

Figure 2. Presence of massive ascites with abdominal girth 120 cm.

Furthermore, she was also noted to have an ovarian mass measuring 5 x 5 cm on the transvaginal ultrasound, and the CECT abdomen and pelvis confirmed the presence of a right adnexal mass likely representing an ovarian tumour with pelvic lymphadenopathy. The gynaecologists were concerned about the possibility of ovarian carcinoma. Subsequently, she underwent right salphingectomy, omentectomy, appendicectomy, and right pelvic lymph node sampling. The intraoperative findings were

Table 1. Baseline blood investigations

Hb (g/dL)	10.5 (11-16)
Hct (%)	33.3 (37-47)
MCV (fl)	84.1 (76-96)
MCH (pg)	26.5 (27-32)
MCHC (g/dL)	31.5 (30-35)
WBC (10*9/L)	9.1 (4-11)
Platelets (10*9/L)	478
Urea (mmol/L)	2.6 (1.7-8.3)
Na (mmol/L)	131 (135-145)
K (mmol/L)	3.5 (3.5-5)
Creatinine (umol/L)	55 (44-80)
Albumin (g/L)	22 (35-50)
fT4 (pmol/L)	4 (7.9-14.4)
TSH (mU/L)	>100 (0.34-5.6)
Anti-TPO (U/ml)	468.6 (<34)
Antithyroglobulin (U/ml)	770.4 (<155)

oedematous subcutaneous fat, peritoneum and retroperitoneum with normal looking uterus, both ovaries and left fallopian tube. There was a 5 x 5 cm right fimbrial cyst (for which cystectomy was done) and normal omentum, mesentery, bowel and liver. Right external and common iliac lymph nodes were enlarged and other lymph nodes were not palpable. All the histopathological specimens from the right fimbrial cyst, omentum, left and right peritoneum, appendix, right external iliac lymph node and right common iliac lymph node were benign tissues and did not contain any malignant cells. The ascitic fluid also did not reveal any malignant cells and contained predominantly lymphocytes, histiocytes, plasma cells and reactive mesothelial cells. Postoperatively she had a very rapid ascitic fluid accumulation associated with pleural effusion and minimal pericardial effusion. The peritoneal fluid was drained by multiple abdominal paracentesis with results of ascitic fluid analyses pointing to an exudative etiology. The tumour markers such as alpha fetoprotein (AFP), CA-125, carcinoembryonic antigen (CEA) and beta human chorionic gonadotrophin (BHCG) were negative. With these clinical evidences of serositis and the presence of autoimmune thyroiditis, a thorough screening for connective tissue diseases was performed (Table 2).

Table 2. Connective tissue screening results

ANA	reactive (1: 1280), speckled (1: 5120)
ENA	positive for SSA/SSB and RNP
Direct Coombs	Positive
C3 (g/L)	0.29 (0.83 - 1.93)
C4 (g/L)	0.07 (0.15 - 0.57)
Anti-dsDNA	Negative
24 hour urine protein	0.62 g (<0.5g/day)
Full blood picture	Normochromic normocytic anaemia, adequate white blood cell count,no blast or abnormal lymphoid cells, reactive thrombocytosis
ESR	111
CRP	5.8

The fine needle aspiration and cytology of thyroid gland (FNAC) showed lymphoplasmacytic infiltration and few follicles. The follicular epithelium exhibited oncocytic changes consistent with chronic lymphocytic thyroiditis (Hashimoto's thyroiditis).

After 1 month, she started to develop multiple oral ulcers and hair loss. There was mild arthralgia but there was no skin rash or photosensitivity. She was noted to have mild

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nephritis as evidenced by 24-hour urine protein 0.62 g/24hrs (<0.5g/24hrs). Based on the clinical and biochemical manifestations, she satisfied 6 out of 11 criteria for SLE according to the American College of Rheumatology and hence diagnosed as active SLE. She was started on IV methylprednisolone for 3 days followed by hydroxychloroquine and azathioprine. Biochemically, following the levothyroxine replacement, there was a rapid improvement in the thyroid function tests within 2 months and the levothyroxine dose was gradually reduced from 300 mcg to 25 mcg once a day before breakfast (Table 3). She tolerated all the medications well and experienced remarkable improvement with complete resolution of her symptoms following the therapies instituted. The ascites resolved and the facial and periorbital puffiness improved (Figure 3).

Figure 3. Resolution of periorbital and facial puffiness post treatment.

DISCUSSION

Approximately 15 to 20% of patients with systemic lupus erythematosus (SLE) have anti-thyroid antibodies, a higher percentage than is found in normal subjects of the same age. The antibody titres may fluctuate and clinical thyroid disease is associated with the persistent presence of these antibodies. The prevalence of overt thyroid disease appears to be between 3 and 19%, with subclinical or overt hypothyroidism being more common than hyperthyroidism in most studies.[1-3] In a study of 153 SLE patients screened for thyroid disease, there was a significant increase in the prevalence of hypothyroidism (19%), hyperthyroidism (9%), and thyroid antibodies (33%) in comparison with controls (2%, 1%, and 13%, respectively).[1-3] In a study of 3286 Caucasian subjects with Graves' disease (2791 cases) or Hashimoto's thyroiditis (495 cases), there was a significantly increased relative risk of SLE in both diseases, with the relative risk in women being over 10-fold.[4] However, there is limited evidence that the concurrence in the same patient of thyroid disease and connective tissue disease alters the clinical manifestations or natural history of either disorder.

The development of thyroiditis can occur before or after the diagnosis of SLE. In a study of 300 lupus patients, 22 (7%) had thyroid disease. There were 17 (5.7%) cases of hypothyroidism; eight were diagnosed before the onset of SLE, six after, and three simultaneously. There were five cases (1.7%) of hyperthyroidism, two diagnosed before the onset of SLE and three afterwards.[1] The development of lupus may be as long as five years later.[5]

SLE is an autoimmune disorder characterized by involvement of various organs. Inflammation of serous membranes including pericardium and pleura is relatively common (16%) and accepted by American College of Rheumatology as one of the 11 criteria of SLE.[6] However, ascites with lupus peritonitis is extremely rare and has only been described in a small group of patients.[7,8] The mechanism of ascites in SLE may be multifactorial. It is postulated that the deposition of immune complexes in the peritoneum and activation of complements play a crucial role. In addition, vasculitis of peritoneal vessels or the serous membrane of abdominal organs may be related to lupus peritonitis.[8] Nevertheless, other more common causes of exudative ascites have to be ruled out. On the other hand, in this case, one may think the presence of ascites is most likely due to hypothyroidism instead of lupus peritonitis since the incidence is extremely rare. It is important to note that ascites due to hypothyroidism is transudative rather than exudative.

Ito and associates in a review of chronic lupus peritonitis, reported that in all patients treated with steroids, only 13/16 achieved remissions. In 40%, additional immunosuppressant agents were required to manage incomplete remission and recurrence of ascites.[7] The strength of the approach to this case was that an accurate diagnosis was made and she was followed up regularly to monitor her symptoms and biochemical parameters. She underwent extensive investigations to ensure the accuracy

Table 3. Trends of thyroid function tests

Date	27/10/15	2/11/15	15/11/215	30/11/15	10/12/15	22/12/15
FT4 (pmol/L)	4	14	16.7	12.5	18.3	14.1
TSH (mU/L)	>100	16	14.9	6.25	5.4	4.74
Levothyroxine dose (mcg/day)	300	150	150	100	50	25

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of the diagnosis. Hence, appropriate treatments were instituted. The limitation of the approach was a slight delay in diagnosing SLE because of the overlapping symptoms and the concern of malignancy at the beginning resulting in extensive surgeries.

This patient will require life-long monitoring of her thyroid status and adjustment of the thyroid replacement therapy accordingly. There is limited evidence that the presence of both diseases alters the natural history, manifestation or treatment of either disorder. Nevertheless, the concurrence of autoimmune thyroiditis and SLE can pose some risks if she is considering pregnancy. An increased risk of preterm delivery has been noted in pregnant women with SLE and thyroid disease. In a retrospective study of 63 pregnant women with SLE, 37.9 percent of the cohort had thyroid disease diagnosed before, during, or immediately after pregnancy. Preterm delivery occurred in 67 percent of the women who had thyroid disease, compared with 18 percent of the women with SLE who remained free of thyroid disease. Thyroid antibodies did not predict preterm delivery in this group of women.[9]

CONCLUSION

Thyroid disorders are commonly associated with many autoimmune rheumatic diseases such as SLE and it can occur before or after the diagnosis has been made. It is reasonable to assess thyroid function tests in most patients on presentation and periodically thereafter. In addition, it is important to keep vigilant on the development of SLE following a diagnosis of autoimmune thyroid disease. This case illustrates the importance of early recognition of an atypical presentation of wide spectrum multi-systemic diseases such as SLE with regards to thyroid disorders.

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Ethical Consideration
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Statement of Authorship
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Author Disclosure
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CASE REPORT

Ectopic ACTH syndrome – Experience with Etomidate*

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Abstract

For ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS), when surgery is not feasible, or in cases of severe biochemical disturbances, immunosuppression or mental instability, medical therapy with agents such as etomidate is indicated. We present our experience in using etomidate for a 41-year old female with EAS secondary to a malignant mediastinal paraganglioma. We were able to demonstrate that etomidate can be used effectively to control severe hypercortisolism in a lower dose than previously described.

Key words: etomidate, ectopic ACTH syndrome, Cushing's syndrome

INTRODUCTION

Medical therapy is indicated in ectopic ACTH syndrome (EAS) when surgery is not feasible, or in cases of severe biochemical disturbances, immunosuppression or mental instability. A cortisol inhibitor such as etomidate may be used in these situations.

CASE

We report a rare case of a 41-year-old Malay female with an ectopic ACTH-producing malignant paraganglioma. Our patient presented in February 2014 with an acute stroke. She was also found to be diabetic and hypertensive. Three months later, she was readmitted for severe, symptomatic hypokalemia and poorly controlled diabetes. Her attending physician noted her Cushingoid features. On further inquiry, she had proximal limb weakness, easy bruising, amenorrhea and acne for the past 3 months. She also noticed significant weight loss and insomnia. She did not experience any paroxysms of headache, palpitation and diaphoresis. She was referred to an endocrinologist in a private hospital, who diagnosed her to have ACTH-dependent Cushing's syndrome. She had markedly elevated midnight serum cortisol [2609 (<50 nmol/L)] and ACTH [62.04 (2.2-13.2 pmol/L)]. Twenty four-hour urine metanephrine level was not elevated. Further imaging using computerized tomography (CT) scan for localization revealed a large lobulated mediastinal mass in the anterior superior mediastinum, mediastinal lymphadenopathy and multiple lung nodules (Figures 1A and 1B). A CT scan-guided fine needle aspiration showed that the mediastinal mass was of neuroendocrine origin, possibly a thymic carcinoid. It stained positive for ACTH on immunohistochemistry. She was then referred to our hospital for further management.

On our assessment, we noted that the patient had truncal obesity, with a body mass index of 29 kg/m^2 (weight 70 kg, height 1.55 m). She had prominent hyperpigmentation; most conspicuous over her knuckles, palmar creases and knees; multiple ecchymoses; acne; and mild hirsuitism, with Ferriman-Gallwey score of 9.

Oral ketoconazole was given at 200 mg twice daily and then uptitrated to 400 mg three times a day for control of hypercortisolemia while awaiting definitive therapy. She required continuous potassium replacement, insulin (up to 100 units per day) and 3 anti-hypertensive agents, including spironolactone. While awaiting surgery, she developed a left lung abscess. Blood culture yielded *Bacillus sp*. This was resolved after bronchial washout and intravenous meropenem and sulfamethoxazole + trimethoprim. She then underwent debulking surgery of her mediastinal tumor on 13 August 2014. Intraoperatively, a large mass infiltrating into the superior mediastinal tissue and over the pericardial surface of right side of heart was seen. It was adherent to right parasternal area and chest wall. Despite the complexities of her surgery, she had an uneventful recovery. Histopathologic examination of the tumor showed malignant mediastinal paraganglioma with heterogenous Ki67 index, ranging from 20% in most areas to 70%. The tumor cells stained strongly positive for neuron-specific enolase, synaptophysin, chromogranin A and CD56.

After debulking surgery, she remained clinically and biochemically Cushingoid despite ketoconazole treatment [ACTH 59.5 (2.2-13.2 pmol/L)]. Metaiodobenzylguanidine

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Table 1. Biochemical parameters monitored during etomidate infusion

	Date, December 2014																			
	15	**17**	**17**	**17**	**18**	**18**	**18**	**18**	**19**	**19**	**19**	**19**	**19**	**20**	**21**	**22**	**22**	**23**	**24**	**29**
Time		**0838**	**1745**	**1836**	**0238**	**0614**	**1400**	1600	1026	1520	1800	1930	2211	1351	1350	0523	1251	0642		
Etomidate infusion rate, mg/hour	-	-	2.6*	2.6	2.6	2.6[§]	2.6[a]	2.0	1.0	1.0	1.0	1.4[b]	1.4	1.4	1.4	1.4	1.4	1.4	1.4**	-
Hydrocortisone infusion rate, mg/hour	-	-	-	-	-	-	-	-	0.5[†]	0.0[‡]	-	-	-	-	-	-	-	-	-	-
Serum cortisol, nmol/L	2952	4690	-	3224	1942	1384	424	-	1297	-	1477	-	1221	1075	949	888	1153	668	-	19
Serum sodium, mmol/L	-	146	-	147	-	146	142	-	136	-	135	-	-	134	139	144	138	141	-	-
Serum potassium, mmol/L	-	4.0	-	3.2	-	4.6	4.5	-	4.2	-	4.0	-	-	3.5	4.1	4.6	5.1	4.5	-	-
Blood glucose, mmol/L										8.4-14.7						6- 9				

Initiation of etomidate infusion: **Discontinuation of etomidate infusion upon induction of anesthesia; [†]Initiation of hydrocortisone infusion; [‡]Discontinuation of hydrocortisone infusion; [§]Discontinuation of Ketoconazole; [a]Extubation; [b]BP and blood glucose increasing, noted to be more breathless

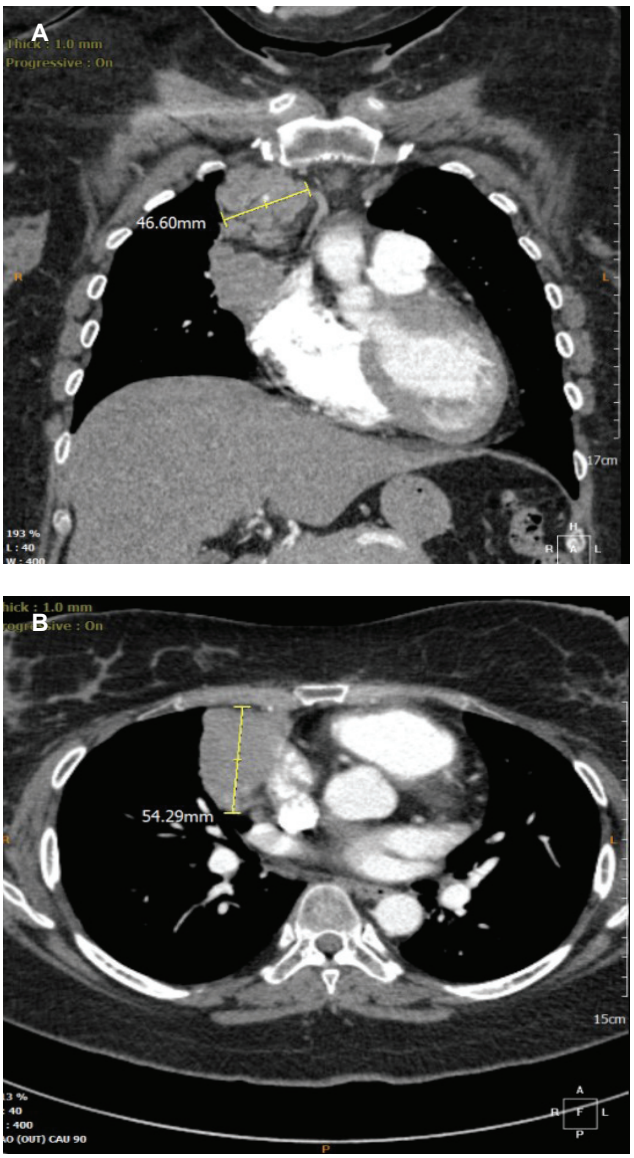

Figure 1. Computerized tomographic scan of the thorax showed a large infiltrative anterior mediastinal mass measuring 5.4 cm x 5.9 cm x 3.8 cm at the anterior superior mediastinum, abutting into right heart margin (coronal view, A). Multiple lung nodules (largest measuring 1.3 cm x 1.1 cm) and mediastinal lymphadenopathy were also noted (axial view, B).

(MIBG) scan showed no evidence of MIBG-avid disease. She was then referred to our oncology team. Since the patient declined chemotherapy, she received 30 cycles of external beam radiation which was completed on 15 December 2014. Throughout radiotherapy, her blood glucose control became more challenging, and she had persistent hypokalemia despite regular potassium supplementation. Following radiotherapy, she developed severe nosocomial pneumonia and steroid-related myopathy requiring subsequent invasive ventilation. In view of uncontrolled severe hypercortisolism despite maximal doses of ketoconazole, she was referred for bilateral adrenalectomy.

Intravenous infusion of etomidate was initiated at the recommended low dose of 0.04 mg/hour under close monitoring in the intensive care unit. Vital signs, blood sugar, serum electrolytes and cortisol levels were monitored. We aimed to achieve partial blockade with a target serum cortisol of 500 to 800 nmol/L prior to surgery. Our patient responded rapidly to etomidate: after 8 hours of infusion, cortisol level was halved; after 20 hours, it was relatively low (424 nmol/L), prompting reduction of etomidate infusion rate. Upon the development of hypocortisolism, as indicated by low blood pressure and the need to discontinue intravenous insulin, intravenous hydrocortisone was started. With etomidate infusing at a rate of 1.4 mg/hour (0.02 mg/kg/hour), we managed to achieve a cortisol level of 668 nmol/L just before adrenalectomy (Table 1). The patient underwent bilateral retroperitoneoscopic adrenalectomy on 24 December 2014. Etomidate infusion was stopped prior to induction of anesthesia. As anticipated, blood pressure and sugar control was more manageable after adrenalectomy.

Repeat CT scan on 13 February 2015 showed a slightly smaller residual mediastinal tumor, multiple subcentimeter mediastinal lymph nodes, multiple lung nodules and sclerotic lesions over vertebrae T3, T5, T6, T8, T9 and T11. Our patient unfortunately succumbed one year later in March 2016 after a sudden cardiorespiratory arrest, presumably due to acute pulmonary embolism.

DISCUSSION

Ectopic ACTH syndrome was first described by Brown in 1928 as "Pluriglandular syndrome: Diabetes of bearded women."[1] It accounts for 5 to 10% of cases of ACTH-dependent Cushing's syndrome. EAS is more commonly

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caused by intrathoracic neoplasms.[2] It typically presents with rapid clinical evolution due to high ACTH levels and the malignant nature of the neoplasm. Apart from the common features of Cushing's syndrome, anorexia, weight loss and anemia may also be found. Hypokalemia occurs in up to 80% of EAS due to the mineralocorticoid effects of markedly elevated cortisol levels and the decreased activity of 11-hydroxysteroid dehydrogenase type 2.[3] Cushing's syndrome secondary to ectopic ACTH-producing mediastinal paraganglioma is extremely rare. To date, less than 5 cases have been reported. Mediastinal paragangliomas arise from chromaffin tissue located in the para-aortic ganglia, with a tendency to invade bordering structures as observed in our patient. Fifty percent of patients are asymptomatic and incidentally diagnosed.[4] Other manifestations include mass effects and hormonal hypersecretion.

Surgical clearance of tumor is the only curative measure in EAS. In cases where surgery is not feasible, medical therapy to control hypercortisolemia is imperative. Other indications of medical therapy include severe biochemical disturbances, such as hypokalemia; immunosuppression; mental instability; or following radiotherapy. Bilateral adrenalectomy may be considered in patients with severe hypercortisolemia or intolerance to oral therapy.[5] Surgical risks may be significantly reduced if cortisol levels are normalized preoperatively. Etomidate is a carboxylated imidazole which inhibits mitochondrial cytochrome P450-dependent enzyme 11β-hydroxylase that catalyzes cortisol conversion from deoxycortisol. It was initially developed as an intravenous hypnotic non-barbiturate induction anesthetic agent, but was noted to increase mortality in critically unwell patients and cause low serum cortisol. The starting dose is 0.04 to 0.05 mg/kg/hour (2.5 to 3.0 mg/hour). Etomidate initiation should be monitored in the ICU setting for close monitoring of plasma cortisol and potassium. Intravenous hydrocortisone may also be used in a "block and replace" strategy, with a serum cortisol target of 500 to 800 nmol/L.[6] There is a clear delineation between higher anesthetic dose and lower doses which inhibits adrenal function. Schulte showed that etomidate only causes prominent sedation at the highest dose of 0.3 mg/kg/hour. In their protocol, etomidate is started at 2.5 mg/hour regardless of body weight, and titrated up to 4 mg/hour according to cortisol level.[7] Etomidate is an effective treatment for hypercortisolism, but is limited to short-term use. It is generally used to "buy time" while awaiting other definitive therapy.

Our patient required a much lower dose of etomidate compared to other protocols. As with many other treatments, the dosages required by Asian patients tend to differ from their Caucasian counterparts. This is possibly due to ethnic differences in the metabolism of medications. From our own experience, we will continue to use a lower starting dose of etomidate on our patients in the future. Close clinical and biochemical monitoring of patients to enable appropriate dose adjustment is essential.

CONCLUSION

Low dose etomidate can be effectively used to control severe hypercortisolism.

Ethical Consideration
Informed consent has been taken before submission of the manuscript.

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

Author Disclosure
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CASE REPORT

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Metastatic Follicular Thyroid Carcinoma as a Cause of Low Serum Thyroxine with a Normal Thyroid Stimulating Hormone Level

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Abstract

Thyroid function is usually normal in differentiated thyroid carcinoma. We describe a case of a female patient who had metastatic follicular thyroid carcinoma (FTC) to the spine and lungs, who was clinically euthyroid but had very low free tetraiodothyronine (fT4) and normal thyroid stimulating hormone (TSH). Free triiodothyronine (fT3) and total T3 (TT3) were normal. Levothyroxine treatment increased fT4 marginally but caused a two- to three-fold rise in fT3 and TT3 along with suppressed TSH. This is likely due to hyperconversion of T4 to T3 from elevation in D2 deiodinase activity in the tumor. This phenomenon has been reported to occur in about 20% of metastatic FTC.

Key words: follicular thyroid carcinoma, increase deiodinase activity

CASE

A 46-year-old female presented to our hospital in 2008 with gradual onset of paraparesis of both lower limbs. She had right hemi-thyroidectomy performed 12 years ago at another hospital. She did not monitor TSH, nor did she receive levothyroxine replacement at any time. Magnetic resonance imaging (MRI) of the spine showed multiple areas of abnormal marrow signals in the spine, involving the T4, T6, T7, T12, L2, L3 and S1 vertebrae. Collapse of the T4 vertebra was seen with posterior cortical margin convexity and associated pre- and para-spinal and anterior epidural soft tissue components, causing compression on the thecal sac with moderate to severe secondary central canal stenosis (Figures 1A and B). Computed tomography (CT)-guided biopsy of the third lumbar spinal lesion revealed tumor cells which were positive for thyroglobulin immunohistochemistry, suggestive of metastatic follicular thyroid carcinoma.

CT scan of the neck showed a remaining homogenous left thyroid gland with no abnormal calcification or nodule. A right-sided pleural effusion with collapse and consolidation of the right lower lobe of the lung was also present. Pleural fluid biochemistry was exudative, but cytology showed nonspecific staining of mesothelial cells and macrophages. It was most likely malignant in origin. Serum thyroglobulin was markedly elevated (3682 mg/mL) and antithyroglobulin antibody was <4 IU/mL.

She refused total thyroidectomy or any surgical intervention for her spinal compression. Local radiotherapy to the spine was then given. As radiotherapy was done in another hospital, we were not aware of the response to treatment. Bisphosphonate therapy was also not given. Due to the extent of disease, palliative care was offered. She defaulted clinic follow-up and was admitted several times for recurrent pleural effusion. The event leading to death 2 years ago was respiratory failure, which may have been due to pulmonary embolism due to chronic immobilization.

Serial thyroid tests showed extremely low fT4 levels with normal fT3, TT3 and TSH. Levothyroxine 100 mcg daily was started, which raised fT4 minimally but increased fT3 to 1.5-fold the upper limit of normal and suppressed TSH even further (Table 1). Cortisol showed appropriate response to Synacthen®: baseline serum cortisol of 749 nmol/L rose to 1236 nmol/L at 30 minutes and 1447 nmol/L at 60 minutes. Adrenocorticotropic hormone, follicular stimulating hormone, luteinizing hormone, estradiol and prolactin were normal.

DISCUSSION

Thyroid hormone production is regulated by both pituitary and peripheral factors. While the secretion of TSH is inhibited by T4 and T3, it is stimulated by thyrotropin releasing hormone. The thyroid follicular epithelial cell is responsible for the biosynthesis of thyroid hormones. As the main product of the thyroid gland, T4 functions as a prohormone which is transformed into the biologically active hormone, T3. Extra-thyroidal conversion of T4 to T3 is regulated by nutritional,

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Table 1. Serial thyroid function test results

Parameter	Reference Value	Date					
		21 May 2013	23 July 2013	15 Oct 2013	20 Jan 2014	12 July 2014	5 Aug 2014
TSH[a], mIU/L	0.27-4.2	1.42	3.76	2.26	3.2	0.008	<0.005
fT4[b], pmol/L	12.0-22.0	0.4	0.8	0.7	0.7	0.3	2.3
TT3[c], nmol/L	0.90-2.60				1.73		4.03
fT3[d], pmol/L	3.5-6.0	4.2			5.3		9.4
LT4[e] dose/day, mcg	N/A	-	-	-	-	100	100

[a]TSH, thyroid stimulating hormone, determined using electrochemiluminescence immunoassay (ECLIA) using COBAS® E Immunoassay Analyzer
[b]fT4, free tetraiodothyronine, determined using ECLIA using COBAS® E Immunoassay Analyzer
[c]TT3, total triiodothyronine, determined using chemiluminescent immunoassay using the Access® Immunoassay System
[d]fT3, free triiodothyronine, determined using chemiluminescent immunoassay using the Access® Immunoassay System
[e]LT4, levothyroxine

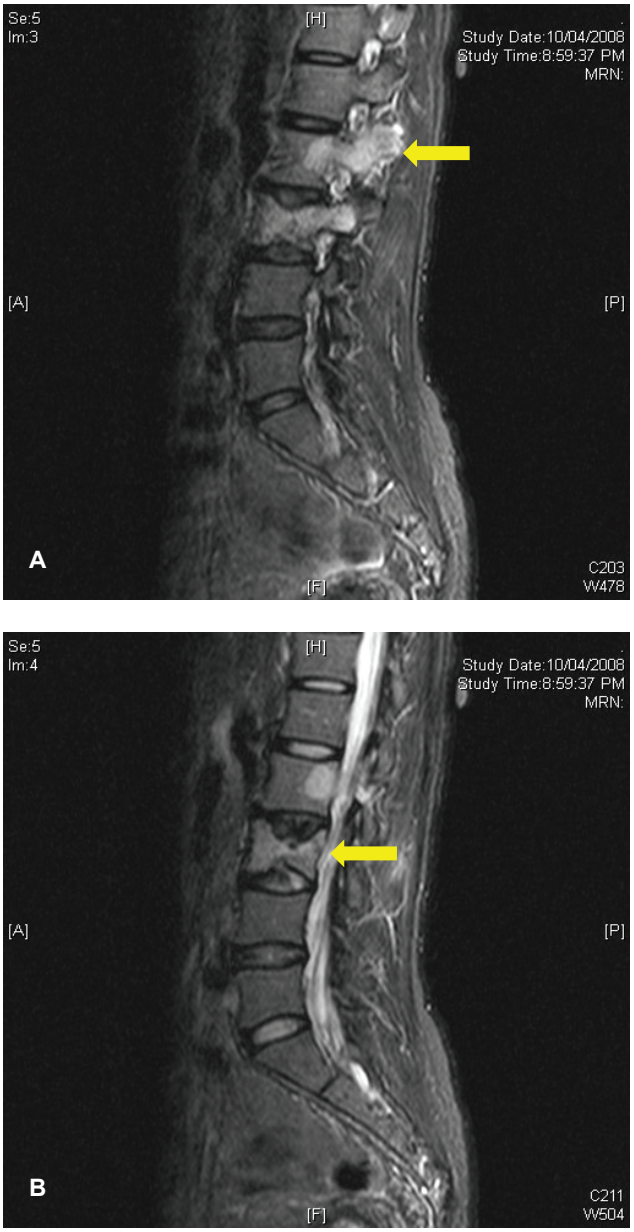

Figure 1. Magnetic resonance imaging of the spine showing vertebral metastases (yellow arrow) on parasagittal (A) and sagittal (B) views.

hormonal and illness-related factors. Approximately 80% of the T3 produced is formed by 5′-deiodination of T4 in extra-thyroidal tissue.[1] Three iodothyronine deiodinases (D1, D2, D3) have been identified.

T4 and TSH are usually undisturbed in thyroid carcinoma. However, in a minority of cases of metastatic follicular thyroid carcinoma, an elevated serum T3 to T4 ratio is seen. Several studies have evaluated the expression of deiodinase activity in thyroid neoplasms. D1 activity has been found to be reduced in papillary, follicular and anaplastic thyroid carcinomas. In contrast, a high level of D2 activity has been reported in metastatic follicular thyroid carcinoma, resulting in an increased fractional conversion of T4 to T3.[2-4]

D1 and D2 activities were assayed in the tumor resected from a patient in a previous case report.[2] The tumor D2 converted 73 ± 3% of T4 to T3, compared to 26 ± 3% in the normal human thyroid. Most of these patients presented with either bulky primary tumors or metastatic disease. Akira et al., found that 20% of patients with massive metastatic follicular carcinoma had T3 thyrotoxicosis while on thyroxine treatment, whereas none of the patients with papillary or medullary thyroid carcinoma exhibited this phenomenon.[5]

Our patient had very low serum fT4, in the range of 0.4 to 0.7 pmol/L, with normal levels of TSH, fT3 and TT3. When exogenous thyroxine was started, fT4 increased marginally, with a consequent suppression of TSH and increase in fT3 and TT3. This is an indirect evidence of hyperconversion of T4 to T3, likely due to a high D2 activity. However, the activity of deiodinase was not evaluated in the tumor tissue of our patient.

In these patients, frequent monitoring of T3 levels along with fT4 and TSH should be done to avoid overzealous treatment with exogenous thyroxine. Unfortunately, we were not able to titrate and optimize the dose of levothyroxine in this patient, as she defaulted follow-up and only returned later with other complications.

CONCLUSIONS

It is rational to consider elevated D2 deiodinase activity in follicular thyroid carcinoma as a cause of a low T4 with normal TSH. This increases the conversion of T4 to triiodothyronine, making measured T3 levels normal. Thyroid suppression therapy should be titrated according to T3 and TSH levels to avoid T3 thyrotoxicosis.

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Ethical Consideration
Consent from the patient was not obtained because of her demise.

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

Author Disclosure
The authors have declared no conflict of interest.

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ORIGINAL ARTICLE

Unusual Manifestations Associated with Primary Hypothyroidism: Experience from A Tertiary Care Health Center

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Abstract

Hypothyroidism is a commonly diagnosed endocrine disorder. Typical signs and symptoms of hypothyroidism include lethargy, cold intolerance, hoarseness, dry skin, constipation, delayed relaxation phase of deep tendon reflexes, and bradycardia. However, some patients may present with unusual signs and symptoms of hypothyroidism which can result in diagnostic confusion.

Besides the usual clinical manifestations of primary hypothyroidism, some signs are very unusual and not commonly recorded. The treating physician may not be familiar with them. Hence, timely identification of these unusual presentations is very important for early intervention and treatment.

Key words: primary hypothyroidism, Van Wyk-Grumbach syndrome, Kocher-Debre-Semelaigne syndrome

INTRODUCTION

Primary hypothyroidism is a common autoimmune disorder of paediatrics as well as the adult population, and may be associated with unusual manifestations, e.g., calf muscle hypertrophy, pericardial effusion, precocious puberty, etc. The prevalence varies from 10-12% in the Indian population.[1] Hypothyroidism, presenting with classic manifestations is readily diagnosed and treated. Occasionally, patients present with less commonly recognised symptoms, making the diagnosis less apparent. Such atypical presentations may be suggestive of another disease or pathological entity. Therefore, the initial focus of attention gets diverted away from hypothyroidism towards investigating for other diseases. We considered it instructive to compile a report about such patients, as it emphasizes the need to be aware of the unusual presentations of hypothyroidism and to consider hypothyroidism when confronted with such atypical clinical manifestations.

CASE 1

An 11-year-old female child presented with complaints of growth failure, fatigue, puffiness of face, hoarseness of voice, and deafness for 1 year. She also gave a history suggestive of proximal muscle weakness, hair loss, constipation, and cold intolerance. Her antenatal, natal, and postnatal history were unremarkable as were her past and treatment history. There was no history of any radiation exposure. No other member of the family was affected.

On general examination, her pulse rate was 70/min, regular, all peripheral pulses palpable; BP was 86/70 mm Hg with no postural variation. The presence of coarse facial features, depressed nasal bridge, facial and periorbital puffiness, dry skin, and acanthosis nigricans was noted. She weighed 19.2 kg, her height was 108 cm (both below third percentile); arm span was 104 cm, the upper segment to lower segment ratio was 0.9. Her IQ was normal. Systemic examination revealed bilateral bulky calf muscles, delayed contraction and relaxation of ankle jerks, and pseudomyotonia of calf muscles with negative Gower's sign (Figure 1). Her gait was normal. The rest of the nervous system and other systemic examination were within normal limits. The investigation performed showed hemoglobin of 9.4 g% with normocytic normochromic red blood cells on peripheral smear. The total and differential leucocyte count and platelet counts were normal. Renal and kidney function tests were normal. Urinary examination showed no abnormalities. The bone age was only 5.3 years (by Tanner White House 2). Audiometry showed conductive hearing loss.

Thyroid hormone deficiency was evident as serum T4 was <1.0 μg/dl (4.5-12.0), serum T3 was <0.25 ng/ml (70-130), and serum TSH was 1186.0 μIU/ml (0.30-5.0). A primary autoimmune etiology was confirmed by raised anti-TPO antibody titre >1300 U/ml. Serum CPK was raised to 1062 U/L and aPTT was prolonged for 47.90 s (34.90). Ultrasonography of the thyroid gland suggests diffuse bilateral enlargement of thyroid lobes.

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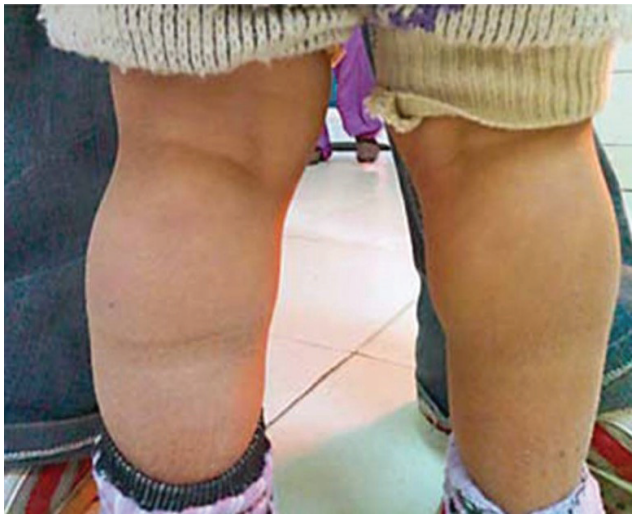

Figure 1. Pseudohypertrophy of the calf muscles.

A diagnosis of autoimmune thyroid disease causing primary hypothyroidism, was made and she was treated with 50 μg thyroxine once a day. On follow-up after 3 months, she showed significant improvements in her symptoms, thyroid function tests and regression in the volume of the calf muscles was noted. Repeat TSH after 3 months was 2.54 μIU/ml.

CASE 2

A 26-year-old married female presented with a chief complaint of menorrhagia for the last 3 months with intermittent abdominal pain for the last month. She had been bleeding heavily for the last 12 days, along with the passage of clots. Over the last 3 months, her cycle interval had increased from 45 to 60 days and bleeding had increased in duration and amount. Her menarche was at a normal age of 11 years followed by regular cycles until the last 3 months. There was history of weight gain and malaise for last 2-3 yrs. Her physical examination revealed weight 75 kg, height 156 cm and BMI 30.8. She had an apathetic expression. Her pulse was 64 bpm and BP 124/92 mm Hg. Her IQ was normal. She was pale with periorbital puffiness, dry skin and swelling over hands and feet and delayed reflexes. The thyroid gland was not enlarged and there was no galactorrhea. On abdominal examination, an abdominopelvic mass reaching upto the umbilicus was felt, which was cystic, non-tender and mobile. Her laboratory tests revealed mild anemia with a dimorphic picture on peripheral blood film. Ultrasound of the abdomen and pelvis showed bilateral enlarged multicystic ovaries. The uterus was normal with endometrial thickness of 6.4 mm. Her TSH 124.6 IU/L (0.2–4.6 IU/L), total T_4=1.2 μg/dL (5–12.5 μg/dL), T_3=12.5 ng/dL (60–180 ng/dL)]. Ultrasound of the thyroid showed small thyroid lobes with heterogenous coarsened echo pattern suggestive of chronic thyroiditis. Antithyroid peroxidase was positive 1300 U/ml (positive >50). Patient was started on 50 ug of thyroxine and gradually increased to 125 ug. The acute bleeding episode was controlled with oral progesterone and hemostatic drugs. She was started on oral iron supplemenation and calcium. By 6 weeks, both the ovarian cysts had resolved completely. At the 3rd month follow up, the patient was euthyroid with TSH level of 3.67 μIU/ml along with normal menstrual cycles and weighed 64 kg.

CASE 3

An 18-year-old female presented to the outpatient department with complaints of gradually progressive swelling over her legs over 3 months. There was no diurnal or postural variation, and it did not respond to diuretics previously prescribed to her. In addition, she had gained 5 kgs weight since 1 year, associated with malaise, fatigability and intolerance to cold. On further questioning, her relatives confirmed that her voice had become hoarse. She also took medications for relieving constipation. The patient was a non-smoker and non-drinker, with no family history of any chronic illness or thyroid disorders.

On examination, her skin was dry and scaly. Her pulse rate was 78/min, bilaterally symmetrical with normal rate, rhythm and volume. She was afebrile, having a normal blood pressure with no postural variation. Her eyes were slightly protruding with normal conjunctiva (Figure 2). A soft, diffuse swelling over her neck without any nodularity or overlying skin changes was observed suggestive of goitre. Bilateral, non-pitting edema was noticed below her knees. There was no evidence of tremor on outstretching her fingers. The rest of the systemic examination was within normal limits.

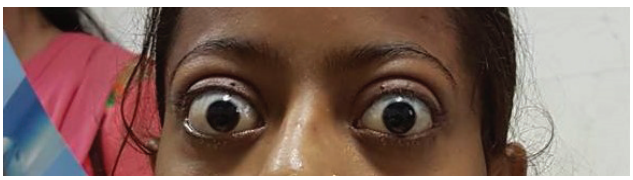

Figure 2. Hypothyroid ophthalmopathy.

On investigating further, haemogram, ECG, kidney and liver function tests were within normal limits. Fundus examination and perimetry was normal. Thyroid function tests revealed the presence of overt hypothyroidism with a thyrotropin (TSH) level of 94.1 μIU/ml (normal: 0.4-5), free 3,5,3′-triiodothyronine (FT3) of 1.76 pg/dl (normal: 1.8-4.2) and free thyroxine (FT4) of 0.54 ng/dl (normal: 0.8-1.9).Thyroid receptor antibody (TRAb) was 147 U/L (normal range: 0-9 U/L), anti-thyroid peroxidase antibody (Anti TPO Ab) titre was >3000 IU/ml (normal range: 0-50 IU/ml), suggestive of Hashimoto's autoimmune thyroiditis. Ultrasound study of thyroid revealed bilateral enlargement of the thyroid gland with normal vascularity and absence of any nodular changes. Exophthalmos was documented with by Hertelex ophthalmometry. Clinical activity score (CAS) was 0 and a "NOSPECS" score was class 1.

ONLINE FIRST | May 9, 2017 | https://doi.org/10.15605/jafes.032.01.12

Subsequently she was started on levothyroxine replacement therapy (dosage 1.6 μg/kg body/wt.). Over the next 6 months, there was gradual regression of pedal edema. She was relieved of her gastrointestinal symptoms and reported feeling more energetic than before. However, her eye changes were more or less unchanged and she continues to present himself at regular intervals for follow up.

CASE 4

A 33-year-old female presented to the emergency department with complaints of insidious and gradually progressive breathlessness, along with swelling of both feet. There was no history of medical illness and drug history in the past. Vital signs on admission were recorded (temperature, 37°C; blood pressure, 86/54 mm Hg; heart rate, regular at 68 beats/min). On examination, the apex beat was not felt and the heart sounds were soft and distant. The JVP was raised (6 cm). Chest auscultation revealed bilateral basilar crepitations, and there was mild tenderness in right upper quadrant of the abdomen. Her SpO2 was 95%, and other vitals were stable. Electrocardiogram showed heart rate of 68/min with low voltage pattern with electrical alternans. Bedside echocardiogram demonstrated small heart size with massive pericardial effusion and signs of early diastolic right ventricular (RV) collapse (Figures 3 and 4). There was swinging motion of heart within large effusion, prominent respiratory alteration of RV dimension with right atrial (RA) and RV collapse during diastole. Pericardial effusion was noted in the pericardial cavity and all cardiac chambers were of small size with predominant diastolic heart failure. A provisional diagnosis of pericardial effusion with cardiac tamponade was made. Investigations revealed elevated Pro BNP levels (>1000 pg/ml). Renal functions were slightly deranged (Creatinine 1.6 mg/dl, BUN 30 mg/dl) with normal electrolytes. Liver functions showed elevated transaminases (SGOT 140 IU/L, SGPT 80 IU/L). A thyroid profile revealed TSH=300 mIU/L (N=0.5-4.2 mIU/L), T4 (total)=3 μg/dl (N=5.01-12.45 μg/dl), consistent with hypothyroid state. Serum Anti TPO antibody 448.70 U/ml (N=<65). Ultrasound study of the abdomen showed presence of mild hepatosplenomegaly, minimal ascites and evidence of increased systemic venous pressure. We transferred the patient immediately to the Intensive Care Unit for pericardiocentesis. Thyroxine replacement was started. Unfortunately, the patient's condition deteriorated after 3 days. She went into a state of refractory shock, unresponsive to fluids and vasopressors. We suspected an adrenal crisis, and gave her intravenous hydrocortisone (100 mg TID). However, she could not be resuscitated and expired on the 4th day of hospitalization.

CASE 5

An 18-year-old man presented with a history of enlargement of the testes for the last 10 years. He had a normal birth and normal childhood development.

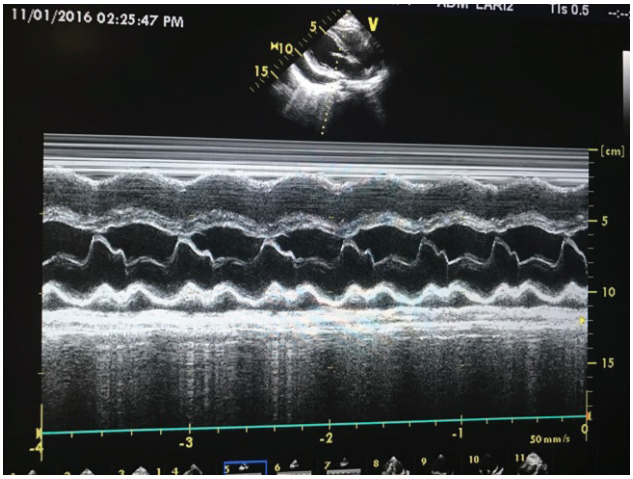

Figure 3. Apical four chamber view shows right atrial and right ventricle diastolic collapse.

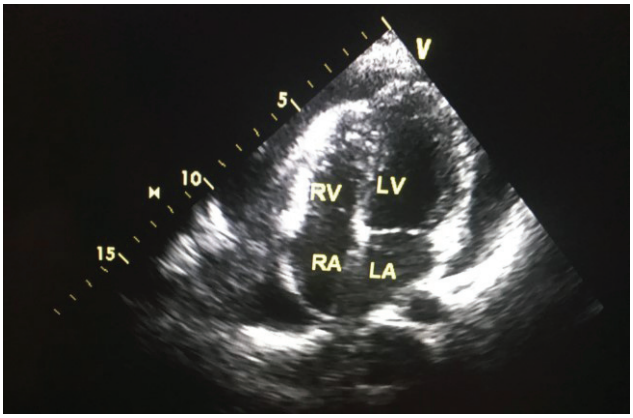

Figure 4. M-mode echo at the level of mitral valve in parasternal long axis shows diastolic right ventricle collapse.

However, he had failed to gain height during his adolescent years, with no evidence of development of axillary hair, pubic hair, gynecomastia, beard and moustache. There was no history of weight gain, nor any suggestion of mental retardation. On examination, his height was 126 cm (less than 3rd percentile), weight of 36 kg (less than 3rd percentile), body mass index of 22.7 kg/m^2, body surface area of 1.10 m^2, arm span of 124 cm. The mid parental height was calculated to be 160 cm. His sexual maturity score was axillary hair (A) stage 1, pubic hair (P) stage 1 with a testicular volume of 20 ml (Figure 5). He had coarse facies, dry skin, brittle nails, calf muscle hypertrophy and delayed relaxation of ankle reflexes. There was no evidence of goitre. His investigations revealed a normal haemogram, renal and liver functions. Bone age was 7.2 years (Tanner Whitehouse 2 staging). Hormonal profile was consistent with primary hypothyroidism [TSH >100 mIU/L, T4 (total)=2.1 μg/dl]; anti-thyroid peroxidase antibody levels were raised (500 units/ml). FSH, LH and testosterone levels were within normal limits. Ultrasound revealed enlarged testicular volume (right = 24.5 ml, left = 24 ml) with no evidence of varicocele or fluid collection. The patient was subsequently started on levothyroxine

ONLINE FIRST | May 9, 2017 | https://doi.org/10.15605/jafes.032.01.12

replacement and is being followed up regularly for progress of pubertal development. On regular follow up, testicular size remained the same; however, axillary and pubic hair appeared and patient had considerable catch up growth.

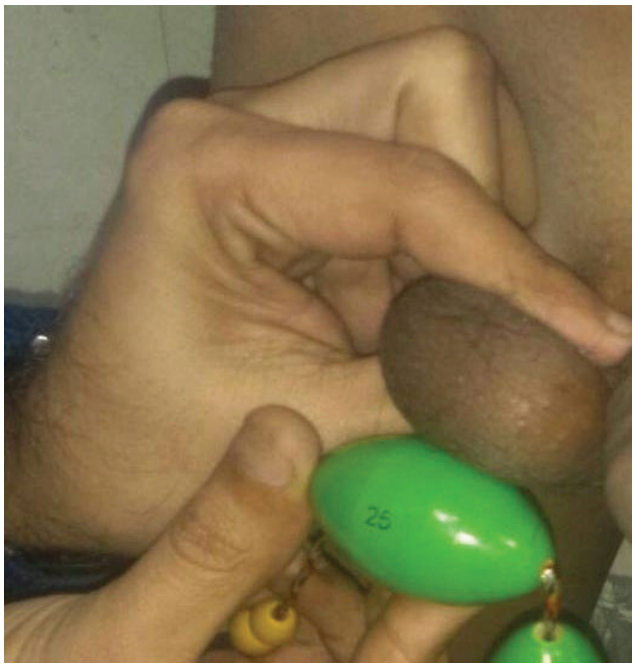

Figure 5. Testicular volume >25 ml bilaterally, with no pubic hair in hypothyroid patient.

CASE 6

An 18-year-old male patient was diagnosed to have primary hypothyroidism 6 months back following weight gain, edema and facial puffiness of 3 years duration. His initial thyroid function tests showed the following T4: 2.3 μg/dl (5.01-12.4) T3: 0.35 ng/ml (0.6-1.81) and thyroid stimulating hormone (TSH): 180 μIU/ml (0.35-5.50) and he was started on levothyroxine, with significant improvement of symptoms. He was referred to our hospital after her developed myoclonus for the previous 1 month, 2 months after thyroxine replacement therapy.

On examination, he was conscious, with cognitive impairment and had memory loss for recent events, with the poor attention span, difficulty in finding words, dyscalculia and dysgraphia. His mini mental status examination (MMSE) was 11 suggestive of moderate cognitive impairment. He also had myoclonus, involving both upper limbs and lower limbs.

On investigation, blood routine examination and erythrocyte sedimentation rate were normal and liver function tests, kidney function tests, electrolytes calcium and magnesium were normal, as was the arterial blood gas analysis. His most recent TFTs showed normal T3 and T4 levels, with mild elevation of TSH (TSH-9.1 μIU/ml). Anti-thyroid peroxidase antibody was positive (>1300 IU ml). His electroencephalogram (EEG) showed a diffuse slow wave activity and magnetic resonance images (MRI) non-specific white matter changes (Figures 6 and 7). Cerebrospinal fluid (CSF) study had normal cytology, but slightly increased protein of 69.2 mg% (N=10-50 mg%). Antinuclear antibody titer, anti-double-stranded deoxyribonucleic acid, hepatitis B surface antigen, anti-hepatitis C virus, lupus anticoagulant and Venereal Disease Research Laboratory (VDRL) tests were carried out to evaluate the cause of decreased cognitive function, myoclonus and seizures, which were all negative. CSF protein electrophoresis was normal.

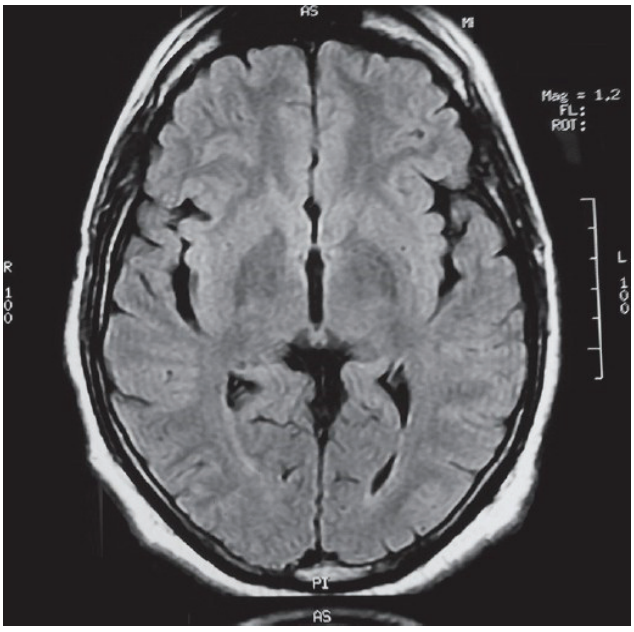

Figure 6. Magnetic resonance images showing non-specific white matter changes in primary hypothyroidism.

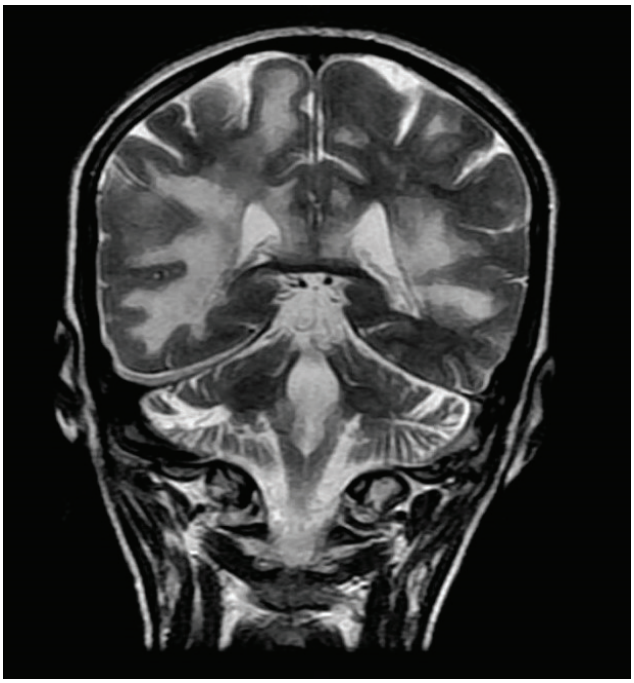

Figure 7. Magnetic resonance images showing non-specific white matter changes in primary hypothyroidism.

ONLINE FIRST | May 9, 2017 | https://doi.org/10.15605/jafes.032.01.12

Table 1. Unusual manifestations associated with primary hypothyroidism

Atypical Presentation	Male (107)	Female (149)	Total (256)
Koecher-Smeglaine-Debre Syndrome	02 (1.87%)	03 (2.01%)	05 (1.95%)
Multicystic ovaries	00 (0%)	02 (1.34%)	02 (0.78%)
Hypothyroid ophthalmopathy	00 (0%)	02 (1.34%)	02 (0.78%)
Massive pericardial effusion	01 (0.93%)	01 (0.67%)	02 (0.78%)
Van Wyk-Grumbach Syndrome	01 (0.93%)	00 (0%)	01 (0.39%)
Hashimoto's encephalopathy	01 (0.93%)	00 (0%)	01(0.39%)
Pseudotumor cerebri/ pituitary hyperplasia	00 (0%)	01 (0.67%)	01 (0.39%)

In view of these neurologic symptoms, associated with high titers of serum anti-thyroid antibodies and the exclusion of other possible causes of encephalopathy, patient was diagnosed with "steroid-responsive encephalopathy and associated autoimmune thyroiditis" (SREAT)/Hashimoto's encephalopathy. He was started on IV methyl prednisolone 1 g/day for 3 days and was shifted over to oral prednisone 1 mg/kg/day. There was a marked improvement in his symptoms with no further episodes of myoclonus or seizures. One month after discharge, the patient reported a sustained improvement in all parameters, including memory and cognition, making it possible for his to return to an almost normal routine. His MMSE had improved to 26 and he was seizure free. The prednisone dose was tapered over 3 months without the recurrence of symptoms.

CASE 7

A 28-year-old female presented to the Emergency Department with a one day history of altered sensorium. She had a history of generalised headache of six months duration, easy fatigability, coarseness of facial features, pedal edema and huskiness of her voice for the last 3 months. She had developed diplopia and diminution in vision over the previous 20 days. She also had a history of irregular menses for 5 years. On examination, pulse rate was 78 beats/minute and regular. Cranial nerves were normal except for right lateral rectus paresis. Fundus was normal. There were no focal neurological deficits. Deep tendon reflexes were normal. Routine blood investigations were normal, except low hemoglobin (6.4 gm/ dL). Her hormonal profile showed raised thyrotrophin stimulating hormone (TSH) (>300 μIU/dL, range 0.30-5.5) and low T3 (12.2 ng/dL, range 60-200) and T4 (0.86 microgram/mL, range 4.5-12.0). Prolactin was 65 IU/dL. Further investigation showed positive anti-TPO antibody >1300 [N<65]. A possible diagnosis of an intracranial space occupying lesion was entertained, but magnetic resonance imaging (MRI) of brain showed diffuse pituitary enlargement (Figure 8). A diagnosis of autoimmune thyroiditis and primary hypothyroidism with pituitary hyperplasia was suspected. She was started on oral L-thyroxine 75 mcg/day and low dose of steroids. At 6 months follow-up, she was doing well and T3, T4 and TSH levels were in normal range. Follow-up imaging was not performed as the patient was lost to follow up.

In our case series, the female to male ratio was found to be 1.4:1. The sex distribution of the various unusual manifestations in our primary hypothyroidism patients is given in Table 1.

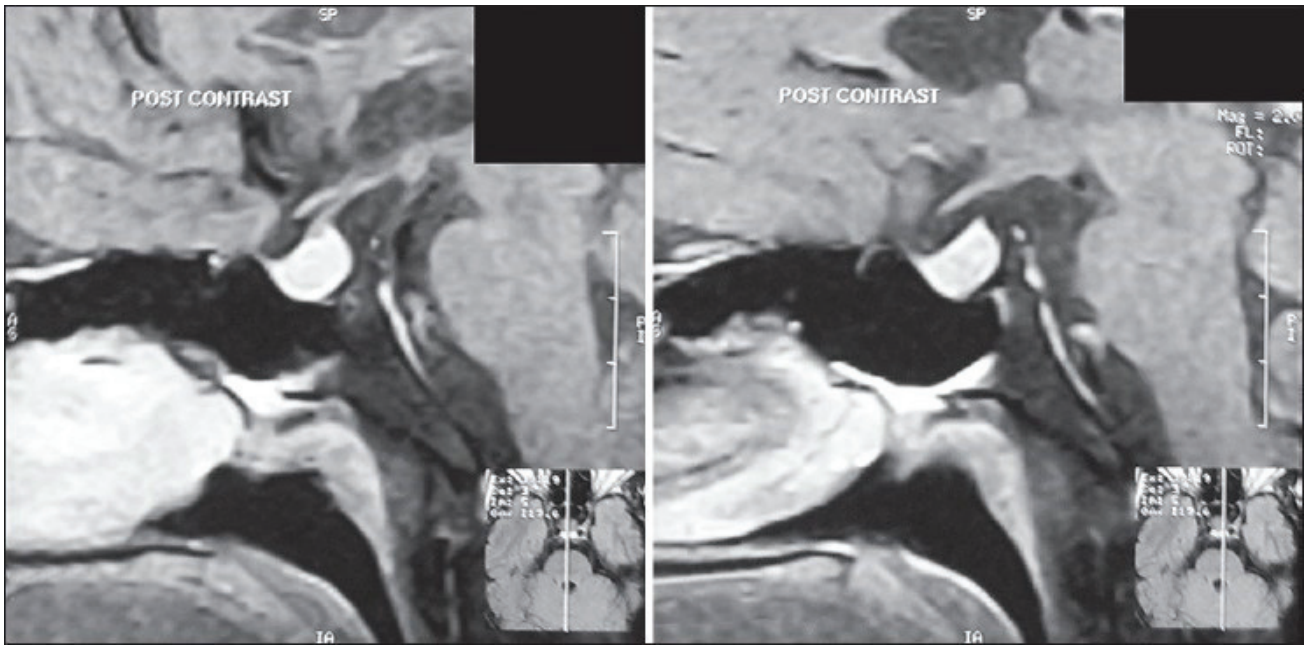

Figure 8. Magnetic resonance images showing pituitary hyperplasia in primary hypothyroidism.

ONLINE FIRST | May 9, 2017 | https://doi.org/10.15605/jafes.032.01.12

DISCUSSION

Hypothyroidism is failure of the thyroid gland to produce enough thyroid hormone to meet the metabolic needs of the body.[1] Hypothyroidism presents with a myriad of subtle and nonspecific manifestations like weight gain, poor concentration, depression, fatigue, muscular weakness, menstrual irregularities, short stature, etc. Some features of hypothyroidism are more suggestive like dryness of skin, proximal myopathy, constipation, cold intolerance and dry brittle hair.[2] The presentation of hypothyroidism depends on various factors like age and sex.[1] In 2003, a large study involving 40,000 patients attending an Omani health facility revealed that almost half of the patients were asymptomatic, while fatigue was evident as the most common symptom presenting in 30%; the other common presenting features were constipation, weight gain, and carpal-tunnel syndrome. Sleep apnoea, snoring, menorrhagia, dysphagia and dysarthria were seldom present.[3]

There are some unusual manifestations of hypothyroidism reported in the medical literature. As their exact prevalence in a hypothyroid population has not been studied epidemiologically, they often prove to be diagnostic challenges. The patients presenting with such manifestations are often misdiagnosed because of unawareness amongst the primary care providers, ultimately leading to a long delay in treatment and poor therapeutic outcomes. The care of such patients can be improved by familiarizing primary care providers with these unusual manifestations. In the present report, we document the presence of unusual presenting manifestations of hypothyroidism in a cohort of 256 patients diagnosed with primary hypothyroidism within a 2 year period in a tertiary care centre.

In our study the most common unusual presenting feature was Koecher-Debre-Smeglaine Syndrome (KDSS), which was present in five pediatric patients (2 males and 3 females) out of 256 hypothyroid patients. KDSS usually presents in the age group between 18 months and 10 years with the combination of hypothyroidism, calf muscle pseudo-hypertrophy, delayed muscle contraction and delayed relaxation of reflexes, along with percussion myxoedema.[4] The adult variant of KDSS is known as Hoffman's Syndrome. Muscles of the extremities, limb girdle, trunk, hands and feet are commonly involved. The affected muscles are bulky, rubbery or firm, hypotonic and weaker than healthy muscles, hence the descriptive term "Herculean muscles." The involved muscles do not show any specific microscopic features and the underlying pathogenesis is still obscure, although the accumulation of glycosaminoglycans and glycogen are thought to play a role.[4,5] KDSS shows a good response to levothyroxine therapy, as was seen in our patients.

The other relatively common atypical presentation in our study was multicystic ovaries found in two patients. Hypothyroidism is a rare cause of ovarian hyperstimulation syndrome (OHSS) which usually occurs in the setting of exogenous FSH treatment.[6] Hypothyroidism is usually overlooked as a cause of ovarian cysts and patients may undergo surgery without any improvement.[6] A number of theories have been proposed to explain the development of multicystic ovaries in hypothyroid patients. The homologous structure of TSH and FSH causes stimulation of ovarian FSH receptors (specificity-spillover) by excessively raised serum TSH levels in patients with untreated hypothyroidism.[7] Multicystic ovaries can be caused by a differential increase in FSH concentrations along with low LH concentrations due to modification of GnRH pulse frequency by increased TRH in hypothyroid patients.[8] Hyperprolactinemia possibly due to elevated hypothalamic TRH may suppress LH secretion. Also, the clearance of FSH is reduced in hypothyroidism, and there may be activating FSH receptor mutations enhancing the effect of elevated TSH on the ovaries.[6] These multicystic ovaries are extremely important to diagnose in primary hypothyroid patients who may undergo unnecessary surgery since levothyroxine therapy resolves the condition, as was apparent in our study.

Two women presented with orbitopathy. Graves' ophthalmopathy (GO) occurs in close temporal relation with hyperthyroidism but rarely can occur in hypothyroid and even in euthyroid subjects. The prevalence of GO in euthyroid and hypothyroid subjects ranges from 1.6% to 8.4%.[9] The symptoms differ between hyperthyroid and hypothyroid GO patients in various aspects. GO in hypothyroid patients is more asymmetrical with lesser soft tissue involvement and less marked clinical manifestations.[9] TRAbs are present in 69% of euthyroid and hypothyroid patients with GO. The number further increases to 75% when AntiTPO and TRAbs are considered together.[9] The mean TBI concentration is less in hypothyroid and euthyroid patients with ophthalmopathy as compared to hyperthyroid patients during the initial 6 months.[9]

We had 2 patients who presented with massive pericardial effusion as the primary clinical manifestation of hypothyroidism. Although mild pericardial effusion is common cardiovascular manifestation of hypothyroidism, the occurrence of massive pericardial effusion is a rare phenomenon.[10] Pericardial effusion (PE) in hypothyroidism is a part of the spectrum of polyseropathy characterized by extravasation of albumin and inadequate lymphatic drainage. The pericardial fluid is typically straw colored with high concentration of globulins and lymphocytes.[11,12] Treatment of hypothyroidism is mandatory along with pericardiocentesis.

One child with primary hypothyroidism presented with the rare syndrome known as Van Wyk-Grumbach syndrome (VWGS). This refers to the occurrence of

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paradoxical isosexual precocious puberty along with short stature and delayed bone age in a case of long standing untreated primary hypothyroidism.[13] The VWGS syndrome is seen more commonly in girls.[4,5,14] It presents as precocious isosexual puberty, delayed bone age, vaginal bleeding and ovarian cystic changes in girls and as isolated testicular enlargement (macro-orchidism) in boys without phallic enlargement, pubic hair development, or morning erections. Short stature and delayed bone age are seen in both.[4,5,14] This occurs as a result of high TSH levels in primary hypothyroidism stimulating ovarian and testicular FSH receptors leading to isosexual precocious puberty. The theory is supported by the fact that VWGS does not occur in secondary or tertiary hypothyroidism and the degree of precocity is directly proportional to the TSH concentration.[4,5,14]

In our study, we found one patient presenting with "steroid-responsive encephalopathy and associated autoimmune thyroiditis (SREAT)/Hashimoto's encephalopathy. "Steroid-responsive encephalopathy and associated autoimmune thyroiditis (SREAT) is a rare steroid responsive encephalopathy presenting with persistent or fluctuating neurological and neuropsychological deficits associated with anti-thyroid antibodies.[15] The diagnosis is often difficult because of varied subtle manifestations and rarity of the syndrome. The exact pathophysiology is unknown but various hypotheses have been proposed like autoimmune cerebral vasculitis, toxic effects of thyroid-stimulating hormone on the central nervous system and neuronal reaction mediated by antibodies.[16] Anti-thyroid antibodies are considered as the markers of autoimmunity but they probably do not have a role in pathogenesis.[15] The EEG changes are nonspecific in 90-98% of patients, while brain MRI may show abnormalities in 49% patients, namely cerebral atrophy, focal cortical abnormality, diffuse subcortical abnormality and non-specific subcortical focal white matterabnormality.[15] The syndrome is steroid responsive while in 5% non-responsive cases azathioprine, IVIG, or plasmapheresis can be tried.[15]

Lastly, one patient with primary hypothyroidism in our study presented with a pituitary mass. In this situation, the decreased levels of thyroid hormone lead to loss of negative feedback, resulting in increased secretion of TRH from hypothalamus and TSH from pituitary. Under constant TRH stimulation, pituitary thyrotropes become hyperplastic and hypertrophied and present as a pituitary mass.[17] Although sellar enlargement is more common in primary hypothyroid children than in adults, patients seldom present with neurological signs of sellar expansion, unlike adults who may present with headache and other neurological symptoms.[17]

CONCLUSION

Besides the usual clinical manifestations of primary hypothyroidism, there are others that are very unusual,and hence are not easily recognised by the treating physician. The timely identification of these atypical presentations is very important for early intervention and treatment of hypothyroidism.

Ethical Consideration
Informed consent has been taken before submission of the manuscript.

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

Author Disclosure
The authors have declared no conflict of interest.

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CASE REPORT

Blepharophimosis Ptosis Epicanthus Inversus Syndrome (BPES) Type 1 in an Indian Family

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Abstract

Blepharophimosis ptosis epicanthus inversus (BPES) is a relatively rare congenital disorder, which usually presents with classical eye manifestations. In some cases, it is associated with premature ovarian failure (POF). BPES is of two types, type I and type II. Type I is associated with POF along with eyelid malformations, while Type 2 has only eyelid malformations.

Here, we report a family of BPES, in whom two sisters presented with secondary amenorrhea. On eye examination, they have blepharophimosis, ptosis, epicanthus inversus and telecanthus. Investigations revealed hypergonadotropic hypogonadism. Their father also has similar eye manifestations. Diagnosis of BPES type I was made and both were started on hormone replacement therapy.

To make timely diagnosis of BPES, every patient with POF should specifically be checked for eye manifestations.

Key words: blepharophimosis ptosis epicanthus inversus syndrome (BPES), secondary amenorrhea, primary ovarian failure

INTRODUCTION

Blepharophimosis ptosis epicanthus inversus syndrome (BPES) is a rare congenital eyelid disorder that is inherited as an autosomal dominant trait, with an estimated incidence of 1 in 50,000 births.[1] Blepharophimosis was first reported by Von Ammon in 1841. Vignes first associated blepharophimosis with ptosis and epicanthus inversus in 1889. It is characterized by shortened horizontal palpebral fissure (blepharophimosis), impaired function of levator palpebrae superioris of upper eyelid (ptosis), a vertical skin fold arising from the lower eyelid that inserts medially into the upper lid (epicanthus inversus) and an increased inner canthal distance (telecanthus).[2] Zlotogra et al., in 1983 described two types of BPES, Type I and Type II. Type I is associated with premature ovarian failure (POF) in the affected female, in addition to the classical eye findings, while Type II has only eye features.[3]

The diagnosis of BPES is primarily made by combination of typical facio-ocular features, with clinical and biochemical features of primary ovarian insufficiency. For diagnostic purpose, genetic analysis is not needed. However, both types of BPES are caused by mutations of the forkhead transcriptional factor 2 (FOXL2) gene, that is located on the long arm of chromosome 3 (3q23).[4]

In this paper, we report a family of two female siblings, who have all the eye manifestations of BPES along with amenorrhea, while their father has only ophthalmic manifestations.

CASE

We describe an Asian Indian family of 2 female and 2 male siblings. Both sisters, who were 22 years and 19 years of age, presented to the Endocrinology OPD, with complaints of bilateral drooping of the eyelids, dimness of vision since early childhood and secondary amenorrhea for 4 years and 2 years, respectively.

There was no history of puffiness of face, swelling of eyes, constipation, deafness, proximal myopathy, any chronic illness, mental retardation, chemotherapy, radiation, pelvis surgery, absence of tears and hyperpigmentation. Their antenatal, natal and postnatal histories were unremarkable. General examination revealed normal stature with absence of low set ears, short fourth metacarpal, shield chest, cubitus valgus, web neck and low posterior hairline. Both sisters have normal secondary sexual characteristics (Tanner stage A+ P4 B5) and attained menarche at age of 14 years. On ophthalmologic examination there was bilateral ptosis,

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Table 1. Anthropometry and hormonal profile

Parameters	Patient 1	Patient 2	Normal range
Age (years)	22	19	
Weight(kg)	39.8	41.2	
Height(cm)	151	155.5	
BMI(kg/m2)	17.48	17.04	
Amenorrhea duration (years)	4	2	
Horizontal palpebral fissure (mm)	19	20	33.7 ± 1.8
Vertical palpebral fissure (mm)	4	3.5	11.7 ± 1.6
Epicanthus inversus	Present	Present	
Inter canthal distance (mm)	38	39	32.7 ± 1.5
LH (IU/L)	32	33	0.69-7.15
FSH (IU/L)	44	42	0.40-6.50
Estradiol (pmol/L)	2.72	<2.72	91.8-1505
Uterine length (cm)	5.6	5.5	5-8 (pubertal)
Right Ovary (cm^3)	2.6	2.5	>2.8 (pubertal)
Left Ovary(cm^3)	2.5	2.7	>2.8 (pubertal)
Endometrial thickness (mm)	4	4	>7 mm (pubertal)

blepharophimosis and epicanthus inversus (vertical skin fold arising from the lower eyelid that inserted medially into the upper lid). The length of both horizontal palpebral fissures were 19 mm in the older sister and 20 mm in the younger sister, which were less than the normal adult Indian female measurement of 33.7±1.8 mm. The length of both vertical palpebral fissures were 4 mm in the older sister and 3.5 mm in the younger sister, which were less than the normal adult Indian female measurement of 11.7 ± 1.6 mm. The distance between the medial canthi (telecanthus) was 38 mm in the older sister and 39 mm in the younger sister, which were more than the normal adult Indian female measurement of 32.7 ± 1.5 mm (Table 1) (Figure 1).[5] Visual acuity was decreased in both eyes. The father also has similar eye findings of blepharophimosis, ptosis, epicanthus inversus and telecanthus (Figure 2).

Laboratory investigations revealed normal hemogram, renal function test, hepatic function test, electrolytes, and prolactin. Investigation also revealed raised FSH values above 40 IU/L on two occasions, 1 month apart, with raised LH and low estrogen. Ultrasound of the pelvis showed atrophic ovaries, small uterus with endometrial thickness of 4 mm in both sisters. Chromosomal analysis revealed normal 46,XX karyotype. Cytogenetics and molecular genetic analysis were not done due to unavailability and financial constraints. All the hormonal investigations were done by chemiluminescence immunoassay using Abbott ARCHITECT i1000sr immunoassay analyzer.

On the basis of typical clinical history, examination findings and laboratory evaluation, a diagnosis of type 1 BPES was formed in both sisters and they were started on hormone replacement therapy (estrogen and progesterone) with calcium and vitamin D supplementation. Need for eye surgery and fertility issue were discussed. Written informed consent from to publish the case report and images has been taken and is approved by the local ethics committee.

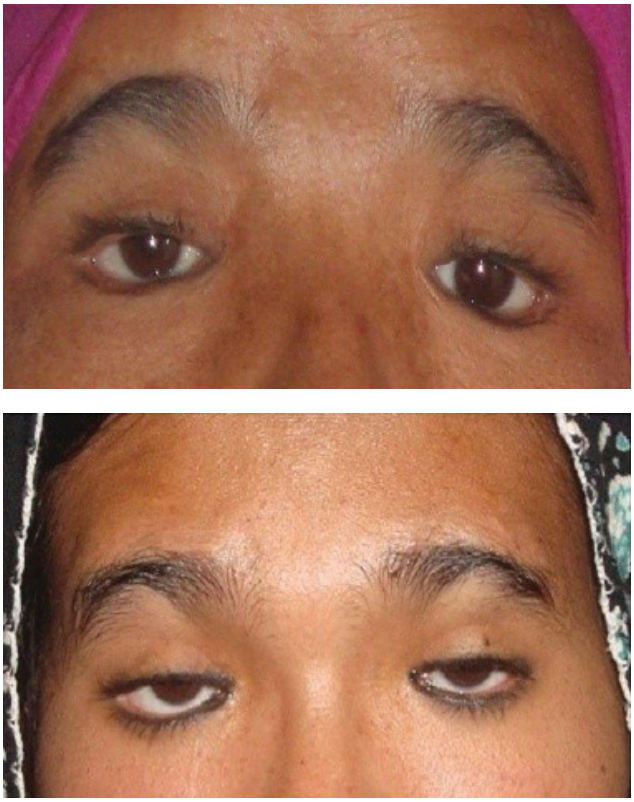

Figure 1. Characteristic clinical features of the patients with blepharophimosis, ptosis, epicanthus inversus syndrome (BPES). Both patients have small palpebral fissures, ptosis of the eyelids, and epicanthus inversus.

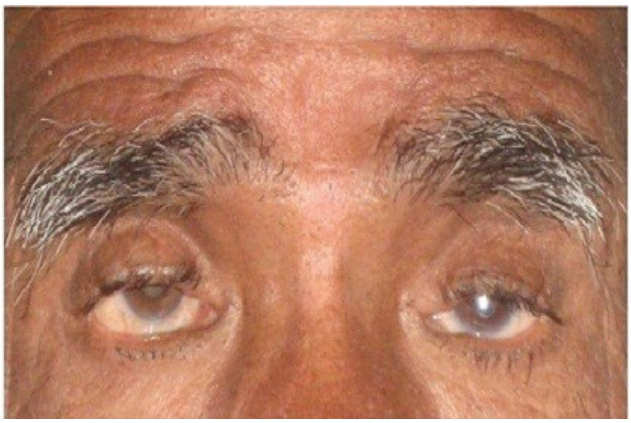

Figure 2. Characteristic clinical features of the patients with blepharophimosis, ptosis, epicanthus inversus syndrome (BPES). The father also has small palpebral fissures, ptosis of the eyelids, and epicanthus inversus.

DISCUSSION

BPES is a complex eyelid malformation, characterized by four major features: blepharophimosis (narrowing of horizontal aperture of the eyelids), ptosis (drooping of upper eyelid), epicanthus inversus (a skin fold arising from the lower eyelid and running inwards and upwards) and telecanthus (lateral displacement of the inner canthi with normal interpupillary distance). BPES type I includes the four major features and POF; BPES type II includes only the four major features. Other ophthalmic

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manifestations that can be associated with BPES include lacrimal duct anomalies, amblyopia, strabismus, and refractive errors. Minor features include a broad nasal bridge, low set ears, and a short philtrum.[4,6]

The definition of POF is amenorrhea, hypoestrogenism, and elevated serum gonadotropins in women less than 40 years of age. More than 4 months of amenorrhea and two serum FSH levels of more than 40 IU/L obtained more than one month apart in women aged <40 years are the suggested criteria for diagnosing POF.[7]

In the Indian population, mean age of BPES cases was 12 ± 8.4 yrs (range 4-32 years), with the majority of cases between 4-8 yrs. This finding is consistent with studies from other parts of the world that have reported that majority of cases present before 8 yrs of age. In our case, patients present at 22 and 19 yrs of age after the onset of amenorrhea.[1]

Townes and Muechler, Fraser et al., Smith et al., and Panidi et al., described families affected with POF and eye features of BPES.[8-10]

The genetic pathophysiology of BPES is due to a FOXL2 gene mutation which is responsible for BPES type I and II, which is located on the long arm of chromosome 3 (3q23). Four types of deletions in chromosome 3q has been described in BPES (46,XY,del 3qter; 46,XY,del 3q26.3; 46,XX,del 3q24-25 and 46,XY,del 3q26-qter). Patients who are cytogenetically normal are further evaluated for molecular analysis for FOXL2 sequence variations. Complete or partial loss of FOXL2 protein function leads to development of BPES types I and II respectively. The FOXL2 gene instructs the proteins involved in eyelid muscles and ovarian development. More than 100 FOXL2 gene mutations have been identified in BPES, which includes frameshift insertions, nonsense mutations and missense mutations.[1]

Mati et al., showed that the form of BPES associated with premature ovarian failure maps to 3q22-q23, the same chromosomal region as does the form without POF.[11] By positional cloning, Crisponi et al., identified the FOXL2 gene and identified mutation resulting in truncated proteins in affected individuals with both Type I and II BPES. FOXL2 was selectively expressed in the mesenchyme of developing mouse eyelids and in adult ovarian follicles; in adult humans, it appeared predominantly in the ovary.[12] In our patients, cytogenetic and molecular analysis could not be done beyond karyotyping because of financial constraints.

Treatment of BPES is eyelid surgery which involves a medial canthoplasty for correction of the blepharophimosis, epicanthus inversus, and telecanthus at age three to five years, typically followed a year later by ptosis correction, a one-stage procedure has also been described. Premature ovarian failure is treated with hormone replacement therapy (estrogen and progesterone), fertility is addressed with reproductive technologies such as embryo donation and egg donation.[6]

BPES is usually inherited in an autosomal dominant manner but autosomal recessive inheritance has also been reported in one consanguineous family. Prenatal testing for pregnancies at increased risk is possible if the pathogenic variant in the family has been identified.[6]

CONCLUSION

BPES can either present as only typical eye findings or combined with primary ovarian failure. Therefore, the possibility of BPES must be borne in mind in any patient presenting with POF and associated characteristic eye features. If available, molecular characterization and genetic evaluation may be useful for a more definitive diagnosis and genetic counseling. Family pedigree construction is also important to identify the pattern of inheritance.

Ethical Consideration
Informed consent has been taken before submission of the manuscript.

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

Author Disclosure
The authors have declared no conflict of interest.

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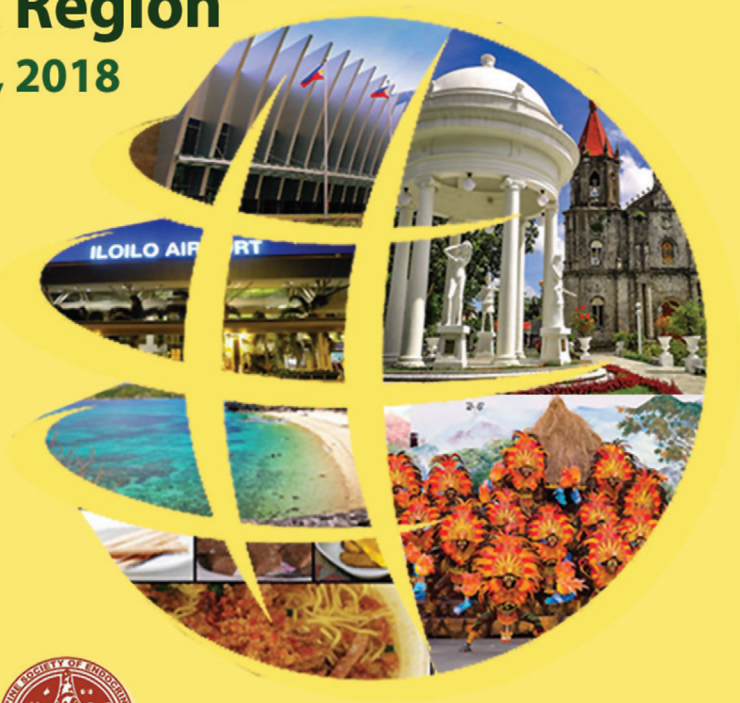

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Case Reports
The abstract should be from 50 to 75 words and should not be structured. A manuscript for case reports should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words.

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, affiliations, ORCID iD, specific role/s in writing the manuscript and email address) ☐ Indicate in the letter the corresponding author and provide complete contact information (post address, telephone, fax number, e-mail address)
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ORAL EXAMINATION

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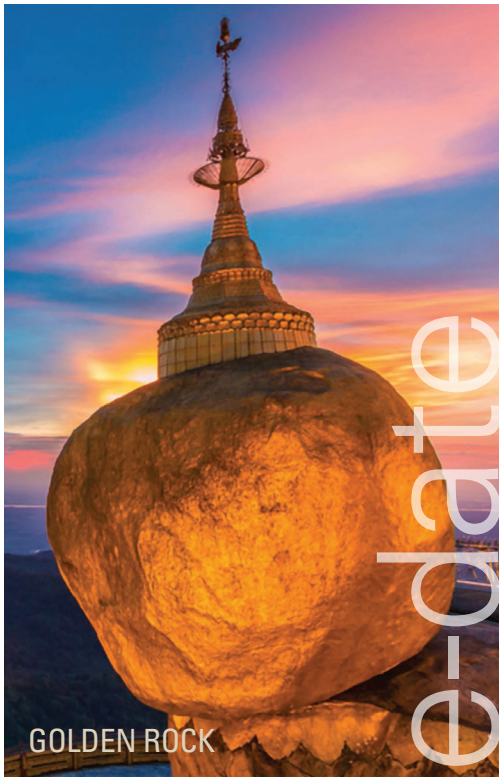

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