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Keeping Our Authors' Trust

During one of our editorial board meetings in 2018, the question was posed of whether we are to accept articles which cite sources from predatory or suspected predatory publications. Predatory journals are deceptive publications that charge article processing fees and provide rapid publication without the benefit of peer review and editorial quality checks. The discussions revolved around the doubtful credibility of an article that is published in a predatory journal. Ultimately, the board decided that if such an article is cited to support articles submitted to JAFES, it lessens the credibility of the submitted article, *and* would reflect on the credibility of JAFES. We informed the authors about this resolve and advised them that we cannot accept their article if the reference in question is retained.

This situation made us realize another dimension of our role in maintaining the integrity of scientific scholarly information. On the one hand, we have invested significantly in refining our editorial policies, ethical standards, and publication operations, to provide authors a high-quality open access platform for their findings. We exerted efforts to be indexed in Scopus, Directory of Open Access Journals, and the Western Pacific Region Index Medicus, and continuously working on inclusion in PubMed and ISI Clarivate. We have established a rigorous article selection process, which begins with an initial editorial board deliberation, a double-blind peer review system through an international pool of experts, and supplemental statistical, and radiologic and pathologic image reviews by in-house statisticians, radiologists, and pathologists, respectively, and culminates with a second round of editorial deliberation.

On the other hand, recognizing the preponderance of deceptive publications, we need to exercise due diligence to guard against citation of information from journals of questionable credibility. It is remarkable to note that such journals do get included in literature searches and even get cited. To some degree, prior to 2018, we have been consulting Jeffrey Beall's list of predatory journals[1,2] to review article references. But this year, after encountering several more article submissions with questionable references, JAFES has begun using Cabell's "Blacklist,"* a subscription-based service which lists 65 criteria for blacklisting of predatory journals. Originally meant to help researchers know where *not* to publish, we now recognize the blacklist's additional value as an integral reference by editors to decide what *not* to allow to be cited.

To further enhance the quality of articles that JAFES publishes, we are newly introducing changes in our **Author Forms**. We added stipulations in the **Author Declarations** that the manuscript and supplemental materials submitted by authors do not infringe any copyright or violate any other intellectual property rights of others; and that they have obtained written permission from copyright or intellectual property right owners for all copyrighted/patented works that are included in the manuscript. This is to address authors who may inadvertently be using diagrams, photographs, or figures that are already published elsewhere, without proper attribution and permission. We included a certification that the author does not refer or cite predatory or suspected predatory journals.

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We shall also require submission of the accomplished **EQuaTOR Network checklist** relevant to the type of research. The checklists are based on reviews of best practices on ethical scholarly publication by experts around the world. This move will ensure that all the items necessary for complete reporting on study findings are included in the submitted manuscript. To increase transparency and assist us in settling authorship disputes, we added a Section on **Author Contribution Disclosure** based on CRediT by the Consortia Advancing Standards in Research Administration Information (CASRAI) showing the 14 standardized roles of authors.

Part of our commitment to scientific integrity is our commitment to the authors, who have entrusted JAFES their work, and this commitment extends to protecting their rights to their own work. After deliberations, it has been resolved that the author copyright shall no longer be transferred to JAFES. By signing the **Author Publishing Agreement,** authors shall retain copyright and grant JAFES the right to publish and distribute their work through 100% Open Access, and to enforce a Creative Commons user license (CC-BY-NC) to guide other authors, scientists, and other users, on the proper use of the author's work.

With these and other future improvements in the way we manage the JAFES, we aim to not only remain relevant and be the publication of choice in endocrinology in the region, but more importantly, to keep the authors' trust that we are working with them to ensure the quality, permanence, and visibility of their work.[3] This way, ultimately, we aim to keep all our readers' trust too.

Elizabeth Paz-Pacheco
Editor-in-Chief

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LETTER TO THE EDITOR

In response to the article *'Transient Pseudohypoaldosteronism in an Infant: A Case Report'* by T. Latt et al., published in JAFES Vol. 33 No. 1.

Severe Hyponatremia in a 6-month-old Infant

Joanna Mańdziuk, Magdalena Okarska-Napierała, Ernest Kuchar

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We want to congratulate Latt and colleagues on the article describing a case of a patient with transient pseudohypoaldosteronism.[1] Electrolyte derangements in course of this rare entity may be much more severe, as in our patient presenting with hyponatremia of 103 mmol/L. We feel that we can contribute to the topic by reporting our patient and discussing hyponatremia management.

We admitted a 6-month-old girl with irritability and 580 g weight loss within a month, presenting with severe dehydration. Laboratory tests revealed profound derangements: Na^+ 103 mmol/L, K^+ 7.8 mmol/L, Cl^- 76 mmol/L, metabolic acidosis and hyperaldosteronism (aldosterone 1857 ng/dl). Abdominal ultrasound revealed bilateral megaureters. Urine test confirmed a urinary tract infection (UTI).

Neurologic sequelae of both severe hyponatremia and its overly rapid correction are life-threatening. Therefore, careful therapeutic strategy must be provided. The safe rate of severe hyponatremia correction varies in the literature. Guidelines concerning adult patients with hyponatremia agree on the limit of correction being 10 mmol/L/d.[2] Nevertheless, for patients posing high risk for osmotic demyelination, such as patients with hyponatremia <110 mmol/L, recommendations for natremia correction vary from 8 mmol/L to 6 mmol/L/d.[2] Somers et al.,[3] in their review about hyponatremia in children recommend the rate of correction of 8 mmol/L/d, as grade 1a recommendation.

Another issue is achieving the target correction rate. Some authors suggest universal equations to predict the change in natremia. However, they can be inaccurate as they do not refer to dynamic sodium balance changes (due to, e.g., changing aldosterone and antidiuretic hormone release). The safest method of controlling natremia correction seems to be monitoring natremia every 4-6 hours, as suggested by Spasovski et al.,[4] who also state that in case of correction exceeding 10 mmol/L in the first 24 hours or 8 mmol/L in consecutive days, re-lowering serum sodium is warranted.

We want to present the scheme of severe hypovolemic hyponatremia treatment that may help clinicians dealing with this electrolyte imbalance.

Initially, increasing serum sodium by 5 mmol/l within 4 hours is frequently recommended,[5] which one can achieve following a simple equation:

sodium dose [mmol] = TBW x 5 = 0,6 x body mass [kg] x 5 = 3 x body mass

TBW – total body water

The preferred initial fluid for hypovolemic hyponatremia correction is 0.9% NaCl, with Na concentration of 15 mmol/100 ml, which means that preferred initial dose of 0.9% NaCl is 20 ml/kg/4 hours. By measuring sodium concentration after 4 hours one can assess patient's response to treatment and predict further change.

Further sodium correction should not exceed 8 mmol/L/d, which means 2 mmol/L/6 hours. This can be achieved by regular, every 6 hours, controls. Fluid sodium content should be guided by serum sodium, fluid volume – by patient's water need. In our patient, after initial quick correction of serum sodium we continued with hypotonic fluid (0.3% NaCl + 5% glucose) which guaranteed slower rate of correction as recommended. We corrected hyponatremia within 4 days (Table 1). The girl responded well to therapy, and after three months follow up, her physical and neurological development is appropriate for age.

Table 1. Consecutive sodium concentration values in our patient

Day	Hour	Sodium level [mmol/L]
1	19:33	103
1	22:05	107
2	06:30	110
2	09:40	115
2	15:16	118
2	20:00	107
3	00:06	117
3	06:18	119
3	12:42	120
3	16:44	123
3	19:40	126
4	00:01	125
4	13:38	127
5	13:36	136

To conclude, management of severe hyponatremia can provide a challenge for physicians. We feel that success can be achieved by regular, at least every 6 hours checking of serum sodium and adequate fluid therapy.

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Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

Malaysian Consensus Statement for the Diagnosis and Management of Acromegaly

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Abstract

In Malaysia, acromegaly is under-recognised with only 10-15% of the expected number of cases from prevalence estimates, having been diagnosed and managed in established endocrine centres with access to multidisciplinary care. This is mainly due to lack of awareness and standardised approach in diagnosing this disease resulting in delay in diagnosis and management with suboptimal treatment outcomes. This first Malaysian consensus statement on the diagnosis and management of acromegaly addresses these issues and is based on current best practices and latest available evidence so as to reduce the disease burden on acromegaly patients managed in the Malaysian healthcare system.

Key words: acromegaly, consensus, Malaysia, growth hormone excess

INTRODUCTION

Acromegaly is an uncommon clinical syndrome resulting from excessive growth hormone (GH) production. In most cases, it arises from a GH secreting pituitary adenoma with resultant increased production of insulin-like growth factor-1 (IGF-1) from the liver. Both hormones exert characteristic changes and growth effects on major organ, skeletal and soft tissues. The resultant insulin resistant state, leads to predisposition of developing glucose intolerance, metabolic dysfunction and increased cardiovascular risk with associated co-morbidities such as hypertension, obstructive sleep apnoea (OSA) and arthritis. OSA in acromegaly is due to osseous and soft tissue changes which lead to narrowing and collapse of the upper airway during sleep. The pituitary tumour, typically a macroadenoma, can contribute to local mass effect with complications such as visual disturbance and hypopituitarism.

Main aims of treatment in acromegaly are to reduce and restore GH and IGF-1 levels to normal range, as this is associated with control of symptoms, prevention and control of complications, and reduction in morbidity and mortality. Treatment choices include surgical, medical and radiation therapy (RT) needing long-term multidisciplinary monitoring.

Currently there are no available guidelines addressing the diagnosis and management of patients with acromegaly in Malaysia. As the disease is chronic, associated with multiple co-morbidities and complications requiring multidisciplinary care, it is important to establish evidence-based guidelines to standardise screening, diagnosis, management and long-term follow-up of these patients. This manuscript presents the first Malaysian Consensus Statement for the Diagnosis and Management of Acromegaly in Malaysia.

METHODOLOGY

This consensus statement is based on latest best practice recommendations of the Endocrine Society[1] and American Association of Clinical Endocrinologists (AACE)[2] guidelines, and a comprehensive review of current medical literature. The recommendations were then developed with consensus building through face-to-face meetings by a multidisciplinary group of Malaysian specialists involved in the care of acromegaly patients consisting of endocrinologists, neurosurgeons, radiologists, radiation oncologists and laboratory specialists. The local recommendations were then carefully formulated taking into consideration the Malaysian healthcare system and the local availability and accessibility of diagnostic procedures and management options for patients with this disease. This was then circulated to a group of external reviewers in the same specialities and practicing within Malaysia for further review and feedback, which were taken into consideration resulting in these final recommendations.

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epidemiology

Acromegaly is a rare disease with significant risk of mortality. Based on existing data from western countries, the prevalence of acromegaly is approximately 70-80 cases per million population (cpmp) and its incidence, 3-11 cpmp/year.[3-6] However, data from some Asian countries have approximated the prevalence of acromegaly at 28 cpmp and its incidence at 4 cpmp/year.[7] Males and females are equally affected by the disease.[3,4,7] The mean age of diagnosis is from mid-forties to early fifties[3,7-9] however, there is an average of 4-7 years of delay in confirming diagnosis from the onset of GH hypersecretion.[3,4,10]

There are at present very limited Malaysian epidemiological data available for acromegaly. From unpublished observational data of the Malaysian Acromegaly Registry, acromegaly appears to be seriously under-recognised and under-diagnosed in the country, with fewer than 150 patients being managed at established endocrine centres. However, from the case series collected, the ratio of male to female is similar with other countries.

The most common cause of acromegaly, accounting for >95% of cases is GH-secreting pituitary tumours arising from somatotroph cells.[1] The majority of the pituitary tumours (70%) are macroadenomas (≥1 cm in diameter) whilst the rest are microadenomas (<1 cm in diameter).[3] In the hands of high-volume pituitary surgeons, patients with microadenomas are expected to have 80-90% chance of surgical cure.[3] On the other hand, patients with macroadenoma are expected to have 40-50% chance of surgical cure. Achieving disease control in these patients with macroadenoma is challenging even with combination treatment of pituitary surgery, RT and medical therapy. These treatment options are notably costly, so a sensible and schematic selection of patients for specific modalities of treatment is paramount. It is important to note that individuals with uncontrolled disease have at least a 2-fold increase in mortality risk compared to the general population.[1,11-13] The most common cause of mortality in acromegaly is from cardiorespiratory diseases.

Clinical features

The most common complaints bringing patients with acromegaly to consult their primary care doctors, that lead to further tests to confirm diagnosis are headache and acral enlargement.[14] The latter feature usually comprises of lower jaw enlargement and protrusion (prognathism) with dental malocclusion, overbite and interdental separation[15] and, increasing ring and shoe size.[10,16]

Acromegaly is also associated with various co-morbidities. Data from the Malaysian Acromegaly Registry show that co-morbidities commonly encountered are diabetes mellitus, hypertension, cardiac diseases, OSA and multinodular goitre.

Other features that may be associated with acromegaly are visual field defects (typically bitemporal hemianopia), hyperprolactinemia, hypopituitarism (comprised of hypogonadism, hypothyroidism and hypocortisolism), colonic polyps, visceromegaly, carpal tunnel syndrome (CTS) , large joint pains, oily perspiration (mainly noted by hand examination) and multiple skin tags.[16,17]

Diagnosis

Clinical diagnosis

In the local context, if any clinician encounters a patient with acral enlargement of the face, hands or feet with two or more co-morbidities or features associated with acromegaly, biochemical screening is then indicated. The clinical features suggestive of Acromegaly include the presence or complaints of headache, diabetes mellitus, hypertension, heart disease of uncertain aetiology, OSA, colonic polyps, large joint pains, CTS, sweaty/oily hands or multiple skin tags.

In Malaysia, efforts have been carried out to educate primary care physicians regarding early recognition of clinical features of acromegaly. Regional level disease awareness talks by endocrinologists to primary care doctors have been carried out to highlight the disease and it's comorbidities and complications and emphasising the need for earlier diagnosis at the primary care level. Promotional educational material have been developed in the form of posters and video clips and distributed to all government primary care clinics. A screening algorithm will also soon be introduced to ease and facilitate the referral pathway of suspected cases of Acromegaly to receive prompt review by an endocrinologist at the nearest hospital.

Biochemical diagnosis

Biochemical screening should be performed promptly where clinically indicated and serum IGF-1 assessed if the test is available and accessible. In Malaysia, serum IGF-1 testing is limited and only available at endocrine laboratories at a single central government hospital, few university hospitals and private hospitals. Where the test is not accessible, referral should be made to an endocrinologist for biochemical screening and confirmation of acromegaly. Serum IGF-1 is measured as an initial screening test as it is the most sensitive and specific test for diagnosis. The levels should be interpreted using assay-specific age and gender matched reference ranges developed by the assay manufacturer. In Malaysia, different laboratories are using different assays which result in differences in the reference ranges. There are also various conditions that may elevate (e.g., puberty, pregnancy and hyperthyroidism) or lower (e.g., malnutrition, liver failure, renal failure, oral oestrogen use, untreated hypothyroidism and uncontrolled diabetes) serum IGF-1 levels. Interpretation of results will need careful consideration of the clinical context of the patient.[18,19]

An oral glucose tolerance test (OGTT) in patients with elevated IGF-1 that fails to suppress GH confirms diagnosis of acromegaly. At times it is justified to proceed simultaneously with an OGTT without waiting for IGF-1 levels in patients with a very high index of clinical suspicion to minimise diagnostic delay. The nadir GH level is seen between 60-120 minutes following an oral glucose load thus, GH measurements are recommended to be taken at 0, 60 and 120 minutes during the OGTT[2,20] and failure to supress GH levels to <1 mcg/L during OGTT (at 120 minutes) is considered diagnostic of acromegaly.[1]

There are instances however, where there may be discordance in IGF-1 and GH levels, i.e., elevated IGF-1 with nadir GH <1mcg/L during OGTT. With improvement in the sensitivity of modern GH assays, it has been established that in normal individuals, the nadir GH is <0.3 mcg/L.[21] Depending on the sensitivity and accuracy of the GH assay used, some authorities advocate using a cut-off of 0.4 mcg/L during an OGTT to diagnose acromegaly.[2] Therefore, when a highly sensitive GH assay is used in the context of an elevated serum IGF-1, a nadir GH above 0.4 mcg/L is consistent with a diagnosis of acromegaly. Discussion with a laboratory biochemist is required to establish sensitivity of GH assay in use.

Random GH or mean GH levels are not suitable or recommended to be used for making the initial diagnosis of acromegaly due to poor specificity.[1]

Imaging

Magnetic resonance imaging (MRI) of the pituitary (MR pituitary) with and without contrast is the neuroimaging investigation of choice in patients with acromegaly confirmed by biochemical diagnosis. All patients with likely exposure to contrast agents should have their serum creatinine and estimated glomerular filtration rate (eGFR) tested to identify individuals that are at potential risk of developing contrast induced nephrogenic systemic fibrosis. Patients with eGFR <30 ml/min/1.73m^2 should not have contrast administered.

MR pituitary is the preferred diagnostic imaging modality to evaluate sellar and parasellar tumours, offering high contrast and multiplanar thin cuts[22] which enable the evaluation of small soft tissue changes.

MR pituitary protocols should include pituitary sequences, 3 mm thick slices with Coronal T1WI /T2WI /T1 post-gadolinium and Sagittal T1WI /T1 post-gadolinium with or without a dynamic study. Optional added brain sequences include, T2WI axial and T1 axial post-contrast sequences. A dynamic MR pituitary may be useful particularly when functioning microadenomas are suspected as, it obtains images within seconds after administration of gadolinium.[23]

Computed tomography (CT) scan of the pituitary is only suggested in patients where MRI is contraindicated, as anatomical details are less defined.[2] Locally, this is already less commonly done. However, if necessary, CT should be done with use of contrast and must include multiplanar reformats.

Management

The management of acromegaly involves multimodal therapy.[1,2,24,25] Individualised treatment decisions should ideally be made following multidisciplinary team (MDT) discussions involving endocrinology, neurosurgery, neuroradiology, oncology, ophthalmology and pathology specialities. Hence, the management of acromegaly patients in Malaysia should be centred in major public, university and private hospitals with availability of specialists in these disciplines.

The main goals in acromegaly treatment[1,2] are tumour shrinkage, reduction of GH (<1 mcg/L) and normalisation of IGF-1,[26] resolution of clinical symptoms, improvement in co-morbidities and reduction in long-term mortality.

Surgery, is the recommended first line treatment[1,2] of acromegaly. Medical therapy with somatostatin receptor ligands (SRL) and dopamine agonists (DA) such as cabergoline are also available.

Locally, despite advancements in surgical techniques and medical therapy, RT[27] still has an important role as salvage therapy. Indications for RT include patients unfit for or who refuse surgery, residual or recurrent tumours not amenable to repeat surgery or failed medical therapy.[27,28]

Surgery

In Malaysia currently, most patients diagnosed with acromegaly, are recommended trans-sphenoidal surgery as the first line of treatment followed by medical therapy and RT, should surgery not be curative.[1,2,29] A well-coordinated multidisciplinary team approach in the surgical management of acromegaly can offer optimal treatment with better outcomes and lower morbidity.[1]

The goal of surgery is to achieve cure and to avoid life-long post-operative hormonal replacement therapy. Aggressive and complete removal of GH secreting tissue is therefore advocated whenever possible, whilst attempting to identify and preserve the remaining normal pituitary tissue.[2]

The ability to rapidly normalise GH and IGF-1 levels, compared to medical and RT, makes trans-sphenoidal surgery (TSS) the treatment of choice.[29,] For large and invasive tumours, debulking surgery is suggested to relieve compressive symptoms and to enhance response to medical therapy.[1,2] Therefore, it is also advocated in patients where surgical cure is not feasible due to tumour location or invasiveness. [29] Repeat surgery is recommended when there is elevated IGF-1 in the presence of an accessible residual or recurrent tumour.

Pre-operative evaluation should consist of imaging and management of co-morbidities. MRI is the recommended imaging modality of choice for pre-operative evaluation and surgical planning followed by dynamic contrast-enhanced multisection CT scan when MRI is contraindicated or not available. High resolution MRI with pituitary protocol helps in localising the tumour and visualising fine anatomic details surrounding the tumour and its neighbouring structures as well as presence of haemorrhage or tumour necrosis. MRI for Image Guided Surgery protocol is recommended for removal of macroadenoma with cavernous sinus invasion, destruction of sellar floor, poor pneumotisation of sphenoid sinus, repeated surgery and microadenoma with normal size sellar turcica.

On the other hand, computer assisted imaging navigation provides a pre-operative and intraoperative 3-dimensional (3-D) mapping of tumour margins in relation to surrounding tissues which, can be useful during the pre-operative planning. It serves as a guide to safe resection whilst preserving critical functions, ensuring patient safety and improving outcomes. Additionally, high resolution CT scan may be required in the presence of significant bony enlargements within the nasal cavity and skull

base to determine the necessity of an adjunct endonasal surgical procedure.

Selective adenomectomy via trans-sphenoidal-trans-nasal route should be the preferred surgical technique as it emphasises targeted and minimally invasive approaches. This is done by using either an operating endoscope or microscope for visualisation and microsurgical techniques.[1,2]

For tumours that are not visualised well on MRI, the possibility of an ectopic neuroendocrine tumour producing GHRH should be considered, even though very rare. For those undergoing transphenoidal surgery with unidentifiable tumour intraoperatively despite confirmative biochemical analysis, partial hypophysectomy may be considered. In failed remission, a more aggressive approach during repeat surgery may be required. Other alternative approaches can include conventional microscopic sublabial trans-septal approach and endoscopic assisted trans-nasal microsurgery.

For large tumours with significant extension to suprasellar, intraventricular, lateral, parasellar or fronto-temporal regions, cavernous sinus invasion or involvement of critical neurovascular structures, transcranial surgery is recommended. In large and invasive tumours, multiple approaches may be required.

Reconstruction of the sellar defect after tumour removal with vascularised mucoperiosteum-mucoperichondrium nasoseptal flap is recommended for large defects or in the presence of an intraoperative cerebrospinal fluid (CSF).

Additionally, Image Guided Surgery protocol is strongly recommended when normal anatomical landmarks of the nasal cavity and endonasal skull base are altered or destroyed by a large tumour or previous surgery.

Medical therapy

SRL is offered as secondary treatment in the presence of residual disease without mass effects after primary surgery.[1,2,25] As long-term indefinite use of SRL is heavily limited by its cost in the Malaysian setting, most patients are offered other definitive treatment options such as repeat surgery and/or RT. As such, the most common indication of SRL would be as bridging therapy while awaiting the effects of RT or to control co-morbidities while awaiting the second surgery.

SRL is also an option as primary medical therapy in macroadenomas with extrasellar extension particularly into the cavernous sinus, without mass effect or chiasmal compression where surgical cure is unlikely.[1,2] Other indications of SRL as primary therapy should be in patients who are poor surgical candidates (e.g., age and co-morbidity restrictions)[1,2] and those who refuse surgery. As a pre-operative treatment, SRL has limited use to those with severe pharyngeal thickness, sleep apnoea or heart failure to improve surgical outcomes.[1,30]

The two commonly used SRL in Malaysia are the intramuscular (IM) octreotide long-acting release (LAR) and subcutaneous (SC) lanreotide depot formulations that are administered four weekly. IM octreotide LAR is available in 20 mg and 30 mg doses and SC lanreotide is only available in 120 mg dose formulation. Most physicians in Malaysia do not use a test dose of short acting (SA) octreotide prior to commencing the long-acting formulation. In terms of efficacy, both octreotide LAR and lanreotide are similar[1,2,31] with an expected GH control to safe levels (<2.5 mcg/L) and/or IGF-1 normalisation in 34-55% of patients.[32-36] With SRL, a clinically relevant reduction in tumour volume (>20%) is seen in 53-63%[37,38] of patients.

SC lanreotide has an added benefit of convenience in a pre-filled ready to use pen that allows partner or self-injection[39] compared to IM octreotide LAR which requires reconstitution and administration by a healthcare professional. With improvement in clinical, biochemical parameters and reduction in tumour size, physicians may extend the dosing intervals up to 8-12 weekly for octreotide LAR and 6-8 weekly for SC lanreotide in order to improve cost effectiveness.[40,41] However, if SRL standard dosing does not achieve control, the frequency may be increased to every 3-weekly (for lanreotide 120 mg and octreotide 30 mg) for better disease control.[42,43] The main adverse events are abdominal cramps and diarrhoea that are usually temporary. However, more severe side effects such as formation of gall bladder sludge and stones require an abdominal ultrasound only if patients present with symptoms of gall bladder disease.[1]

Pasireotide LAR, a second generation SRL can be used in selected cases when octreotide LAR or lanreotide fail to control IGF-1, as data show better efficacy with this agent.[35,44,45] However, its use is limited by very high cost and to patients without poorly controlled glucose, as there is a high rate of worsening hyperglycaemia seen in up to 70% of treated patients.[35] Though pegvisomant, the GH receptor antagonist is the most effective medical therapy for acromegaly[46] it is currently unavailable in Malaysia.

DA is another option in medical therapy for acromegaly. It is mainly used for mild residual disease (IGF-1 <2 times upper limit of normal; ULN)[47] or when cost limits the use of SRL, and has the added benefit of being orally administered. DA is used regardless of prolactin co-secretion. Though accepted as a less effective form of treatment, these drugs may be used in Malaysia as bridging therapy as it is less costly in comparison to SRL. Cabergoline is the only DA that has been widely studied and recommended for use in acromegaly[47,48] with 30% of patients reaching normalised IGF-1 when used as a single agent. The dose of cabergoline is between 1.5-3.5 mg/week and patients should be warned of its side effects such as nausea, hypotension and headaches prior to initiating treatment. All patients on cabergoline should have an annual clinical cardiovascular examination to detect valvulopathy.[49] Echocardiogram (ECHO) should be reserved for patients with audible murmur, on cabergoline ≥3 mg/week for more than five years or equivalent cumulative dose, and those who maintain treatment after the age of 50 years.[49]

Combination treatment with SRL and DA is recommended in patients who have only partial control with SRL monotherapy[50,51] with 42-44% of patients uncontrolled on single therapy reaching normal IGF-1 levels with combination therapy.[2,50] Generally considered a weak agent, selective oestrogen receptor modulators (SERMs) or oral oestrogen[2,52] may be used in combination with

SRL and DA. This may be an option in patients with mild disease who cannot afford the use of SRL. However, this combination is not commonly practiced in Malaysia and experience is therefore limited.

Radiotherapy

Indications for intensity modulated radiotherapy (IMRT), fractionated stereotactic radiotherapy (FSRT) or stereotactic radiosurgery (SRS) are normally reserved for residual or recurrent tumour cases where risk of surgery is high or when patients refuse surgery. RT services including FRST are available in four out of five Ministry of Health, Malaysia centres. IMRT is available in all centres whilst SRS is offered in Kuala Lumpur General Hospital and the National Cancer Institute. Therefore, fractionated RT with 1.8-2 Gray (Gy) per day (up to a total dose of 50.4-54 Gy) is the recommended standard approach toward irradiating secreting pituitary adenomas. This results in tumour growth control in 80-90% and normalisation of GH/IGF-1 in 50-60% of patients at 10 years.[53] Rapid decrease in GH occurs in the first two years followed by progressive, slow decrease over 10-20 years.[54] Median onset of biochemical remission is between 7-10 years.[55] Hypopituitarism occurs in up to 60% of treated patients and its onset follows a similar time course as the development of remission. Optic neuropathy (1-5%), brain necrosis (<1%), cerebrovascular accident and second intracranial neoplasms (1-2%) are long-term side effects that should be followed up.[55] Fractionated RT should be delivered using 3-D conformal radiation technique with CT image acquisition[53] and is consistent with local practice. IMRT and FRST are preferred, as it significantly reduces dose of radiation to normal tissues and incidence of long-term toxicities.[53]

SRS is preferred[56] if appropriate equipment such as linear accelerator, gamma knife or Cyberknife, and trained personnel are available. Minimum distance of tumour to optic chiasm of 3 mm needs to be fulfilled for this approach to be possible.[53] A margin dose of 18-25 Gy is recommended. Though long-term tumour control rate of 80-90%, similar to fractionated RT, is achievable, its strength lies in earlier normalisation of GH/IGF-1 as early as 1.4 years (median 4.5 years).[55] Risk of long-term side effects are further reduced, even though hypopituitarism still remains common reaching up to 50% in some case series.[28,53]

As data is conflicting in different case series,[54,55] interruption of somatostatin analogue during RT should not be routinely adopted in our setting. Patients who have received RT should be monitored with GH/IGF-1 and hormonal profiles annually.[1]

Monitoring

GH and IGF-1 levels should be monitored to assess treatment efficacy and to detect persistent or recurrent disease. Regular assessment of possible development of hypopituitarism, co-morbidities and complications should be carried out.

Post-surgical monitoring

Monitoring patients post-surgery should include both biochemical and imaging studies. The recommendation for IGF-1 level and random GH measurements is at 12 weeks post-surgery.[1] Immediate post-operative measurement of GH is not recommended in the local context. GH value of <1 mcg/L at 12 weeks and a normal IGF-1 value (after age-dependent normalisation) by 3-6 months are consistent with surgical remission.[2] GH level <1 mcg/L indicates "control" and normalisation of mortality risk.[1,57] If the GH is >1 mcg/L, we suggest to measure nadir GH levels after an OGTT.[1]

Following a surgical cure, all patients should have at least an annual IGF-1 level with the addition of OGTT if there is any suspicion of recurrence clinically or based on IGF-1 levels.[2,57] Although most cases have concordant GH and IGF-1 levels, discordant levels can be seen in about 35% of patients with active acromegaly.[58] A repeat testing of GH and IGF-1 levels is suggested 3-4 months after a discrepant result.[59] However, there is no specific guideline on the management of patients with discordant GH and IGF-1 levels.

The first post-surgical MR pituitary should be done at least 3-4 months after the surgery[2,60-62] and subsequently based on disease activity.[2] In patients with pre-operative visual field defects, visual field testing should be done regularly post-surgery.[1]

As there is no available consensus on frequency of post-operative pituitary hormone assessment, based on current local practice, we recommend that it be performed at 3- and 6-months post-surgery and annually thereafter. Hypopituitarism is a significant complication of either continued tumour growth compromising normal pituitary function, or consequences of loss of pituitary function post-surgery or post-radiotherapy.

Monitoring patients receiving medical therapy

For patients who are on medical treatment with SRL or DA, it is recommended to monitor both GH and IGF-1 levels to assess response to treatment. GH and IGF-1 levels should ideally be monitored 4-6 weeks after any dose change.[2] It is also recommended to monitor adverse events associated with SRL such as gastrointestinal and metabolic disorders.

OGTT should not be used to monitor treatment response to SRL, as it is unreliable. Disease monitoring should be done using IGF-1 and random GH levels.[63]

Monitoring patients receiving radiotherapy

Patients receiving RT are at risk of developing hypopituitarism, radiation-induced secondary tumours and radionecrosis. The recommendation is for annual assessments to evaluate pituitary function for hypopituitarism and monitoring of GH and IGF-1 levels.[2,57] Visual acuity and visual field should be closely monitored by regular formal testing to assess any damage to the optic chiasm or optic nerves following RT.

Monitoring of co-morbidities

Cardiovascular and cerebrovascular events are the main causes of death in patients with acromegaly. Cardiovascular risk factors should be appropriately treated and monitored. Patients with symptoms of OSA should have an overnight polysomnography done. ECHO and electrocardiography (ECG) should be performed in patients with suspected cardiac disease. Screening for hypertension and diabetes should be regularly performed.

Patients should also be monitored for signs and symptoms of CTS and arthropathy whilst bone densitometry should be performed in patients with history of hypogonadism or fractures.[2] All patients should undergo colonoscopy once diagnosed with acromegaly[1,2] and repeated either every five years in patients with a colonic polyp at screening or with persistently elevated IGF-levels, or 10 years in those without any polyps at screening and controlled disease.[1] Ultrasound of the thyroid should be performed if there is palpable thyroid nodularity[1] in view of increased risk of thyroid cancer in acromegaly.[64]

CONCLUSION

There are significant challenges in the management of patients with acromegaly in Malaysia. There need to be better awareness of the condition among primary care doctors and other specialities due to the heterogeneity of GH-related morbidity presentation. There is a need for improved screening to identify patients and earlier referral to endocrinologists for confirmation of diagnosis and treatment initiation.

A multidisciplinary team should assess each newly diagnosed acromegaly patient to ensure individualised plan of treatment. Comprehensive care and follow-up should be accessible via a dedicated pituitary clinic led by an experienced endocrinologist, with access to neuroimaging and endocrine laboratory facilities that provide appropriate assays for prompt measurements of GH and IGF-1.

This consensus has been developed to standardise the management of this uncommon disease in Malaysia. A prompt and optimal resource allocation and utilisation for the management of acromegaly will enable patients to achieve a good quality of life with reduction of chronic complications and co-morbidities. Ultimately, this strategy will contribute to true cost savings and reduce this disease burden on the Malaysian healthcare system in the long-term.

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Review Article

A Systematic Review on the Association between Lipid Accumulation Product Index and Type 2 Diabetes Mellitus*

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Abstract

Introduction. Excess fat accumulation contributes to the development of type 2 diabetes mellitus (T2DM). Lipid accumulation product (LAP) is an index computed from waist circumference and triglycerides, which represents increased lipotoxicity. We aim to study the relationship of LAP index and T2DM and its utility as a predictor for T2DM development.

Methodology. A literature search in PubMed and Cochrane database was performed to retrieve and review studies reporting the association between LAP and T2DM.

Results. Two cross-sectional studies from Japan and the United States, and one cohort study from Iran were obtained. A high LAP was associated with a higher risk of T2DM [odds ratio (OR) 19.1, 95% confidence interval (CI) (6.6-55.5) for women; and OR 7.4, 95% CI (5.1-10.8) for men].

Conclusion. LAP was strongly associated with T2DM. Its utility in predicting the development of T2DM needs to be confirmed.

Key words: lipid accumulation product, type 2 diabetes mellitus, insulin resistance, obesity

INTRODUCTION

The prevalence of obesity has escalated globally, invariably affecting low- to middle-income countries. The prevalence of global obesity has increased by about 8.1% in men and 8.2% in women from 1980 to 2013.[1] In a shorter period of time, the prevalence of obesity in adult Indonesians from 1993 to 2007 has also increased rapidly by 11% in men and 13 to 16% in women.[2] The most common etiology for this rapid increase in obesity in low- to middle-income countries is lifestyle change toward high calorie intake and sedentary behavior leading to positive energy balance.[3-5]

Positive energy balance eventually leads to hypertrophy of adipocytes and ectopic lipid accumulation in multiple organs in the body.[6,7] Lipids that overly accumulate outside the non-adipose tissues will be ineffectively oxidized.[8] These unoxidized excess fatty acids lead to abnormal lipid accumulation, which further results to pancreatic beta cell failure, fatty liver, reduced insulin-stimulated glucose uptake in muscle and myocardial insulin resistance.[9] In the end, excessive fat accumulation will contribute to the development of insulin resistance and type 2 diabetes mellitus.

Body mass index (BMI), a common marker of obesity that can be used in measuring lipid accumulation, might not completely represent abnormal adipose tissue deposition.[7,10] Lipid accumulation product (LAP) is an index of lipid accumulation that is computed from waist circumference and triglycerides (TG). LAP was found to have the ability to represent lipotoxicity.[11] Previous studies have reported the relationship between LAP index and the incidence of T2DM.[11-12] However, the cut-off point of LAP index which may contribute to the development of T2DM is still uncertain. Moreover, because the current LAP index formula was derived from a Caucasian population, its applicability in different ethnic groups needs to be further explored. We aim to evaluate the relationship of LAP index and T2DM and its potential as a predictor for T2DM development. In addition, the cut-off point of LAP index associated with T2DM was also evaluated.

METHODOLOGY

This systematic review followed recommendations from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). Literature search was performed from September 10 to 11, 2018 in PubMed

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and Cochrane Central Trial Database - EMBASE. The formulated research question is: "Is LAP index associated with T2DM?" We used the terms: [[lipid accumulation product (Title/Abstract)] OR LAP (Title/Abstract)] AND diabetes (Title/Abstract) in PubMed. For the Cochrane Central Trial Database - EMBASE we used the terms: LAP in Title Abstract Keyword OR lipid accumulation product in Title Abstract Keyword AND diabetes in Title Abstract Keyword AND predictor in Title Abstract Keyword. We included studies that were published within the last 10 years, in English, conducted on humans, and among adult subjects. Grey literature, interventional studies and poor-quality studies were excluded in this review.

Retrieved articles were reviewed independently by two investigators (GA and DLT) in order to gain potentially relevant articles. All disagreements on inclusion/exclusion were discussed and resolved by consensus. Two reviewers (GA and DLT) independently extracted data from included studies. Information on study background (journal, title, year of publication), background characteristics (country, study design, sample, and duration of observation), cut-off point of LAP index, and odds ratio/hazard ratio of LAP index for incidence of T2DM were extracted. All relevant studies were assessed for risk of bias using the Newcastle Ottawa Scale (NOS) in order to be included in the review. Studies with NOS score above 7 were considered as high-quality; a score of 6 to 7 was considered as moderate; and a score less than 6 was considered as poor-quality.

ethics approval and consent to participate

This study was approved by the ethics committee of the Faculty of Medicine Universitas Indonesia (No 1293/UN2. F1/ETIK/2018).

ReSULTS

Our comprehensive search identified 83 publications. After removing duplicates and screening by title and abstract, a total of 7 studies matched the research question. After retrieving the full manuscripts, 3 studies were excluded. These were due to interventional design or diagnostic nature. One study recruited subjects with metabolic syndrome. A total of 2 cross-sectional studies and one prospective cohort study were included in the synthesis, which were performed in Japan, the United States and Iran, respectively (Table 1).[11,12,14] The search and selection process based on the PRISMA flow diagram is outlined in Figure 1. The largest population included 10,170 patients, while the longest duration of follow-up was 6 years.

LAP index cut-off point

All of the included studies performed the analysis separately according to gender. The study by Wakabayashi et al., analyzed the LAP index cut-off point using receiver operating characteristic (ROC) curve analysis.[12] The area under the curve (AUC) values for LAP index with diabetes were 0.763 (0.709-0.816) for women and 0.764 (0.742-0.787) for men, with cut-off points of 21.1 for women and 37.2 for men.[12] The other two studies by Bozorgmanesh et al., and Kahn et al., used quartiles as reference, and considered LAP index values in the 4th quartile as high.[11,14] In the study by Kahn et al., a LAP index of 66.1 for the 4th quartile was considered high.[11] There is no data on the quartile values in the study by Bozorgmanesh et al (Table 1).[14]

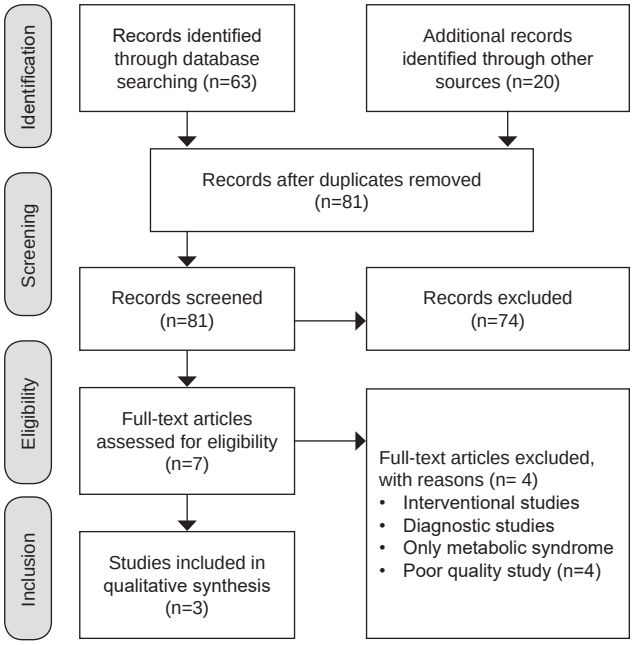

Figure 1. Preferred reporting items for systematic review and meta-analyses flow diagram.

Odds ratios for T2DM

Wakabayashi et al., demonstrated a strong association between LAP index and T2DM in the Japanese population.[12] Using the cut-off values for LAP index of 21.1 and 37.2 for women and men respectively, the OR for T2DM in subjects with high LAP index was 19.09, 95% CI (6.57-55.50) for women; and 7.40, 95% CI (5.10-10.75) in men (Table 1 and Figure 2).

The study by Kahn et al., compared LAP index and BMI for identifying T2DM. The LAP, BMI and homeostatic model of insulin resistance (HOMA-IR) variables that were skewed were logarithmically (ln) transformed. They found that the standardized T2DM OR for (ln)LAP was larger compared to (ln)BMI in each age and sex group. The greatest difference in standardized OR between LAP index and BMI was observed in younger women [5.55, 95% CI (3.48-8.84) versus 2.35 (1.82-3.04)], while the smallest difference was seen in older men [2.33, 95% CI (1.89-2.86) versus 1.95 (1.49-2.54)]. In addition, the upper quartiles of the LAP index (cut-off points of >66.1 for men and >60.4 for women) was found to be associated with more than twice the likelihood of 4th quartiles of BMI for having diabetes (Table 1, Figure 2).[11]

The study by Bozorgmanesh et al., consisted of both cross-sectional and longitudinal analyses. Based on their cross-sectional analysis, LAP index is a strong predictor of diabetes in young individuals, especially among women. LAP had almost consistently stronger association (higher coefficient of determination, R^2) with baseline fasting plasma glucose (FPG) and 2-hour post-challenge plasma glucose (2h-PCPG) than BMI, especially in women (10.2 versus 6.9 and 17.3 versus 9.8, respectively). In younger

Table 1. Summary of included studies

Author	year	Population	Design	LAP[a] index cut-off point	Result
Kahn et al[11]	2006	9,180 (4,733 women and 4,447 men) US[b] civilians age ≥18 years	Cross-sectional	4th Quartile 4 1st Quartile 4th Quartile of LAP index ≥66.1	LAP[a] index is superior to BMI[c] for identifying adults with diabetes. The greatest difference in standardized OR[d] was seen in younger women [5.55, 95% CI[e] (3.48-8.84) versus 2.35 (1.82-3.04)]. The smallest difference was among older men [2.33 (1.89 -2.86) versus 1.95 (1.49-2.54)].
Wakabayashi et al[13]	2014	10,170 (3,267 women and 6,903 men) Japanese age 35 to 40 years	Cross-sectional	ROC[i] curve analysis: AUC[j] for women: 0.763 (0.709-0.816) AUC[j] for men: 0.764 (0.742-0.787) Cut –off points: 21.1 for women 37.2 for men	The prevalence of a high LAP index was calculated to be 23.7% in women and 28.8% in men. The OR[d] for diabetes in subjects with high LAP[a] index was 19.09, 95% CI[e] (6.57-55.5) in women and 7.40, 95% CI[e] (5.10-10.75) in men after adjusting for age, smoking, alcohol consumption and regular exercise.
Bozorgmanesh et al[15]	2010	8,671 (4,989 women and 3,682 men) age ≥20 years in Tehran, Iran	Cross-sectional and longitudinal cohort	Quartile 4 versus quartile 1 (no data given for quartile values)	Cross-sectional analysis: LAP[a] index is a strong predictor of diabetes and in young individuals, especially among women. The OR[d] of LAP[a] with the prevalence of T2DM[f] was 2.1 (1.8-2.5), p<0.001 for age 20-49 years old and 1.5 (1.3-1.8) for age ≥50 years old. Longitudinal analysis: LAP[a] index was better in predicting T2DM[f] compared to BMI[c] but relatively similar to WHpR[g] and WHtR[h]. OR[d] for prediction of T2DM[f] prevalent in young women (age 20-49) was higher in LAP[a] than BMI[c] [2.1, 95% CI[e] (1.8-2.5) versus 1.6,(1.5-1.9), p<0.001.

[a] LAP, lipid accumulation product
[b] US, United States
[c] BMI, body mass index
[d] OR, odds ratio
[e] CI, confidence interval
[f] T2DM, type 2 diabetes mellitus
[g] WHpR, waist-hip ratio
[h] WHtR, waist-height ratio
[i] ROC, receiver operating characteristic
[j] AUC, area under the curve

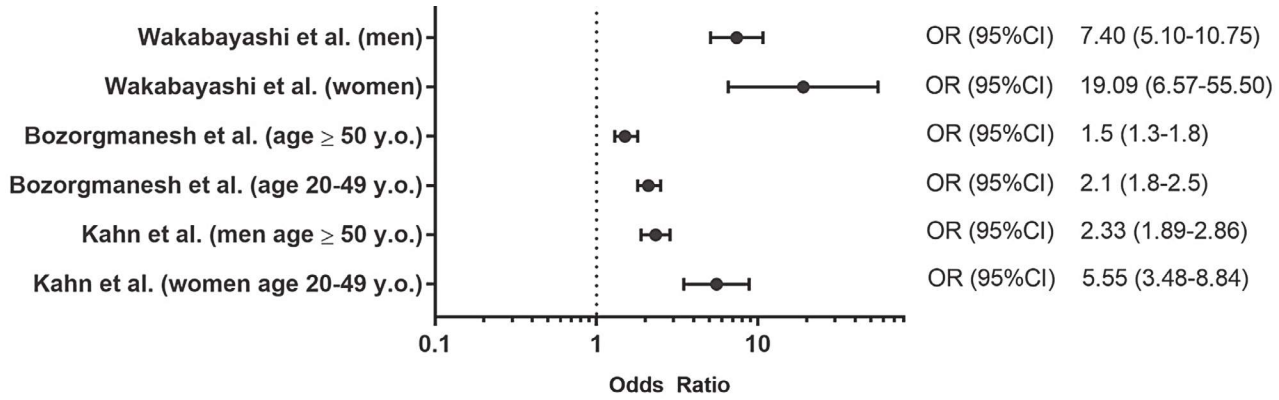

Figure 2. The odds ratio of LAP index and T2DM among the included cross-sectional studies.

Table 2. Critical appraisal and bias risk analysis of the selected articles using the Newcastle Ottawa Scale Study

	Selection	Comparability	Outcome	Total
Kahn et al.[11]	****	**	***	9
Wakabayashi et al.[13]	****	**	**	8
Bozorgmanesh et a.l[15]	****	**	***	9

women (ages 20 to 49 years) and older men (age 50 years and above), the LAP explained greater variability than waist-to-height ratio (WHtR) and waist-to-hip-ratio (WHpR) in the baseline levels of FPG (7.2, 3.6 and 4.6 in women; 5.6, 3.2 and 3.6 in older men; respectively) and 2h-PCPG (8.5, 5.1 and 4.9 in women; 8.8, 6.3 and 6.5 in older men) (Table 1 and Figure 2). In the longitudinal analysis, LAP index performed similarly with BMI, WHtR and WHpR in both sexes and across age groups to predict the incidence of T2DM. The LAP index was only superior compared to BMI in younger men (ages 20 to 49 years).[14]

Study quality

The critical review and bias risk analyses were conducted by using the Newcastle Ottawa Scale (Table 2). All of the included studies were identified as good quality as they reached a score of more than 7.[11-12,14] One study did not report funding sources which may contribute to the risk of bias.[11]

DISCUSSION

Studies have shown that excessive fat accumulation could lead to adipocyte dysfunction and an increase in the risk of T2DM, as well as other cardiovascular risks.[15] This study is the first systematic review to provide evidence on the association of LAP index, a practical equation for estimating body fat accumulation, with T2DM.[11-12,14]

In most population-based studies, BMI, waist circumference, WHpR and WHtR are the most common measures of obesity. Although studies have demonstrated the utility of BMI in assessing population-based mortality and disease-specific morbidity, there are some limitations in using BMI alone to diagnose obesity. First, BMI has an inherent inability to distinguish weight associated with muscle or fat mass. Second, BMI does not characterize body fat distribution, a known determinant of metabolic risk.[15-16] In this aspect, WHpR and WHtR might better represent central obesity, particularly visceral fat, which has been reported to be strongly associated with T2DM. In this study, we observed that LAP index had stronger relationship with T2DM in comparison to BMI, but not to WHpR and WHtR.[14] However, the evidence on the predictive power of LAP on T2DM is still limited and insufficient.

The available studies on LAP and T2DM used different approaches in determining the LAP index value that may contribute to the incidence or development of T2DM. In addition, the studies included different ethnic backgrounds, particularly Asian and Caucasian.[11-12,14] Ethnicity may influence body fat composition as Asians tend to have higher abdominal adiposity.[17] Hence, the cut-off point of LAP index which may related of T2DM still cannot be confirmed, and may possibly vary according to each population.

The stronger relationship of T2DM and LAP index compared to BMI but not WHpR and WHtR can be explained in several possible ways. First, simple measurement of central obesity might be sufficient to identify T2DM. This measurement mostly measures visceral fat, which plays an important role in the development of chronic low-grade inflammation and insulin resistance, and eventually to the development of T2DM. Second, because the formula for LAP index also includes waist circumference, it already includes a measurement of central obesity. We may then speculate that the lipolysis process, represented by TG levels, may also be related to central obesity. Thus, the addition of TG levels in the formula does not add precision in identifying or predicting T2DM.

It is important to note that in the 3 different populations included in our analysis, we observed different of cut-off values for the LAP index. The available calculated cut-off point using AUC analysis was in the Japanese, while the other studies used quartiles as the cut-off point.[11-12,14] Many studies have shown that different ethnic and age groups are correlated with different levels of insulin resistance and body fat composition.[18-19] For the same BMI as Caucasians, the body fat percentage in Asians would be 5 to 7% higher in Indian men; 8% in Indian women; 1 to 4% in Japanese women; 5% and 7% for Indonesian men and women from Malay ancestry, respectively; and 1.3% and 1.7% for Indonesian Chinese men and women, respectively.[7,20-25] To this end, as the LAP index was developed using Caucasian populations, further studies are needed to determine a specific LAP index formula for Asians.

Conclusions

The LAP index was superior to BMI in identifying T2DM risk, but not to WHpR and WHtR. However, the current available studies were not sufficient to establish the role of LAP index in predicting T2DM. Since the current LAP index was developed from studies on Caucasian populations, further research is needed to evaluate the cut-off values for that could be used effectively in identifying or predicting T2DM in other populations.

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All authors certified fulfillment of ICMJE authorship criteria.

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Clinical Features of girls with Turner Syndrome in a Single Centre in Malaysia*

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Abstract

Objectives. Diagnosis of Turner syndrome in Malaysia is often late. This may be due to a lack of awareness of the wide clinical variability in this condition. In our study, we aim to examine the clinical features of all our Turner patients during the study period and at presentation.

Methodology. This was a cross-sectional study. Thirty-four (34) Turner patients were examined for Turner-specific clinical features. The karyotype, clinical features at presentation, age at diagnosis and physiologic features were retrieved from their medical records.

Results. Patients with 45,X presented at a median age of 1 month old with predominantly lymphoedema and webbed neck. Patients with chromosome mosaicism or structural X abnormalities presented at a median age of 11 years old with a broader clinical spectrum, short stature being the most common presenting clinical feature. Cubitus valgus deformity, nail dysplasia and short 4th/5th metacarpals or metatarsals were common clinical features occurring in 85.3%-94.1% of all Turner patients. Almost all patients aged ≥2 years were short irrespective of karyotype.

Conclusion. Although short stature is a universal finding in Turner patients, it is usually unrecognised till late. Unlike the 45,X karyotype, non-classic Turner syndrome has clinical features which may be subtle and difficult to discern. Our findings underscore the importance of proper serial anthropometric measurements in children. Awareness for the wide spectrum of presenting features and careful examination for Turner specific clinical features is crucial in all short girls to prevent a delay in diagnosis.

Key words: Turner syndrome, short stature, webbed neck, lymphoedema, karyotype

INTRODUCTION

Turner syndrome occurs in approximately 1 in 2500 female live births.[1] This syndrome is usually diagnosed in females with characteristic features with an absence of one X chromosome in their karyotype (45,X). However, studies have shown that 45,X karyotype accounts for only 45-50% of all cases of Turner syndrome.[2] Up to 55% of Turner syndrome have other karyotypes including 46,X,i(X)(q10), 46,X,r(X), 45,X/46,XX, 46,X,del(Xp), and 46XY.[2]

Clinical features of classic Turner syndrome with 45,X include short stature in the majority, delayed puberty and infertility in 60-90%, left- sided cardiac anomalies in 50% and renal defects in one-third of cases.[3-5] Other clinical features seen in these patients are short webbed neck, low-set ears, multiple pigmented naevi, oedema of hands and feet, short metacarpals or metatarsals and cubitus valgus deformity. Studies have shown that cardiovascular malformations are more common in classic Turner with 45,X karyotype compared to non-classic Turner with chromosome mosaicism or structural X abnormalities.[4,5-7]

Even though the karyotype of a patient with Turner syndrome does not reliably determine its phenotype or clinical features, patients with mosaic 45,X or structural X chromosomal abnormalities may have less or subtle clinical features compared with patients with 45,X. For instance, normal puberty and fertility are more commonly reported in mosaic Turner patients.[8] Amongst Turner patients with structural X chromosomal abnormalities, ring X-chromosome may also convey a distinct phenotype. Notably these patients may have severe mental retardation, growth retardation and multiple congenital anomalies, which are usually not found in the 45,X patients.[9,10] On a different note, Turner patients with presence of SRY or other Y-chromatin harbor a risk of developing gonadoblastoma in the streak gonads.[11] Management include prophylactic excision of the abnormal gonads.

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Human growth hormone has been shown to be effective in improving the growth of Turner syndrome patients to prevent short adult stature. Treatment has to be initiated early to achieve a satisfactory outcome. Unfortunately, Turner syndrome is often diagnosed late due to lack of awareness of the variability in clinical features and karyotypes. Hence, the aim of our study is to compare the age at diagnosis between 45,X Turner syndrome and the non-classic Turner syndrome and to evaluate the association between age at diagnosis and karyotype. We also aim to evaluate the association between clinical features at presentation and karyotype. These Turner patients are also examined thoroughly for clinical features of Turner syndrome and the association between clinical and physiologic features of Turner syndrome and karyotype are evaluated. We hope that this knowledge may help to heighten awareness and enhance early diagnosis of Turner syndrome so that counseling and appropriate management may be instituted as soon as possible.

Table 1. Classification of Turner Syndrome (n=34) based on karyotype

	Karyotype	N(%)
1. Group A		
Monosomy X	45,X	16 (47.1%)
2. Group B		
X mosaicism	45,X/46,X+1Mar (n=3)* 45,X/46,X+2Mar (n=1)* 45,X/46,XX (n=3)	7 (20.6%)
Y mosaicism	45,X/46,XY (n=2) 45,X/47,XYY (n=1) 45,X/46,X+Mar.ish dic(Y;Y) (n=1)	4 (11.8%)
Ring X	45,X/46,X, r(X) (n=3) 45,X/46,X, r(X)/ 47,X, +2r(X) (n=1)	4 (11.8%)
Isochromosome Xq	46,X,i(Xq) (n=2)	2 (5.9%)
Isochromosome Xp	45,X/46,X,i(Xp) (n=1)	1 (2.9%)
	Total	34 (100%)

* Lymphocytes examined by fluorescent in situ hybridization were negative for SRY gene probe and positive for X pericentromeric probe.

MeTHODOLOgy

We conducted a cross-sectional study over a 1 year period from 2015 to 2016 in Universiti Kebangsaan Malaysia Medical Centre (UKMMC). All karyotype proven Turner patients who were on active follow up in the paediatric endocrine clinic and aged more than 6 months were selected for the study. A total of 34 patients were included in the study. In all cases, Turner syndrome was diagnosed based on karyotype findings using G-banding technique on at least 30 cells performed by the cytogenetic unit at PPUKM. FISH studies using centromeric X, centromeric Y and SRY gene probes were carried out on at least 100 nuclei in selected cases, i.e., in patients with Turner phenotype where karyotype was found to be normal, in patients with detectable marker chromosomes and in patients with detectable Y chromosome.

All patients were classified into 2 groups based on their karyotype. Sixteen patients (47.1%) were in Group A, i.e., 45,X and 18 patients (52.9%) were in Group B, i.e., chromosome mosacism with more than one cell line or structural abnormality of the X chromosome. Table 1 shows the karyotype distribution of the study group. The median age was 14.7 years (11-20.4 years) in Group A and 17.3 years (12.5-22.1 years) in Group B (Table 2).

Throughout the study, these patients underwent thorough clinical examination by the same researcher during their routine clinic visits. This clinical examination included all clinical features of Turner syndrome as stated in Table 3, anthropometric measurements and pubertal staging by method of Tanner. For patients aged more than 2 years and who can stand properly as instructed, height was measured using the Harpenden stadiometer. Patients younger than 2 year or those who could not stand properly as instructed, length was measured using an infantometer. Short stature was defined as height or length less than 3rd percentile on the NCHS (National Child Health Statistics) growth chart and below the target height range for the mid parental height in patients aged ≥2 years. For Turner patients who had been started on growth hormone therapy, their pre-treatment heights were obtained from their respective medical records. Short stature was only determined in 14 patients in group A and 18 patients in group B aged ≥2 years.

The plasma FSH values and pubertal staging of all subjects were reviewed from their medical records. Delayed puberty was defined by presence of exaggerated rise in plasma FSH >10 IU/L and the absence of clinical signs of spontaneous puberty (Tanner stage 2 breast development) by 12 years of age. Delayed puberty was only determined in 11 patients in group A and 15 patients in group B who were aged ≥12 years. Arrested puberty was defined by a lack of pubertal progression over one year or more.

Other physiologic features, i.e., cardiac abnormalities, mental retardation, hearing abnormalities, thyroid disorders, impaired carbohydrate metabolism and renal abnormalities were obtained from medical records. The presence of cardiac abnormalities was confirmed by echocardiography. The presence of hearing and thyroid abnormalities were confirmed by audiology assessment and abnormal thyroid function tests. All subjects in the study had undergone echocardiography, audiology assessment, renal ultrasound and thyroid function screening at diagnosis and/or during follow up.

Impaired carbohydrate metabolism was confirmed by HbA1c and fasting blood glucose (FBG) before and during growth hormone therapy. For Turner patients who were not on growth hormone treatment, HbA1c and FBG were performed by 10 years of age. Patients who had an abnormal HbA1c or FBG underwent an oral glucose tolerance test (OGTT). Impaired carbohydrate metabolism was defined as presence of impaired fasting glucose, impaired glucose tolerance or diabetes mellitus. Impaired fasting glucose was defined by FBG level of 5.6-6.9 mmol/L and impaired glucose tolerance was defined by a 2- hour postload glucose of 7.8 to <11.1 mmol/L during an OGTT.[12] Diabetes mellitus was defined by a FBG of ≥7.0 mmol/L or 2 hour postload glucose of ≥11.1 mmol/L during an OGTT.[13] Only 14 patients in Group A and 16 patients in Group B underwent screening for impaired carbohydrate metabolism.

Table 2. Age at diagnosis and clinical features at presentation

	group A N=16	group B N=18	OR (95% CI)	*P* value
*Current age (years)	14.7 (11.0- 20.4)	17.3 (12.5-22.1)		0.32
Age at diagnosis				
<12 months old	11 (68.8%)	4 (22.2%)	7.7 (1.66 to 35.69)	0.009
1-12years	5 (31.3%)	8 (44.4%)	0.57(0.14 to 2.32)	0.43
≥13years	0 (0%)	6 (33.3%)	0.06(0.003 to 1.14)	0.06
*Overall age at diagnosis	1 month (0- 4.3 years)	11 years (0.75-13.4 years)		0.005
Clinical Features at Presentation				
Lymphoedema	9 (56.3%)	1 (5.6%)	21.86 (2.31 to 206.46)	0.007
Webbed neck	6 (37.5%)	0 (0%)	22.91 (1.17 to 448.48)	0.04
Short stature	4 (25%)	8 (44.4%)	0.42 (0.10 to 1.80)	0.24
Delayed/arrested puberty	0 (0%)	4 (22.2%)	0.10 (0.005 to 1.973)	0.13
Developmental delay	0 (0%)	3 (16.7%)	0.13 (0.006 to 2.815)	0.2
Clitoromegaly	0 (0%)	1 (5.6%)	0.35 (0.01 to 9.31)	0.53
Spinal bifida	0 (0%)	1 (5.6%)	0.35 (0.01 to 9.31)	0.53
Hearing deficits	1 (6.3%)	0 (0%)	3.58 (0.14 to 94.32)	0.44

* Age is in median with IQR (Q1-Q3)

Table 3. Clinical features detected during the study and physiologic features of the study group

Clinical features	group A (N=16) n(%)	group B (N=18) n(%)	OR (95% CI)	*P* value
Webbed neck	11 (68.8%)	3 (16.7%)	11.0 (2.16 to 56.10)	0.004
Short neck	15 (93.8%)	7 (38.9%)	23.57 (2.52 to 220.34)	0.006
Edema of hands/feet	9 (56.3%)	3 (16.7%)	6.43 (1.32 to 31.37)	0.02
Ptosis	6 (37.5%)	3 (16.7%)	3.00 (0.61 to 14.86)	0.18
Low set ears	13 (81.3%)	10 (55.6%)	3.47 (0.73 to 16.53)	0.19
Scoliosis	5 (31.3%)	3 (16.7%)	2.27 (0.45 to 11.59)	0.32
Hypertelorism	8 (50%)	7 (38.9%)	1.57 (0.40 to 6.14)	0.52
Pigmented naevi	10 (62.5%)	13 (72.2%)	0.64 (0.15 to 2.72)	0.55
* Short stature	14 (100%)	17 (94.4%)	2.49 (0.09 to 65.76)	0.59
Nail dysplasia	15 (93.8%)	16 (88.9%)	1.88 (0.15 to 22.88)	0.62
Short 4th/5th metacarpals or metatarsals	14 (87.5%)	15 (83.3%)	1.40 (0.20 to 9.66)	0.73
Micrognathia	8 (50%)	8 (44.4%)	1.25 (0.32 to 4.83)	0.75
Widely spaced nipples	12 (75%)	14 (77.8%)	0.86 (0.18 to 4.19)	0.85
Cubitus valgus	15 (93.8%)	17 (94.4%)	0.88 (0.05 to 15.37)	0.93
Physiologic features				
Cardiac abnormalities	8 (50%)	2 (11%)	8 (1.38 to 46.81)	0.02
Mental retardation	0 (0%)	6 (33.3%)	0.058 (0.003 to 1.135)	0.06
# Delayed puberty	11 (100%)	11 (73.3%)	9.0(0.43 to 187.02)	0.16
Hearing abnormalities	7 (43.8%)	5 (27.8%)	2.02(0.49 to 8.43)	0.33
Thyroid disorders	0 (0%)	3 (16.7%)	0.13 (0.006 to 2.82)	0.2
Renal abnormalities	1 (6.3%)	0 (0%)	3.58 (0.14 to 94.31)	0.44
** Impaired carbohydrate metabolism	1 (7.1%)	2 (12.5%)	0.54 (0.044 to 6.668)	0.63

* Short stature was only determined in patients aged ≥2 years old (14 patients in Group A and 18 patients in Group B)
# Delayed puberty was only determined in 11 patients in Group A and 15 patients in Group B who were aged ≥12 years
** Impaired carbohydrate metabolism was only screened for 14 patients in Group A and 16 patients in Group B

As an IQ assessment was not carried out in our study to ascertain the degree of intellectual impairment, mental retardation was defined by significant developmental delay or intellectual impairment in need of special education. To identify potential delays in the diagnosis of Turner syndrome, information on the age at diagnosis and clinical features at presentation were retrieved from the medical records.

This study had been approved by the ethics committee of UKMMC (Project code number FF-2015-337). Written informed consent had been obtained from the patients.

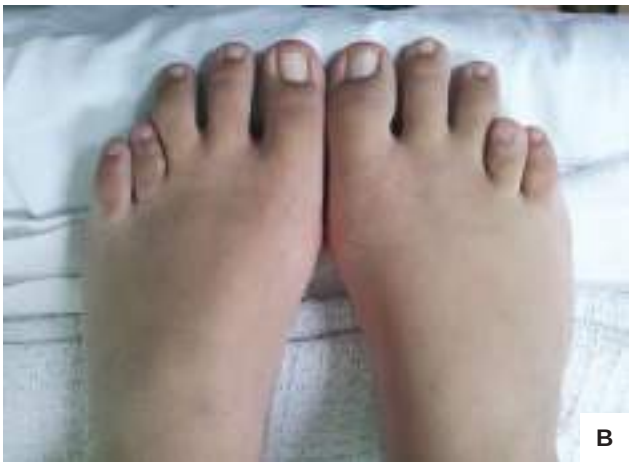
Statistical analysis

Categorical data was expressed as frequency and percentage. Numerical values were expressed as median and inter-quartile range. Group medians were compared using Mann- Whitney U test. Categorical variables were compared using Chi Square test and Fisher's exact test. All statistical analyses were performed using IBM SPSS (Version 25). A p value <0.05 was considered statistically significant.

ReSULTS

Age at diagnosis and clinical features at presentation

The median age at presentation was 1 month (0-4.3 years) in Group A and 11 years (0.75-13.4 years) in Group B. In Group A, 68.8% of the patients presented during infancy compared to 22.2% in Group B (OR 7.7, 95% CI 1.66 to 35.69, p=0.009). In Group A, the predominant clinical features at presentation were lymphoedema and webbed neck. These features were significantly more common in Group A than Group B (56.3% vs 5.6% for lymphedema and 37.5% vs 0% for webbed neck). The majority of patients in Group B (77.7%) presented later after 1 year of age. Out of the patients in Group B who presented beyond infancy, 42.9% were of ages ≥13 years. The initial presentation for Group B was more varied, with short stature being the commonest (44.4%), followed by delayed/ arrested puberty (22.2%) and developmental delay (16.7%). Lymphedema (5.6%) and webbed neck (0%) were uncommon presentation (Table 2).



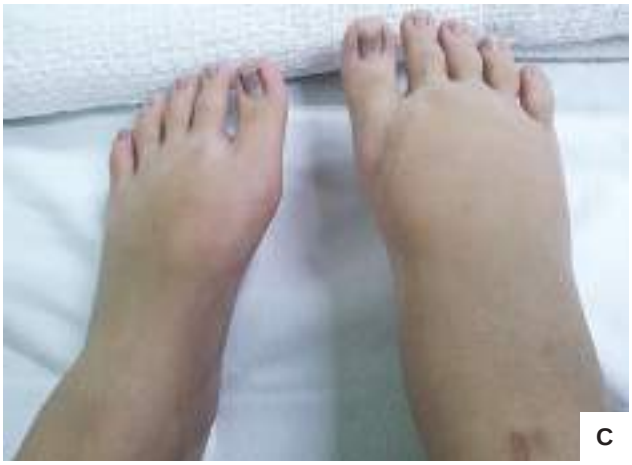


Figure 1. (A) Low set ears, micrognathia and short webbed neck in a 12-year-old with 45,X karyotype. **(B)** Short 4th and 5th metatarsals and hypoplastic nails in a 16-year-old girl with 45,X karyotype. **(C)** Right foot lymphoedema, bilateral hyperconvex and hypoplastic nails in a 11-year-old girl with 45,X karyotype.

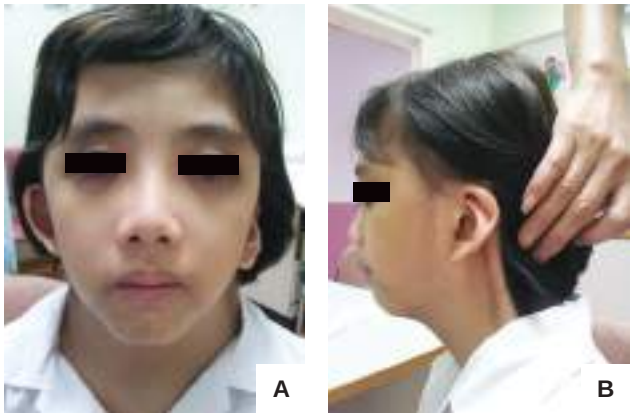


Figure 2 (A & B). Low set ears, hypertelorism, micrognathia, short webbed neck, left eye strabismus, pigmented nevus depicted in a 14-year-old girl with 45,X/47,XYY karyotype.

Figure 3. 24-year-old girl with 45,X/46,X,r(X) karyotype untreated with growth hormone showing cubitus valgus and short stature with a final height 19 cm below the mid-parental height which is indicated by the level of the Harpenden stadiometer head-block.

Two patients in Group B had unusual presentation. One of them had presented with spinal bifida, Arnold Chiari malformation and communicating hydrocephalus at birth. Clinical features of Turner syndrome were also present, i.e., oedema of hands and feet, nail dysplasia, low set ears and scoliosis. G-banded chromosome karyotyping showed 45,X/46,X,i(Xp). Another patient had presented with mild clitoromegaly at birth. Karyotyping revealed 45,X/46,XY. She subsequently underwent prophylactic gonadectomy at 1 year of age. Histopathologic Examination (HPE) of the gonads showed immature semiferous tubules with sertoli cells but no malignant cells.

Clinical features detected during the study

Clinical features of Turner syndrome as listed in Table 3 were more commonly detected in Group A than Group B. Short neck (OR 23.57, 95% CI 2.52 - 220.34, p=0.006), webbed neck (OR 11.0, 95%CI 2.16 - 56.10, p=0.004) and edema of hands/feet (OR 6.43, 95% CI 1.32 to 31.37, p=0.02) were significantly more common in Group A than Group B. Short stature was present in 100% of patients in Group A compared to 94.4% in Group B (Only one patient in Group B did not have short stature). There was no statistical significant difference between both the groups (p=0.59). Cubitus valgus deformity, nail dysplasia and short 4th/5th metacarpals or metatarsals were also common clinical features in both Group A and Group B, occurring in 85.3-94.1% of all the Turner patients. Again there was no statistical significant difference between the groups (Table 3). Figures 1 to 3 illustrate the clinical features detected by clinical examination during the study.

Physiologic features

The prevalence of cardiac abnormalities in our study was 29.4%. Cardiac abnormalities were significantly more common in Group A compared to Group B (OR 8, 95% CI 1.38 to 46.81, p=0.02) (Table 3). The commonest cardiac abnormality was coarctation of aorta, which accounted for seven out of the eight patients in Group A and one out of the two patients in Group B with cardiac abnormalities. Other cardiac abnormalities detected were aortic stenosis in one patient in Group A and hypoplastic aortic arch in one patient in Group B. Amongst the ten patients with cardiac abnormalities, nine (90%) had neck webbing and six (60%) had edema of the hands or feet, suggesting a coexistence between aortic arch structural abnormalities and lymphoedema.

Delayed puberty, hearing abnormalities and renal abnormalities were more common in Group A than Group B. However, the differences were not statistically significant. Delayed puberty was diagnosed in 100% group A and 73.3% group B patients who were ≥12 years of age (p=0.16) (Table 3). Four out of fifteen (26.7%) patients in group B had spontaneous onset of puberty, whereby two had 45,X/46,XX mosaicism and two had ring X-chromosome. All the subjects in the study group, including the four patients with spontaneous puberty had elevated plasma FSH >10IU/L. Out of these four, three had spontaneous menarche but developed secondary amenorrhoea, requiring hormonal replacement therapy.

None (0%) of the patients in Group A had mental retardation whereas six out of eighteen (33.3%) in Group B had mental retardation (Table 3). Amongst patients with mental retardation, three had karyotype 45,X/46,X+Mar, two had karyotype 45,X/46,X,r(X) and one had karyotype 45,X/46,X,i(Xp). Three patients in Group B had subclinical hypothyroidism secondary to autoimmune thyroiditis, and none in Group A. Two out of the three patients required thyroxine replacement. One patient in group A had dysplastic left kidney, and none in group B. None of our patients had horseshoe kidney. One patient in Group A had impaired fasting glucose. In Group B, one patient had diabetes mellitus on gliclazide and one had impaired glucose tolerance. Two out of the three patients with impaired carbohydrate metabolism were overweight. Impaired carbohydrate metabolism did not occur during growth hormone therapy.

DISCUSSION

Monosomy X or 45,X karyotype accounted for 47.1% of our cohort of Turner syndrome. This figure is consistent with other reports whereby monosomy X makes up 45% to 50%. of the karyotype of girls with Turner syndrome.[2] However, in contrast to other studies where isochromosome Xq forms the majority of patients in the non-classic Turner group,[2] our study showed that isochromosome Xq was uncommon and accounted for only two out of eighteen (11.1%) of our non- classic Turner group. This discrepancy might have been due to the small sample size of our cohort.

Short stature was the universal clinical feature seen in both groups. Patients with 45,X tended to present early in life at the median age of 1 month. Lymphoedema and webbed neck were the prominent clinical features leading to early presentation in this group before short stature became apparent. Webbed neck and lymphoedema were rare presenting features at diagnosis (Table 2) and uncommon clinical features in group B (Table 3). This might have been a reason for late diagnosis in these patients until peripubertal age when short stature became obvious or when delayed puberty set in which prompted medical consultation.

In addition to short stature, cubitus valgus deformity, nail dysplasia and short 4th / 5th metacarpals or metatarsals were common physical features across both groups. These characteristics may however be subtle and not easily discernible clinically. Unrecognised short stature and the failure to detect subtle clinical features in Turner syndrome could have led to late diagnosis of patients in Group B at median age of 11 years. It is noteworthy that 33.3% of patients in Group B presented at the age of ≥13 years, hence would miss the opportunity for height restoration with early growth hormone therapy.

The clinical features of short stature and skeletal abnormalities seen in 45,X is due to haploinsufficiency of the *SHOX* gene that has escaped X inactivation and is located in the terminal pseudoautosomal region Xp22.3.[13,14] It has been inferred that the lymphogenic genes residing at Xp11.3 could be responsible for the lymphoedema and webbed neck phenotype seen in Turner syndrome.[14,15] *USP9X (DFRX)*, a gonadal dysgenesis gene which maps to Xp11.4, is implicated in ovarian failure.[14] The diaphanous gene *(DIAPH2)* located on the Xq arm is required for normal ovarian function.[15] The smaller proportion of abnormal cells bearing the 45,X karyotype seen in our mosaic patients in group B could explain the lower prevalence of clinical features in group B compared to group A. This notion is however controversial as the karyotype of these patients is only performed on cultured lymphocytes from peripheral blood, and does not take into account the karyotype of body tissues, e.g., skin, brain, heart and ovaries which might be different.

The prevalence of cardiac abnormalities in Turner syndrome reported by other authors ranges from 20% to 50%, with biscupid aortic valve and coarctation of aorta as the leading causes.[4,6,16] Correlation between cardiac abnormalities and karyotype has been suggested in some

studies.[6,8,17] The largest patient series by Mazzanti et al., on 594 Turner patients showed that patients with 45,X were more likely to be associated with neck webbing and more serious cardiac abnormalities especially coarctation of aorta and partial anomalous pulmonary venous return.[6] Patients with structural X abnormalities were more likely to have bicuspid aortic valve and aortic valve disease.[6] In our study cohort, the prevalence of cardiac abnormalities was 29.4%. Coarctation of aorta was the predominant cardiac defect in our Turner patients with 45,X, comprising 87.5% of total cardiac defects in this group. Only two of the patients in our non-classic Turner group had cardiac abnormalities, comprising of coartation of aorta in one patient and hypoplastic aortic arch in another. The coexistence of webbed neck and congenital heart disease which has been reported by other authors[6,17] was also implicated in our study. It has been postulated that aberrant fetal lymphatic drainage could have caused disturbances to intracardiac blood flow and led to left sided cardiac abnormalities.[18]

Spontaneous puberty is reportedly more common in 45, X mosaicism than monosomy X. For instance, spontaneous puberty has been documented in 6% of patients with monosomy X compared to 54% of patients with 45X/46XX karyotype.[9] In our study, none of the patients with 45,X had spontaneous puberty. Spontaneous puberty onset however occurred in 26.7% of our patients with 45,X mosaicism, consisting of two patients with 45,X/46,XX, and 2 others with large ring X chromosomes. Large ring chromosomes have relatively distal break points which could preserve the critical regions where the ovarian failure genes map. There have been few cases of patients with large ring chromosome reported to be fertile and transmitted their r(X) to their offsprings.[19-21]

Most Turner patients have normal intelligence, with only specific deficits in visuospatial, psychomotor, social and nonverbal problem solving skills. The occurrence of mental retardation is greatest amongst Turner patients with ring chromosomes and marker chromosomes.[9,10,22,23] In our study, mental retardation was found in two out of four (50%) patients with ring X chromosomes and three out of four patients (75%) with marker chromosomes. The more severe phenotype could be a result of deletions in critical regions in the small ring Xs and marker chromosomes as well as failure of X inactivation. Mental retardation was also a feature in one patient with 45,X/46,X,i(Xp). The developmental delay found in this patient could be explained by the underlying Arnold Chiari malformation associated with hydrocephalus and spinal dysraphism.

The majority of our patients with non-classic Turner syndrome were diagnosis late in life at the median age of 11years. Even though short stature, cubitus valgus deformity, nail dysplasia and short 4th/ 5th metacarpals or metatarsals were very common clinical features in both 45,X and non- classic Turner syndrome, under recognition of these features had led to delayed diagnosis. This suggests an inadequacy in our community based health screening programme in detecting children with short stature as well as poor awareness among clinicians of the broad clinical spectrum and subtle phenotype that can be seen in non- classic Turner syndrome.

In a study by Sävendahl and Davenport,[24] lymphoedema was an important feature which led to the diagnosis in most of the girls diagnosed in infancy. Girls who were diagnosed during childhood or adolescence were found to have Turner-specific features and/or a history of lymphoedema. The diagnosis was however delayed an average of 5.3 years after faltering of their heights below the 5th centile. Screening guidelines were proposed following their study whereby girls with at least one of the following features, i.e., unexplained short stature (height below the 5th percentile); peripheral lymphoedema; webbed neck; delayed puberty (no signs of puberty by age 12.5 years) and coarctation of aorta required karyotype analysis for Turner syndrome.[24] It was also proposed that girls with at least two of the following features, i.e., nail dysplasia, short 4th metacarpal bone, strabismus and high arched palate) to be screened for Turner syndrome.[24]

Limitations in our study include a small study population sample size from a single centre. The assessment of clinical features during the study was by one single investigator and this may constitute bias in identification of subtle features. Knowledge of the patients' karyotype could also have caused bias. This study is however the first study in Malaysia which examined the age at diagnosis, presentation, clinical features and karyotype of patients with Turner syndrome.

CONCLUSION

Turner syndrome with monosomy X may be diagnosed early due to their association with webbed neck and lymphoedema. However, Turner patients with mosaic 45,X or structural X chromosomal abnormalities often present late. They lack the obvious clinical features of short webbed neck and lymphoedema. They can present with a wider clinical spectrum and have more subtle clinical features. We recommend accurate height measurement and careful detailed examination of all girls with clinical features suspicious of Turner syndrome. Karyotyping with or without florescent in-situ hybridization (FISH) should be performed to confirm the diagnosis so that appropriate management may be instituted early to prevent morbidities such as short stature, delayed/absent puberty, osteopenia and psychosocial issues.

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ORIGINAL ARTICLE

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Prevalence of Hypoglycaemia among Insulin-Treated Pregnant Women with Diabetes Who Achieved Tight glycaemic Control*

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Abstract

Objectives. To determine the prevalence of hypoglycaemia using continuous glucose monitoring system (CGMS) among insulin-treated pregnant women with diabetes whose glycosylated haemoglobin (HbA1c) were <6.0% and identify the risk factors associated with hypoglycaemia occurrence.

Methodology. We conducted a cross-sectional study using 6-days CGMS to detect the prevalence of hypoglycaemia in 31 insulin-treated pregnant women with diabetes who achieved HbA1c <6.0%. Patients were required to log-keep their self-monitoring blood glucose (SMBG) readings and hypoglycaemia events.

Results. Eight women experienced confirmed hypoglycaemia with additional seven experienced relative hypoglycaemia, giving rise to prevalence rate of 45.2% (one had both confirmed and relative hypoglycaemia). Nine relative hypoglycaemia and 17 confirmed hypoglycaemic events were recorded. Sixteen (94%) out of 17 confirmed hypoglycaemia events recorded by CGMS were asymptomatic and were missed despite performing regular SMBG. Nocturnal hypoglycaemia events were recorded in seven women. Univariable analysis did not identify any association between conventional risk factors and hypoglycaemia events in our cohort.

Conclusion. Insulin-treated pregnant women with diabetes who achieved HbA1c <6.0% were associated with high prevalence of hypoglycaemia. Asymptomatic hypoglycaemia is common in our cohort and frequently missed despite regular SMBG. Present study did not identify any association between conventional risk factors and hypoglycaemia events in our cohort.

Key words: hypoglycaemia, continuous glucose monitoring system, pregnancy, diabetes mellitus

INTRODUCTION

Maternal hyperglycaemia is associated with increased risk of major malformations, pregnancy loss, macrosomia, birth complications, infant with excess adiposity and subsequently higher risk of developing obesity and metabolic syndrome as children.[1-4] Treatment to achieve normoglycaemia has been demonstrated to improve perinatal outcomes in numerous randomised studies.[5] The recommended glycosylated haemoglobin (HbA1C) target in pregnancy is less than 6.0% if this can be achieved without hypoglycaemia.[6] However, striving to achieve tight glycaemic control increases the risk of hypoglycaemia.[7] In a study on pregnant women with type 1 diabetes, data recording by continuous glucose monitoring system (CGMS) for 72 hours detected nocturnal hypoglycaemia (defined as interstitial glucose <2.8 mmol/L, recorded by CGMS) in up to 76% of the study population. The mean HbA1c level in their study population was 6.1±1.2%[8] Nielsen et al., in another study demonstrated that 45% of women with type 1 diabetes experienced at least one episode of severe hypoglycaemia during pregnancy. The authors defined hypoglycaemia as capillary blood glucose <4 mmol/L, and severe hypoglycaemia when the patients required help from another person to actively administer oral carbohydrate or injection of glucagon or glucose. The median HbA1c in women who experienced severe hypoglycaemia was 7.0% (interquartile range 5.9–10.9) in their study.[9] High incidence of hypoglycaemia was not only detected in women with type 1 diabetes, but also among women with gestational diabetes mellitus (GDM).[10] In the study, the authors defined hypoglycaemia as glucose <2.8 mmol/L, detected by either CGMS or glucometer. The reported incidence of hypoglycaemia differs greatly between studies mainly due to different study populations, methodological variation and used of different threshold to define hypoglycaemia.

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Mild hypoglycaemia may be inconvenient or frightening to patients whereas severe hypoglycaemia can lead to severe morbidity and death.[9,11] Frequent hypoglycaemia not only affect the mother, but has also been shown to be associated with intrauterine growth restriction.[6] Hence, a balance needs to be sought between achieving the targets to prevent complications due to maternal hyperglycaemia as well as avoiding maternal hypoglycaemia.

The tool traditionally used to treat and manage diabetes is self-monitoring of blood glucose (SMBG) using glucometer. However, intermittent SMBG using glucometer fails to provide complete insight on the pattern of glycaemia profiles with regards to the direction and recent history of the blood glucose level. A better appreciation and understanding of the effect of these two extremes, hyper- and hypoglycaemia in pregnancy, has been made possible by the advent of CGMS technology, which is able to provide a profile of glycaemic patterns throughout a 24-h period and has been shown to improve glycaemic control, reduce hypoglycaemia occurrence, lower birth weight and reduced risk of macrosomia compared to those managed using SMBG.[12-14] Continuous glucose monitoring (CGM) may also be particularly beneficial among those with hypoglycaemia unawareness, nocturnal hypoglycaemia and/or frequent hypoglycaemic episodes.[15,16]

Despite increasing numbers of investigators using this technology in pregnancy, there are limited studies that look into the occurrence of hypoglycaemia among pregnant women with diabetes.[8,10] A previous study had demonstrated an association between HbA1c level <6.5% and risk of severe hypoglycaemia during early pregnancy in type 1 diabetes.[7] Nevertheless, literature search revealed that, to date, none has looked into the prevalence of hypoglycaemia among insulin-treated pregnant women with diabetes when their HbA1c were <.6.0%. Hence, the present study aims to determine the prevalence of hypoglycaemia using CGMS among insulin-treated pregnant women with diabetes who achieved tight glycaemia control with HbA1c level <6.0%. This study also attempts to identify the risk factors associated with occurrence of hypoglycaemia.

MeTHODOLOgy

We conducted a cross-sectional study using CGMS (iPro™2 Professional CGM developed by Medtronic) to detect the prevalence of hypoglycaemia events among pregnant women with diabetes who achieved tight glycaemic control with HbA1c level of <6.0%. This study was carried out from June 2015 to December 2015. All pregnant women with diabetes who attended the follow up at Combined Endocrine-Obstetric Clinic Tengku Ampuan Rahimah Hospital, Klang and who had fulfilled the inclusion and exclusion criteria were recruited. The inclusion criteria were 1) diabetes in pregnancy including type 1 diabetes, type 2 diabetes and GDM, 2) on insulin therapy, of any dose, 3) HbA1C <6.0% and 4) age >18. The exclusion criteria were 1) known or suspected haemoglobinopathies, 2) renal failure with serum creatinine above the normal reference range, 3) recent blood transfusion within three months prior to the enrolment of the study, 4) not willing to check a minimum of four blood glucose readings each day and 5) decided to fast during Ramadan Month despite counselling regarding the risks.

The classification and diagnosis of diabetes followed were based on the guideline recommended by the American Diabetes Association.[17] GDM was defined as diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes, using "one-step" 75-gram oral glucose tolerance test with cut-off fasting plasma glucose values of 5.1 mmol/L and two hours of 8.5 mmol/L. HbA1c was measured using ion-exchange high performance liquid chromatography (HPLC), with National Glycohaemoglobin Standardisation Program (NGSP) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference system. No previous study has been performed to determine the prevalence of hypoglycaemia events among pregnant women with diabetes whose HbA1c's were treated to target of less than 6.0%. A relevant study was performed on 34 pregnant women with type 1 diabetes of any HbA1c levels where the prevalence of hypoglycaemia was reported as 76%.[8] In order to achieve 15% precision in estimating prevalence rate of 76%, 31 patients were recruited into present study.[18]

Out of the 229 women who were screened for eligibility of entering into the study, 46 women fulfilled the criteria. Eligible patients were informed about the study protocol and written informed consent was obtained prior to the commencement of the study. Thirty-seven women consented for the study. Patients were managed and counselled as per usual clinical practice including dietary advice, target weight gain, target glucose level, technicality of insulin injection and titration. Patients were encouraged to carry out daily usual routine during the six days of CGMS, including self-management of diabetes control. They were also oriented on frequency of capillary blood glucose testing using glucometer in order to calibrate the sensor data, log-keeping on the SMBG, food diary, physical activities, medications and other events (such as feeling of hypoglycaemic and/or hyperglycaemic symptoms, or illness). Following insertion of the CGMS device, interstitial glucose were recorded and stored every five minutes for the following six days. Upon completion of the study and after reports were generated, patients were educated regarding the effects of food, activities and medications on blood glucose levels and advised on adjustment if necessary. Six patients were excluded from the analysis because of withdrawal of consent (n=1), sensor manufacturing defect (n=1), steroid therapy (n=1) and dislodged sensor (n=3).

Criteria for discontinuation or withdrawal of patients were as in Supplement 1.

The following are the outcome variables and their corresponding definitions:[1,19,20]

1. Confirmed or documented hypoglycaemia was defined as blood glucose level of less than 3.0 mmol/L, recorded either by SMBG or CGMS (for at least 20 minutes).
2. Severe hypoglycaemia was defined as a hypoglycaemia event that requires assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
3. Asymptomatic hypoglycaemia or hypoglycaemia unawareness was defined as a documented hypoglycaemia event not accompanied by typical symptoms of hypoglycaemia.

4. Relative hypoglycaemia was defined as an event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured blood glucose concentration ≥3.0 mmol/L.
5. Nocturnal hypoglycaemia was defined as a hypoglycaemia event that occurs between 00:00 and 06:00 hours.

The study had been approved by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia.

Statistical analysis

Demographic and baseline characteristics were expressed using mean and standard deviation (SD) for continuous variables (median with interquartile range were used for non-parametric variables). Test for normality was by using skewness and kurtosis. Numbers with proportions were used for categorical variables. Characteristics of the patients for categorical variables between group with hypoglycaemia and group without hypoglycaemia were compared using Fisher's Exact test; for continuous variables, independent-samples T test was used (Mann Whitney U test was used for non-parametric variables). Univariable analysis was used to identify the risk factors associated with occurrence of hypoglycaemia. The results were expressed as odd ratios (OD) and 95% confidence intervals (CI). The associations were considered to be significant if *p* value <0.05. Analyses of the data were made using the SPSS package version 23.

ReSULTS

A total of 20 women with preexisting diabetes mellitus and 11 women with GDM were recruited into present study. Mean age of the overall cohort was 33.6±4.3 years. Malays formed the majority of the study cohort reflecting the ethnic composition of Malaysians' general population. The mean HbA1c at recruitment was 5.3%±0.5 (Table 1). The duration of disease was very short (≤3 years) in most of the patients except two (six and eight years respectively). Majority of the women (n=26) were on basal boluses, of these 22 women on short acting human insulin and neutral protamine hagedorn (NPH), three women on rapid acting analogues (two aspart and one lispro) and NPH, one woman on short acting human insulin and detemir . The remaining patients were on basal (n=3, all on NPH) and basal plus two (n=2, both on NPH and short acting human insulin).

During the study period, there were eight women who experienced confirmed hypoglycaemia and seven women who experienced relative hypoglycaemia with capillary glucose levels ranges from 3.3-3.8 mmol/L, giving rise to prevalence rate of 45.2% (14 women, as one had both confirmed and relative hypoglycaemia events). Nine events of relative hypoglycaemia and 17 confirmed hypoglycaemic events were recorded during the study periods with the nadir glucose level below the threshold of detection value by CGMS, i.e., <2.2 mmol/L. Of all the 17 confirmed hypoglycaemia events recorded by CMGS, almost all (94%) were asymptomatic and were missed despite performing regular SMBG daily. Patients experienced a mean of 1.9±1.1 episodes

Table 1. Baseline clinical data in 31 diabetes women according to occurrence of hypoglycaemia in pregnancy

	All (n=31)	Hypo (n=14)	No hypo (n=17)	*p* value
Age (in years)	33.6±4.3	34.5±3.7	32.8±4.6	0.283
Ethnicity				
1. Malay	17 (54.8%)	11 (78.6%)	6 (35.3%)	
2. Non-Malay (Chinese, Indian, Others)	14 (45.2%)	3 (21.4%)	11 (64.7%)	0.029
BMI (kg/m^2)	30.8 (5.9)	29.9 (4.7)	31.0 (5.1)	0.427*
Gestational age (weeks)	28.0±4.5	28.0±4.3	28.0±4.8	1.000
Trimester				
1. Second	12 (38.7%)	6 (42.9%)	6 (35.3%)	
2. Third	19 (61.3%)	8 (57.1%)	11 (64.7%)	0.724
Haemoglobin (g/L)	117±9	118±11	117±8	0.718
BP (mmHg)				
1. Systolic	117.5±12.2	119.1±8.6	116.1±14.7	0.491
2. Diastolic	74.0±9.8	73.6±8.6	74.4±10.9	0.845
Type of diabetes				
1. Preexisting #	20 (64.5%)	10 (71.4%)	10 (58.8%)	
2. Gestational	11 (35.5%)	4 (28.6%)	7 (41.2%)	0.707
Type of insulin				
1. Human insulin	27 (87.1%)	10 (71.4%)	17 (100.0%)	
2. Insulin analogue	4 (12.9%)	4 (28.6%)	0 (0%)	0.032
Total insulin dose (unit/day)	45.5±22.4	46.9±21.2	44.4±24.0	0.763
Insulin dose (unit/kg)	0.6±0.3	0.6±0.3	0.5±0.2	0.403
HbA1c (%)	5.3±0.5	5.4±0.5	5.3±0.4	0.377
HbA1c				
1. <5.0%	7 (22.6%)	2 (14.3%)	5 (29.4%)	
2. 5.0% – 5.9%	24 (77.4%)	12 (85.7%)	12 (70.6%)	0.412

Abbreviation: Hypo= Hypoglycaemia; N= number; HbA1c=Haemoglobin A1c; BP= blood pressure; BMI= body mass index
Categorical variables are expressed as number (percentage)
Continuous variables are expressed as means±standard deviation
* Non-parametric variables are expressed as median (interquartile range)
# All were type 2 diabetes

of hypoglycaemia during the six days study period. The mean duration of hypoglycaemia experienced by each patient during the six days study period was 48.8±29.2 minutes. None of the women had severe hypoglycaemia. Nocturnal hypoglycaemic events were recorded in seven women (three experienced both daytime and nocturnal hypoglycaemia, whereas four experienced only nocturnal hypoglycaemia). The remaining seven women experienced only daytime hypoglycaemia. There were five women who did not comply with regular SMBG necessary for calibration of the CGMS resulting in loss of some CGMS data.

There was no significant difference between women who developed hypoglycaemia compared to those who did not with regards to baseline characteristics include age, body mass index, gestational age, recruitment HbA1c level, haemoglobin level, systolic blood pressure and diastolic blood pressure (Table 1). Malay ethnicity appeared to be associated with higher proportion of hypoglycaemia rate.

None of the women was in their first trimester, 12 (38.7%) were in the second trimester and 19 were (61.3%) in the third trimester. Six out of 12 women (50.0%) in the second trimester compared to eight out of 19 women (42.1%) in the third trimester experienced hypoglycaemia (p=0.724). There was no significant difference between preexisting diabetes mellitus who experienced hypoglycaemia when compared to GDM (p=0.707). There were only four women on insulin analogue and all of them experienced hypoglycaemia during the study period. Women who experienced hypoglycaemia used higher daily insulin dose compared to those who did not. However, this difference was not statistically significant (0.6±0.3 vs. 0.5±0.2 unit/kg, p=0.403).

Univariable analysis demonstrated a crude association between ethnicity and hypoglycaemia events (OR 6.72; 95% CI 1.33-33.91; p=0.021). However, the other conventional risk factors of hypoglycaemia did not significantly relate with occurrence of hypoglycaemia (Table 2).

Table 2. Factors associated with the risk of hypoglycaemia event

	Univariable analysis	
	Crude OR (95% CI)	***p* value**
Age	1.10 (0.92-1.32)	0.277
Ethnicity		
Malay	6.72 (1.33-33.91)	0.021
Non-Malay	1.00	
BMI	0.99 (0.86-1.11)	0.740
Trimester		
Second	1.38 (0.32-5.88)	0.667
Third	1.00	
Type of diabetes		
Preexisting	1.75 (0.39-7.92)	0.467
Gestational	1.00	
Duration of diabetes	0.79 (0.48-1.30)	0.349
Mean insulin injection/day	1.42 (0.58-3.44)	0.444
Insulin dose (unit/kg)	3.46 (0.20-58.78)	0.390
HbA1c categories		
<5 %	0.4 (0.07-2.48)	0.325
5.0-5.9 %	1.00	

Abbreviation: OR = odd ratios; CI = confidence intervals; BMI= body mass index; HbA1c=Haemoglobin A1c
Type of insulin was not analysed due to zero cell count

DISCUSSION

To our knowledge, this is the first study that evaluates the prevalence of hypoglycaemia among pregnant women with diabetes who achieved a tight glycaemic control with HbA1c <6.0%. Hence, all trimesters of pregnant women and all types of diabetes were included in order to provide an overall picture of the prevalence. This study demonstrated high prevalence of hypoglycaemia among insulin-treated pregnant women with diabetes when their HbA1c levels were less than 6.0%. The prevalence rate in current study is comparable with other studies among cohort of type 1 diabetes during their early pregnancy, where the risk was well recognised to be highest.[7,9,21,22]

The present study adopted blood glucose level <3.0 mmol/L for definition of hypoglycaemia, as per recommendation of the International Hypoglycaemia Study Group.[20] This threshold value has been agreed to have serious clinical and health-economic consequences. A uniform hypoglycaemia definition would also permit meta-analysis of various studies as a statistical tool to increase power when comparing various interventions. Previous studies used difference threshold values ranges from 2.8 mmol/L to 3.9 mmol/L to define hypoglycaemia, making comparison between studies very challenging.[8-10,22-24]

The gold standard for the measurement of glucose traditionally is with plasma glucose using a high-precision enzymatic laboratory method (glucose oxidase, glucose dehydrogenase, or hexokinase).[25] Since 1987, however, glucometers have been standardised to report plasma-adjusted values within 15% from those obtained by a laboratory reference method and are now recognised and widely used as the standard of care for adjustment of therapy.[25,26] The current study adopted CGMS in additional to a glucometer as the method of detection for hypoglycaemia. Interstitial glucose measured by CGMS is highly correlated with meter glucose (r=0.91–0.92) with the overall mean absolute relative difference of 11.0%.[27-30]

Our study recorded 94% of hypoglycaemia unawareness including nocturnal hypoglycaemia, which were missed despite performing regular intermittent SMBG. The high incidence of hypoglycaemia unawareness during pregnancy may relate, in part, to the loss of counterregulatory hormones reported in women with preexisting diabetes, particularly growth hormone and epinephrine.[31,32] With the advent of CGMS which can reveal hypoglycaemia unrecognised by intermittent blood glucose determinations, this can provide a useful tool to guide clinicians in adjusting diabetes therapy and to guide patients to improve adherence to the management regimes. On the basis of the additional information provided by continuous monitoring that recorded hypoglycaemic events, the therapeutic regimen (insulin therapy, diet adjustment, or both) was changed in seven (88%) of the eight women. Previous studies have shown improvements in pregnancy outcomes and duration of hypoglycaemic episodes with CGM.[8,10,13,33] However, the present study was not designed to explore this.

The incidence of hypoglycaemia has been reported in previous studies to be highest in early pregnancy and lowest in the third trimester.[7,34-36] It has been suggested

that pregnancy related hyperemesis gravidarum, increased insulin sensitivity during early pregnancy, insulin independent feto-placental glucose uptake, over-insulinisation of previously poorly controlled diabetes, a transient decline in progesterone secretion during the late first trimester, luteo-placental shift in progesterone secretion, or other hormonal shifts might be the contributing factors for severe hypoglycaemia in early pregnancy.

Unexpectedly, none of the woman in current study was in their early pregnancy stage at recruitment, which could reflect the time interval needed to intensify the treatment regime before achieved target HbA1c <6.0%, i.e., most women would have surpassed the first trimester period when they have achieved their HbA1c target. Determining the prevalence rate of hypoglycaemia without including this high-risk category will definitely underestimate the actual prevalence in our patients' cohort. Besides, it also weakened the power to detect any association between gestational age and hypoglycaemia occurrence.

A HbA1c level of less than 6.5% has been shown to be associated with risk of hypoglycaemia.[7] However, in the current study, it appears that when HbA1c was below 6.0%, any further reduction of HbA1c did not predict further risk of hypoglycaemia.

Among those pregnant women with type 1 diabetes, it has been reported that a 10 years' longer diabetes duration was associated with 1.6 (95% CI 1.0-2.4) odds of developing severe hypoglycaemia.[7] However, none of our study patients had type 1 diabetes and the majority of them had very short disease duration. Hence, the present study did not demonstrate similar association.

Only four women were on insulin analogues and their insulin regimes were changed prior to the study recruitment as they experienced hypoglycaemia when they were treated with human insulin. It appeared that they continued to experience hypoglycaemia despite being shifted to insulin analogues. However, there is no data available to compare the relationship between changing treatment regime with duration and severity of hypoglycaemia. A recent randomised trial compared prandial insulin aspart with human insulin in type 1 diabetes either switching them preconceptionally or during early pregnancy demonstrated trends toward improved risk of severe hypoglycaemia in the aspart group but the difference was not statistically significant.[22,23] More importantly, switching to insulin analogues after human insulin treatment during pregnancy did not seem to worsen the risk of hypoglycaemia.[22,37]

Evers et al., demonstrated in their study that a daily insulin dose 0.1 unit/kg or higher were risk indicators predictive for severe hypoglycaemia during the first trimester.[7] The current study did not demonstrate a similar association among those women during their second and third trimesters. Besides, the mean daily insulin dose used in their study (0.7±0.3 unit/kg) was also higher compared to our study population (0.6±0.3 unit/kg), which might predispose their study cohorts to higher hypoglycaemia risk.

Others possible predictors for hypoglycaemia in pregnancy are history of severe hypoglycaemia pre-pregnancy and hypoglycaemic unawareness.[9,32,38] None of our study patients with preexisting diabetes mellitus has a history of severe hypoglycaemia pre-pregnancy.

The sample size recruited in the present study, which was calculated based on prevalence rate from the previous relevant study, was a major limiting factor due to the cost of CGMS. Consequently, the power to detect a relationship between various variables and hypoglycaemia may have been too small. For the same reason, we did not pursue with multivariable analysis. Besides, sample size calculated was based upon a study among type 1 diabetes with a different cut-off definition for hypoglycaemia. Future studies to identify the risk factors associated with hypoglycaemia in this cohort of patients should consider focusing on the very high-risk group, i.e., type 1 diabetes in their early pregnancy. Further research should also study maternal and neonatal outcomes in order to elucidate how the benefits of strict glycaemic control can be balanced with the markedly increased risk of hypoglycaemia during pregnancy. In order to maintain near-normoglycaemic state without episodes of hypoglycaemia, it is of utmost importance that besides considering to relax the strict glycaemic target, patients at risk should receive appropriate self-management education including carbohydrate counting with clear insulin dose adjustment instruction, risk of hypoglycaemia unawareness and more frequent SMBG including midnight glucose monitoring for those at risk of nocturnal hypoglycaemia. Another approach will be utilisation of CGMS technology, whenever it is feasible to discover the occurrence of hypoglycaemia especially amongst patients with preexisting diabetes mellitus. However, the cost of CGMS will be the limiting factor.

CONCLUSION

In conclusion, this study demonstrated that insulin-treated pregnant women with diabetes who achieved HbA1c <6.0% were associated with high prevalence of hypoglycaemia. Almost all (94%) of the confirmed hypoglycaemia events were asymptomatic and were missed despite performing regular SMBG. The conventional risk factors of hypoglycaemia did not significantly related with occurrence of hypoglycaemia in the current study cohort.

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

Author Disclosure
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SUPPLeMeNT 1

Criteria for discontinuation or withdrawal of a patient

1. Experience local irritation such as redness, pain or swelling at the site of sensor insertion and iPro™2 attachment site
2. Experience allergic reaction to adhesive tape
3. Lost to follow up. The patient did not return to the clinic and attempts to contact the patient were unsuccessful.
4. Voluntary withdrawal. The patient wishes to withdraw from the study. The reason of withdrawal, if provided, will be recorded.
5. Patient goes into labour, regardless of stage of labour
6. Patient admitted to hospital for reasons that deems likely to affect glucose control such as infection, poor oral intake, treatment with steroid
7. Miscarriage or intrauterine demise

Note: Data from discontinued or withdrawn women were not interpreted. Discontinued or withdrawn women were followed up as their routine clinic visit as per scheduled. Discontinued or withdrawn women were replaced.

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ORIGINAL ARTICLE

Factors associated with In-Hospital Mortality among Patients with Diabetes Admitted for Lower extremity Infections

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Abstract

Objective. To determine the factors associated with in-hospital mortality among diabetic patients admitted for lower extremity infection.

Methodology. This is a retrospective analysis of diabetic patients with lower extremity infection admitted at the UP-Philippine General Hospital. Data was analyzed through multiple logistic regression after multiple imputation was performed for missing data.

Results. 441 patients with diabetes were included in the analysis, of which 98.1% have Type 2 diabetes mellitus; 58.1% were males and the mean age of the cohort was 56.7±11.1 years. The mortality rate was 11.1% over the 3-year period from 2015 to 2017, of which 46% died from myocardial infarction (MI). Multivariate logistic regression showed the following were associated with increased likelihood of in-hospital mortality: non-performance of surgery (OR=4.22, 95%CI 1.10-16.27, *p*=0.036), elevated BUN (OR=1.06, 95%CI 1.01-1.11, *p*=0.016), MI (OR=27.19, 95%CI 6.38-115.94, *p*=0.000), respiratory failure requiring mechanical ventilation (OR=26.14, 95%CI 6.28-108.80, *p*=0.000), gastrointestinal bleeding (OR=10.08, 95%CI 1.87-54.38, *p*=0.007), hospital-acquired pneumonia (OR=9.46, 95%CI 2.52-35.51, *p*=0.001) and shock (OR=7.09, 95%CI 2.17-23.22, *p*=0.001).

Conclusion. In the in-patient setting, morbidity and mortality is high among diabetic patients with lower extremity infection. Non-performance of surgery, elevated BUN, MI, respiratory failure requiring mechanical ventilation, gastrointestinal bleeding, hospital acquired pneumonia and shock are associated with in-hospital death.

Key words: diabetes, diabetic foot infection, mortality, hospitalization

INTRODUCTION

Diabetic foot disease remains the leading cause of non-traumatic lower extremity amputation. Foot ulcers, in association with infection or gangrene, precede amputations in 75-85% of cases.[1] Approximately 9% of patients with diabetes admitted at hospitals have active foot disease. Half of this group will have active foot disease as the reason for admission.[2] After an initial event of hospitalization for diabetic foot ulcer, the rates are high for ulcer recurrence (60.9%) and amputations (43.8%). Furthermore, long-term studies have found poor quality of life and increased mortality among these patients even after amputation and discharge.[1,3,4]

Management of diabetic foot disease requires a multidisciplinary approach to adequately address the various pathological processes contributing to the disease. At the University of the Philippines-Philippine General Hospital (UP-PGH), the Diabetes Extremity Care Team (DECT) was established in 1996 with the aim of providing comprehensive surgical and medical care. The major objective of this team approach is to decrease the rates of major amputations and mortality. A retrospective study done 3 years after the formation of the DECT reported a decrease in the mortality rate of patients from 13.8% to 8%. However, no decrease in major amputation rate was observed.[5] Furthermore, additional retrospective studies published last 1999 and 2009 showed suboptimal quality of care in this patient group.[6,7] There was a non-significant trend in mortality increase during 2005, 2006 and 2007 (2.6%, 9% and 8.5%, respectively) compared to 1999 (4.6%). From 1998 to 2007, the time from admission to surgery ranged from 7.5 to 10.9 days. In addition, the mean time to antibiotic administration ranged from 7.5 to 16.7 hours. This is far from the recommended window of 1 hour from recognition of severe sepsis/septic shock to first antibiotic administration and likely contributed to increased mortality.[8] Department data from June 2014 to August 2016 showed a significantly higher mortality rate compared to previous reports, wherein there were 53 in-hospital deaths among 445 admissions (11.9%) under the DECT.

Diabetic patients with foot disease have prolonged hospital stay and greater in-hospital mortality, which widely ranged from 1.1% to 40.5%.[9-13] Few studies have

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examined the factors that are associated with mortality among hospitalized diabetic patients with foot disease.[12-15] However, potential factors such as delay in surgery and initiation of antibiotics, and development of in-hospital complications such as infection, hypoglycemia, MI, renal failure, stroke and respiratory failure and their influence on in-hospital death among diabetic patients with lower extremity infection has not been adequately studied.

The present study was undertaken to examine the factors potentially associated with in-hospital mortality such as clinical and biochemical characteristics, type of surgical treatment received and in-hospital complications. Furthermore, the mortality rate and causes of death among diabetic patients admitted with lower extremity infection were also studied. The early recognition and management of the identified in-hospital complication may help decrease the mortality rate among these patients. Findings of this study will aid in the creation of a risk stratification strategy that will identify high risk patients needing urgent medical and surgical care as well as provide data that will inform an institution-based treatment pathway.

MeTHODOLOgy

Study design and study population

This is a retrospective analytical study conducted at the UP-PGH, a tertiary government hospital in Manila, Philippines. The records of 506 consecutive admitted patients with diabetes referred to the DECT from January 2015 to December 2017 were reviewed. All patients were ≥18 years old, diagnosed with diabetes mellitus according to the American Diabetes Association (ADA) criteria and had signs of infection involving the lower extremity. Patients who refused treatment for infection control, life-extending measures, or those who were discharged against medical advice were excluded from the analysis.

The sample size calculation was estimated based on the risk of dying among diabetic patients with extremity infection who develop in-hospital MI from our registry. A logistic regression of death on occurrence of MI with a sample size of 435 admitted patients with diabetic foot infection (of which 89% are without MI and 11% had MI) achieves 90% power at 5% significance level to detect a change in probability of death from the baseline value of 0.16 to 0.50. This change corresponds to an odds ratio of 5.25. An adjustment was made since a multiple regression of MI on the other independent variables in the logistic regression is assumed to have an R-squared of 0.60.

This study was approved by the University of the Philippine Manila Research Ethics Board (UPREB) Panel. Since the research was limited to use of existing records, informed consent was waived. Patient codes were used to de-identify patients in the data collection forms. All data gathered was kept strictly confidential.

Data collection

The in-hospital charts of all patients admitted under the DECT from January 2015 to December 2017 were screened for eligibility. The patient's demographic profiles, clinical presentation, medical history and physical findings were reviewed from the medical records. This included the patient's age, sex, smoking status and medical conditions. Patients were classified as smokers if they smoked ≥100 cigarettes per lifetime, currently smoking or stopped less than 1 year. They were considered former smokers if they smoked ≤100 cigarettes per lifetime, quit ≥1 year. Those who smoked <100 cigarettes per lifetime were considered never smokers. Patients were diagnosed with diabetes based on medical history, present intake of diabetes medications or if they fulfill the ADA criteria for the diagnosis of diabetes mellitus. Those who had a blood pressure of ≥140/90 mmHg or were taking antihypertensive medications were diagnosed with hypertension. The diagnosis of coronary heart disease was based on the presence of anginal chest pain, exertional dyspnea, history of MI, unstable angina, prior revascularization procedures or as diagnosed by a physician. Neuropathy was considered present if the patient had evidence of loss of sensation using the monofilament test, vibration sense on tuning fork test or as diagnosed by a physician based on symptoms. Retinopathy was diagnosed based on funduscopic examination by an ophthalmologist or history of retinal surgery. Peripheral arterial disease was diagnosed by an ankle brachial index of <0.9 with claudication, significant occlusion on arterial Doppler studies or as diagnosed by a physician based on symptoms. Cerebrovascular disease was defined as a history of an acute focal neurologic deficit of sudden onset that was irreversible within 24 hours, evidence of stroke on neuro-imaging or as assessed by a physician.

The wound classification was based on the University of Texas Diabetic Foot Classification System. Classification of Body Mass Index (BMI) was based on the World Health Organization/International Association for the Study of Obesity/International Obesity Task Force (WHO/IASO/IOTF).

Values of routine laboratory tests taken on admission were documented and included the following: complete blood count, creatinine, calculated eGFR based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, blood urea nitrogen, alanine transaminase, aspartate transaminase, serum sodium, potassium, albumin, total calcium, magnesium, chloride, international normalized ratio (INR), random blood sugar, capillary blood glucose on admission, HBA1c and lipid profile results. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated by dividing the neutrophil or platelet counts, respectively, by the number of lymphocytes from the initial complete blood count.

The hospital course of each patient was followed from admission until death or discharge. Amputations above the ankle were classified as major amputations. Digit, ray and trans-metatarsal amputations were considered minor amputations. The time intervals from admission to the first antibiotic dose and first surgery were documented. In-hospital complications were reviewed based on the medical records and include the following: hypoglycemia, hospital-acquired pneumonia, MI, stroke, transfusion of packed red blood cell (PRBC), gastrointestinal bleeding, renal failure requiring dialysis and respiratory failure needing assisted ventilation. Hypoglycemia was defined based on the ADA classification of hypoglycemia.[16] Hospital-acquired pneumonia was defined as

development of new lung infiltrates with clinical evidence that the infiltrate was infectious in origin, associated with new-onset fever, purulent sputum, leukocytosis or decrease in oxygenation presenting 2 or more days after hospitalization or as diagnosed by the attending physician. Stroke was defined as an acute focal neurologic deficit of sudden onset that is irreversible for 24 hours or results in death not due to other non-vascular cause, or evidence of infarction or intracerebral hemorrhage by neuro-imaging. Myocardial infarction was defined based on an elevated cardiac troponin (>99th percentile or a >20% increase if with elevated baseline value) associated with at least one of the following: symptoms of myocardial ischemia, new ischemic electrocardiogram (ECG) changes or new left bundle branch block, development of pathological Q-waves on the ECG, imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality or identification of intracoronary thrombus by angiography. Patients with sudden death but without biomarkers were diagnosed to have had MI if attending physician deemed it was the cause of death. Shock was defined as systolic arterial pressure less than 90 mmHg or mean arterial pressure less than 70 mmHg associated with evidence of tissue hypoperfusion. Gastrointestinal bleeding was defined as a clinical event documented by the attending physician such as coffee-ground emesis, hematemesis, hematochezia or melena, or endoscopic evidence of active bleeding from the upper or lower gastrointestinal tract.

Data analysis

The demographic, clinical and laboratory characteristics of patients who were discharged or who died during admission were summarized using means and standard deviations (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed using frequencies and percentages. Shapiro-Wilks test was used to test for normality of data.

Pearson chi-square and Fisher's exact tests were used to compare categorical parametric and nonparametric data, respectively. Independent t-test was used to compare continuous variables. Variables were assessed for collinearity and excluded in the multivariate logistic regression. We used multiple imputation by chained equation (MICE) to impute missing data in the covariates. All available auxiliary variables capturing the clinical profiles of the patients were included in the imputation to support missing-at-random assumption. We estimated average associations across 10 imputed data sets. The effect size from the multivariate analyses was reported as odds ratios (OR) for inpatient mortality. Confidence intervals (CI) are given at 95% and p-values less than 0.05 were considered significant. STATA 13 was used for data analysis.

ReSULTS

From January 2015 to December 2017, there were 506 diabetic patients with lower extremity infection referred to the DECT. Four hundred and seventy-one records were reviewed and 35 charts could not be retrieved. Out of the 471 patients, 30 were excluded from the study. Of the final 441 patients, 49 (11%) died during hospitalization. The causes of deaths were as follows: 23 (46.9%) due to MI, 13 (26.5%) from refractory septic shock, 7 (14.3%) with respiratory failure and 6 (12.2%) with fatal arrhythmia. The death occurred prior to any surgical intervention in 35 (71.4%) patients and 14 (28.6%) were post-operative mortalities. The mean duration from admission to death was 17.7±14.4 days.

The demographic and clinical characteristics are summarized in Table 1. The mean patient age of the cohort was 56.7±11.1 years. Patients who died were significantly older than those who were discharged with mean ages of 55.2±10.9 and 60.6±11.9 years old, respectively. Overall, majority of patients were males (58.1%) and were within the normal BMI category for Asians (46%). Almost all patients had type 2 diabetes mellitus (98.1%), with 57 (13%) patients diagnosed within one month from admission and four of whom eventually died.

Microvascular and macrovascular complications were common in both groups. The most common microvascular complication was neuropathy, which was present in 287 (65.1%) patients. Likewise, the most common macrovascular complication among the cohort was peripheral arterial disease which was present in 110 patients (24.9%). The presence of retinopathy, pre-existing coronary heart disease and peripheral arterial disease was more frequent in the mortality group. Other common comorbidities were hypertension, renal disease and dyslipidemia which were present in 239 (54.2%), 190 (43.1%) and 188 (42.6%), respectively. Eighty patients (18%) already had a prior amputation.

Table 2 summarizes the laboratory results of the patient cohort. Patients had leukocytosis and anemia on admission. Renal function was significantly poorer in the mortality group as shown by the higher BUN and creatinine, as well as a lower eGFR. Overall, glycemic control was poor as reflected by the RBS [median 9.9 mmol/L (IQR 9.7)] and HBA1c (mean 9.85±3.4%).

The wound classification of diabetic foot ulcers in patients with foot involvement is presented in Appendix A. Majority of the wounds were University of Texas stage 3 (69.6%) and grade C (51.3%). 22 patients (5%) presented with necrotizing fasciitis, four of whom died during admission.

All patients received antibiotic treatment. The median time to first antibiotic administration was longer among those who were discharged alive but the observed difference between the two groups was not statistically significant [4.3 hours (IQR 13.6) vs 6.3 hours (IQR 11.6), p=0.2]. The median length of hospital stay was 17 days (IQR 13) for the entire cohort.

Table 3 summarizes the surgical procedures performed during hospital stay. Any form of surgery for infection control was performed in 315 patients (71.4%). Major amputation was performed in 233 patients (50.6%). There were fewer deaths among patients who underwent BKA. Overall, surgery was performed 11 days (IQR 10) after admission and did not significantly differ between two groups.

The in-hospital complications are summarized in Table 4. Occurrence of at least one hypoglycemic episode

Table 1. Demographic and clinical characteristics of diabetic patients with lower extremity infection

	Total n=441	Discharged n=392	Mortality n=49
Age in years, mean (SD)	56.7 (11.1)	56.2 (10.9)	60.6 (11.9)
Sex, n (%)			
Male	256 (58.1)	224 (57.1)	32 (65.3)
Female	185 (41.9)	168 (42.9)	17 (34.7)
BMI (kg/m^2), mean (SD)	23.50 (3.9)	22.54 (3.6)	23.58 (3.9)
<18.5	12 (4.4)	11 (4.5)	1 (3.3)
18.5-22.9	127 (46.0)	108 (43.9)	1 (63.3)
23-24.9	62(22.5)	58 (23.5)	4 (13.3)
25-29.9	58 (21.0)	54(22.0)	4 (13.3)
>30	17 (6.16)	15 (6.1)	2 (6.7)
Smoking, n (%)			
Smoker	92 (20.9)	82 (20.9)	10 (20.4)
Previous smoker	107 (24.3)	97 (24.7)	10 (20.4)
Never smoker	242 (54.9)	213 (54.4)	29 (59.2)
Type of Diabetes, n (%)			
Type 1 DM	6 (1.4)	6 (1.5)	0
Type 2 DM	433 (98.1)	385 (98.2)	48 (98)
Secondary diabetes*	2 (0.5)	1 (0.3)	1 (2)
Newly-Diagnosed Diabetes**, n (%)	57 (12.9)	53 (13.5)	4 (8.2)
Duration of Diabetes in months (SD)	93.37 (94.5)	93.44 (95.5)	92.86 (87.9)
Treatment of diabetes, n (%)			
Insulin Only	42 (9.5)	38 (9.7)	4 (8.2)
Oral diabetes medication only	238 (54.0)	212 (54.1)	26 (53)
Insulin and oral medication	55 (12.5)	50 (12.8)	5 (10.2)
None	106 (24)	92 (23.4)	14 (28.6)
Microvascular complications, n (%)			
Retinopathy	205 (46.5)	185 (47.19%)	20 (40.82%)
Nephropathy	226 (51.3)	197 (50.26%)	29 (59.18%)
Neuropathy	287 (65.1)	261 (66.58%)	26 (53.06%)
Macrovascular complications, n (%)			
Cerebrovascular disease	43 (9.8)	36 (9.2)	7 (14.3)
Coronary heart disease	63 (14.3)	48 (12.2)	15 (30.6)
Peripheral arterial disease	110 (24.9)	92 (23.5)	18 (36.7)
Co-morbidities, n (%)			
Hypertension	239 (54.2)	207 (52.8)	32 (65.3)
Renal Disease	190 (43.1)	163 (41.6)	27 (55.1)
Dyslipidemia	188 (42.6)	168 (42.7)	20 (40.8)
Prior amputation	80 (18.1)	67 (17.1)	13 (26.5)
Dialysis prior to admission	48 (10.9)	38 (9.7)	10 (20.4)
Liver Disease	16 (3.6)	11 (2.8)	5 (10.2)
Pulmonary Tuberculosis	16 (3.6)	13 (3.3)	3 (6.1)
COPD	7 (1.6)	5 (1.3)	2 (4.1)

COPD - Chronic Obstructive Pulmonary Disease
* 1 patient with Acromegaly and 1 patient with Steroid-induced Diabetes
** Diagnosed within 1 month from admission

was common and occurred in 160 of patients (36.3%), with 27 episodes (6.1%) classified as severe hypoglycemia based on the ADA classification. Blood transfusion was required in 285 patients (65.4%). Development of shock, renal failure requiring dialysis, blood transfusion, respiratory failure requiring mechanical ventilation, hospital-acquired pneumonia, MI, and gastrointestinal bleeding were more frequent in the mortality group.

Univariate analysis revealed 22 factors with crude association with mortality as shown in Appendix B. After removal of collinear variables and adjusting for covariates, analysis showed that in-hospital complications increased the likelihood of dying during hospitalization due to lower extremity infection among patients with diabetes. Myocardial infarction, respiratory failure requiring mechanical ventilation, gastrointestinal bleeding, hospital-acquired pneumonia and shock were found to be associated with higher risk of in-hospital mortality (Table 5). Similarly, for every 1 mmol/L increase in BUN seen on admission, there is a corresponding 6% increase in the odds of dying. Likewise, patients who did not undergo any form of surgery for source control were also 4.2 times more likely to die during hospitalization.

DISCUSSION

This study shows that the in-hospital mortality rate among patients with diabetes admitted for lower extremity infection was 11.1%. This figure is comparable to that reported by Costa et al., in a Brazilian cohort of patients.[15] However, the reported in-hospital mortality rates vary widely from 1.1% to as high as 40.5% depending on the hospital setting.[9-13] Majority of our patients had cardiac or pulmonary complications as the underlying causes of death. This is similar to a study involving 283 predominantly diabetic patients who underwent major lower extremity amputation wherein cardiac and respiratory complications were significant risk factors for death during hospitalization.[14]

Table 2. Laboratory characteristics of diabetic patients with lower extremity infections

	Total n=441	Discharged n=392	Mortality n=49	*p*-value
WBC (10^9/L), median (IQR)	17.1 (13.6)	16.7 (13.7)	20.3 (12.9)	0.032
Hemoglobin g/L, median (IQR)	9.9 (3.4)	10(3.5)	8.9 (3.8)	0.172
Platelet (10^9/L), mean (SD)	402.3 (168.4)	409.3 (169.4)	346.7 (150.4)	0.014
Neutrophil (%), mean (SD)	80.3 (11.1)	79.6 (11.2)	86.2 (8.2)	0.0001
Lymphocyte (%), median (IQR)	10(10)	11(10)	6(5)	0.000
N-L Ratio, median (IQR)	8.3 (10.5)	7.5(10.3)	14.8(13.5)	0.000
P-L Ratio, median (IQR)	224.7(172.9)	221.5(165)	263.3(201.9)	0.099
Creatinine (mmol/L), median (IQR)	110(139)	103(264.5)	199(234)	0.000
BUN (mmol/L), median (IQR)	8.5(9)	7.7(8.2)	14.2(15.2)	0.000
eGFR (ml/min/1.73 m^2), median (IQR)	54.7 (63.6)	58.9(60.9)	24 (34.6)	0.000
Na (mmol/L), mean (SD)	131.5(10.4)	131.5 (10.6)	131.6 (8.5)	0.930
K (mmol/L), median (IQR)	4.3 (1.2)	4.3(1.2)	4.5(1.1)	0.241
Cl (mmol/L), mean (SD)	95.7 (10.2)	95.4 (10.2)	97.8 (10.2)	0.125
Albumin (g/L), mean (SD)	28.7 (12.2)	28.6 (7.2)	29.9 (29.8)	0.496
Calcium (mmol/)L, mean (SD)	2.29 (0.29)	2.30 (0.20)	2.20 (0.66)	0.018
Mg (mmol/L), mean (SD)	0.79 (0.34)	0.78 (0.36)	0.85 (0.21)	0.175
HBA1c (%), mean (SD)	9.85 (3.40)	9.93 (3.40)	8.75 (3.25)	0.155
ALT (U/L), median (IQR)	31 (28)	30.5 (27)	39 (31)	0.070
AST (U/L), median (IQR)	32 (25)	32 (24.5)	43 (40)	0.011
INR, mean (SD)	1.19 (0.40)	1.17 (0.36)	1.38 (0.64)	0.001
RBS (mmol/L), median (IQR)	9.9 (9.7)	10.3 (9.6)	8.1 (6.6)	0.565
CBG (mmol/L), median (IQR)	11.6 (10.2)	11.9 (10.2)	10.9 (10.9)	0.082
Cholesterol (mmol/L), mean (SD)	3.55 (1.40)	3.62 (1.43)	2.85 (0.73)	0.004
Triglyceride (mmol/L), median (IQR)	1.3 (0.9)	1.31(0.9)	1.4(0.82)	0.486
HDL (mmol/L), median (IQR)	0.59 (0.3)	0.61 (0.4)	0.51(0.3)	0.026
LDL (mmol/L), mean (SD)	2.18 (0.95)	2.23 (0.96)	1.63 (0.59)	0.001

WBC - white blood cell count; N-L ratio - Neutrophil to Lymphocyte Ratio; P-L ratio - Platelet to Lymphocyte ratio; BUN - Blood urea nitrogen; eGFR - estimated glomerular filtration rate; Na - Sodium; K - Potassium; Cl - Chloride; Mg - Magnesium; HBA1c - Hemoglobin A1c; ALT - alanine aminotransferase; AST - aspartate aminotransferase; INR - international normalized ratio; RBS - random blood sugar; CBG - capillary blood glucose; HDL - High-Density Lipoprotein; LDL - Low-Density Lipoprotein

Table 3. Surgical procedures performed

	Total n=441	Discharged n=392	Mortality n=49	*p*-value
Number of patients who had surgery, n (%)	315 (71.4)	297 (75.8)	18 (36.7)	0.000
Debridement, n (%)	49 (11.1)	45 (11.4)	4 (8.2)	0.486
Minor amputation, n (%)	42 (9.5)	41 (10.5)	1 (2.0)	0.058
Major amputation, n (%)	223 (50.6)	210 (53.6)	13 (26.5)	0.000
BKA	178 (40.4)	173 (44.1)	5 (10.2)	0.000
AKA	46 (10.4)	38 (9.7)	8 (16.3)	0.152
Hip disarticulation	2 (0.4)	2 (0.5)	0	-
Revascularization, n (%)	2 (0.4)	2 (0.5)	0	-
Time from admission to first surgery (days), median (IQR)*	11(10)	13(14)	11(17)	0.653

BKA - Below Knee Amputation; AKA - Above Knee Amputation
* n=302

Our subjects had a mean age of 56.7±11.1 years and were predominantly males. The cohort is slightly older than the previous population of diabetic patients with foot infection in our hospital described in 2007, wherein the mean age was 55±11 years old.[17] In other reports, the age of diabetic patients admitted for foot disease varies between 54.3 to 64.3 years.[13,15,18,19] Increasing age has been found to be a risk factor for in-hospital mortality among diabetic patients with foot disease.[12,15] One study reported that age >75 years old was associated with increased in-hospital mortality in diabetic patients admitted for foot disease.[12] However, our study did not find age as a factor for in-hospital death. This may be due to dissimilarities in the ages of the population. Our patient cohort is younger and only 5% were more than 75 years of age.

Majority of our patients had microvascular complications, with retinopathy documented in 46.5%, nephropathy in 51.3% and neuropathy in 65%. These complications are commonly observed in patients with long-standing diabetes (>10 years) and these numbers likely underestimate the true prevalence of these conditions due to the retrospective design of the study. The high prevalence of microvascular complications highlights the need for routine screening for such conditions during hospitalization of patients with diabetes mellitus as hospital stay is a good opportunity for these patients to be assessed by different specialists involved in their care. PAD was observed in 24.9% of the study population. The presence of both neuropathy and PAD are independent risk factors for ulcer development and limb loss in diabetic patients.[15] This relationship between PAD and increased risk of amputation emphasizes the need for a comprehensive vascular assessment among diabetic foot patients. Coronary heart disease was present in 14.3% of patients but this likely underestimates the true prevalence of this disorder as patients may have occult disease. In our study, the presence of PAD and pre-existing coronary heart disease was crudely associated with mortality in univariate analysis but the association was not significant after correcting for multiple variables.

Table 4. In-hospital complications among diabetic patients with lower extremity infection

	Total n=441	Discharged n=392	Mortality n=49	*p*-value
Any hypoglycemia episode, n (%)	160 (36.3)	137 (35)	23 (46.9)	0.100
Severe hypoglycemia, n (%)	27 (6.1)	20 (5.1)	7 (14.3)	0.011
PRBC transfusion, n (%)	285 (65.4)	247 (63.5)	38 (80.9)	0.018
Shock, n (%)	71 (16.1)	37 (9.4)	34 (69.4)	0.000
Respiratory failure requiring mechanical Ventilation, n (%)	52 (11.8)	19 (4.9)	33 (67.4)	0.000
Myocardial infarction, n (%)	51 (11.6)	22 (5.6)	29 (59.2)	0.000
Hospital-acquired pneumonia, n (%)	51 (11.6)	27 (6.9)	24 (49)	0.000
Renal failure requiring dialysis, n (%)	38 (8.6)	25 (6.4)	13 (26.5)	0.000
Gastrointestinal bleeding, n (%)*	25 (5.7)	13 (3.3)	12 (24.5)	0.000
Stroke, n (%)	4 (0.9)	2 (4.1)	2 (0.5)	0.063

PRBC - Packed Red Blood Cell
* Includes both upper and lower gastrointestinal bleeding

Table 5. Multivariate analysis of factors associated with in-hospital mortality

Variable	OR	95% CI	*p*-value
Myocardial infarction	27.19	6.38 to 1115.94	0.000
Respiratory failure requiring mechanical ventilation	26.14	6.28 to 108.80	0.000
Gastrointestinal bleeding	10.08	1.87 to 54.38	0.007
Hospital-acquired pneumonia	9.46	2.52 to 35.51	0.001
Shock	7.09	2.17 to 23.22	0.001
No surgery	4.22	1.10 to 16.27	0.036
Blood urea nitrogen	1.06	1.01 to 1.11	0.016

In terms of laboratory parameters, both groups were anemic on admission (hemoglobin <11 g/dL) and required transfusion with packed red blood cells in two-thirds of patients (65.4%). The anemia is likely multifactorial resulting from infection, chronic kidney disease or poor nutrition. When analyzed in our multiple logistic model, anemia did not increase the likelihood of mortality contrary to another report.[15] Both groups had elevated creatinine and BUN, with eGFR <60ml/min during admission. These findings are likely secondary to sepsis, preexisting renal disease and/or volume depletion. Of interest, elevated BUN was found to be associated with in-hospital mortality in this study and has not been previously reported in this patient population. The elevated BUN and its relationship to increased mortality in this population is uncertain. However, in a study involving 4176 critically ill patients admitted to the ICU due to various medical conditions, BUN was independently associated with a higher risk of death.[20] As BUN levels are routinely taken during hospitalization, this laboratory test represents a readily available tool to risk stratify patients who have a higher risk of in-hospital death. This can be used in combination with other reported laboratory parameters associated with in-hospital death such as albuminuria and elevated WBC count (>12.0 x10^9/L) in this patient population.[12]

In our study, the grade and stage of the diabetic foot ulcer were not associated with mortality. There was a slight increase in the major amputation rate from 48.6% in 2008 to 50.6% in this study.[17] This rate is higher compared to international reports that ranged from 21% to 24.4%.[14,18] Overall, the median time interval from admission to surgery for source control was 11 days (IQR 10), which is even longer compared to the 9.8 days last 2007.[17] The delay in intervention in our hospital setting is mainly due to the lack of an available operating room, the need for medical optimization of the patient, correction of anemia or no initial consent for surgery.

Patients who did not undergo any surgical intervention had an increased likelihood of mortality of 3.5 times. This finding supports the notion that prompt source control of infection should be done as soon as medically practical after the diagnosis of sepsis has been made to improve outcomes.[21,22] Furthermore, after initial resuscitation and stabilization of the patients with septic shock, source control should be done within 6-12 hours.[8] However, our study did not show any association between delayed time to first antibiotic treatment (>60 minutes) and surgery with mortality. This may be due to the fact that majority of the patients in both groups had delayed antibiotic treatment and surgery hence there was no adequate comparator to assess this association.

Severe hypoglycemia occurred more frequently in the mortality group (14.3% vs 5.1%). There was crude association between severe hypoglycemia and mortality in our study but this was not significant after adjusting for confounders. Hypoglycemia has been linked to higher mortality rates in hospitalized patients with diabetes, while hyperglycemia has been linked to impaired wound healing.[23,24] This stresses the importance of carefully balancing glycemic control with hypoglycemia avoidance.

In this study, gastrointestinal bleeding was associated with 10-fold increase in the likelihood of death during hospitalization and highlights the need for routine stress ulcer prophylaxis. The development of shock, respiratory failure requiring assisted ventilation, hospital-acquired pneumonia and MI also markedly increased the odds of dying among diabetic patients with lower extremity infection. Development of these in-hospital complications indicate a need for more aggressive treatment and possible early subspecialty referral if necessary. In particular, those who are high risk for adverse cardiovascular events based on clinical risk stratification may warrant additional non-invasive testing for proper risk stratification.

This study has several limitations. First, due to the retrospective nature of the study design, missing data is inevitable when reviewing medical records. However, we tried to offset this by doing multiple imputation of missing data. Second, important physical findings such as the ankle brachial index, test for loss of proprioception and funduscopic examination were not performed in all of the patients and the true incidence of PAD, neuropathy and retinopathy are likely underestimated. Third, findings of this study apply to diabetic patients admitted in a tertiary hospital with limited resources and

availability of operating rooms allotted for infectious cases such as diabetic foot ulcers. This limits the applicability of our data to patients with similar situations. Fourth, the odds ratios of the factors associated with in-hospital death are broad indicating that the precision is low or that the sample size for logistic regression analysis may be small. Hence, these findings should be confirmed through studies with a larger population. Finally, causality cannot be established between the factors identified and death due to the retrospective nature of the study. However, this study was able to analyze a comprehensive set of multiple variables including in-hospital complications as it relates to mortality thereby adding to our understanding of the hospital course of this patient group. Furthermore, our data highlights the complex nature of lower extremity infections among patients with diabetes mellitus wherein patients present with multiple diabetes complications, comorbidities and frequent hospital complications that need to be considered in treating this population.

CONCLUSION

In our setting, the in-hospital mortality rate among patients with diabetes admitted for lower extremity infection was 11.1%. In-hospital complications such as development of shock, MI, respiratory failure, hospital-acquired pneumonia and gastrointestinal bleeding were associated with increased risk of in-patient death. Additionally, elevated baseline BUN and non-performance of surgery for source control were also associated with increased likelihood of death. Patients identified to have high risk for cardiovascular events, and those who develop in-hospital complications, warrant more aggressive approach to treatment, including source control.

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All authors certified fulfillment of ICMJE authorship criteria.

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APPeNDIX

Appendix A. University of Texas wound classification for infections with foot involvement*

	Total n=392	Discharged n=344	Mortality n=48	*p*-value
UT Grade				
A	0 (0)	0 (0)	0 (0)	0.887
B	21 (5.3)	19 (5.5)	2 (4.2)	
C	201 (51.3)	177 (51.5)	24 (50)	
D	170 (43.4)	148 (43)	22 (45.8)	
UT Stage				
1	65 (16.6)	61 (17.7)	4 (8.3)	0.246
2	54 (13.8)	46 (13.4)	8 (16.7)	
3	273 (69.6)	237 (68.9)	36 (75)	
Necrotizing Fasciitis	22 (5.6)	18 (5.2)	4 (8.3)	0.329

UT - University of Texas
* Data presented as n(%)

Appendix B. Univariate analysis of factors associated with in-hospital mortality

Variable	Crude OR	95% CI	*p*-value
Respiratory failure requiring mechanical ventilation	40.49	19.04 to 86.09	0.000
Myocardial infarction	24.39	11.94 to 49.79	0.000
Shock	21.75	10.85 to 43.60	0.000
Hospital acquired pneumonia	12.98	6.55 to 25.69	0.000
Gastrointestinal bleeding	9.46	4.02 to 22.21	0.000
Stroke	8.30	1.14 to 60.29	0.037
No surgery	5.38	2.88 to 10.06	0.000
Renal failure requiring dialysis	5.30	2.50 to 11.25	0.000
Coronary heart disease	3.16	1.60 to 6.23	0.001
eGFR ≤15 (ml/min/1.73 m^2) on admission	2.80	1.23 to 6.39	0.014
Severe hypoglycemia	2.80	1.13 to 6.95	0.026
PRBC transfusion	2.29	1.09 to 4.82	0.029
INR	2.26	1.13 to 4.52	0.021
Peripheral arterial disease	1.89	1.01 to 3.54	0.046
Blood urea nitrogen	1.06	1.03 to 1.08	0.000
Age (years)	1.04	1.01 to 1.07	0.008
Neutrophil lymphocyte ratio	1.03	1.02 to 1.05	0.000
Creatinine	1.002	1.001 to 1.003	0.003
Platelet count	0.997	0.995 to 0.999	0.015
Cholesterol	0.671	0.506 to 0.891	0.007
Low density lipoprotein	0.525	0.359 to 0.768	0.001
Major amputation	0.313	0.161 to 0.608	0.001

OR - Odds ratio
eGFR - estimated glomerular filtration rate; INR - international normalized ratio

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ORIGINAL ARTICLE

Development of a Patient Decision Aid on the Choice of Diabetes Medication for Filipino Patients with Type 2 Diabetes Mellitus*

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Abstract

Objective. To develop a locally adapted patient decision aid (PtDA) on treatment intensification among Filipino patients with Type 2 Diabetes Mellitus and to test the feasibility of using PtDAs in a low middle-income country

Methodology. A qualitative approach and an iterative process of development of a PtDA were employed for this study. We describe the process of developing a Filipino version of the Diabetes Medication Decision Aid. This PtDA was designed to help the patient choose the appropriate treatment intensification based on his own values and preferences, in consultation with his physician. The process involved decisional needs assessment through focus group discussions and key informant interviews, systematic literature review, iterative process of the development of a PtDA with clinical encounters (pilot testing), and preliminary field testing.

Results. Decisional needs assessment revealed that Filipino patients are open to participate in shared decision-making if given the opportunity, including those with low socioeconomic status who likely have low health literacy. Physicians prefer to have visual aid tools to help them support their patient's decision-making. A PtDA prototype of a set of flash cards in Filipino was created and revised in an iterative method. We developed a more visually appealing tool after inputs from the expert panel and patient advisory group. Its use during clinical encounters provided additional insights from patients and clinicians on how to improve the PtDA. Preliminary field testing showed that its use is feasible in the target patient population.

Conclusion. Filipino patients, clinicians, and diabetes nurse educators have contributed to the creation of the first Filipino PtDA for diabetes treatment intensification.

Key words: decision aid, decision support technique, decision support model, patient decision making, interactive health communication, risk communication

INTRODUCTION

The increasing array of new anti-diabetic agents and the rising uncertainty on the single "best" choice of add-on therapy to metformin has led the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) to emphasize the need for patient-centered care and shared decision-making (SDM).[1] Studies show only small differences between agents in terms of glucose control, which may be less likely to have a differential long-term impact on an individual patient.[1–4] The decision about the next add-on medication may not be clear cut and involves trade-offs (e.g., glucose lowering efficacy, side effects, impact on weight, cost, and patient's routine).[5] As such, SDM plays a particularly important role in this situation where the available evidence does not provide the clear "best" option for the patient. It also provides an opportunity for physicians to involve patients in a conversation about the advantages and disadvantages of the various treatment options.[6]

SDM is a patient-centered approach that engages both the physician and the patient in a discussion about reasonable treatment choices, with each one bringing in his own "expertise" into the conversation—the clinician is expected to be an expert on the clinical evidence while the patient is the expert on his illness experience, daily routine, and values. SDM also recognizes that clinical evidence alone may be inadequate to guide treatment decisions at all times.[7] In endocrinology, 60% of recommendations from current clinical practice guidelines from various societies are supported by low to very low quality of evidence whilst only 14-15% of the recommendations are based on high quality evidence.[8,9]

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On the other hand, patients and physicians may not want to nor be comfortable with patients taking part in decision making about diabetes medications.[10] In fact, impediments to SDM include patient's perceived lack of knowledge, low self-efficacy (i.e., belief that one cannot perform SDM), and the fear of making decisions about medications.[11] Thus, physicians must be provided with tools to effectively engage patients in SDM. In addition, facilitators for SDM also rely immensely on physician motivation and their perception that SDM can make an impact on patient outcomes.[10]

Patient decision aids (PtDAs) are tools used in SDM to facilitate patient participation in healthcare decision-making. They can be in the form of web-based tools, videos, treatment cards, or worksheets.[7] Unlike educational materials, PtDAs provide information in preparation for a decision to be made, which includes the various options and their corresponding advantages, disadvantages, and outcomes. In a Cochrane review of 115 trials involving 34,444 participants, PtDAs were shown to increase patient knowledge, informed patient choices, increased participation in decision making, improved decision self efficacy, and reduced decisional conflict (remained undecided).[12] However, despite the rapid pace of development in the field of SDM,[10] the impact of this approach on medication adherence, cost reduction, and clinical outcomes is still lacking.[12,13] Due to this, SDM may be more appropriate for treatment decisions in chronic care, such as diabetes, which requires more active participation and commitment to maintain medication and lifestyle regimens in the long term.[14–17] As such, different versions of PtDAs have been developed to engage patients in a conversation about decisions on initiation or intensification of diabetes treatment.[18–23] These PtDAs have been tested in RCTs and, similarly, have been found to improve patient's knowledge and increased patient involvement in SDM,[5,13,21,24] reduced decisional conflict,[5,21,24] promoted realistic expectations, and promoted autonomy in making decisions.[21]

It has been argued that SDM and the use of these PtDAs are applicable only to well-educated middle class patients and for high-income countries.[25] However, patients with lower literacy levels, when provided with well-presented information on evidence, can participate well and potentially benefit the most from increasing knowledge on medication options.[26] To date, no PtDAs have been developed and published in the field of endocrinology in the Philippines or from any other low-middle income country.

We aim to develop a locally adapted PtDA to help Filipino patients with poor glycemic control despite being on one or two medications decide on treatment intensification. We also aim to test the feasibility of using PtDAs in a low middle-income country.

MeTHODOLOgy

The study was done in three-phases: 1) the creation of the PtDA prototype (including decisional needs assessment); 2) pilot testing (alpha testing); and, 3) preliminary field testing (beta testing). This process was adapted from the International Patient Decision Aids Standards (IPDAS) Collaboration and the Ottawa Decision Support Framework (ODSF).[27-28] The University of the Philippines Manila Research Ethics Board approved this study. Figure 1 shows the overall flow of the study.

Phase I: Creation of the PtDA prototype

Decisional needs assessment

Participants

Patients were recruited from the outpatient clinics of the University of the Philippines-Philippine General Hospital (UP-PGH) General Medicine, Family Medicine, Diabetes, and Faculty Clinics through convenience sampling. Adult patients aged 18 years old and above who have a physician diagnosis of type 2 diabetes mellitus (T2DM) and were already on one or two medications for T2DM were invited to participate in the patient decisional needs assessment. Those who consented were included in the focus group discussions

Physicians recruited for the professional needs assessment included doctors from specialties directly taking care of patients with T2DM in our hospital. These were comprised of internists (IM), family medicine (FM)

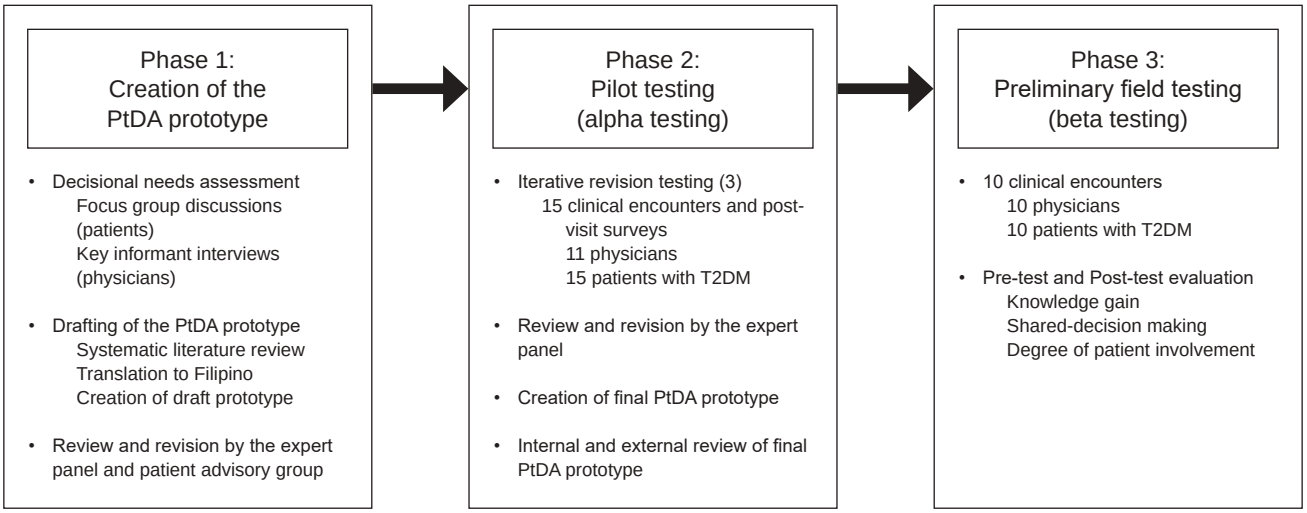

Figure 1. The study flow diagram.

physicians, and endocrinologists, including fellows-in-training. We recruited physicians in the spectrum of early, mid, and late career to be able to capture a wide array of perspectives on SDM.

Methods

Focus group discussions (FGDs) and key informant interviews (KIIs) were conducted with patients and physicians, respectively, to determine their views and perceptions on making decisions, explore the concept of SDM including barriers and facilitators to SDM, and the factors to consider when choosing diabetes medications.

Four FGDs with 5 to 9 participants each were conducted to assess patient decisional needs. Informed consent was obtained from all the participants prior to the start of the discussion. A moderator facilitated the group discussion aided by a set of guide questions. All sessions were video recorded and transcribed verbatim prior to analysis. FGDs were conducted until themes had reached point of saturation.

Ten key informant interviews (KIIs) were conducted to assess the professional needs of clinicians who will be the potential end-user of the PtDA. Semi-structured KIIs were video recorded and also transcribed verbatim.

Drafting of the PtDA prototype

Literature review and translation to Filipino

The Diabetes Mellitus Medication Choice Decision Aid was adapted with permission from the Mayo Clinic.[29] The original English version was sent to the *Komisyon sa Wikang Filipino* (KWF [Commission on the Filipino Language]) for initial translation. The Filipino translation was revised upon the discretion of the researcher for improved comprehensibility by lay patients. The first revision of the prototype was sent back to the KWF to check for errors in grammar, spelling and translation.

To update the information presented in the PtDA, we did a systematic literature search on PubMed for evidence on the effectiveness, effects on weight, and safety including rates of hypoglycemia and adverse effects of the different medications for diabetes that are available in the Philippines. All network meta-analyses, traditional meta-analyses, RCTs, and clinical practice guidelines were critically appraised for directness, validity, and applicability prior to inclusion into the evidence base of the PtDA. Cost of medications was surveyed from local pharmacies. The range of costs was presented in the PtDA where applicable.

Review by the expert panel and patient advisory group

The draft prototype was presented to an expert panel composed of physicians (two endocrinologists, a family medicine physician, and an internist) and 3 diabetes nurse educators; as well as to a patient advisory group composed of 3 patients with T2DM to assess comprehensibility, clarity, and value of information. They were oriented on the scope and purpose of the study and the PtDA. Results of the decisional needs assessment were shown to them. Members of the patient advisory group were asked to role-play a clinical encounter using the PtDA prototype administered by one of the investigators. The draft of the prototype was evaluated and critiqued in two separate group discussions by the expert panel and the patient advisory group. It was then revised according to suggestions from the group discussions prior to evaluation in actual clinical encounters.

Phase 2: Pilot testing (Alpha testing)

Participants

A convenience sample of clinicians (IM and FM residents and endocrinology fellows), and patients from the UP-PGH General Medicine, Family Medicine, Diabetes, and Faculty Clinics were invited to participate in the study. Eligible patients included adult Filipino patients age ≥18 years of age, with a physician diagnosis of T2DM, currently on mono- or dual therapy of oral anti-diabetic medication/s, with an HbA1c within the past 3-6 months of greater than or equal to 7.5%, and were advised by their physician to consider additional anti-diabetic medication to achieve glycemic targets. Subjects were identified through chart review of patients who were scheduled to undergo a check up on that clinic day or were referred for inclusion by their respective physicians. Informed consent was obtained prior to enrolment into the study.

We excluded patients who were pregnant and those who cannot speak or understand Filipino. Other patients excluded were those who require very complex care or with poor health status, i.e., requiring long-term care, with severe cognitive impairment, or with end stage chronic illness that will impair them from fully participating in a discussion and significantly limit medication choices. End stage chronic illness included the presence of stage III-IV congestive heart failure (CHF), oxygen dependent lung disease, end stage renal disease requiring dialysis, or metastatic cancer.

Clinicians recruited for the pilot testing included physicians who provide consultations for patients with T2DM in our hospital such as those from IM, FM, and Endocrinology. However during the recruitment process, only IM residents and Endocrinology fellows-in training consented to participate in the study.

A convenience sample of 3 to 5 clinicians and 6 to 7 patients participated in each iteration.

Procedure

An iterative process was utilized in developing the final prototype PtDA. Prior to the use of the prototype during an actual clinical encounter, clinicians were oriented about the nature of the study, the purpose of the PtDA, and how to use it. When the patient agrees to participate, the physician administered the PtDA prototype. Each clinical encounter was expected to last for 5 to 30 minutes. During the actual clinical encounter, the physicians encouraged the patient to participate in deciding what medication will be added to his current regimen. At the end of the consult, the physician and the patient were expected to arrive at a decision on treatment intensification. Aside from choosing an add-on medication, patients were also allowed to choose not to intensify treatment as long as she/he understood the risks of such an option. This was followed by a semi-structured interview of the patient and physician to gather insights on the usability, acceptability,

comprehensibility, and visual appeal of the PtDA, as well as other suggestions on how to improve it. All clinical encounters were recorded through video recording. The video recordings were reviewed to see if and how the PtDA facilitated discussion on medication choice and how well it was utilized.

After each iteration, the PtDA prototype was revised according to the feedback obtained from the clinical encounters as discussed with the expert panel. The revised prototype was then used in the next iteration. These iterations were repeated until an acceptable version of the PtDA for field testing was made.

The final prototype of the PtDA was reviewed by a group of 4 practicing endocrinologists from our hospital who were not included in the development of the PtDA. The reviewers assessed content including accuracy and completeness of information. The PtDA was revised further to reflect comments from the external review prior to preliminary field testing. An investigator also evaluated adherence to the IPDAS checklist to ensure the quality of the PtDA.

Phase 3: Preliminary field testing (Beta testing)

The aim of this phase of the study was to test the feasibility of a study formally evaluating the effectiveness of the final version of the PtDA.

Participants

A convenience sample of 10 sets of patients and clinicians who met the selection criteria used in the pilot testing were recruited for this phase.

Procedure

Pre-test and post-test evaluations were performed for each clinical encounter. To evaluate knowledge gained among patients, we administered a 10-item multiple-choice test containing questions related to the diabetes medications discussed in the PtDA. The Filipino version of the Shared Decision Making Questionnaire (SDM-Q9)[30] was used to evaluate whether the final PtDA was able to facilitate SDM among the participants. The SDM-Q9 is a tool used to investigate the effectiveness of PtDAs as an intervention aimed at the implementation of SDM.[31] It is a 9-item questionnaire with a 6-point Likert scale (*completely disagree* to *completely agree*) with a total score that ranges from 0 to 54 transformed into a 100-point scale. Patients were asked to answer the SDM-Q9 questionnaire during a pre-test (evaluating their most recent consultation for their diabetes) and a post-test (pertaining to the consultation using the PtDA).

The degree of patient involvement during each clinical encounter was evaluated by two physician raters using the OPTION scale, a 12-item questionnaire that measures what degree clinicians involve patients in decision-making.[32-33] The primary investigator and another physician not involved in the development of the PtDA observed the video recordings of the clinical encounters. The card selection, medication choice, and duration of encounter were also recorded. Both physician raters used the OPTION Manual to guide the rating process.

ReSULTS

Phase I: Creation of the PtDA prototype

Decisional needs assessment: Patients

Four FGDs were conducted to elicit patients' views on their decisional needs in relation to their DM medications. The data analysis and results of the FGDs will be discussed in detail in a separate paper. Table 1 shows the characteristics of patients that were included in the FGDs.

Briefly, the points that emerged which were relevant to the development of the PtDA included the following:

1. Patients are willing to participate in decision-making for their own care if given the opportunity.
2. There is a subset of patients who prefer to leave the decision-making to their doctors who they perceived to be the expert in their illness.
3. Some of the patients find it difficult to grasp the concept of decision-making for their own care.
4. The most difficult decisions to make were those that involve the transition to an insulin-based regimen or the addition of an expensive medication.
5. Aside from cost and method of administration, other factors that they consider when choosing or agreeing to a medication include side effects such as hypoglycemia, allergy and gastrointestinal effects.
6. Only some physicians spend time to discuss medication choice with their patients.
7. Few physicians ask for their patient's opinion regarding treatment options.
8. Activities that help reduce decisional conflict include facilitation of external sources of free or cheap medicines and educational activities at the outpatient clinic.
9. Factors that facilitate decision-making include availability of information from their doctors that patients can understand, more time spent by their clinician explaining their condition, and clarification of risks and benefits of treatment. They consider family members, fellow patients, and their doctors as allies in decision making.

Decisional needs assessment: Physicians

Ten physicians were interviewed to assess decisional needs of clinicians treating patients with T2DM. Table 2 shows the characteristics of physicians included.

The following is a summary of findings from the KIIs that helped inform the PtDA development.

1. Some patients prefer that their doctors make the decision for them. On the other hand, more empowered patients, usually the younger ones, prefer to participate in SDM.
2. Some physicians prefer to choose the medications for their patients especially if it is an oral medication. In contrast, initiating insulin requires a more detailed explanation from the physician.
3. The most difficult type of decision for patients to make is transitioning to an insulin-based regimen or the addition of a more expensive medication
4. Family members help facilitate decision-making of patients. Elderly patients who rely on their children for financial support most often need help from them to decide on an add-on medication.

Table 1. Demographic and clinical characteristics of patients included in the focus group discussions for decisional needs assessment

Characteristic	n=24
Age, n (%)	
≤40 years	4 (17)
41-60 years	14 (58)
60 year	6 (25)
Mean (SD)	53 (9.1)
Sex, n(%)	
Male	8 (33)
Female	16 (67)
Education, n (%)	
At least elementary school graduate	
At least high school graduate	11 (46)
At least college graduate	9 (37)
Postgraduate	4 (17)
Employment, n (%)	
Retired	6 (25)
Unemployed	9 (37.5)
Employed	9(37.5)
Physician, n (%)	
Consultant	9 (37)
Fellow	14 (58)
Resident	1 (4)
Duration of Type 2 DM, n (%)	
<10 years	12 (50)
10-20 years	8 (33)
>20 years	4 (17)
Number of DM meds, n (%)	
1	9 (38)
2	7 (29)
≥3	8 (33)
mean (SD)	1 (0.3)
Type of DM medication, n (%)	
Oral agent/s only	10 (42)
Insulin only	2 (8)
Both oral agent and insulin	12 (50)
History of hypoglycemia, n (%)	
No	8 (33)
Yes	16 (67)

Table 2. Characteristics of key informants

Characteristic	n=10
Age	
<40 year old	4
40-60 years old	5
>60 years old	1
Area of practice	
Metro Manila	8
Outside of Metro Manila	2
Specialty	
Family Medicine	2
Internal Medicine	1
Endocrinology	7
Type of physician	
Consultant	8
Fellow-in-training	2
Years in practice[a]	
<10 years	4
10-20 years	4
>20 years	2

[a] including years in training

5. Barriers to SDM include lack of time, skills, knowledge (on the different options), resources (materials to aid SDM), and motivation to use SDM or to change one's habits.
6. Patients who are not receptive to new treatment options, i.e., being close-minded, is also an important barrier to SDM.
7. All the physicians prefer to have visual aid tools to help them support their patient's decision-making.
8. Aspects of medications that are important to consider when choosing medications include side effects, cost, and efficacy. Size of tablet is also important to consider but to a lesser degree.
9. The PtDA will not only help educate patients but also help doctors be informed about treatment options and the evidence base to support them.
10. The PtDA is a potential tool that can correct patient's misconceptions and misinformation about medications.

Scope and design of the PtDA

This Diabetes Medication decision aid for Filipino patients with T2DM aims to facilitate a patient's participation in decision-making during a consultation with his physician. This PtDA was designed to help the patient choose the appropriate treatment intensification to his existing diabetes treatment regimen based on his own values and preferences. It is a set of flash cards comparing different drugs based on domains that are important to consider when choosing medications. It is intended for use during a clinical encounter if add-on therapy is being considered.

Literature review

Information on the rate of hypoglycemia and magnitude of HbA1c reduction was extracted from two network meta-analyses.[2,34] Information on the daily routine for the use of the medications was gathered from the Full Prescribing Information from the US Food and Drug Administration or from the manufacturer. Data for weight change were collected from three network meta-analyses[2,35] for metformin, sulfonylureas, pioglitazone, DPP4 inhibitors, and SGLT-2 inhibitors, while data for liraglutide and insulin (Insulin glargine and Neutral Protamine Hagedorn, NPH) were from two randomized controlled trials (RCTs). Information on side effects were extracted from several meta-analyses for pioglitazone (edema, heart failure, fractures),[36–38] DPP4 inhibitors (headache and dizziness),[39] and SGLT-2 inhibitors (polyuria, orthostatic dizziness, urinary tract infection, and genital yeast infection),[40] while those for liraglutide (nausea and vomiting, diarrhea, and nasopharyngitis)[41] and insulin (local skin reaction, worsening of retinopathy)[42] were from two RCTs. Information on daily sugar testing was based on one meta-analysis[43] and a consensus guideline from the International Diabetes Federation[44] except for liraglutide which was gathered from a European expert recommendation.[45]

First PtDA prototype

The original English version of the Diabetes Medication Choice decision from the Mayo Clinic was composed of 6 domains: hypoglycemia, daily routine, weight change, HbA1c reduction, daily sugar testing, and side effects. After the initial translation, the phrase "blood sugar" which was translated to "*asukal sa dugo*" (blood in the sugar) by KWF was revised back to "blood sugar" since the latter is more readily understood by Filipino patients. After the translation to Filipino, the first prototype was redesigned to include cost (Figure 2). All figures were updated to reflect the most current information based on literature review. DPP4 inhibitors and SGLT2 inhibitors were included in the list of medications, as they have become more widely available since the time of the original decision aid. Liraglutide was not included because albeit locally available, it is not widely used in the country due

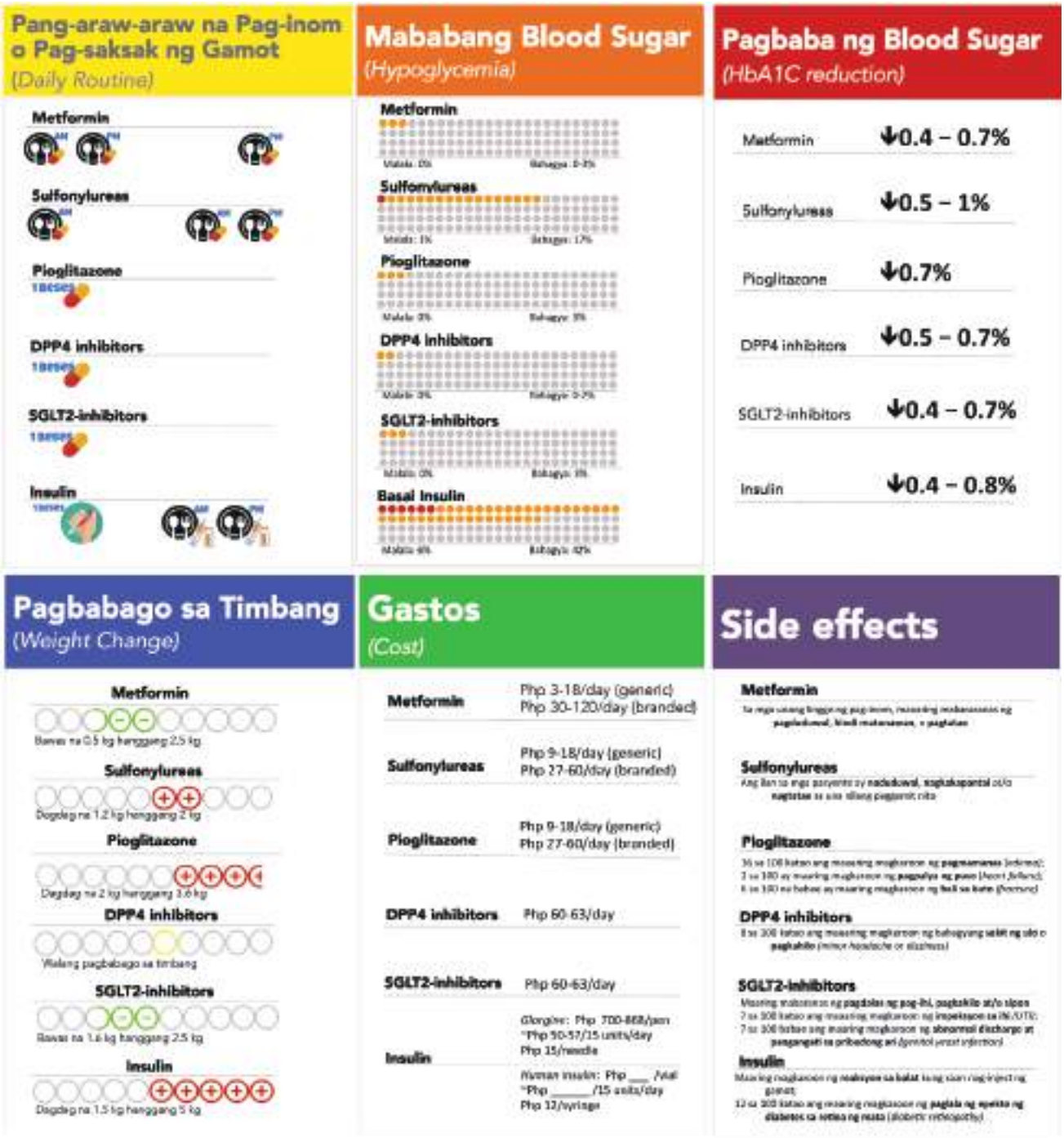

Figure 2. The first prototype of the Filipino Diabetes Medication Decision Aid.

to limited accessibility and high cost. Data on side effects were presented as frequencies (x in 100 patients) rather than percentages to represent absolute risk.

Review by the expert panel and patient advisory group

The following revisions were made to the first prototype of the PtDA based on the recommendations of the expert panel:

1. Included liraglutide in the list of medications because it is an available option for patients that should be offered to patients.
2. Revised the icons in the daily routine card to reflect the relation of tablet intake or medication injection to a meal and the interval between intake instead of just indicating "once a day."
3. Used a single color in the weight change card to indicate that a particular weight change (i.e., weight gain) may not always have a negative impact on the patient.
4. Presented HbA1c reduction as a vertical bar graph instead of plain numbers to better illustrate differences in efficacy of glucose lowering.
5. Used photographs of coins and bills for the prices to better illustrate the differences in total projected expenditure per day.
6. Presented prices for generics drugs for simplification.
7. Added the cost for sugar testing in the cost for insulin.
8. Presented side effects as illustrations to improve comprehensibility for the patients.
9. Added a card on daily sugar testing to reflect recent expert consensus recommendations.[43,44]

10. Included a clinician's guide to serve as general instructions for use during a clinic consultation.

Further revisions were made based on the issues raised by the patient advisory group. They suggested using 2 colors to differentiate weight gain or loss because it was not quickly understood despite the use of "+/-" signs. To simplify further, they suggested using the same icons for the same side effects. They also emphasized the importance of the skill of the clinician explaining the cards. Additional inputs included use of more appropriate terms such as "*pagturok*" (to prick or inject) instead of "*pagsaksak*" (to stab)(Figure 3).

Phase 2: Pilot testing (Alpha testing)

Three iterations composed of 15 clinical encounters were conducted after the initial revision of the prototype. Duration of use ranged from 3 to 12 minutes with a median time of 5 minutes. Seven internal medicine residents and 4 endocrinology fellows participated in the clinical encounters.

During the actual clinical encounters, we observed that some patients did not know what hypoglycemia was, hence an infographic on the symptoms of hypoglycemia was incorporated at the back of the hypoglycemia card. In the original HbA1c reduction card, one patient and one physician did not clearly recognize that the colored horizontal bars were actually a horizontal bar graph. Hence, the degree of HbA1c reduction was revised into a downward vertical bar graph to reflect decrease in HbA1c. We also added a section in this card on "Target HbA1c: ____" and "*Ang inyong* HbA1c:_____" (Your HbA1c) to emphasize individualization of glycemic target. Some patients had difficulty reading the graphics hence some of the physicians and patients requested for bigger size cards.

All of the patients found the PtDA helpful and easy to understand. They related that it was easier for them to understand and know what to expect with the use of a new medication. They emphasized the importance of the clinician guiding them through the decision-making process. They were able to ask questions and clarify aspects of their medications. All of the patients would like to be involved in decision-making related to their health.

In one of the clinical encounters, one of the patients could not read or write. With a skilled clinician explaining the PtDA, the patient was able to successfully maneuver the cards and eventually decide which medication he preferred. During the post-visit interview, we found that he indeed understood the contents clearly and was satisfied with the decision he made despite his limitations with literacy and numeracy. In contrast, we observed that elderly patients who had low literacy had more difficulty understanding the PtDA, needed more time going through the cards, and would frequently veer away from the conversation.

On the other hand, all of the physicians found the PtDA comprehensible and easy to administer for willing patients. Most of the physicians found that the use of a PtDA in the form of a visual aid made it easier for them to explain aspects of the medications to the patients. The PtDA was most helpful in patients who have decisional conflict and those who are willing to be involved in decision-making. For patients who still had decisional conflict after administration of the PtDA, it was suggested that a copy of the cards be given to the patient to be reviewed at home. One of the physicians related that the PtDA served as a reminder that as physicians, we also needed to take into account what is also important to the patient, including their values and preferences. All of the physicians were interested in incorporating SDM in their practice. Likewise, they found the PtDA to be potentially useful in their practice if such a tool was readily available. Both patients and clinicians expressed satisfaction and positive reception of their experience on the use of the PtDA.

Phase 3: Preliminary field testing

Nine residents and one endocrinology fellow-in-training participated in the preliminary field testing. Table 3 shows the characteristics of patients included in the preliminary field testing with their decision patterns.

Clinical encounters had a median duration of 8.5 minutes (range 5 to 25 minutes). Drug efficacy as shown through degree of HbA1c reduction was the primary concern of most of the patients (5/10) having been the first choice card of most patients and the most frequently picked card overall. Cost was the secondary consideration of majority of the patients (5/10). Other cards that were commonly picked were daily routine, weight change, daily sugar testing, and side effects. Although none of the patients chose the hypoglycemia card, we decided to retain this card because this aspect was important to bring into the conversation on diabetes medication. In terms of medication choice, SGLT2 inhibitor was the most commonly preferred medication, followed by DPP4 inhibitor and sulfonylurea. One of the patients decided to maximize his dose of metformin instead, before deciding whether to add a medication at the next consultation.

Majority of the patients (9/10) exhibited gain in knowledge and improvement in SDM Q9 scores (6/10). The PtDA was also able to promote patient involvement by clinicians with a median OPTION score of 47 points (range 32 to 53 points, possible minimum and maximum score 0 and 100 points, respectively).

DISCUSSION

In this paper, we described the development of a locally adapted Filipino version of the Diabetes Medication decision aid, which aims to facilitate SDM between the Filipino patient and his physician. The Filipino Diabetes Medication decision aid is a user-centered tool that involved the target users (i.e., both health care professionals and Filipino patients) in every step of its development. It was created in accordance with the standards set by the IPDAS. The content is based on the current available evidence on the benefits and risks of the different treatment options for diabetes. It is visually comprehensible to the Filipino patient, and was well-received by both clinicians and patients, who expressed enthusiasm and satisfaction with its use.

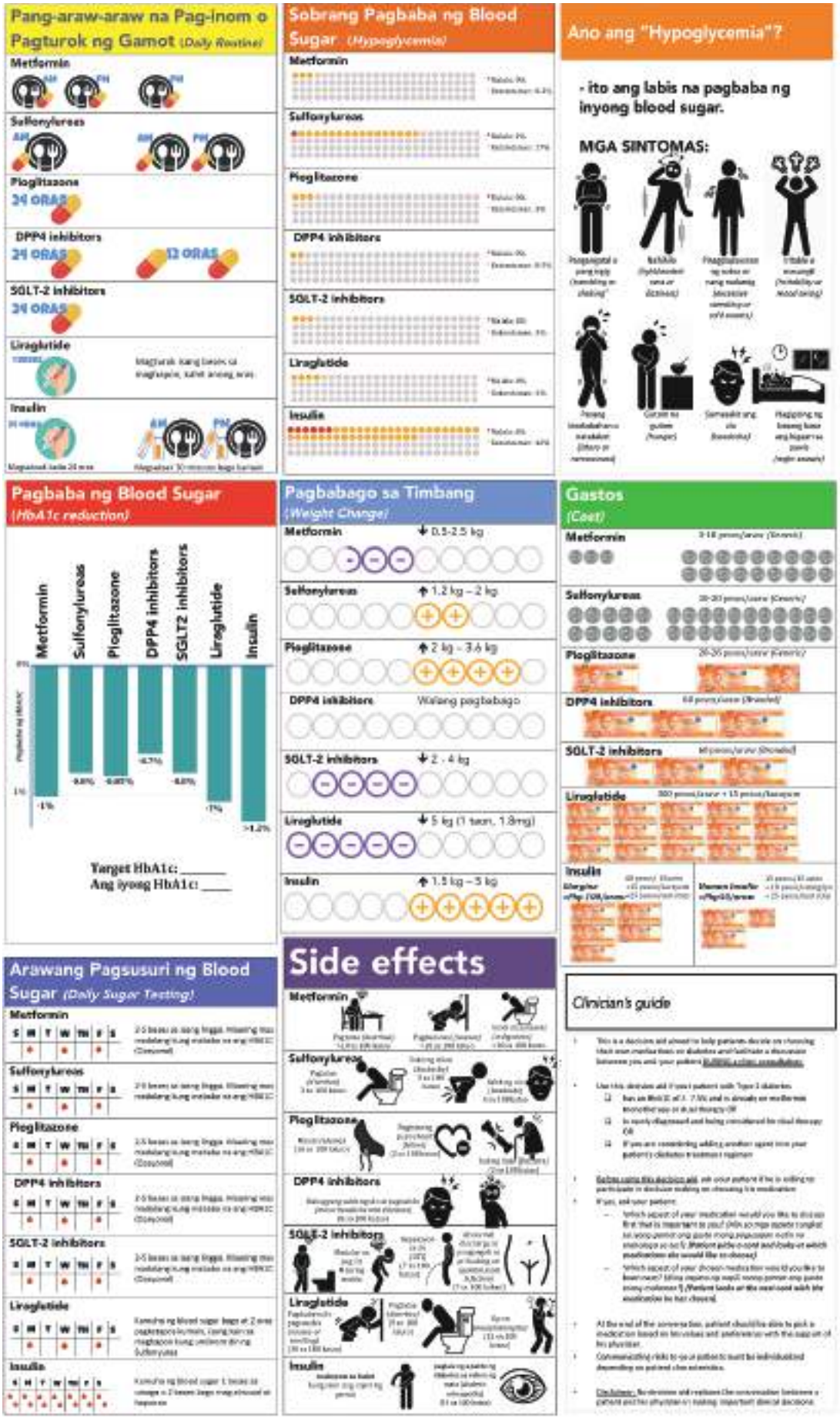

Figure 3. The final prototype of the patient decision aid for Filipino patients with diabetes mellitus©.

Table 3. Characteristics of patients and their corresponding choices of domain cards and medication (Preliminary field testing)

Pt	Age/ Sex	Location	education	Type of MD	Duration of Consult (mins)	HbA1C	Hypo-glycemia	DM duration (yrs)	Number of DM meds	Medication choice	Card choice 1	Card choice 2	Card choice 3
1	51/F	Urban	College	Resident	25	7.9	Yes	1	1	SU	sugar testing	cost	daily routine
2	48/F	Urban	High School	Fellow	16	9.3	No	7	2	Pioglitazone	HbA1C reduction	cost	N/A
3	44/F	Rural	Vocational	Resident	24	8.1	No	4	2	SGLT2i	HbA1C reduction	cost	weight change
4	56/F	Rural	High School	Resident	7	10.9	Yes	1	1	SU	HbA1C reduction	cost	side effects
5	73/F	Urban	Grade School	Resident	7	10.1	No	4	1	DPP4i	daily routine	cost	HbA1C reduction
6	51/F	Rural	College undergrad	Resident	7	8.3	Yes	8	2	Insulin	HbA1C reduction	side effects	N/A
7	56/F	Urban	High School	Resident	16	8.3	No	8	2	DPP4i	sugar testing	HbA1C reduction	weight change
8	66/M	Rural	Vocational	Resident	7	9.5	No	18	1	SGLT2i	weight change	HbA1C reduction	cost
9	50/F	Rural	College	Resident	5	10.8	No	new	1	SGLT2i	weight change	sugar testing	N/A
10	61/M	Urban	College undergrad	Resident	10	7.7	No	0.5	1	Increased Metformin dose	HbA1C reduction	daily routine	Side effects

N/A – not applicable; SU- Sulfonylurea; SGLT2i – SGLT2 inhibitor; DPP4i – DPP4 inhibitor

During the development process, we also incorporated elements of the approach to development of PtDAs by Mayo Clinic, which was used in the creation of the original Diabetes Medication Choice PtDA.[29] The patient advisory group was asked to role-play as if they were in a diabetes consultation and then provided reflections of their experience collectively. Compared to the original PtDA, the Filipino version was very graphic, with less textual information. We also incorporated a card containing brief instructions for the clinician on how to use the PtDA. A reminder to individualize HbA1c targets and compare it with the patient's present level was also included in the HbA1c reduction card. A similar decision aid on diabetes treatment intensification, the PANDAs decision aid, is an online interactive multimedia PtDA that requires at least 25 minutes to view.[18] Since access to the Internet by our patients and in the clinic is limited in our setting, we opted to focus on paper-based cards to be used during a clinical consultation.

The pilot testing and the preliminary field testing showed that PtDA is feasible to use in a low middle income country, since both Filipino physicians and patients found it acceptable and satisfactory to use. In all the clinical encounters, patients were able to arrive at a decision without significantly increasing consultation time. There were also other perceived benefits of the PtDA that were not commonly cited in development of diabetes PtDAs. The PtDA served as a reminder to physicians not accustomed to SDM—to involve patients in decision-making and facilitate a conversation between doctors and patients instead of having a one-way discussion. In addition, it not only informed patients on treatment options but also updated physicians as well.

In this study, the patients' most important considerations when choosing a medication were method of administration (injectable versus oral agent), cost, rate of hypoglycemia, and side effects. Facilitators of SDM included increasing time spent, providing more information, and support from family, fellow patients, and their doctors. From the clinician's point of view, physicians were not able to incorporate SDM in their practice due to lack of time, skills, resources, motivation to use SDM and to change one's habits. Similarly, in a systematic review[10] on the barriers and facilitators to implement SDM in clinical practice as perceived by health care professionals, the most common barriers were time pressure, lack of applicability due to patient profile, and lack of applicability due to the clinical situation. On the other hand, the most commonly identified facilitators included motivation of the health care professional, perception of a positive impact on patient outcomes and on the clinical process.

In a RCT evaluating the effects of skills development workshop and the use of risk communication aids on SDM, clinicians significantly increased their involvement of patients with a 12.9- and 10.6-point increase in OPTION score from baseline with the use of these tools, respectively.[46] Furthermore, the addition of skills development in SDM to the use of risk communication aids, increased patient involvement incrementally. Using such aids coupled with skills in SDM resulted in perceived higher patient and clinician agreement on treatment, patient satisfaction with information, clinician satisfaction with decision, and overall satisfaction with the consultation.[46] As such, the use of PtDAs in our setting, where this concept is relatively new to both patients and physicians in actual clinical practice, warrants not only its introduction but also accompanying skills training on SDM and the use PtDAs in order to maximize its benefits.

The population where the PtDA was tested included patients who had low socioeconomic status and who were more likely to have lower health literacy. Lower health literacy has been associated with higher decision uncertainty and regret. Adults with low health literacy have also been shown to have less desire for participation and question-asking.[47] Despite the low health literacy in our population, most preferred to participate in decision-making and were able to satisfactorily use the PtDA. On the other hand, some patients prefer to leave the decision

to the doctor, who they perceive as the expert. As such, this PtDA may not be used in patients who are not engaged.

A person's ability to effectively use a PtDA is determined by both their health literacy skills and the quality and suitability of the PtDA.[48] Creators of PtDAs are encouraged to design tools that can be accessed and understood by patients across the health literacy spectrum.[47] One of the intentions of this study was to create a tool that could cater to Filipinos with low literacy levels. In a systematic review looking at health literacy in PtDAs,[47] some of the specific features that improved comprehension for low literacy individuals included presenting numerical information in tables or pictographs, using the same denominator, and using natural frequencies (1 out of 100) to help patients understand probabilities. We incorporated these features in the present PtDA with a simple graphic display with less textual information as compared to the original. In the study evaluating the Greek version of the Diabetes Medication Choice Decision Aid,[49] majority of the patients (72%) recruited were high school graduates or undergraduates. Likewise, they were able to implement the Greek PtDA with a positive reception from both patients and clinicians. Supporting patients with low literacy by providing well designed tools favorably change the inequity in health care, as the average patient with low socioeconomic status and limited education appear to be at a disadvantage when handling seemingly complex information.[50] The present PtDA may mitigate the effects of low literacy among Filipino patients but this needs to be confirmed in a formal evaluation study.

We observed that elderly patients who had low literacy took longer, had poor comprehension, and would frequently deviate from the topic. Use of PtDAs among older people had similar benefits with improved risk perception, knowledge, and patient involvement. However, the evidence supporting effectiveness of PtDAs in older adults are still limited, as most studies are small and heterogenous.[51] In a study on the impact of cognitive aging on decision making, older adults were found to rely on simpler strategies and took longer to process information.[52] In the study, despite the challenges observed among the older patients, there was no trend towards a difference in knowledge gain, degree of patient involvement, and expressed satisfaction towards its use despite the challenges. Although the PtDA may have some limitations in the older population because it was not specifically designed for them, there may still be evidence to support its use, but the conversation may need participation from a family member or companion who knows the patient's routine and preferences.

The limitation of this study is its external applicability to patients of higher income and higher literacy levels including those who go for consultations in private clinics.

We recommend the introduction of the Filipino Diabetes Medication decision aid among health care professionals caring for people with T2DM to promote awareness and integration of SDM in clinical practice. A formal evaluation of the impact of this PtDA in a large and broader Filipino population is recommended. Skills training on SDM and on the use of PtDAs is of paramount importance in order to achieve its benefits, improve patient and doctor satisfaction, increase uptake among physicians, without undue disruption in the overall clinic workflow of a busy practice.

CONCLUSION

Using a qualitative method and an iterative process of tool development, patients, clinicians, and diabetes nurse educators have contributed to the creation of the first Filipino patient decision aid on diabetes treatment intensification. This patient decision aid will help generate a conversation on shared decision-making between patients and clinicians on medication options for diabetes.

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

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The primary author reports grants from GX International, Inc, other from AstraZeneca Philippines, outside the submitted work. In addition, she has a Philippine copyright (Registration number 0209-1775) for the decision aid developed and mentioned in the article.

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*To avail of the high resolution version of the patient decision aid, kindly email the corresponding author at apmacalaladjosue@up.edu.ph.

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ORIGINAL ARTICLE

The Effectiveness of Conducting Home Visits by Medical Students among Malaysians with Type 2 Diabetes: A Retrospective Analysis

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Abstract

Background. Medical students at the International Medical University (IMU), Seremban, Malaysia were required to assess patients at home over a period of two years as a part of their curriculum. The students conducted six visits to educate their patients and help them utilize available resources to manage their disease.

This study aims to examine whether patients with diabetes visited improve their control of their disease, specifically in terms of their HbA1c measurement.

Methodology. We used a retrospective, matched before and after study design to prevent biased levels of effort by students conducting the home visits over two years. Information was obtained through reports written by IMU students. Convenient sampling was used to select outpatients undergoing treatment 'as usual' from a health clinic and were subsequently matched as controls.

Results. There was a significant decrease in the mean HbA1c among 57 patients with diabetes who were CFCS subjects [from 8.4% (68 mmol/mol) to 7.3% (57 mmol/mol) $p<0.001$], while the mean HbA1c levels among 107 matched control subjects rose significantly from 7.9% (63 mmol/mol) to 8.3% (67 mmol/mol) ($p=0.019$) over a similar period. The two groups were controlled for most biological and socioeconomic variables except for comorbidities, diabetic complications and medication dose changes between groups.

Conclusion. Behavioural intervention in the form of home visits conducted by medical students is an effective tool with a dual purpose, first as a student educational initiative, and second as a strategy to improve outcomes for patients with diabetes.

Key words: home visits, medical students, type 2 diabetes, glycated hemoglobin, Malaysia

INTRODUCTION

Out of the 17% of Malaysian adults who suffer from type 2 diabetes mellitus (T2DM), only 20% of these patients achieve optimal control of their disease.[1] There is growing evidence that home visits focusing on patient education and behavioral intervention help improve glycemic control in patients with diabetes.[2] The initiatives undertaken by community health workers among African Americans, Latinos[3] and Mexican Americans[4] appear to support the need for home visits. Similar success was seen in home visits conducted by nurses[5,6,7] or pharmacy students.[8] Home visits are used often in conjunction with telephone calls,[3,5,9] newsletters[4] and group discussion or classes.[3,7] A systematic analysis of these studies show there is significant improvement in glycemic control,[2] with longer intervention programs (2 years)[4,8] showing a bigger decrease in HbA1c values than shorter (3 months) ones.[5,6] These studies have been done across countries and cultures from the United States[3,4,8] to Thailand[7] (Table 1).

Medical students at the International Medical University (IMU) undergo a Community and Family Case Study (CFCS) program as a part of their curriculum.[10] This program emphasizes holistic patient care from a family-oriented and communal perspective. Students, in pairs or rarely, a team of three, select a patient, with any disease, from the hospital or primary care clinic. Subsequently, these patients are followed up at their own homes. These visits span a period of 2 years, commencing from the third year of medical studies; during which these patients continue regular clinic follow-up. During the six periodic home visits, in addition to discussing the progress of the patient's illnesses, the students explore several behavioral themes that are relevant to their patients. Each visit lasts an average of 1.5 hours in the relaxed atmosphere of the patient's residence.

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Table 1. Results of previous studies on the effectiveness of home visits on HbA1c level of patients with diabetes

Authors	estey AL, Tan MH, Mann K	Couper JJ, Taylor J, et.al.	Stroup J, Kane MP, Busch RS, et al	Taylor KI, Oberly KM	Wattana C, Srisuphan W, Pothiban L, et al	Spencer MS, Rosland AM, Kieffer EC, et al	Rothschild SK, Martin MA, Swider SM, et al
Journal	Diabetes Educ 1990; 16: 291–295.	Diabetes Care 1999 22:1933-37	Am J Pharm Educ 2003; 67: 91	Biol Res Nurs 2005; 6: 207–215	Nurs Health Sci 2007; 9: 135–141	Am J Public Health 2011; 101: 2253–2260	Am J Public Health 2014; 104: 1540–1548
Type of patients	T2DM	T1DM	T2DM	T2DM	T2DM	T2DM African and Latino Americans	T2DM Mexican Americans
Location of study	Halifax, Canada	South Australia	Albany, New York	Calgary, Canada	Eastern Thailand	Detroit, Michigan	Chicago
Population studied	Patients referred for diabetes education who completed 3 day education program	Adolescents with a mean HbA_{1c} of >9.0 %	HbA_{1c} of >10.0 %	Excluded those pending surgery, recently hospitalized and with severe complications	>35 years Excluded those with severe complications and changed treatment during program	>18 years Exclude serious diabetic complications	>18 years Exclude major end-organ complications
Sample size	N=28 control=25	N=37 control=32	N=30 control=40	N=20 control =19	N=75 control=72	N=72 control =92	N=73 control =71
Intervention agent	Registered nurse	Diabetes educator	Pharmacy students	Nurse	Nurse researcher	Community health worker	Community health workers
Type of Intervention	four telephone calls (6 min) and one home visit (38 min)	monthly home visits (45-60 min) weekly phone contact (5-10 min)	Students observed the faculty member during the first interaction and conducted the second meeting themselves under the supervision of the faculty member then conducted the remainder of their home visits without supervision	4-5 nurse visits (30-45 min) 1 dietician visit 1 exercise specialist (optional) consult In home or place of patient's choosing	small group diabetes education class (120 min), four small group discussions (90 min), two individual home visit sessions from the researcher (45 min), and a patient education manual	(1) diabetes education classes, (2) 2 home visits of about 60 minutes each in length per month to address participants' specific self-management goals (3) 1 clinic visit with the participant and his or her primary care provider (4) phone call once every 2 weeks	36 home visits, or a bilingual control newsletter delivering the same information on the same schedule
Study duration	3-months	6 month	2 years	3 months	24 weeks	6 months	2 years
Mean pre-HbA1c level	6.3±1.1%	11.1±1.3%	11.2±1.3%	7.69%	8.08±1.87%	8.6 (8.1, 9.2)%	8.5±2.2%
Mean post-HbA1c level	5.6±0.7%	9.7±1.6%	10.0±2.0%	7.40%	7.40±1.25%	7.8 (7.3, 8.3)%	7.64%

The themes for each of the visits are: 1) family structure and life cycle, 2) illness behavior, self-care, complementary medicine and cultural aspect of health care, 3) epidemiological study of biological, physical and social environment affecting the illness, 4) preventive care, 5) hospitalization and illness experience and 6) community resources.

Throughout these visits, students observe how their patients cope with their illness in their home environment and their challenges.[10] They were also tasked to assess their patients' needs, plan/carry out suitable interventions, and evaluate the outcomes of their initiative. They prepare individual reports and present their findings to their respective mentors. The CFCS program was designed not only to have an impact on the students' learning process, but also to contribute to the overall care of the patients who may benefit from these student encounters. The patients gain more insight and this improved their self-efficacy to care for themselves.

A large number of the selected patients had type 2 diabetes mellitus (T2DM) in view of the increased prevalence of this disease in Malaysia.[11] Therefore, this study explored the influence of student visits on the control of diabetes among such patients.

MeTHODOLOgy

Study Population

We undertook a retrospective, matched before and after study,[12] examining the portfolios of students who had completed their CFCS reports. We included only patients diagnosed with T2DM. These patients were followed up for 2 years with home visits beginning 2013-2015 and ending 2015-2017. During this time they continue their T2DM follow up at outpatient government clinics. These reports were then compared with controls taken from a government health clinic. Patients who died before the end of study were excluded. As these patients lived within a 15 km radius from Seremban, a municipality 60 km south of Kuala Lumpur, we matched them with controls conveniently sampled from a public outpatient health clinic, Klinik Kesihatan Seremban, matching T2DM patients with HbA1c readings at least 18 months apart for gender, age (±5 years) and years since diagnosis (±3 years).

Both CFCS patients and matched controls continue their follow-up with their outpatient clinic doctors at frequencies decided by their doctors.

Instruments

Glycated hemoglobin (HbA1c) was chosen as an indicator for glycaemic control as it is a widely used index determining blood glucose control of diabetic patients.[13] It also serves as a strong predictor of diabetic complications.[14]

A data extraction sheet was designed and used to obtain salient patient information. Besides demographic data and HbA1c readings, the information sheet also collected information about co-morbid conditions, medications, diabetic complications, pre- and post-weight (kg), body mass index (kg/m^2), random blood glucose (mmol/L) and blood pressure (mmHg). Data were obtained anonymously from patients attending follow-up consultations at the primary care clinic without any identifying information.

The Students' CFCS study guide is available as an Appendix. It details the objectives, process, activities and learning references of the programme which cover many areas that impact on the patient's knowledge and attitude on health. In addition, the actual conversation during the visit impacts the patients emotionally individually.

Statistical Analyses

The data collected were coded and entered into Statistical Package for Social Science for statistical analysis (SPSS Version 19.0, IBM Corp, USA). Chi-Square test was used to analyze categorical data in the study. Independent and paired T-test, Wilcoxon rank test or Kruskal-Wallis test was employed as appropriate. A power analysis was done through the G*Power software (version 3.1.9, University of Kiel, Germany).

Based on what other educational and behavioral interventions of similar duration have produced, we estimated an HbA1c difference of 0.9% between the groups,[3,4,8,9] and calculated the sample size needed to give a result with a confidence interval (CI) of 95%, 5% margin of error and power of 80%, with a baseline HbA1c of 8.0% (64 mmol/mol) with a standard deviation of 1.3% and found we required a sample size target of 75, half as intervention patients and half as controls. However, we targeted twice the number of controls to CFCS patients to better represent patients undergoing usual outpatient care, as they were readily available.

ethical Considerations

This study was approved by the International Medical University Joint Ethics and Research Committee (CSc-sem6 (38)2016) and registered in the National Medical Research Registry (NMRR-16-2782-31914).

ReSULTS

Population Characteristics

We obtained a total of 197 CFCS reports. Of these, 73 (37%) were patients diagnosed with T2DM. The drop-out rate was 21.9%. This attrition rate was due to the exclusion of sixteen (16) of these reports as there was an absence of two HbA1c readings more than 18 months apart, despite effort being made to trace the details from their respective follow-up clinic. We included 106 controls.

The demographic profile of the CFCS patients and controls are given in Table 2. Race is noted and analyzed because risk factors and prevalence of many diseases in Malaysia are associated with ethnicity. Not all patients had complete glucose, BMI, BP, medication, co-morbid and complications data. Co-morbidities recorded included hypertension, obesity, dyslipidemia, coronary artery disease, stroke and a range of others including gout, rheumatoid arthritis and asthma. For analysis, patients were grouped into those with two co-morbid or

Table 2. Characteristics of study patients and control group, Seremban, Malaysia 2013-2017

	CFCS patients (%) n=57	Controls (%) n=106	*p* value
Age (mean)	61.3±8.5 y	61.8±8.0 y	0.70*
gender			
Males	29(50.9)	54(50.9)	1.0†
Females	28(49.1)	52(49.1)	
Race			
Malays	14(24.6)	29(27.4)	
Chinese	18(31.6)	35(33.0)	0.60**
Indians	25(43.9)	42(39.6)	
years since diagnosis (mean)	14.5±9.0 y	12.5±8.3 y	0.14*
Medication			
Oral agents only	31 (54.4)	59 (55.7)	
Insulin only	12 (21.1)	10 (9.4)	0.08**
Oral agents + Insulin	14 (24.6)	37 (34.9)	
Co-morbidities	(n=56)	(n=106)	
0-2	44	102	<0.001**
3 and more	12	4	
Complications	(n=54)	(n=106)	
0-1	41	101	0.01**
2-3	13	5	
Mean Values±SD			
HbA1c	8.4±1.5% (n=57)	7.9±1.6% (n=106)	0.07*
Glucose(mmol/l)	11.1±4.3 (n=46)	9.9±3.7 (n=87)	0.08*
BMI(kg/m^2)	27.9±5.2 (n=43)	27.6±4.9 (n=102)	0.71*
Systolic BP(mmHg)	136±14 (n=50)	137±19 (n=104)	0.71*
Diastolic BP(mmHg)	80±10	75±15	0.002*

less and those with three or more. Diabetic complications included nephropathy, eye disease and neuropathy. Patients were grouped into those with one or no complication, or, two or more. The two groups were well matched for age (p=0.70), gender (p=1.0) and race (p=0.60) but less so for years of diabetes (p=0.14). The groups were also not different for initial blood glucose (p=0.08), BMI (p=0.71) and systolic blood pressure (p=0.71). They were however not similar for diastolic blood pressure (p=0.002), co-morbidities (p<0.001) and complications (p=0.01). The initial HbA1c for the two groups was approaching significant difference (p=0.07).

Outcome

Paired t-tests showed a significant decrease in the HbA1c and glucose level of CFCS patients (p<0.001) (Table 3). The effect size of 0.96 at a CI of 95% and the margin of error of 5% was obtained. This gave a statistical power of 99%. There was also a small decrease in BMI (p=0.08) and systolic blood pressure (p=0.06) approaching significance. On the other hand, control patients showed a significant rise in HbA1c (p=0.019) over the follow up period. There was no significant change in glucose, BMI (p=0.62) and blood pressure (systolic, p=0.22 diastolic p=0.96) in the control group.

Subgroup analysis

Table 4 examines the change in HbA1c within the two groups. Gender, race, age, medication patients were on, prevalence of co-morbidities or complications were not significantly associated with the change in HbA1c in either group over the study period.

DISCUSSION

Main Findings

This study demonstrates a significant improvement in HbA1c and blood glucose over the two-year period during which the patients were visited by the students. We could not identify any correlation with factors such as gender, race, age, the patient's current medications, and prevalence of co-morbid or associated complications to account for the HbA1c change. Therefore, factors such as

Table 3. Outcome measures of the patients and control group, Seremban, Malaysia 2013-2017

CFCS	Before±SD (n)	After±SD (n)	*p* value
HbA1c	8.4±1.5% (57)	7.3±1.3% (57)	<0.001
Glucose (mmol/l)	11.1±4.3 (46)	7.9±2.9 (45)	<0.001
BMI (kg/mm2)	27.9±5.2 (43)	27.8±6.6 (30)	0.08
Systolic BP(mmHg)	136±14(50)	132±11(50)	0.06
Diastolic BP(mmHg)	80±10 (50)	79±8 (50)	0.37
Controls	**Before±SD (n)**	**After±SD (n)**	***p* value**
HbA1c	7.9±1.6% (106)	8.3±1.8% (106)	0.02
Glucose (mmol/l)	9.9±3.7 (87)	10.3±3.9 (87)	0.35
BMI (kg/mm2)	27.6±4.9 (102)	27.6±4.7 (102)	0.62
Systolic BP(mmHg)	137±19(104)	139±19 (104)	0.22
Diastolic BP(mmHg)	75±11 (104)	75±11 (104)	0.96

Paired t-test

Table 4. Change and correlation of HbA1c within patients and control group, Seremban, Malaysia 2013-2017

	CFCS patients (n) Mean % change of HbA1c±SD	***p* value**	**Controls (n)** Mean % change of HbA1c±SD	***p* value**
gender				
Male	-1.08±1.5 (29)	***0.82****	0.32±1.2 (54)	***0.76****
Female	-1.04±1.6 (28)		0.36±1.7 (52)	
Race				
Malay	-0.75±1.8 (14)		0.42±1.7 (29)	
Chinese	-1.22±1.5 (18)	***0.65****	0.08±1.0 (35)	***0.53****
Indian	-1.11±1.4 (25)		0.50±1.7 (42)	
Duration of diabetes				
1 - 10	-0.86±1.5 (22)		0.29±1.2 (55)	
11–20	-1.44±1.8 (21)	***0.25****	0.33±1.7 (32)	***0.48****
21– 30	-0.87±1.1 (10)		0.60±1.9 (19)	
31- 40	-1.22±0.2 (4)		0.20 (1)	
Age group				
36- 45 y	-1.5±2.0 (4)		-0.25±1.8 (4)	
46-55 y	-0.55±2.1 (8)		0.63±1.6 (19)	
56-65 y	-0.91±1.4 (23)	***0.62****	0.40±1.4 (48)	***0.51****
66-75 y	-1.35±1.4 (21)		0.17±1.6 (30)	
76-85 y	-0.5 (1)		0.22±1.3 (5)	
Diabetes medication				
Oral	-0.99±1.6 (31)		0.38±1.4 (59)	
Insulin	-0.75±1.3 (12)	***0.46****	0.77±2.1 (10)	***0.70****
Oral+insulin	-1.48±1.5 (14)		0.16±1.4 (37)	
Complication				
0-2	-0.95±1.4 (44)	***0.88****	0.29±1.4 (101)	***0.45****
2-3	-1.32±1.7 (12)		0.55±2.6 (5)	
Co-morbidities				
0-1	-0.75±1.6 (13)	***0.44****	0.27±1.2 (44)	***0.66****
2-3	-1.11±1.3 (41)		0.39±1.6 (64)	

* Wilcoxon test, **Kruskal-Wallis test

individual preparedness to listen and change, as well as how the team of students communicated with the patients arguably played a major role.

Among the notable features of the CFCS program was the home setting in which the intervention was conducted. Patients more likely felt they could inquire about any uncertainties without the time limitation inherent in a visit to a doctor's clinic. An average of 1.5 hours was spent by students for each home visit, which is much longer than the consultation time during follow-ups in the clinic. One unhurried visit cannot be compared to many short visits. In addition, the home setting may also contribute to better reception of knowledge, as patients may feel more comfortable and relaxed in their own environment.

Students were not authorized to change the patients' medication dosage. They were only responsible for advice on medication compliance. Having clear instructions to assess, plan, execute and evaluate self-care interventions, the students were able to effect a change in behavior over this period. The components of the students' engagement with patients were mentioned in the introduction, but it would not be possible to identify specifically which were the most important; one important factor may have been simply the rapport that was built up. Nevertheless, any changes of medication in the two-year period were not recorded in this study in either group; this may have impacted the results.

The increase in mean HbA1c levels among control patients was unexpected. Nevertheless, in any cohort, patients with diabetes often start with a mild to moderately elevated HbA1c value which increases over time due to poor control and disease progression;[15] therefore, snapshots over two years can show that decline, which has been also noted in a similar study.[4]

Strengths

A case-control design is arguably a more suitable method to explore the objectives of this study compared to a randomized controlled trial. Klein reasons that it is more appropriate for observing decision making in action naturally.[16] If the students knew that the HbA1c of their patients was an outcome measure of a study, or even that their case was being specially observed, they might have put in extra effort to get their patient to do well. A retrospective study observes the intervention as is normally is. Unlike other studies where intervention arm includes home visits but also other tools, such as telephone calls to counsel patients or small group meetings, this study consists only of home visits and nothing else besides a phone call by the students to arrange the visit.

Limitations

The two groups were fairly well matched except for the prevalence of co-morbidities and diabetic complications, factors that were not considered in the matching process. The difference in co-morbidities and complications was not anticipated. However, it was not unexpected, as many students recruited their CFCS patients from among patients who had been admitted to the Seremban Hospital; such patients might have more co-morbidities and complications compared to patients recruited conveniently from an outpatient clinic. The control group was thus not ideal but it would have been technically very difficult to match for hospital admissions.

The recordings of parameters in the two groups were taken over a range of time and not at exactly the same time and in the same setting for each patient. While readings such as BMI and HbA1c are not likely to vary, more labile readings, such as glucose and blood pressure might be more prone to variation. There are minor biological sample variations between different HbA1c machines. All control patients at Klinik Kesihatan Seremban would have been tested using the same machine (Bio Rad Laboratories); however, CFCS patients were seen in different clinics using different machines but likely of the same make. Not all patients carried out self blood glucose monitoring at home, hence this could not be studied. Increments in patients' medication dosage in both groups during the study period were not taken into account in this study and this could be a confounder. The sample size was not large enough for subgroup analysis as the study was not designed with that in mind, and could not have been, because we had no clue which factors might show a trend of being significant and to what measure.

CONCLUSION

Given that diabetes mellitus is one of the most common chronic diseases, it is important that we understand how to improve compliance to prescribed medication and lifestyle changes. Home visits can make a difference and students can be an important part of the process.

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ORIGINAL ARTICLE

A Randomized Controlled Trial on the Effectiveness of Short Message Service (SMS) Reminders in Improving Postpartum Follow-up among gestational Diabetes Mellitus Patients

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Abstract

Objective. This study assessed whether short message service (SMS) reminders would improve follow-up rate among gestational diabetes mellitus (GDM) patients by 12 weeks postpartum.

Methodology. In this single-center, single-blind randomized controlled trial, we assigned 308 patients with GDM to either of 2 arms, usual care alone versus usual care with SMS reminders. In the usual care group, 154 patients received a 10-minute short lecture on GDM and a 75 g oral glucose tolerance test (OGTT) request prior to discharge. In the SMS group, 154 patients received twice a week SMS reminders at 4 weeks, 8 weeks, and 10 weeks after delivery in addition to usual care. The primary outcome was clinic visit within 6 to 12 weeks postpartum with a 75 g OGTT result.

Results. In our population, the overall follow-up rate was 19.8% (61/308). Follow up rates were 20.1% (31/154) for the usual care group and 19.5% (30/154) for the SMS. The addition of SMS reminders was not associated with an increase in follow-up rate at 12 weeks postpartum (adjusted RR 0.98, 95% CI 0.63-1.52; *p*=0.932). The use of insulin or metformin for GDM control was associated with increased follow-up (adjusted RR 1.92, 95% CI 1.20-3.07; *p*=0.006).

Conclusion. SMS reminders did not improve postpartum follow-up rate among GDM patients at 12 weeks postpartum.

Key words: gestational diabetes, short message service, reminder system

INTRODUCTION

The prevalence of gestational diabetes mellitus is reported to be as high as 14% among Filipinos, based on the ASEAN Federation of Endocrine Societies (AFES) Study Group on Diabetes in Pregnancy.[1] Following GDM, 35 to 60% of women develop type 2 diabetes within 10 years.[2] The incidence of postpartum glucose intolerance among Filipino GDM patients was reported to be as high as 42% (overt diabetes in 7.3% and prediabetes in 34.7%).[3] Subclinical glucose intolerance during pregnancy is also associated with a dose-related increase in cardiovascular disease later in life.[4] Taking into account these long-term implications, early identification of postpartum type 2 diabetes mellitus risk and glucose intolerance is imperative. This can be done by postpartum glucose screening as this presents an opportunity for education and primary diabetes prevention.[5]

The Philippine Clinical Practice Guidelines on the Diagnosis and Management of Diabetes Mellitus recommend that women with GDM be screened for persistent glucose abnormality at 6 to 12 weeks postpartum.[2] However, in our institution, follow-up rates are generally poor, as most are lost to follow-up after discharge from the hospital. Studies from the United States and Australia also report low postpartum screening, with rates ranging from 19 to 73%.[5,6] There are efforts to increase awareness focusing mainly on education, as it has been demonstrated that women who are better educated on the importance of postpartum testing are more likely to follow-up.[7-9] The need to identify simple and innovative strategies to augment current care protocols may serve to improve postpartum glucose testing and follow-up. Among GDM patients, postpartum postal reminders, telephone calls and emails were shown to increase screening rates as reported by other studies.[10,11] A meta-analysis of postpartum screening practices among Asian women with a known history of GDM showed that postpartum testing rate ranged from 13 to 82% during routine care, as compared to 67 to 95% of women who received SMS or call interventions in the studies.[12] The intention behind putting a reminder system in place orovides not only an avenue for continuity of care, but also a continual of awareness of the risk for development of diabetes.[11]

In 2015, our National Telehealth Center reported that there were 114.6 million mobile connections in the country.[13] Given the widespread use of texting and mobile phones and the evidence to support their use, numerous text messaging programs for health promotion have

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been developed.[14] Studies on the use of short message service in health care, particularly among human immunodeficiency virus patients and persons with type 2 diabetes mellitus, showed improved adherence to treatment and increased appointment attendance.[15] Locally, SMS as an adjunct to standard diabetes care has been shown to improve adherence to diet and exercise, supporting disease self-management.[16] An SMS reminder system among postpartum GDM patients in Australia was demonstrated to increase overall postpartum screening rate.[17] In a local study on GDM patients which implemented persistent SMS reminders or calls for scheduled postpartum 75 g oral glucose tolerance test (OGTT), the reported follow-up rate was 71.6%.[3]

Given the prevalent use of mobile phones among Filipinos and the low cost of text messaging (PhP 1.00 equivalent to ~USD 0.020 per standard 160-character SMS), a reminder system through text messaging may prove to be an inexpensive, effective, feasible and culture-appropriate strategy to improve rates of postpartum glucose testing and follow-up.

This study aimed to compare the effectiveness of SMS reminders in addition to usual care in improving follow-up and postpartum glucose testing among GDM patients. We also determined the association of follow-up and socio-demographic and perinatal characteristics, including clinical and neonatal outcomes, and among postpartum GDM patients. We also described self-reported barriers and facilitators for postpartum testing.

MeTHODOLOgy

Study design and participants

This study was a single-blind randomized controlled trial that was conducted at the Philippine General Hospital, a tertiary teaching hospital in Manila. A concurrent qualitative method approach through survey questions was used to identify self-reported barriers and facilitators for postpartum follow-up. Ethics approval was obtained from the University of the Philippines Manila Research Ethics Board.

Participants were eligible for inclusion if they were diagnosed with GDM during their most recent pregnancy by their physician, or based on criteria from the International Association of Diabetes and Pregnancy Study Group (IADPSG) or the Philippine Obstetric and Gynecology Society (POGS). They should have access to a personal mobile phone (not a shared phone), be able to read and write in Filipino, have normal capillary blood glucose (CBG) upon discharge [fasting blood glucose (FBG) <108 mg/dL and 2-hour postprandial blood glucose (PPBG) <144 mg/dL] and with written informed consent. The diagnosis of GDM based on the IADPSG and POGS criteria is summarized in Table 1.

The following were excluded from the study: pre-gestational/overt diabetes (type 1 or type 2 diabetes mellitus), history of intake of drugs that can affect glucose metabolism (e.g., steroids, beta agonists), history of long term medical or surgical condition that can affect glucose metabolism (e.g., post-pancreatectomy, acromegaly, Cushing's syndrome), multiple gestation and perinatal death in the most recent pregnancy (Table 1).

Table 1. Criteria for diagnosing gestational diabetes mellitus and overt diabetes in pregnancy

	IADPSg [a]	POgS [b]
Gestational diabetes[c]		
75 g OGTT[d]:		
Fasting plasma glucose, mg/dL	≥92	≥92
1-hour post-load plasma glucose, mg/dL	≥180	
2-hour post-load plasma glucose, mg/dL	≥153	≥140
Overt diabetes[c]		
Fasting plasma glucose, mg/dL	≥126	≥126
HbA1c, %	≥6.5	≥6.5
Random plasma glucose, mg/dL	≥200[e]	≥200[e]

[a] International Association of Diabetes and Pregnancy Study Groups
[b] Philippine Obstetrical and Gynecological Society
[c] Criteria for diagnosis entails at least one abnormal value
[d] Oral glucose tolerance test
[e] Plus confirmation with fasting glucose or HbA1c

Sample size calculation for 2 independent proportions assumed an estimated baseline follow-up rate of 20%. Stata version 13.0 sample size calculator was used to estimate the sample size. To detect a 15% absolute improvement in follow-up from 20% to 35%, with 80% power, at 95% confidence interval, 5% error, and accounting for 10% data loss inherent in SMS, the sample size needed was computed at 308.

Description of study procedure

All participants admitted for delivery who were referred to the Section of Endocrinology, Diabetes and Metabolism for co-management of GDM, were assessed for eligibility. The primary investigator obtained informed consent if they met the inclusion criteria.

Eligible participants were randomized to either usual care or SMS (in addition to usual care) groups. Randomization was carried out in a 1:1 ratio using a computer-generated random allocation sequence. Allocation of treatment was done by third party personnel, using sequential sealed opaque envelopes. The outcome assessor and primary physician were blinded to treatment allocations. Blinding of the participants was not possible due to the nature of the intervention. Baseline socio-demographic characteristics, GDM status and maternal and fetal outcomes were abstracted from inpatient records and written in data collection forms. Additional information not indicated in the inpatient records was obtained by interview by the primary investigator.

Study intervention

Prior to discharge, the usual care group received a 10-minute lecture on postpartum GDM care and a 75 g OGTT request form. Explicit instructions were given pertaining to the laboratory location and timing of testing at 6 to 12 weeks postpartum. Follow-up visit with test results was also advised.

In addition to the above usual care, the SMS group received twice a week SMS reminders. The SMS were sent at 4, 8 and 10 weeks after delivery: one SMS on a weekday (Wednesday) and one on a weekend (Saturday). The messages in Filipino language contained a short reminder on different aspects of GDM postpartum care

and reiteration of written instructions for follow-up (Appendix A). The participants were not required to reply to these reminders. The content of the SMS was derived from a discussion with an endocrinologist who is also a medical informatics specialist. The SMS were sent manually by the study investigators. The overall cost of sending the text messages for the 154 participants in the SMS group was PhP 924.00, equivalent to USD 17.74 to 19.67 based on the current exchange rate during the course of the study. No monetary incentive was given to the participants to avoid any effect on follow-up.

An independent outcome assessor evaluated the participants on clinic follow-up. The date and results of the OGTT were recorded. If the OGTT results were abnormal, the participant was referred to her respective endocrinologist for subsequent follow-up and intervention. At the end of the clinic consult, each participant was asked a survey question on why they came for follow-up (Appendix B). If the participant belonged to the SMS group, she was asked the number of SMS reminders received.

All the participants who did not follow-up at 12 weeks postpartum were contacted through voice call to answer the survey questions (Appendix B). Responses were recorded verbatim. If a participant could not be reached on the first call, SMS were sent and she was again contacted on a different day. At least 3 attempts at varied times and on different days were made to reach the participant. The patient was then listed as not contactable if any of the following were encountered: phone number cannot be completed as dialed, subscriber cannot be reached, phone number is unattended or out of coverage area, call ended or dropped, wrong number, or ringing but with no answer on all attempts.

Outcome assessment

The primary outcome was follow-up defined as a clinic visit within 12 weeks postpartum with 75 g OGTT results. The follow-up rate for each group was calculated as the number of participants who followed-up divided by total number of participants in the group multiplied by 100. Participants who did not come for follow-up or came for clinic visit after the 3-month time period were labeled as non-follow-up. Participants who did not bring an OGTT result on clinic visit were considered as follow up, given another OGTT request and advised to come back within the time period.

Responses to survey questions were examined and grouped for emerging themes, and then classified as self-reported barriers and facilitators to postpartum follow-up.

Data analysis

Descriptive analyses were performed and bivariate analyses were run by follow-up status. The percentages across independent variables by follow-up status were calculated. The significance of the main effects of the different independent variables on the follow-up status was determined by bivariate analysis using Mann-Whitney U test for continuous data, while chi-square and Fisher's exact tests were used to compare categorical data. Bivariate analysis was initially performed to have an idea of the nature of the strength of association of each independent variable and the outcome variable. A bivariate test resulting to a p value ≤0.25 was considered a candidate for the multivariable model. Multivariate logistic regression with backward selection strategy was then performed to determine the factors associated with follow-up, while taking into account all other associated factors. The significance level for removal of a variable in the model was 0.05. Risk ratios (RR), 95% confidence interval (CI), and p values were derived. All statistical analyses were performed using Stata 14 for Windows® (StataCorp LP, College Station, TX, USA). Outcome comparisons were made according to treatment allocation, on an intention-to-treat analysis.

ReSULTS

Recruitment and participant flow

Recruitment was performed from April 2017 until March 2018 when the pre-specified sample size was reached. Follow-up of study outcomes was completed by June 2018. Out of the 336 participants assessed for eligibility, 28 were excluded. Twenty-four met different exclusion criteria: 12 had overt diabetes, 2 did not meet postpartum glucose cut-offs and were sent home on diabetes medication, 4 did not have a personal mobile phone, 4 had twin gestation in the index pregnancy, one had required long-term steroid treatment during the postpartum period for idiopathic thrombocytopenia, and one had neonatal death. There were 3 patients who did not give consent to participate, while another was excluded because of poor comprehension of instructions from a speech impediment (Figure 1).

Participants were randomized to either usual care (n=154) or SMS (n=154) groups. It was presumed that 151 participants received their text reminders. Three participants reported that no text reminders were received due to change of phone number, subscriber identity module (SIM) card malfunction and inability of mobile unit to receive SMS. A total of 81 (26.3%) participants could not be contacted at the end of the follow-up period [34 (22%) from the usual care group and 46 (30%) from the SMS group]. At the end of the study, these participants were considered as non follow-up, in accordance with an intention-to-treat analysis. During the follow up period, one participant died due to eclampsia in the immediate postpartum period.

Socio-demographic characteristics of included women

There were no significant differences in socio-demographic characteristics between the 2 groups. The mean age for both groups was 31 years. Approximately 60% of participants have college level education. The distribution of other demographic (monthly household income, employment status and parental status) and anthropometric characteristics [pre-pregnant weight and body mass index (BMI)] were similar in both groups (Table 2).

Perinatal factors

There were no significant differences in maternal factors between the groups . Antenatal 75 g OGTT results were available for 295 participants. The 13 patients without

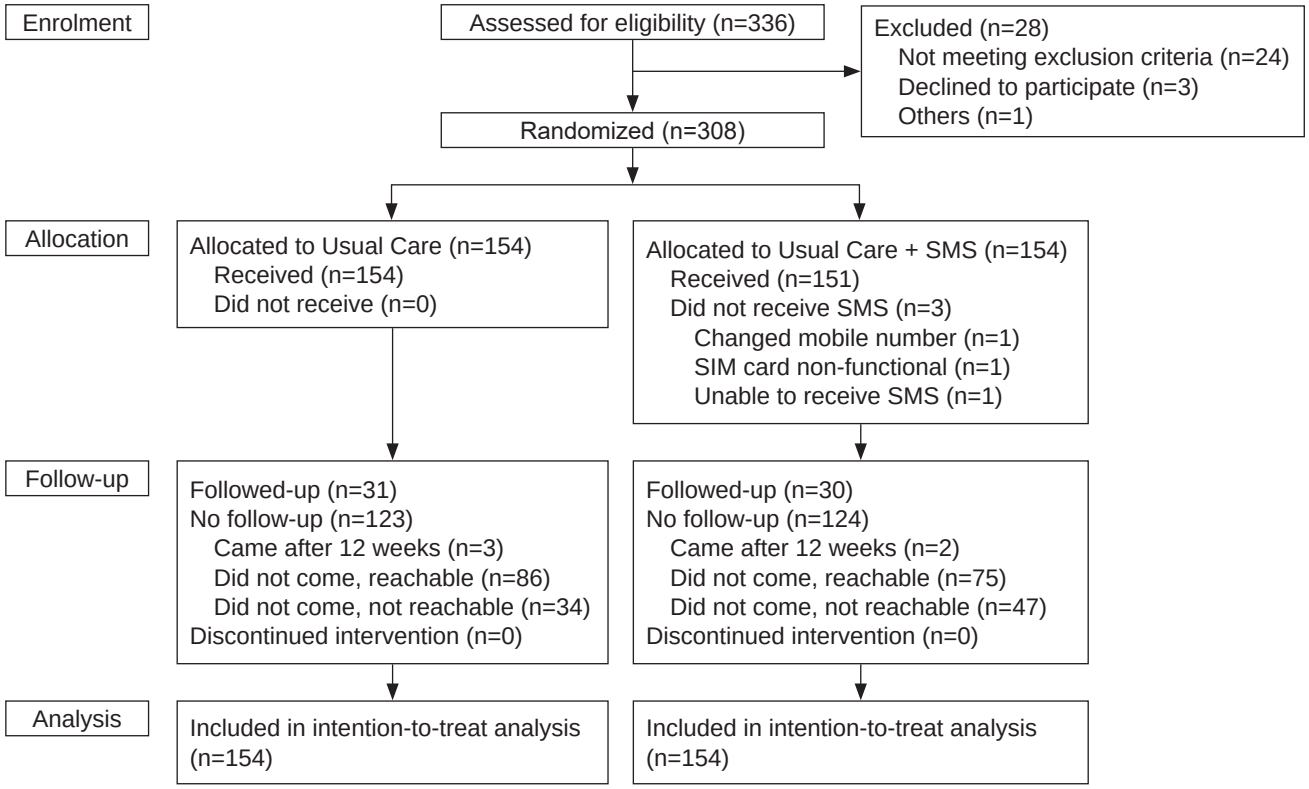

Figure 1. Participant flow diagram.

Table 2. Socio-demographic and anthropometric characteristics at trial entry

Characteristic	Total (n=308)	Usual care (n=154)	Usual care + SMS[a] (n=154)
Age in years (%)			
≤19	5 (1.6)	3 (1.9)	2 (1.3)
20-29	111 (36.4)	56 (36.4)	55 (35.7)
30-39	157 (51.0)	75 (48.7)	82 (53.2)
≥40	35 (11.4)	20 (13.0)	15 (9.7)
Mean age, year (SD[a])	31.6 (6.3)	31.5 (6.4)	31.7 (6.2)
Highest level of education (%)			
Secondary and below	122 (39.6)	58 (37.7)	64 (41.6)
College level and above	186 (60.4)	96 (62.3)	90 (58.4)
Employment status (%)			
Unemployed	189 (61.4)	98 (63.6)	91 (59.1)
Employed	119 (38.6)	56 (36.4)	63 (40.9)
Parental status (%)			
Single parent	15 (4.9)	7 (4.6)	8 (5.2)
With partner	293 (95.1)	147 (95.5)	146 (94.8)
Monthly household income[c] (%)			
Below minimum wage	112 (36.4)	59 (38.3)	53 (34.4)
Minimum wage and above	196 (63.6)	95 (61.7)	101 (65.6)
Mean pregestational weight, kg (SD)	56.1 (10.2)	56.6 (10.5)	55.7 (9.9)
Pregestational BMI BMI[d], kg/m^2 (%)			
Underweight	15 (4.9)	9 (5.8)	6 (3.9)
Normal	179 (58.1)	89 (57.8)	90 (58.4)
Overweight	90 (29.2)	44 (28.6)	46 (29.9)
Obese	24 (7.8)	12 (7.8)	12 (7.8)
Mean pregestational BMI[d], kg/m^2 (SD)	23.9 (4.1)	24.1 (4.1)	23.8 (4.2)

[a] SMS, short message service
[b] SD, standard deviation
[c] Based on the 2012 Family Income and Expenditure Survey, Philippine Statistics Authority
[d] BMI, body mass index

actual OGTT results on admission were physician-diagnosed and on active outpatient follow-up with an endocrinologist during their current pregnancy (Table 3).

More participants in the SMS group had a history of preterm delivery (3.9% in the usual care, 9.1% in the SMS groups). On the other hand, more participants in the usual care group delivered pre-term in the index pregnancy (19.5% in the usual care, 7.1% in the SMS groups). Consequently, a higher rate of neonatal hypoglycemia was recorded in the usual care compared to the SMS group (22.1% versus 13.6%, p=0.053) but this difference did not reach statistical significance. Birth weights and neonatal ICU admissions were similar in both groups (Table 3).

Table 3. Maternal factors at trial entry

Factor	Total (n=308)	Usual care (n=154)	Usual care + SMS[a] (n=154)
GDM [b] control (%)			
Diet	256 (83.1)	125 (81.2)	131 (85.1)
Insulin/metformin	52 (16.9)	29 (18.8)	23 (14.9)
Gravidity (%)			
Primigravid	86 (27.9)	48 (31.2)	38 (24.7)
Multigravid	222 (72.1)	106 (68.8)	116 (75.3)
Past obstetric history (%)			
GDM [b]	13 (4.2)	9 (5.8)	4 (2.6)
Preterm delivery	20 (6.5)	6 (3.9)	14 (9.1)
Abortion/stillbirth	68 (22.1)	31 (20.1)	37 (24.0)
Macrosomia[c]	15 (4.9)	7 (4.6)	8 (5.2)
Neonatal death	13 (4.2)	6 (3.9)	7 (4.6)
Gestational hypertension	21 (6.8)	8 (5.2)	13 (8.4)
Other past medical history (%)	91 (29.6)	45 (29.2)	46 (29.9)
Smoking (%)	14 (4.6)	8 (5.2)	6 (3.9)
Family history of diabetes[d] (%)	110 (35.7)	58 (37.7)	52 (33.8)
Breastfeeding (%)	307 (99.7)	153 (99.4)	154 (100.0)
Mode of delivery[e] (%)			
Spontaneous or assisted vaginal delivery	142 (46.1)	75 (48.7)	67 (43.5)
Caesarean section	166 (53.9)	79 (51.3)	87 (56.5)
Neonatal Outcomes[f] (%)			
Gestational age at birth			
Preterm	41 (13.3)	30 (19.5)	11 (7.1)
Full term	267 (86.7)	124 (80.5)	143 (92.9)
Birthweight			
Small for gestational age	9 (2.9)	5 (3.2)	4 (2.6)
Appropriate for gestational age	286 (92.9)	142 (92.2)	144 (93.5)
Large for gestational age	13 (4.2)	7 (4.6)	6 (3.9)
Neonatal hypoglycemia	55 (17.9)	34 (22.1)	21 (13.6)
Neonatal intensive care unit admission	80 (26.0)	44 (28.6)	36 (23.4)

[a] SMS, short message service
[b] GDM, gestational diabetes mellitus
[c] Neonatal death in previous pregnancies (excluding current/index pregnancy)
[d] Limited to first-degree relatives
[e] Pertains to index pregnancy
[f] Definitions are based on guidelines used by Department of Pediatrics, Section of Neonatology, Philippine General Hospital

Table 4. Postpartum follow-up rates and glucose status

Outcome	Total	Usual care	Usual care + SMS[a]
Follow-up status (%)	(n=308)	(n=154)	(n=154)
Follow-up	61 (19.8)	31 (20.1)[b]	30 (19.5)[b]
No follow-up	247 (80.2)	123 (79.9)	124 (80.5)
Postpartum glucose status (%)	(n=66)	(n=34)	(n=32)
Normal	42 (63.6)	24 (70.6)	18 (56.2)
IFG[c]	11 (16.7)	3 (8.8)	8 (25.0)
IGT[d]	6 (9.1)	2 (5.9)	4 (12.5)
IFG[c] + IGT[d]	2 (3.0)	1 (2.9)	1 (3.1)
Type 2 DM[e]	3 (4.6)	2 (5.9)	1 (3.1)
Unknown	2 (3.0)	2 (5.9)	0 (0)

[a] SMS, short message service
[b] p=0.886
[c] IFG, impaired fasting glucose
[d] IGT, impaired glucose tolerance
[e] DM, diabetes mellitus

Postpartum follow-up and glucose status

A total of 66 participants came for postpartum visit, resulting to an overall follow-up rate of 19.8%. Five participants (3 from the usual care and 2 from the SMS groups) came after the prescribed 6 to 12 week postpartum period and were then considered as non-follow-up. The difference in follow-up rates between groups was not statistically significant (Table 4).

Among those who were able to return for follow-up, 42 (63.6%) had normal glucose status. Nineteen (28.8%) had pre-diabetes, with impaired fasting glucose (IFG) as the most common condition (11 participants, 16.7%). Type 2 DM was newly diagnosed in 3 (4.6%) participants. Two (3%) had unknown glycemic status because the postpartum OGTT was not done at that time of clinic visit (Table 4).

The study was only powered to detect a difference in the follow-up rates between the usual care and SMS groups. The factors associated with follow-up were explored nonetheless to better characterize our population of GDM patients. A bivariate analysis was done to determine the association of demographic and maternal characteristics, including clinical and neonatal outcomes and follow-up (Appendix C). Participants were more likely to come for postpartum follow up if they were older, had a monthly household income at or above minimum wage, and used insulin or metformin for glycemic control during pregnancy. After adjusting for these factors, the addition of SMS to usual care did not increase follow up after 12 weeks postpartum (adjusted RR 0.98, 95% CI 0.63-1.52; p=0.932). Patients who used insulin or metformin during pregnancy were twice more likely to follow-up after delivery (adjusted RR 1.92, 95% CI 1.20-3.07; p=0.006) (Table 5).

Table 5. Logistic regression analysis of factors associated with follow-up

	Unadjusted RR[a] (95% CI[b])	*p* value	Adjusted RR[a] (95% CI[b])	*p* value
Study group				
Usual care	1.00 (reference)		1.00 (reference)	
Usual care + SMS[c]	0.97 (0.62-1.52)	0.886	0.98 (0.63-1.52)	0.932
Monthly household income				
Below minimum wage	1.00 (reference)		1.00 (reference)	
Minimum wage and above	1.48 (0.89-1.06)	0.132	1.37 (0.82-2.27)	0.218
Age	1.02 (0.99-1.06)	0.213	1.01 (0.97-1.05)	0.446
GDM[d] control				
Diet	1.00 (reference)		1.00 (reference)	
Insulin/metformin	2.06 (1.30-3.27)	0.002	1.92 (1.20-3.07)	0.006

[a] RR, relative risk
[b] CI, confidence interval
[c] SMS, short message service
[d] GDM, gestational diabetes mellitus

Because of the significant number of participants who did not follow-up, a post hoc per protocol analysis was performed, excluding 34 patients from the usual care group and 47 from the SMS group who were unreachable at the end of 12 weeks (Appendix D). The results were similar in both intention-to-treat and per-protocol analyses.

Self-reported barriers and facilitators for postpartum follow-up

The participants who came for postpartum reassessment were asked about their reasons for follow-up. The most common reason cited by the responders (n=66) was the need to to know their glucose status after pregnancy. Among those who did not follow-up, most reported child care difficulties as the reason for not returning for clinic visit. Table 6 cites the themes identified as facilitators and barriers for follow-up based on open-ended responses.

Table 6. Identified barriers and facilitators to follow-up

Themes	n
Facilitators	
Desire to know the outcome of blood sugar test results after pregnancy/desire to get better	47
Prevent diabetes	14
Obtain more information on diabetes	13
Monitor health condition/control diabetes	6
Doctor/advice from the doctor	4
Personal safety	3
One's self and/or family	3
Having prior gestational diabetes	2
Fear of outcome of diabetes	2
Text reminder	1
Given laboratory request	1
Keeping one's word/promise to return for follow-up	1
Barriers	
Child care difficulties	
No one to care for baby	
Unable to bring baby with her for follow-up	
Cannot leave home because of other children	50
Sick baby	
Baby too young to be brought out of the house	
Breastfeeding	
Transfer of residence, temporarily or permanently leaving Metro Manila	
Work	
Returned to work	37
Busy with work	27
No leave allowed	
Clinic schedule in conflict with work schedule	
Limited finances	
No budget for OGTT[a]	
Resources allotted for baby	24
No funds for follow-up (including fare and food during clinic visit)	
Patient got sick	
Postpartum depression	6
Caesarean section surgical site infection	
Other postpartum and puerperal complications	
Long distance from clinic location/long commute	
Followed-up with another physician/in another center or clinic	6
nearer to home or work place	5
Bad weather	4
Patient forgot	4
Need to care for sick relative	2
Lost laboratory request/no OGTT[a] done yet	2
Unable to fast	2
Fear of fasting while breastfeeding	
Inadequate fasting	
Patient died	1
Wrong number	1

[a] OGTT, oral glucose tolerance test

DISCUSSION

The results indicate that SMS reminders in addition to usual care did not improve follow-up among GDM patients at 12 weeks postpartum in our center. In addition, the postpartum testing rates were suboptimal (<50%) for both groups. We found that the use of insulin or metformin for GDM control was significantly associated with higher follow-up rate, among the various factors examined. Identification of self-reported facilitators and barriers to follow-up gave us an overall context of the suboptimal outcome of postpartum follow-up in our setting.

Our findings are similar to the results of the DIAMIND study. The investigators reported that SMS reminders did not increase postpartum OGTT, fasting plasma glucose or HbA1c completion, despite a higher overall screening rate of 82%. This was attributed to the concurrent receipt of postal reminders under the national reminder scheme and an OGTT recommendation in the follow-up treatment plan.[17] The findings of a study done in an Asian population reported a better follow-up rate in contrast to our study, at 66.6 to 94.9%, after being recalled by SMS reminder, phone call or invitation to join in studies.[12] A high follow-up rate was reported by Malong in a similar Filipino cohort, possibly attributable not only to persistent SMS or call reminders, but also because the cost of OGTT was free for the patients.[3] While employing a reminder system similar to the aforementioned studies, we investigated the effect of SMS reminders alone, without any concurrent reminder system or monetary incentives that may have affected the rate of follow-up. Another difference is that all of the studies had considerably longer follow-up duration of up to a mean of 22.8 months.[3,12,17] Our trial specified follow-up within the recommended 6 to 12 weeks postpartum. This may possibly coincide with the period of adjustment

to new parenting roles, which took precedence over postpartum follow-up, regardless of an SMS reminder. This was also observed in a study on a South Asian population in Australia. Although majority of the women were aware of the importance of OGTT screening, they struggled with the lack of support in the immediate postpartum period, and many were unable to attend for routine OGTT screening at 6 weeks postpartum leading to postponement of testing.[18] While SMS may seem like a simple platform to employ behavioral intervention, it may not be the case for this particular subset of patients.

The open-ended responses to the survey questions provided insight into the reasons for lack of follow-up. Logistics such as child care difficulties, work and transfer of residence were identified by the participants as the most common reasons for non-follow-up. From those who were unable to return for follow-up, 5 patients had attended postpartum consult in a center within closer proximity to their home or workplace. Financial limitation was cited as the fourth most common reason for non-follow-up based on the survey. Postpartum follow-up is not covered by PhilHealth, our national social insurance program, making it an out-of-pocket expense. Follow-up visits possibly take a low priority in resource allocation for some individuals. These concerns come into play in any behavioral outcome and may have played a major role in the low overall follow-up rates. These barriers to follow-up cannot be addressed by any reminder system alone.

Another technology-based consideration is that about 26.3% of our participants were deemed not reachable by the end of the study period. Our pre-specified data loss at 10% may have underestimated real life attrition among those receiving SMS intervention in our setting.

The use of insulin or metformin for GDM control was significantly associated with higher follow-up in our trial. Apart from the additional intervention of medication use, these women are compelled to come for more regular antepartum follow-up particularly for medication adjustment and monitoring. This may have allowed for more physician-patient interaction and more opportunities to make the patients aware of their condition and the implications on their health, as opposed to their diet-only counterparts. This factor, along with older age, nulliparity and higher income or education, were identified to be predictors of higher follow-up rates in a review by Tovar.[6] With the exception of nulliparity, we also found the same factors to be associated with higher follow-up based on bivariate analysis.

Identification and description of self-reported facilitators and barriers to postpartum follow-up gave us an overall context of the low rate of follow up in our setting. We observed that follow-up was not mechanistic, in that the addition of reminders does not necessarily result to better rates of postpartum follow-up.

We also noted that the results of early postpartum glucose profiles in our study are similar to the rate of early postpartum glucose status in Asian countries. These studies observed incidences of 3.9 to 41.8% for prediabetes, and 2.8 to 20.6% for overt diabetes within 12 weeks postpartum.[3,11] Postpartum glucose abnormalities in our trial may have been under-reported, given a follow-up rate of only 19.8%.

Limitations and Recommendations

As a public tertiary referral center, the patients seen in our institution belong mostly to lower income brackets. Majority of our referrals came from service consults in the Department of Obstetrics and Gynecology. Fewer than 10% of patients came from the private wards, making higher income brackets less represented in our cohort. Future studies may look into better income bracket representation, especially because follow-up is an out-of-pocket expense for our patients.

Improved SMS intervention design aimed at making messages more engaging and persuasive should be a consideration for similar projects in the future. Personalized messages and a two-way versus a one-way SMS design may be more effective, as this allows for more interaction and versatility.[19,20] Quantification of the actual effect of the SMS intervention is difficult to ascertain and remains a limitation of technology-based intervention.

We were not able to contact 26.3% of the participants by the end of the study period. Although no difference in results were seen statistically when this group was excluded from analysis, this remains a significant percentage of the study population. Because we had no control over data loss, a higher attrition rate may be considered in future study designs involving SMS interventions. In addition, other social media platforms which may be more engaging and persuasive, such as a closed Facebook group for GDM patients, can be explored in future studies. Apart from looking for adjunctive methods to increase follow-up, we recommend expanding the sample size to better delineate socio-cultural-economic factors that affect follow-up in our setting, as these were some of the self-reported barriers and facilitators to follow-up. This is the first study in our setting which aimed to identify possible predictors of postpartum follow-up.

The postpartum stage is indeed a challenging period, as can be surmised from the survey responses of the participants. Strategies to make postpartum follow-up universal, more accessible, more affordable and closer to local hospitals and health centers may serve to improve overall follow-up rates. Simplifying postpartum follow-up by incorporating pediatric, obstetric and medical follow up in a single clinic within the same schedule may be a viable option for future healthcare systems planning.

CONCLUSION

SMS reminders did not improve postpartum follow-up rate among GDM patients at 12 weeks postpartum in our setting. Among the factors examined, the use of insulin or metformin was independently associated with increased follow-up rate. Strategies addressing accessibility and affordability of postpartum care may serve to improve overall follow-up rates.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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APPeNDICeS

Appendix A. Teaching material and short message service content

Teaching material	Short message service
Ito ang ABCDEF *ng* GDM *pagkapanganak.* (This is the ABCDEF of GDM after delivery.)	
Assessment: *Ang mga nagka*-GDM *ay pwedeng magka*-diabetes*.* *Anim sa 10 na may* GDM *ay pwedeng magkadiabetes sa loob ng 10 taon. Samakatuwid, mainam na magpakonsulta pagkapanganak.* *Magpasuri ng* 75 g OGTT *at mag* follow-up *6 hanggang 12 linggo pagkapanganak.* (**Assessment**: Persons who have had GDM may have diabetes. Six out of 10 persons who had GDM may have diabetes in the next 10 years. Therefore, it is good to seek consult after delivery. Have a 75 g OGTT done and follow-up 6 to 12 weeks after delivery.)	Sender: PGH OPD DIABETES CLINIC *Ang mga nagka*-GDM *ay pwedeng magka*-diabetes*. Mag-* follow-up *6-12 na linggo pagkapanganak. Dalhin ang resulta ng 75* g OGTT *sa* Medicine Academic Complex Monday 8am. (Persons who have had GDM may have diabetes. Follow-up 6 to 12 weeks after delivery. Bring your 75 g OGTT results to the Medicine Academic Complex Monday 8am.)
Breastfeeding: *Pwedeng makaiwas sa* diabetes *ang pagpapasuso.* *Bukod sa benepisyo ng* breastmilk *sa sanggol, ang breastfeeding ay nagbubunga ng mas mababang peligro ng pagkakaroon ng patuloy na abnormal na blood sugar sa ina.* (**Breastfeeding**: Breastfeeding may help prevent diabetes. Aside from the benefits of breastmilk to the newborn, breastfeeding may confer a lower risk of persistently elevated blood sugar to the nursing mother.)	Sender: PGH OPD DIABETES CLINIC *Pwedeng makaiwas sa* diabetes *ang pagpapasuso. Mag-*follow-up *6-12 na linggo pagkapanganak. Dalhin ang* 75 g OGTT result *sa* Medicine Academic Complex Monday 8am. (Breastfeeding may help prevent diabetes. Follow-up 6 to 12 weeks after delivery. Bring your 75 g OGTT results to the Medicine Academic Complex Monday 8am.)
Contraception: *Mag-agwat ng pagbubuntis para di magka*-diabetes*. Magplano ng pamilya. Ang magkasunod na pagbubuntis ay nagbubunga ng 3x mas mataas na peligro ng* diabetes *sa ina.* (**Contraception**: Provide sufficient time in between pregnancies to avoid diabetes. Practice family planning. Consecutive pregnancies confer a threefold increase in the risk of diabetes in the mother.)	Sender: PGH OPD DIABETES CLINIC *Mag-agwat ng pagbubuntis para di magka*-diabetes*. Mag-*follow-up *6-12 na linggo pagkapanganak. Dalhin ang* 75 g OGTT result *sa* Medicine Academic Complex Monday 8am. (Provide sufficient time in between pregnancies to avoid diabetes. Follow-up 6 to 12 weeks after delivery. Bring your 75 g OGTT results to the Medicine Academic Complex Monday 8am.)
Diet: *Sundin ang tamang* diet *para makaiwas sa* diabetes*.* *Ang tamang* diet *ay kaugnay ng mas mababang panganib ng pagkakaroon ng* diabetes *sa hinaharap.* (**Diet**: Eat a proper diet to avoid diabetes. A proper diet is linked to a lower risk of developing diabetes.)	Sender: PGH OPD DIABETES CLINIC *Sundin ang tamang* diet *para makaiwas sa* diabetes*. Mag-*follow-up *6-12 na linggo pagkapanganak. Dalhin ang* 75 g OGTT result *sa* Medicine Academic Complex Monday 8am. (Eat a proper diet to avoid diabetes. Follow-up 6 to 12 weeks after delivery. Bring your 75 g OGTT results to the Medicine Academic Complex Monday 8am.)
Ehersisyo*:* *Mag-ehersisyo para pumayat at makaiwas sa* diabetes. *Ang* regular *na ehersisyo ay makatutulong sa panunumbalik sa tamang timbang at panatilihing malusog ang pangangatawan.* (**ehersisyo**: Exercise to lose weight and prevent diabetes. Regular exercise helps revert to proper weight and maintain health.)	Sender: PGH OPD DIABETES CLINIC *Mag-ehersisyo para pumayat at makaiwas sa* diabetes*. Mag-follow-up 6-12 na linggo pagkapanganak. Dalhin ang* 75 g OGTT result *sa* Medicine Academic Complex Monday 8am. (Exercise to lose weight and prevent diabetes. Follow-up 6 to 12 weeks after delivery. Bring your 75 g OGTT results to the Medicine Academic Complex Monday 8am.)
Family: *Kailangan ang suporta ng pamilya para iwas* diabetes. *Upang maayos na maisagawa ang* **ABCDeF *ng* gDM,** *hikayating ang suporta ng pamilya.* **Family**: Family support is needed to prevent diabetes. To help follow the **ABCDeF of gDM,** enlist the support of your family.	Sender: PGH OPD DIABETES CLINIC *Kailangan ang suporta ng pamilya para iwas* diabetes*.* Follow-up *6-12 na linggo pagkapanganak. Dalhin ang* 75 g OGTT result *sa* Medicine Academic Complex Monday 8am. (Family support is needed to prevent diabetes. Follow-up 6 to 12 weeks after delivery. Bring your 75 g OGTT results to the Medicine Academic Complex Monday 8am.)

Appendix B. Survey Questions

	Usual Care	Usual Care + SMS
Follow-up	*Ano po ang nag-udyok na inyo na mag*-follow-up*?* (What motivated you to return for follow-up?)	*Ano po ang nag-udyok na inyo na mag*-follow-up*?* *Natanggap niyo po ba ang mga paalala sa* text messages*?* *Ilang paalala po ang inyong natanggap?* (What motivated you to return for follow-up? Did you receive the SMS reminders? How many reminders did you receive?)
No follow-up	*Ano po ang mga dahilan kung bakit hindi kayo nakabalik para sa* follow-up*?* (What are your reasons for not being able to return for follow-up?)	*Ano po ang mga dahilan kung bakit hindi kayo nakabalik para sa* follow-up*?* *Natanggap niyo po ba ang mga paalala sa* text messages*?* *Ilang paalala po ang inyong natanggap?* (What are your reasons for not being able to return for follow-up? Did you receive the SMS reminders? How many reminders did you receive?)

Appendix C. Bivariate analysis of factors associated with follow-up

Characteristic	Total (n=308)		With follow-up (n=61)		No follow-up (n=247)		*p* value
	n or mean	%	n or mean	% within category	n or mean	% within category	
Study group							
Usual care	154	50.0	31	20.1	123	123	
Usual care + SMS[a]	154	50.0	30	19.5	124	124	0.886[b]
Age in years							
≤19	5	1.6	1	20.0	4	80.0	
20-29	111	36.0	16	14.4	95	85.6	
30-39	157	51.0	36	22.9	121	77.1	
≥40	35	11.4	8	22.9	27	77.1	
Mean age, year (SD[c])	31.6 (6.3)		31.4 (6.3)		32.5 (6.0)		
Meadian age, year	32.0		31.0		33.0		0.150[d]
Highest level of education (%)							
Secondary and below	122	39.6	21	17.2	101	82.8	
College level and above	186	60.4	40	21.5	146	78.5	0.384[e]
Employment status (%)							
Unemployed	189	61.4	37	19.6	152	80.4	
Employed	119	38.6	24	20.2	95	79.8	0.899[b]
Parental status (%)							
Single parent	15	4.9	3	20.0	12	80.0	
With partner	293	95.1	58	19.8	235	80.2	0.985[b]
Monthly household income[d] (%)							
Below minimum wage	112	36.4	17	15.2	95	84.8	
Minimum wage and above	196	63.6	44	22.4	152	77.6	0.124[b,k]
Mean pregestational BMI[f], kg/m^2 (SD[c])	23.9 (4.1)		23.9 (3.6)		23.9 (4.2)		
Median pregestational BMI[f], kg/m^2	23.4		23.4		23.3		0.832[d]
Pregestational BMI[f], kg/m^2							
Underweight	15	4.9	2	13.3	13	86.7	
Normal	179	58.1	32	17.9	147	82.1	
Overweight	90	29.2	24	26.7	66	73.3	
Obese	24	7.8	3	12.5	21	87.5	0.282[e]
Basis of diagnosis							
IADPSG[h]	242	78.6	46	19.0	196	81.0	
POGS[i]	53	17.2	11	20.8	42	79.2	0.771
GDM[j] control							
Diet	256	83.1	43	16.8	213	83.2	
Insulin/Metformin	52	16.9	18	34.6	34	65.4	0.003[k]
Gravidity							
Primigravid	86	27.9	17	19.8	69	80.2	
Multigravid	222	72.1	44	19.8	178	80.2	0.992
Presence of any obstetric history							
Yes	108	35.1	21	19.4	87	80.6	
No	200	64.9	40	20.0	160	80.0	0.907[b]
Other past medical history							
Yes	91	29.6	19	20.9	72	79.1	
No	217	70.4	42	19.4	175	80.6	0.759[b]
Smoking							
Yes	14	4.6	1	7.1	13	92.9	
No	294	95.4	60	20.4	234	79.6	0.317[e]
Family history of diabetes							
Yes	110	35.7	24	21.8	86	78.2	
No	198	64.3	37	18.7	161	81.3	0.509[b]
Mode of delivery							
Spontaneous/assisted vaginal delivery	142	46.1	32	22.5	110	77.5	
Caesarean section	166	53.9	29	17.5	137	82.5	0.266[b]
Gestational age at birth							
Preterm	41	13.3	9	22.0	32	78.0	
Full term	267	86.7	52	19.5	215	80.5	0.711
Birthweight							
Small for gestational age	9	2.9	1	11.1	8	88.9	
Appropriate for gestational age	286	92.9	58	20.3	228	79.7	
Large for gestational age	13	4.2	2	15.4	11	84.6	0.916[e]
Neonatal hypoglycemia							
Yes	55	17.9	11	20.0	44	80.0	
No	253	82.1	50	19.8	203	80.2	0.968[b]
Neonatal intensive care unit admission							
Yes	80	26.0	15	18.8	65	81.2	
No	228	74.0	46	20.2	182	79.8	0.783[b]

[a] SMS, short message service
[b] Chi-square test
[c] SD, standard deviation
[d] Mann-Whitney test
[e] Fisher's exact test
[f] BMI, body mass index
[g] Fisher's exact test
[h] IADPSG, International Association of Diabetes and Pregnancy Study Groups
[i] POGS, Philippine Obstetrical and Gynecological Society
[j] GDM, gestational diabetes mellitus
[k] Included in multiple logistic regression analysisDM, gestational diabetes mellitus

Appendix D. Logistic regression analysis of factors associated with follow-up, per protocol analysis, n=227

Variable	Unadjusted association		Adjusted association	
	RR[a] (95% CI[a])	*p* value	RR[a] (95% CI[a])	*p* value
Study group				
Usual care	1.00 (reference)		1.00 (reference)	
Usual care + SMS[b]	1.08 (0.70-1.66)	0.708	1.09 (0.71-1.67)	0.689
Education				
Secondary and below	1.00 (reference)		1.00 (reference)	
College level and above	1.34 (0.85-2.12)	0.203	1.19 (0.75-1.90)	0.452
Monthly household income				
Below minimum wage	1.00 (reference)		1.00 (reference)	
Minimum wage and above	1.38 (0.84-2.25)	0.195	1.23 (0.75-2.04)	0.402
Age, year	1.02 (0.99-1.06)	0.154	1.02 (0.98-1.06)	0.204
GDM[c] control				
Diet	1.00 (reference)		1.00 (reference)	
Insulin/metformin	1.79 (1.15-2.77)	0.009	1.61 (1.04-2.51)	0.032
Mode of delivery				
Spontaneous/assisted vaginal delivery	1.00 (reference)		1.00 (reference)	
Caesarean section	0.75 (0.49-1.15)	0.195	0.70 (0.46-1.07)	0.108

[a] CI, confidence interval
[b] SMS, short message service
[c] GDM, gestational diabetes mellitus
[d] Mann-Whitney test
[e] Fisher's exact test
[f] BMI, body mass index

ORIGINAL ARTICLE

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enhanced Recovery After Surgery (eRAS) Outcomes in Patients with Prior Diagnosis of Diabetes*

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Abstract

Objective. To determine whether a prior diagnosis of diabetes mellitus (DM) is associated with longer postoperative length of stay (LOS) and higher complication rates among patients who underwent colorectal surgery under an Enhanced Recovery After Surgery (ERAS) protocol in a single hospital setting.

Methodology. In a cross-sectional study, we grouped 157 consecutive patients who underwent elective colorectal surgery under ERAS protocol according to preoperative DM status. Patient data was abstracted from the ERAS Interactive Audit Database from January 2016 to December 2017. We compared LOS between groups. Secondary outcomes were postoperative complications, reoperations, pneumonia and wound infection. Categorical and continuous variables were analyzed with Fisher's exact test and student's t-test, respectively, using Stata/SE version 13 with a significance level of p=0.05.

Results. One hundred thirteen subjects did not have diabetes (no T2DM) while 44 patients had type 2 diabetes mellitus (T2DM). Mean postoperative length of hospital stay was 6.4±5.1 days for the no T2DM group versus 5.8±3.8 in the T2DM group (p=0.476). Complications, reoperation rate, pneumonia and wound infection did not differ between groups. Among subjects in the T2DM group, LOS did not differ between patients with preoperative HbA1c ≤7.0% and those with HbA1c >7.0% (5.7±3.7 versus 6.1±4.2 days, p=0.748).

Conclusion. Among patients who underwent colorectal surgery under ERAS protocol, a prior diagnosis of diabetes was not associated with longer LOS or more complications. A preoperative HbA1c of <7% did not affect length of stay in ERAS among patients with T2DM.

Key words: diabetes, ERAS, enhanced recovery, colorectal surgery, diabetes mellitus, length of stay

INTRODUCTION

Enhanced Recovery After Surgery is an evidence-based surgical care protocol that consists of varying interventions that reduce postoperative complications and length of stay. ERAS has been in practice internationally since 2005.[1] At the core of the ERAS philosophy is the modulation of inflammation while attenuating the hypermetabolic response to surgery, optimizing glucose control and providing nutritional support.[2] This philosophy translates into a protocol that consists of 24 preoperative, intra-operative and postoperative elements, each with the goal of early mobilization, early feeding, attenuating surgical stress and inflammation and, ultimately, early discharge (Figure 1).[2-5]

ERAS implementation reduces postoperative complications and length of stay by 50% and 30%, respectively.[4-6] However, there is a dearth of data on patients with diabetes mellitus (DM) and ERAS. The published randomized controlled trials that support ERAS interventions have excluded patients with DM or have included them only in very small numbers.[7,8] A guideline from the United Kingdom recommended the exclusion of patients with a history of diabetes from ERAS programmes, particularly because of the lack of data among patients with diabetes who have undergone ERAS surgery.[9] However, ERAS consensus statements recommend that patients with diabetes may be included provided that their conditions are optimized to international standards.[10]

Among patients who undergo colorectal surgery, 10 to 30% have diabetes mellitus.[11-13] Observational studies suggest that diabetes and hyperglycemia are independent risk factors for 30-day mortality, postoperative length of hospital stay, and complications among patients undergoing in-hospital non-cardiac surgeries, including colorectal surgery.[14,15] The Surgical Care and Outcomes

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** The preliminary results of this study were presented as a poster abstract at the Seoul International Congress of Endocrinology and Metabolism 2018 last April 19-21, 2018 in Seoul Korea, and at the 6th ERAS Society World Congress last May 24-25, 2018 in Stockholm, Sweden.*

Pre admission elements	Preoperative elements	Intraoperative elements	Postoperative elements
Cessation of smoking and excessive intake of alcohol	Structured preoperative information and engagement of patient and relatives or caretakers	Minimally invasive surgical techniques	Early mobilization
Preoperative nutritional screening, assessment and nutritional support	Preoperative carbohydrate treatment	Standardized anesthesia: (Short acting anesthetic, avoiding long acting opioids, mid thoracic/epidural anesthesia for open surgery)	Early intake of oral fluids and solids
Medical optimization of chronic disease	Preoperative prophylaxis against thrombosis	Maintaining fluid balance/avoidance of salt and water overload	Stimulation of gut motility: Use of chewing gums and laxatives and peripheral rather than central opioid blocking agents
	Preoperative prophylaxis against infection	Restrictive use of surgical site drains	Early removal of urinary catheters and IV fluids
	Preoperative prophylaxis against nausea and vomiting/ PONV prophylaxis	Removal of nasogastric tubes before anesthesia reversal	Intake of protein and energy rich nutritional supplements
	No prolonged fasting	Maintenance of normothermia (warm air flow blankets/ warmed IV fluids)	Multimodal approach to opioid sparing pain control
	No or selective bowel preparation		Prepare for early discharge
			Audit of outcomes and process in a multi professional multidisciplinary team on a regular basis

Figure 1. Elements of ERAS protocol (adapted).[1,3]

Assessment Program (SCOAP) suggests that diabetes is associated with increased adverse outcomes in conventional colorectal surgery, with a 2-fold risk of infection and a higher risk of in-hospital mortality and reoperation. Patients with T2DM, particularly those on insulin, are more prone to postoperative morbidity: perioperative glucose levels above 180 mg/dL have been associated with greater risk of infection, reoperative interventions, longer length of stay and death.[16]

It is difficult to conclude from existing literature whether ERAS protocols should include patients with diabetes. The interventions of the ERAS protocol that raise concerns for patients with DM are preoperative carbohydrate loading and routine prophylaxis for postoperative nausea and vomiting (PONV) with steroids.[5-7,9]

In the ERAS protocol, preoperative carbohydrate loading is the administration of a 100 g carbohydrate drink on the night prior to surgery and a 50 g carbohydrate drink 2 hours prior to surgery. Among patients without diabetes, preoperative carbohydrate loading is associated with a small reduction in postoperative length of hospital stay among patients undergoing colorectal surgery. Trials have reported improved perioperative well-being, reduced hunger, reduced blood levels of insulin and insulin resistance on day 2 after surgery.[17-19]

However, among patients with diabetes, high carbohydrate drinks may compromise blood sugar control. In a study by Gustaffson et al., T2DM patients given a 50 g oral carbohydrate load had a higher mean peak glucose [242 mg/dL (13.4±0.5 mmol/L)] compared to non-DM patients [136 mg/dL (7.6±0.5 mmol/L)] despite similar gastric emptying times.[20] Some clinical practice guidelines also recommend against particular elements of ERAS, such as the use of preoperative carbohydrate loading, due to concerns in delayed gastric emptying and a lack of evidence in this area for patients with DM.[19, 21-23]

Preoperative prophylaxis against nausea and vomiting using intravenous dexamethasone is indicated in the ERAS protocol if patient has 2 or more risk factors for PONV. These risk factors include female gender, non-smoker status, history of motion sickness/PONV and opioid use.[2] Administration of systemic steroids, however, causes acute hyperglycemia due to increased hepatic gluconeogenesis, inhibition of glucose uptake in adipose tissue, and alteration of receptor and post-receptor functions.[24] Dexamethasone for PONV prophylaxis has been shown to increase blood glucose from baseline in a dose-dependent manner, to as high as 58±50 mg/dL intraoperatively and 101±71 mg/dL 24 hours postoperatively among patients with diabetes.[25,26]

Since diabetes is associated with increased adverse outcomes in conventional surgery, it is important to examine whether it will also affect surgical outcomes among patients who undergo ERAS. Published literature examining the impact of DM on surgical outcomes of patients undergoing surgery under ERAS is lacking, hence, a general reservation with the use of ERAS protocols among patients who have been diagnosed with DM. The impact of T2DM on outcomes of patients who undergo surgery under ERAS is not clear.

In this study, we aimed to determine whether a prior diagnosis of T2DM was associated with longer LOS and higher complication rates among patients who underwent colorectal surgery under ERAS protocol in a single tertiary hospital. We also aimed to compare length of stay, postoperative complications, reoperation, occurrence of pneumonia and occurrence of wound infection between patients with prior diagnosis of T2DM who achieved HbA1c of ≤7% preoperatively and those with HbA1c >7%.

MeTHODOLOgy

This study was approved by The Medical City (TMC) Institutional Review Board. We conducted a retrospective cohort study using data drawn from TMC ERAS Interactive Audit System (EIAS). Trained abstractors extracted data using standardized definitions as given in https://www.encare.net/healthcare-professionals/products-and-services/eras-interactive-audit-system-eias. We used data from ERAS in a single center, The Medical City-Ortigas, from January 2016 to December 2017.

Data specification

The EIAS (https://www.encare.net/healthcare-professionals/products-and-services/eras-interactive-audit-system-eias) is an online web-based central database designed for interactive audit and research for collecting registry data.

The database was opened in 2007 and is tailored to the ERAS Society guidelines. This was adopted by The Medical City-Ortigas in July 2015. Each patient's data field contains 140 different variables, including patient demographics [preoperative body mass index (BMI), pre-morbid health status] surgical procedures and postoperative outcomes (time to achieve targeted mobility, total length of hospital stay, complications, 30-day mortality). For security purposes in our study, data were de-identified on submission and the database was held on a password and firewall-protected secure internet server. All patients who fulfilled the inclusion and exclusion criteria were referred by their attending surgeons. Data were gathered and encoded consecutively into the EIAS by the ERAS Coordinator.

Subjects

Patients who underwent elective colorectal surgery under the TMC ERAS protocol from January 2016 to December 2017 with data entered into the EIAS were eligible for inclusion. Exclusion criteria were emergency surgery, type 1 diabetes mellitus, intake of steroids prior to admission and procedure, and non-major abdominal surgery. Entries with incomplete data and no known diabetes status were excluded from the analysis.

Clinical risk factors

The EIAS records were used to obtain patient demographic data pertaining to age, gender, BMI, smoking status, alcohol usage, T2DM status, American Society of Anesthesiologists (ASA) physical classification, PONV prophylaxis, preoperative carbohydrate loading, antibiotic prophylaxis before incision and length of operation. Preoperative health status was assessed using the ASA classification.

Subjects were grouped according to their DM status as classified by the EIAS registry: patients who had a diagnosis of diabetes were classified into the T2DM group and those without were classified into the no T2DM group. Under EIAS, patients were classified to have DM based on either a medical history of diabetes elicited from the patient, assessment of the attending physician or the presence of an HbA1c >6.5% on chart review. To attenuate recall and misclassification bias, authors performed chart review for preoperative HbA1c and/or preoperative blood sugar.

Outcomes

The primary outcome was postoperative length of hospital stay, defined as the number of nights in the hospital after primary operation until declared cleared for discharge by the ERAS surgical attending physician. The secondary outcomes were discharge within 30 postoperative days, postoperative complications, reoperation, occurrence of pneumonia and occurrence of wound infection.

Sample size

The sample size was computed using Stata/SE version 13 (StataCorp LP, College Station, TX, USA). This was based on the 45% complication rate of ERAS patients with HbA1c >6% versus the 25% complication rate of patients with HbA1c <6% from the study of Gustaffson et al, using an alpha level of 0.05 and a power of 0.80.[27]

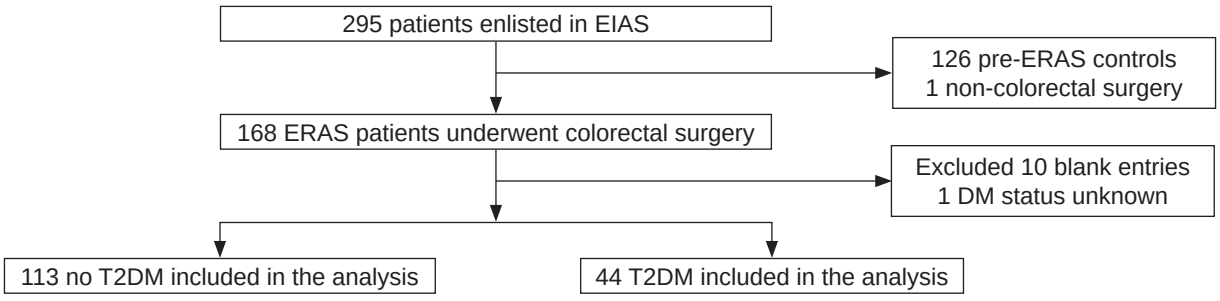
Statistical analysis

Statistical analysis was performed using Stata/SE version 13. We used the independent t-test to compare continuous variables (age, BMI, length of operation, length of stay) and Fisher's exact test for categorical variables (gender, smoking, alcohol use, ASA Physical Classification status, PONV prophylaxis, preoperative carbohydrate loading, antibiotic prophylaxis, reoperation, complications, pneumonia, wound dehiscence, inadequate postoperative glycemic control). A p value of 0.05 was considered significant. A subgroup analysis of the T2DM group was done to compare outcomes between patients with T2DM who had preoperative HbA1c <7.0% and those with higher HbA1c.

ReSULTS

Subjects

From July 2015 to December 2017, a total of 295 patients were enlisted in the EIAS. One hundred fifty eight underwent elective colorectal surgery under TMC ERAS protocol. One patient had unknown T2DM status and was excluded from the analysis. Of the 157 patients included, 113 were in the no T2DM group and 44 in the T2DM group (Figure 2).



ERAS, Enhanced Recovery After Surgery; EIAS, ERAS Interactive Audit System; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus.

Figure 2. Flow diagram of subjects enlisted from the EIAS database.

Patients were mostly female, at their sixth to seventh decade of life and were overweight by Asia-Pacific International Obesity Task Force classification. There was no significant difference in smoking and alcohol use, length of operation, administration of preoperative PONV prophylaxis and preoperative carbohydrate loading. Patients in the T2DM group were older, had a greater percentage of use of laparascopic surgical technique, and had more systemic disease by ASA Classification. In the T2DM group, 34% had a preoperative HbA1c exceeding 7.0% (Table 1).

Outcomes

There were no significant differences in postoperative length of hospital stay, complication rate during primary stay, reoperation, pneumonia and wound infection between the no T2DM and T2DM groups (Table 2).

Table 3 shows the preoperative HbA1c values of the patients in the T2DM group. Among the patients in the T2DM group who underwent colorectal surgery under ERAS, 34% did not have HbA1c <7% within target prior to surgery. The mean HbA1c in this subgroup was 9.0%. The outcomes pertaining to postoperative LOS, complications during primary stay, reoperation and pneumonia were not significantly different in these patients compared to those with preoperative HbA1c ≤7%. None of the patients in our sample had wound or surgical site infection (Table 4).

DISCUSSION

In this study, we compared the postoperative length of stay among patients with and without prior diagnosis of T2DM among patients who underwent major colorectal surgery in an ERAS protocol.

Studies on non-cardiac surgery have demonstrated the association of perioperative hyperglycemia and increased LOS, hospital complications and mortality.[28] The data presented in SCOAP demonstrated that patients with diabetes were more likely to have inadequate perioperative glycemic control, with a 7% increase in infectious complications, and significantly longer length of hospital stay compared to patients without diabetes who underwent colorectal surgery (6.0±8.5 versus 5.3±7.4 days).[16]

Perioperative hyperglycemia may have an indirect effect on length of stay because of its effect on complications.[14] Hyperglycemia is a predictor of nosocomial infection in general surgery.[14, 29-31] Short-term hyperglycemia, with a capillary blood glucose reading >252 mg/dL, is associated with impairment of the immune system seen as abnormalities in neutrophil and monocyte immune cell activity, increased expression of adhesion molecules and E-selectins, increased activation of the cytokine cascade via interleukin-6 and TNF-alpha, and altered microvasculature in response to nitric oxide.[11]

Table 1. Clinical characteristics of patients who underwent colorectal surgery under ERAS[a] protocol

Characteristic	no T2DM[b] (n=113)	T2DM[b] (n=44)	*p* value
Male gender (%)	40 (35.4)	23 (52.3)	0.070
Mean age, year (SD[c])	59.1 (14.2)	65.5 (9.7)	0.007
Mean BMI[d], kg/m^2 (SD[c])	25.0(4.0)	26.3 (5.4)	0.100
Smoker (%)	9 (7.9)	3 (6.8)	0.511
Alcohol usage (%)	2 (1.8)	1 (2.3)	0.630
ASA class[e] (%)			0.000
ASA I: healthy	2 (1.8)	0 (0.0)	
ASA II: mild systemic disease	54 (48.2)	3 (6.8)	
ASA III: severe systemic disease	55 (49.1)	40 (90.9)	
ASA IV: severe, life-threatening systemic disease	1 (0.9)	1 (2.3)	
Preoperative carbohydrate drink (%)	107 (95.5)	39 (88.6)	0.160
PONV[f] prophylaxis (%)	96 (85.7)	35 (79.6)	0.426
Antibiotic prophylaxis (%)	111 (98.2)	44 (100)	1.000
Surgical approach (%)			0.028
Open surgery	73 (65.2)	18 (40.9)	
Standard laparoscopic surgery	25 (22.3)	35 (79.6)	
Hand-assisted laparoscopic surgery	5 (4.5)	5 (11.4)	
Converted to open surgery	9 (8.0)	7 (15.9)	
Mean length of operation, hours (SD)	5.3 (2.5)	5.0 (2.4)	0.498
Preoperative HbA1c >7.0% (%)	N/A	15 (34)	0.000

[a] ERAS, Enhanced Recovery After Surgery
[b] T2DM, type 2 diabetes mellitus
[c] SD, standard deviation
[d] BMI, body mass index
[e] ASA, American Society of Anesthesiologists classification[37]
[f] PONV, postoperative nausea and vomiting

Table 2. Outcomes of patients who underwent colorectal surgery under ERAS[a] protocol

Outcome	no T2DM[b] (n=113)	T2DM[b] (n=44)	*p* value
Mean post-operative LOS[c], day (SD[d])	6.4 (5.1)	5.8 (3.8)	0.476
Discharged within 30 postoperative days (%)	112 (0.99)	43 (97.7)	0.282
Complications during primary stay (%)	37 (33.0)	14 (31.8)	0.521
Reoperation (%)	9 (8.0)	4 (9.1)	0.628
Pneumonia (%)	4 (3.6)	3 (6.8)	0.403

[a] ERAS, Enhanced Recovery After Surgery
[b] T2DM, type 2 diabetes mellitus
[c] LOS, length of hospital stay
[d] SD, standard deviation

Table 3. Preoperative HbA1c values of patients in T2DM group

HbA1c, %	Frequency (%) (n=44)
<5.5	3 (6.8)
5.5 to 5.9	4 (9.1)
6.0 to 6.49	12 (27.3)
6.5 to 7.0	10 (22.7)
7.1 to 7.9	6 (13.6)
8.0 to 8.9	4 (9.1)
9.0 to 9.9	2 (4.5)
>10	3 (6.8)

In a population-based Taiwanese cohort, diabetes conferred a higher risk prolonged LOS [odds ratio (OR) 2.3, 95% confidence interval (CI) 2.16-2.44] and 30-day postoperative mortality (OR 1.84, 95% CI 1.46-2.32).[15]

The impact of glycemic control on surgical outcomes among patients without diabetes who underwent colorectal surgery under a standardized ERAS protocol was demonstrated in a study in Sweden. Patients with preoperative HbA1c >6.0% had longer duration of surgery and greater perioperative blood loss. While a preoperative HbA1c >6.0% was found to confer a 2.9-fold increased risk of postoperative complications (95% CI 1.1-7.9), there was no significant difference in length of hospital stay between the two groups (8.5±5.4 versus 7.3±5.6 days).[27] An exploratory study compared consecutive patients who underwent elective major colorectal procedures under ERAS over the span of one year. Patients with DM had longer median LOS of 7 days with an interquartile range (IQR) of 5 to 15.5 days (n=18, *p*=0.041) compared to than those without diabetes (5 days, IQR 4 to 7.5 days, n=125). The study suggested that a diagnosis of diabetes had a significant impact on LOS even with ERAS interventions. However, the study did not analyze the impact of glycemic control of the patients included in the study.[32]

In our study, in spite of the effects of carbohydrate loading and dexamethasone PONV prophylaxis on short-term hyperglycemia, we observed no difference in LOS or complication rates between the no T2DM and T2DM groups.

ERAS protocols recommend that patients with chronic disease such as diabetes be optimized to international standards.[16] While there is currently no recommended preoperative HbA1c target, this recommendation implies that good glycemic control is a prerequisite to enrolling patients with diabetes to ERAS.[33] In our study, majority of the patients with DM had well-controlled diabetes. This may explain why our results showed that having prior diagnosis of DM was not associated with longer LOS or more complications. Although no difference in outcomes were noted among DM patients who did not achieve an HbA1c <7% prior to surgery, it is important to note that only a small percentage of our sample had poor perioperative glycemic control. Only eleven percent had HbA1c >9%.

Surgical site infections (SSI) can be as high as 15% in patients undergoing colorectal surgery with hyperglycemia in the perioperative period.[16] The use of surgical drains is one such reported risk factor. In our sample, there were no reported wound infections. The limited use of drains, as advocated by the ERAS protocol, could have contributed to fewer surgical site infections.

One factor that has been shown to significantly contribute to length of stay and recovery is the use of laparoscopic surgery.[34] Among the T2DM group, there was a greater proportion of patients who underwent laparoscopic surgery. Our results suggest that the preference for a laparoscopic approach in ERAS may be a contributory factor.

Limitations of the study and recommendations

The varied elements of the ERAS protocol may attenuate the known risk factors for SSI among patients with T2DM. These include the limited use of surgical drains, preference for laparascopic approach and preoperative optimization of chronic diseases such as diabetes. One important outcome that was not measured in this study was postoperative blood sugar. Under the current study protocol, we were unable to document whether ERAS interventions, such as preoperative carbohydrate loading and PONV prophylaxis with dexamethasone, produced clinically significant hyperglycemia. Documentation of postoperative hyperglycemia in patients with and without diabetes who undergo ERAS should be done for future prospective studies, particularly those that examine the individual elements of the ERAS protocol.

Subjects were classified into T2DM and no T2DM groups based on medical history and assessment of attending physicians. Since data on preoperative HbA1c was not available for patients without prior diagnosis of diabetes, this is inadvertently subject to recall bias.

In our study, one patient with T2DM died within 30 postoperative days and one patient had prolonged hospital stay. The differences in secondary outcomes were still not significant between groups. The effect of ERAS on 30-day postoperative mortality, length of stay, complications or outcomes among patients with T2DM cannot be answered by our study design. This important outcome can be determined by comparing data before and after implementation of the ERAS protocol for DM patients.[35,36]

Table 4. Outcomes of T2DM[a] patients grouped by preoperative HbA1c

Outcome	HbA1c ≤7.0 (n=29)	HbA1c >7.0 (n=15)	*p* value
Mean HbA1c, % (SD[b])	6.2 (0.5)	9.0 (2.0)	<0.00001
Mean post-operative LOS[c], day (SD[b])	5.7 (3.7)	6.1 (4.2)	0.748
Complications during primary stay (%)	10 (34.5)	4 (26.7)	0.738
Reoperation (%)	3 (10.3)	1 (6.6)	1.000
Pneumonia (%)	2 (6.9)	1 (6.7)	1.000

[a] T2DM, type 2 diabetes mellitus
[b] SD, standard deviation
[c] LOS, length of hospital stay

There is a need for evidence-based support for the implementation of the ERAS protocol for patients with T2DM undergoing colorectal surgery. The best evidence that will support the use of ERAS protocols among patients with diabetes is a well-powered randomized controlled trial (RCT). Currently, there are no published RCTs that have examined individuals with diabetes randomized to ERAS versus conventional care. A systematic review of MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, conference proceedings and ongoing clinical trials yielded no such high-quality articles that included patients with diabetes undergoing ERAS surgery.[8]

In spite of differences in age and premorbid status, our findings showed that there is no difference in outcomes between patients with prior diagnosis of DM and those without under ERAS. The ERAS protocol has multiple interventions that may contribute to reducing length of stay. While individual ERAS interventions have yet to be examined and deemed appropriate for patients with diabetes, our results show that, for patients with good preoperative glycemic control, the ERAS protocol as a whole does not pose additional harm to the patient with diabetes.

CONCLUSION

A prior diagnosis of T2DM was not associated with longer length of stay or more complications among patients who underwent colorectal surgery under the TMC ERAS protocol. A preoperative HbA1c less than 7% did not affect length of stay in ERAS.

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

Author Disclosure
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ORIGINAL ARTICLE

Country Characteristics and Variation in Diabetes Prevalence among Asian Countries – an ecological Study

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Abstract

Objectives. To determine the variation in diabetes prevalence across Asian countries and its relationship with the quality of health system and socioeconomic characteristics of the country.

Methodology. An ecological analysis was conducted using publicly available data from the World Bank, the World Health Organization and the International Diabetes Federation. Geographical variation in diabetes prevalence across countries was examined using control charts while the relationships between country-level determinants and diabetes prevalence were investigated using linear regression analysis.

Results. The control chart shows special-cause variation in diabetes prevalence in 21 (58%) of the Asian countries; nine countries were below the 99.8% control limits while twelve were above it.

Fifteen (42%) countries suggest common-cause variation. Three country characteristics independently associated with diabetes prevalence were hypertension prevalence (OR 0.39, 95% CI 0.22 to 0.55; *p*-value<0.001), obesity prevalence (OR 0.15, 95% CI 0.13 to 0.18; *p*-value<0.001), and quality of health care governance (OR 0.18, 95% CI 0.04 to 0.34; *p*-value=0.02).

Conclusions. There is a considerable geographical variation in diabetes prevalence across Asian countries. A substantial part of this variation could be explained by differences in the quality of health care governance, hypertension prevalence and obesity prevalence.

Key words: Asia, diabetes, prevalence, health system

INTRODUCTION

The increasing number of people with diabetes worldwide, and the grim consequences of the disease with close to five million deaths each year, makes it one of the largest epidemics in human history.[1] Without effective prevention and management, the burden will continue to increase globally. Type 2 diabetes accounts for 85% to 95% of all cases of diabetes in high-income countries and this estimate may even be higher in low- and middle-income countries.[2]

Asia accounts for more than half of the diabetes prevalence worldwide. Six of the ten top countries with the highest numbers of people with diabetes are Asian countries and this is expected to increase to seven by 2030.[3] The rise in diabetes prevalence among Asian countries is consistently observed although the prevalence vary between country to country.[4] Understanding the variation in health outcomes is key in epidemiological research. According to Deming, variation in an outcome can be due to common cause variation (i.e., variation that is within what is expected) and special cause variation (i.e., variation that is outside what is expected).[5,6] The differences in prevalence of diabetes across Asian countries have not been well addressed. Addressing this gap in knowledge may help improve public health efforts in reducing the disease progress.

Since the prevalence of a chronic disease like diabetes is determined by its occurrence and survival rate, we aim to explain variation in diabetes prevalence among Asian countries by considering health system characteristics (health workforce, health financing, and health governance) and typical diabetes-associated factors (such as affluent lifestyle, hypertension and obesity) within the countries.

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MeTHODOLOgy

Setting

In total, there are 36 countries in Asia. This continent is subdivided in regions namely East Asia (China, Japan, Mongolia, North Korea and South Korea), South East Asia (Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam and Timor Leste), South Asia (Bangladesh, Bhutan, India, Maldives, Nepal and Sri Lanka), and West Asia or East Mediterranean (Afghanistan, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Pakistan, Qatar, Saudi Arabia, Syria, United Arab Emirates and Yemen).

Study design and data acquisition

An ecological study was conducted using publicly available data and reports released by the World Health Organization (WHO)[7], the International Diabetes Federation (IDF)[8] and the World Bank[9]. We extracted data at country level on the determinants and outcome of the 36 Asian countries. Determinants were the factors typically associated with diabetes (affluent lifestyle, hypertension and obesity prevalence) and components of the WHO's building blocks of the health system, e.g., health human resource, healthcare financing and quality of healthcare governance.[10 11]

Health human resources were represented by the ratio of physicians (any specialties) in the country per 1000 population.[7] Healthcare financing was measured by the mean diabetes related expenditure per person per year in US$.[12] Leadership and governance in health was measured using the Worldwide Governance Indicators (WGI); a research dataset by the World Bank built on a survey on the experts' views on political stability, government effectiveness, voice and accountability, rule of law, regulatory quality, political stability and control of corruption of a country. The experts came from various enterprises, regular citizen and experts in industrial and developing countries. The WGI data were gathered from a number of surveys of households and firms, commercial business information providers, non-governmental organizations, and public sector organizations. It is currently used by the World Bank and several other donor agencies to measure the quality of governance of a country.[13] Each of the six parameters in the survey was ranked from -2.5 to +2.5. The ranks were summed up to a total score for the quality of healthcare governance of a country, which ranges from -15 (worst) to +15 (best).[14]

In addition, we considered other factors for each country, such as number of motor vehicles (per 1000 population) which represents affluent lifestyle, prevalence of hypertension above 18 years of age (defined as Systolic Blood Pressure ≥140 OR Diastolic Blood Pressure ≥90 mmHg; age-standardized estimate) and prevalence of obesity above 18 years of age (Body Mass Index ≥25; age-standardized estimate).

As the outcome of interest in this study, we took diabetes prevalence above 18 years of age which was defined as a fasting blood glucose ≥7.0 mmol/L or on medication (age-standardized estimate).[7]

Statistical analysis

We determined the range, mean and standard deviation of diabetes prevalence and the potential determinants. The weighted average of diabetes prevalence was estimated using mixed model analysis.

A Shewhart control chart was used to explore variation of diabetes prevalence across Asian countries to differentiate common cause variation from special cause variation graphically.[5 6]

The control chart depicts the plotting weighted mean of diabetes prevalence on the y-axis against a measure of their precision, i.e., standard deviation on the x-axis. The chart consists of five horizontal lines, one central line with two lines below and above it. The central line represents the weighted mean of diabetes prevalence, while the other two lines above and below the central line indicate 95% limits (2 standard deviations) and 99.8% limits (3 standard deviations) of the weighted mean of diabetes prevalence. We used three standard deviations as the control limits in accordance with the methodological criteria of Shewhart control chart applied in a systematic review by Kotsier et al.[15] Countries with a diabetes prevalence within the control limits (3 standard deviation) are regarded to show common-cause variation while those outside the control limits are considered to show special-cause variation.

Associations between diabetes prevalence and country-level determinants were examined descriptively using bar charts. The pooled country-level of number of physicians per 1000 people, mean diabetes-related health expenditure, quality of healthcare governance, number of motor vehicles per 1000 people, hypertension prevalence and obesity prevalence were plotted using multiple double-bar charts against the average diabetes prevalence of countries located below, within and above the control limits in the control chart.

Relationships between country-level determinants and diabetes prevalence were examined using linear regression analysis in both univariable and multivariable analysis. Two-tailed Wald test at significance level of alpha equal to 5% was used to determine the statistical significance of the association. Stata statistical package version 12 was used to perform statistical analysis.[16]

ethical approval

We used publicly available data, thus no ethical approval was required.

ReSULTS

The prevalence of diabetes varies considerably across Asia, ranging from 5.6% in North Korea to 23% in Qatar, with an average prevalence of 11.6% (SD 4.3%). The countries also showed marked variation in all determinants as shown in Table 1. The ratio of physicians per 1000 population was lowest in Timor Leste (0.07) and highest in Qatar (7.7). The average diabetes-related expenditure per person was 804 US dollars, ranging from 31 to 4,308 US dollars. Ten countries (Japan, Singapore, Qatar, South Korea, United Arab Emirates, Kuwait, Brunei Darussalam, Oman, Saudi

Table 1. Characteristics of the Asian countries (n=36)

Country characteristics	Mean (SD)	Range
Diabetes prevalence (Fasting blood glucose >=7.0 mmol/L or on medication; age-standardized estimate), %	11.6 (4.25)	5.6; 23.0
Number of physicians (per 1000 population), n	1.4 (1.4)	0.07; 7.7
Mean diabetes related health expenditure per person, USD †	804 (1065)	31; 4308
Quality of healthcare governance‡	-2.3 (4.8)	-9.5; 9.4
Number of motor vehicles (per 1000 population), n †	180 (194)	3; 588
Raised blood pressure prevalence (SBP>=140 OR DBP>=90; age-standardized estimate), %	23.8 (4.2)	10.8; 31.4
Obesity prevalence (BMI >= 25; age-standardized estimate), %	39.6 (21.3)	14.5; 78.1

† no data available for North Korea
‡ Measured using Worldwide Governance Indicators which capture six key dimensions of governance (Voice & Accountability, Political Stability and Lack of Violence, Government Effectiveness, Regulatory Quality, Rule of Law, and Control of Corruption).

Arabia and Bahrain) spent more than 1000 US$ on diabetes health-related care per person per year while seven other countries (Myanmar, Bangladesh, Pakistan, Nepal, Laos, Cambodia and India) spent less than 100 US$. The average quality of healthcare governance was generally low with a mean score of -2.3 and only nine countries (Singapore, Japan, South Korea, Qatar, Brunei Darussalam, United Arab Emirates, Malaysia, Oman, and Bhutan) had a positive score indicating good quality healthcare governance. The average number of motor vehicles per 1000 population was 180; ranging from 3 in Bangladesh to 588 motor vehicles per 1000 population in Japan.

Special- and common-cause variations in diabetes prevalence

Figure 1 shows the results of the control chart that explored variation in diabetes prevalence across 36 Asian countries. The weighted mean of diabetes prevalence was 10.5 (99.8% CI 8.8; 12.2). The diabetes prevalence in fifteen (42%) Asian countries was within the 99.8 percent control limits which suggests common-cause variation. The diabetes prevalence in nine (25%) Asian countries was below the control limits while in twelve (33%) Asian countries the diabetes prevalence was higher. Thus, special-cause variation appeared present for twenty-one (58%) Asian countries.

The map in Figure 2 shows the variation in diabetes prevalence across Asian countries. We observed that countries located above the control limit in the control chart (diabetes prevalence >12.2%) are mostly located in the Western part of the continent (the Middle East region) while countries below the control limit (diabetes prevalence <8.8%) like North Korea, Vietnam, Myanmar, Philippines, Timor Leste and Japan are located in the eastern part of the continent.

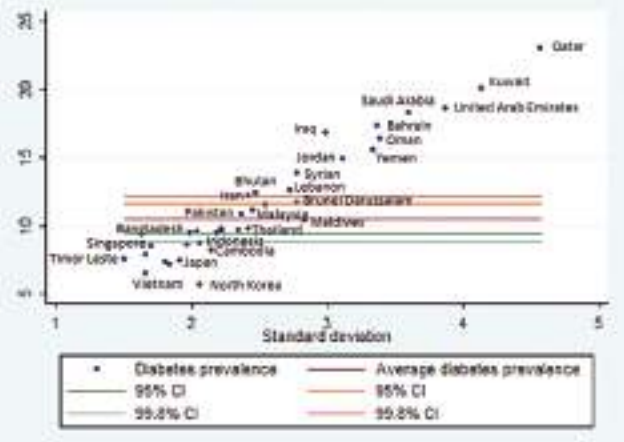

Figure 1. Control chart of diabetes prevalence across Asian countries.

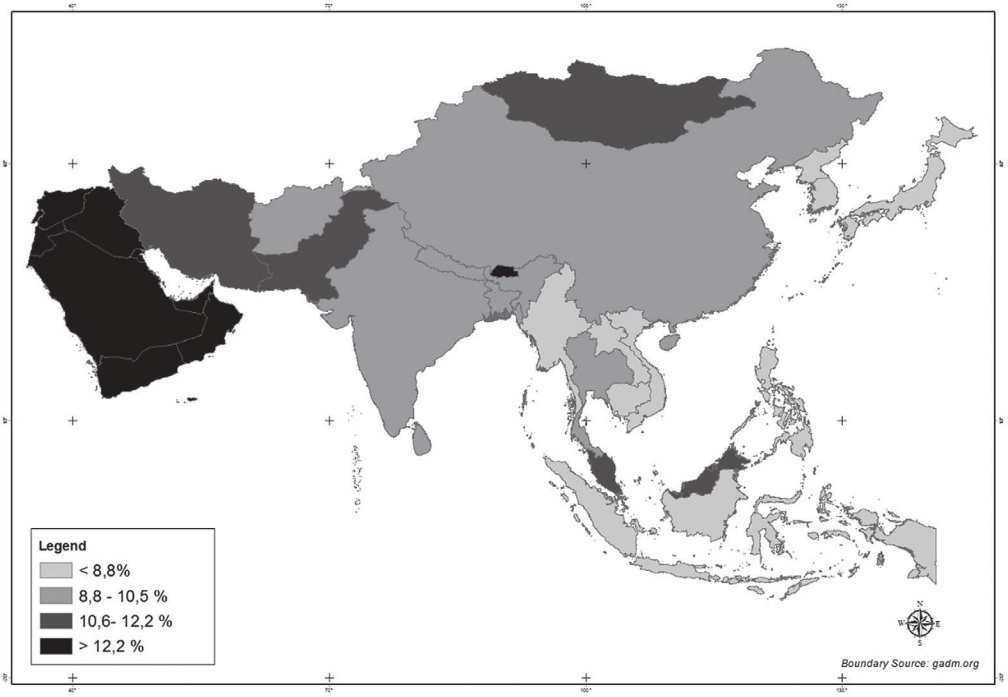

Figure 2. Prevalence of diabetes in Asian countries.

Relationships between country-level determinants and diabetes prevalence

The relationships between country-level determinants and diabetes prevalence are shown in Figure 3 using multiple double-bar charts. The charts show that the diabetes prevalence increases in the same direction as the prevalence of hypertension or obesity. The number of physicians, mean diabetes-related expenditure per person, quality of healthcare governance, and number of motor vehicles showed no linear relationships to diabetes prevalence.

The comparison of characteristics of the countries with the average diabetes prevalence below, within and above the control limits shows positive linear relationships with the country's hypertension and obesity prevalence (Figure 4).

Crude and Adjusted associations

The results of the univariable and multivariable linear regression analyses to examine the association between country characteristics and diabetes prevalence are shown in Table 2. In the final model, three determinants showed

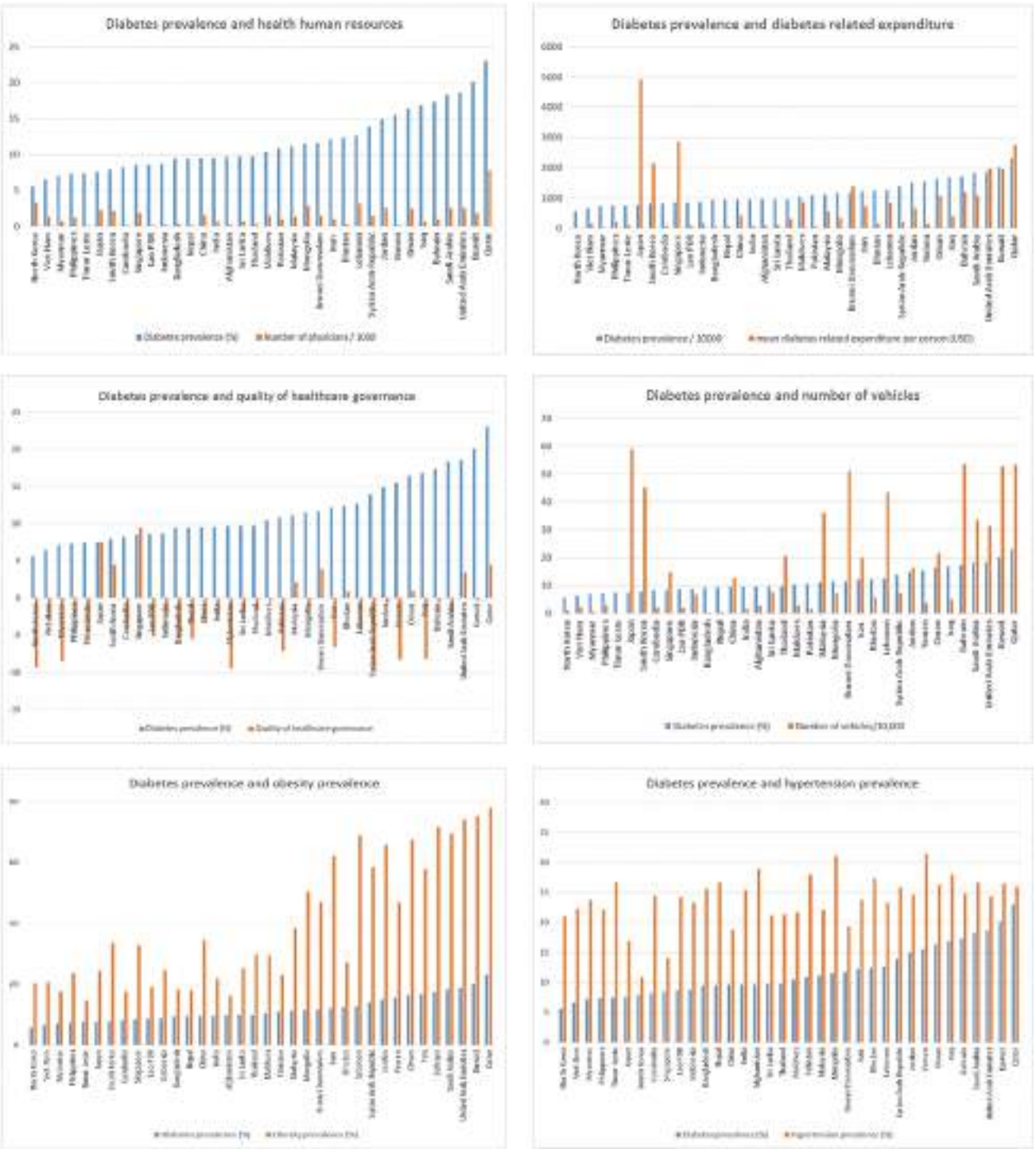

Figure 3. Relationship between country level characteristics and diabetes prevalence in Asia.

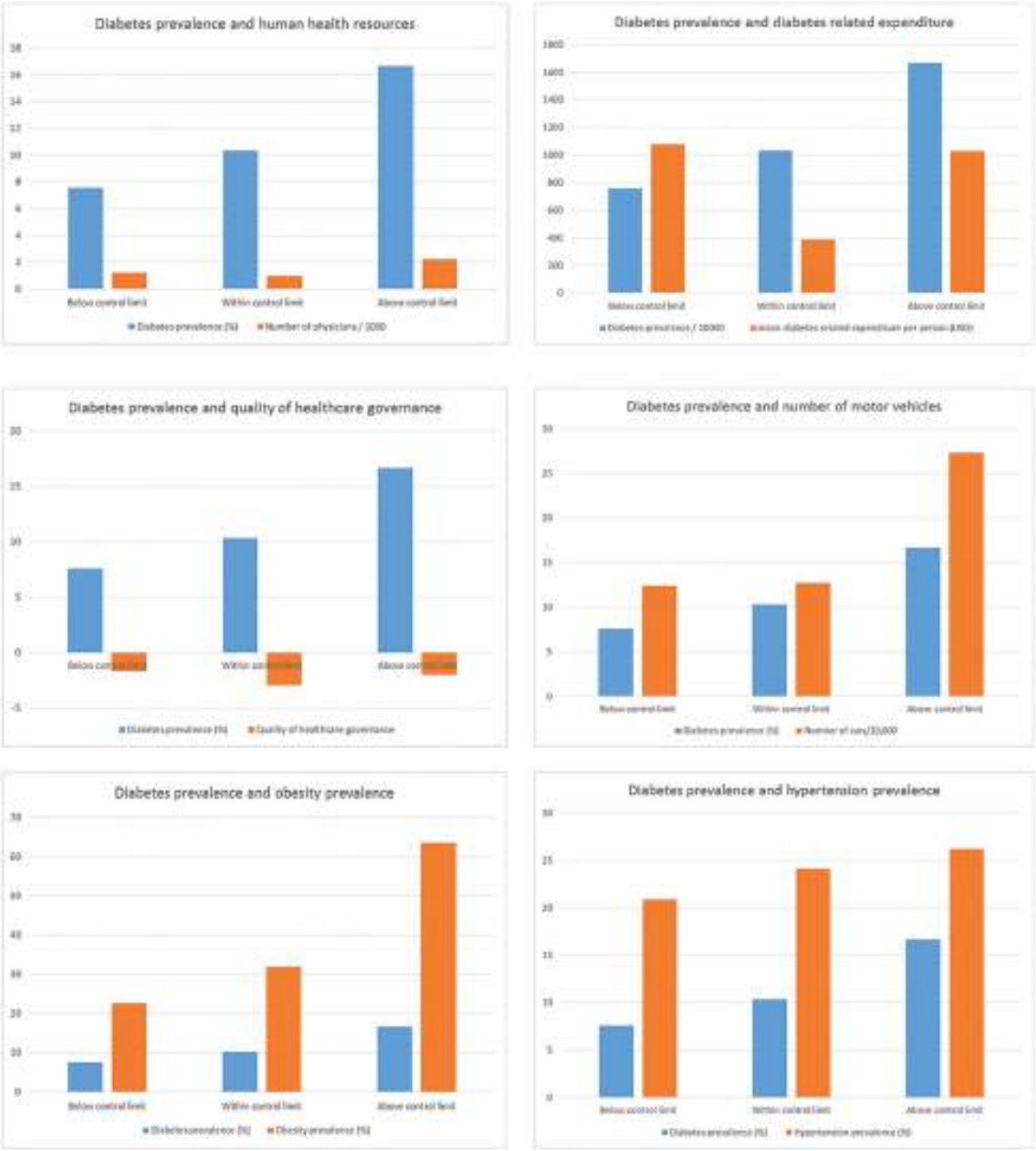

Figure 4. Relationships between country level characteristics and grouped diabetes prevalence (i.e., below control limit, within control limit and above control limit).

Table 2. Associations between Asian country characteristics and diabetes prevalence (n=36)

Country characteristics	Crude OR (95% CI)	Adjusted OR (95% CI)§
Number of physicians (in 1000 population)	1.43 (0.53-2.33)*	###
Mean diabetes related health expenditure per person (USD)†	0.001 (-0.0003; 0.002)	###
Quality of healthcare governance‡	0.15 (-0.16; 0.46)	0.18 (0.04; 0.33)*
Motor vehicles (in 1000 population)	0.01 (0.004; 0.02)*	###
Hypertension prevalence	0.43 (0.11; 0.74)*	0.39 (0.23; 0.55)*
Obesity prevalence	0.18 (0.15; 0.21)*	0.15 (0.13; 0.18)*

† no data available for North Korea
‡ Measured using Worldwide Governance Indicators which capture six key dimensions of governance (Voice & Accountability, Political Stability and Lack of Violence, Government Effectiveness, Regulatory Quality, Rule of Law, and Control of Corruption).
§ Analyzed using multivariable linear regression. Adjusted R-squared= 0.88
* p<0.05
not included in the final model

a significant independent association with diabetes prevalence. Hypertension was the most strongly related to diabetes prevalence. For every percent increase in hypertension prevalence, diabetes prevalence increased by 0.39 percent (95% CI 0.23 to 0.55; $p<0.001$). For every percent increase in obesity prevalence, diabetes prevalence increased by 0.15 percent (95% CI 0.13 to 0.18; $p<0.001$). For every unit increase in the country's quality of healthcare governance, diabetes prevalence increased by 0.18 percent (95% CI 0.04 to 0.32; $p=0.02$). The adjusted R-squared of this model was 0.88, meaning approximately 88% of the variability of diabetes prevalence could be explained by these three determinants.

DISCUSSION

The results of this study show a considerable geographical variation in diabetes prevalence across 36 Asian countries. Countries with the highest diabetes prevalence in Asia are located in the western part of the continent (the Middle East region). Differences in the quality of healthcare governance, hypertension prevalence and obesity prevalence across these countries explain a substantial part of the variation in diabetes prevalence that is observed across Asian countries.

The finding that obesity and hypertension are strongly related to the occurrence of diabetes is in line with associated factors (particularly physical activity, overweight and obesity) that are driving the prevalence of diabetes globally. Across Asian countries, obesity is most common in the Eastern Mediterranean region and lowest in the South-East and East Asia region.[17] Favorable determinants in the eastern part of Asia which might have succeeded in stalling the prevalence of diabetes should be identified. Several studies have reported that sedentary lifestyle and westernized diet,[18] fish and seafood consumption [19], urban exposure [20, 21] and over-dependence on motorized transportation[22] may contribute to the global rise in obesity and diabetes prevalence.

A large population-based cohort study has shown that high normal blood pressure as well as established hypertension are strongly and independently related to the development of type 2 diabetes.[23] Possible underlying mechanisms include endothelial dysfunction which is associated with both elevated blood pressure and insulin resistance which forms the substrate for the development of type 2 diabetes. Second, inflammatory mechanisms associated with hypertension could promote the development of type 2 diabetes.[24] In addition, use of certain blood pressure lowering drugs has been suggested to be related to the occurrence of type 2 diabetes.[25]

With the 4.1 billion people residing in Asia, a single percent increase in hypertension or obesity prevalence may increase the number of people with diabetes in the region by 16 or 6.1 million respectively.

The multivariable analysis suggests that stronger healthcare governance is associated with increased rates of diabetes. A strong health governance at all levels is necessary to ensure that healthcare resources are utilized appropriately to achieve affordable, accessible quality healthcare for all.[11] Typically, when the quality of healthcare governance is good, it is expected to increase the performance of the healthcare system which allows to provide adequate health promotion and prevention of NCDs' risk factors including obesity and hypertension. On the other hand, in the case of chronic diseases such as diabetes, good quality of the healthcare system may lead to earlier and more complete detection of diabetic patients. This may paradoxically even increase the prevalence of diabetes.

Ecologic studies may suffer from what is known as the ecological fallacy.[26] Ecological studies are increasingly rediscovered as powerful tools in the investigation of the population determinants of health, but observations in ecological studies should be interpreted with caution. It should be realized that much of the data utilized in this study were estimated by modeling local data. However, in countries without available local data, estimates were based on modeling using pooled data from countries that were considered similar in geography, ethnicity, and economic development.[17] However, the data have face validity as for example the relationship between obesity and hypertension with diabetes has been well-established. Another limitation of our study is that we only included three of six WHO health systems building blocks as information on other components of the health systems. Other aspects of the management of NCDs such as healthcare delivery, information system, and availability of medical products and technologies may also be relevant but the data are not easily or openly accessible. Diabetes like most NCDs is a chronic disease associated with lifestyle factors. A health system within which each component functions well is necessary for successful detection and management of diabetes.

CONCLUSIONS

This study shows considerable geographical variation in diabetes prevalence across Asian countries. Countries with the highest diabetes prevalence in Asia are located at the western part of the continent (the Middle East region). A substantial part of this variation can be explained by differences in quality of healthcare governance, the prevalence of hypertension and obesity rates. These observations support the view that investments and improvements in healthcare systems provide important opportunities to affect the burden of chronic disease in low and middle income countries, notably by their impact on the occurrence and management of diabetes.

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

Author Disclosure
The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Effectiveness and Safety of Hydroxychloroquine compared to Teneligliptin in uncontrolled T2DM patients as add-on Therapy*

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Abstract

Objectives. Hydroxychloroquine (HCQ) 400 mg is approved by the Drug Controller General of India (DCGI) and recommended by the Research Society for the Study of Diabetes in India (RSSDI) clinical practice recommendations 2017 as add-on therapy after metformin and sulfonylurea in Type 2 Diabetes (T2DM) patients. The aim of this observational study is to compare the efficacy and safety of hydroxychloroquine 400 mg and teneligliptin 20 mg when used as add-on therapy in Indian Type 2 DM patients who were inadequately controlled (HbA1c ≥7.5%) with metformin 1000 mg and glimepiride 2 mg combination.

Methodology. This study is a prospective observational study to be conducted in 2 diabetic centres of Patna city between October 2017 and May 2018 involving 180 patients followed up for 6 months. One group (N=90) of patients received hydroxychloroquine 400 mg + metformin 1000 mg + glimepiride 2 mg, the other group (N=90) received teneligliptin 20 mg + metformin 1000 mg + glimepiride 2 mg. Efficacy was assessed by fasting blood glucose (FBG), post prandial blood glucose (PPBG) and glycated haemoglobin (HbA1c) reduction. Safety was evaluated by the number of hypoglycaemic events and changes in serum creatinine levels. Home based glucose monitoring was used to detect the hypoglycaemic events. Patients who had any type of retinopathy/maculopathy were excluded.

Results. Mean age of entire population was 66±8 years with mean 6±2 years of DM with 102 males. Mean body weight was 71±12 kg. Baseline HbA1c was 8.1±0.3 in the hydroxychloroquine group and 8.2±0.2 in the teneligliptin group.

At 24 weeks there were statistically significant reductions in mean HbA1c in the hydroxychloroquine group (1.1±0.3) as compared to the teneligliptin group (0.82±0.3) (P≤0.001). The mean FBG and PPBG was 169±18 mg/dl and 232±18 mg/dl respectively in hydroxychloroquine group which was reduced to 121±15 mg/dl and 161±19 mg/dl at the end of 24 weeks. In the teneligliptin group, FBG and PPBG was 171±16 mg/dl and 239±21 mg/dl at baseline, which was reduced to 121±15 mg/dl and 161±19 mg/dl respectively in same period of time (P≤0.005). There were 4 incidences of hypoglycaemic events in the hydroxychloroquine group (4.4%) and 6 in the teneligliptin group (6.67%). No patients required medical assistance for hypoglycaemic events. There was no statistically significant change in body weight in both the groups. No marked changes in creatinine levels were found in patients in both the groups.

Conclusion. In conclusion, treatment with hydroxychloroquine 400 mg for 24 weeks reduces glycaemic parameters more aggressively than teneligliptin 20 mg in Indian type 2 diabetes patients.

Key words: hydroxychloroquine, teneligliptin, FBG, PPBG, HbA1c

INTRODUCTION

The incidence of diabetes has increased by multiple folds over the past 40 years in India. Over this time, rapid socioeconomic development and demographic changes, along with increased susceptibility for Indian individuals, have led to the explosive increase in the prevalence of diabetes mellitus in India.[1] The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.

The management of type 2 diabetes mellitus (T2DM) involves lifestyle measures (diet and exercise), oral antidiabetic drugs, and eventually, the use of insulin. Metformin and sulfonylureas (SU) are the most commonly used oral antidiabetic agents. However, SU have a greater tendency to cause hypoglycaemia and weight gain and hence, many patients will eventually need to be shifted to another class of oral antidiabetic agents or insulin therapy.[2] In type 2 diabetic patients, the main pathophysiologic mechanisms of hyperglycaemia involve insulin resistance, impaired insulin secretion and increased hepatic glucose output. Type 2 diabetes is a progressive disease characterized by insulin resistance and diminished insulin secretion.[3] Neither sulfonylureas nor metformin are able to preserve ß-cell function, and many patients

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with type 2 diabetes fail to reach target [glycosylated hemoglobin (HbA1c) <7.0%], despite combined metformin/ sulfonylurea therapy.[4-7] Hence, many patients with type 2 diabetes will eventually require insulin therapy.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, which act in a blood glucose-dependent manner, carries a low risk of hypoglycaemia.[8] In Japan, DPP-4 inhibitors, including teneligliptin (TNL), are the most commonly prescribed antidiabetic drugs,[9] and are suitable for both elderly and dialysis patients.[10] In addition, DPP-4 inhibitors are weight neutral.[11-13]

Hydroxychloroquine (HCQ), a long-standing safe and inexpensive treatment for autoimmune disorders, may theoretically improve glucose tolerance and prevent diabetes. Hydroxychloroquine has a novel mechanism of action, i.e., post receptor inhibition of insulin degradation for reducing blood glucose levels. Reduction in FBG, PPG and HbA1C (0.87-3.3%) is established in various settings.[14-18] Hydroxychloroquine 400 mg is approved by DCGI (Drug Controller General of India) and recommended by RSSDI (Research Society for the Study of Diabetes in India) clinical practice recommendations 2017 as add-on therapy after metformin and sulfonylurea in T2DM patients.

This 24-week open-label, randomized, parallel-group study is to compare the efficacy and safety of hydroxychloroquine 400 mg and teneligliptin 20 mg when used as add-on therapy in Indian Type 2 DM patients who were inadequately controlled (HbA1c ≥7.5%) with metformin 1000 mg and Glimepiride 2 mg combination.

MeTHODOLOgy

This study is a prospective observational study to be conducted in 2 diabetic centres of Patna city in between October 2017 to May 2018 among 180 patients with a 6 month follow up period.

A sample size of 180 subjects, 90 in each arm, is sufficient to detect a clinically important difference of 0.5 between groups in reducing glycaemic level assuming a standard deviation of 1.195 using a two-tailed t-test of difference between means, with 80% power and a 5% level of significance.

Inclusion criteria were (1) weight ≥60 kg,[2] haemoglobin A1c ≥7.5%,[3] treatment with metformin 1000 mg and glimepiride 2 mg for at least 2 weeks prior to the study. Exclusion criteria were[1] type 1 diabetes,[2] severe complications of diabetes, micro or macrovascular, any type of retinopathy/ maculopathy,[3] severe renal and liver dysfunction,[4] severe infections,[5] pregnant or nursing women and those who might be pregnant,[6] alcoholism, and[7] any patients whom the investigators judged to be inappropriate for this study.

Initially, 240 patients were assessed for eligibility, among which 180 patients were selected and continued. There was a 2 weeks run-in period of strict diet control and treatment with metformin 1000 mg and glimepiride 2 mg. All patients were then randomly allotted into two groups. One group (N=90) of patients received hydroxychloroquine 400 mg + metformin 1000 mg + glimepiride 2 mg, other group (N=90) received teneligliptin 20 mg + metformin 1000 mg + glimepiride 2 mg. Efficacy was assessed by FBG, PPBG and HbA1c reduction and safety was evaluated by number of hypoglycaemic events and changes in serum creatinine levels. A blood sugar level below 70 mg/dl is considered as hypoglycaemia and a blood sugar level below 54 mg/dl is considered as sever hypoglycaemia. Home based blood glucose monitoring was used to detect the hypoglycaemic events. Patients who had any type of retinopathy/ maculopathy were excluded.

We performed the current study in accordance with the declaration of Helsinki and the study was carried out after an approval from the ethical committee of the hospital. All subjects were given an explanation of the details of this clinical study and provided written informed consent.

Statistical analysis

The sample size was determined by assuming that add-on treatment drug would improve HbA1c by at least 0.5%, based on a previous study which assessed efficacy of hydroxychloroquine 400 mg and teneligliptin 20 mg in patients with T2DM .[16] It was statistically determined that 90 patients in each group (in account of the potential loss of subjects) were needed to detect a significant difference with at least a power of 80% and statistical significance of 5%. Data was arranged in MS Excel. Student's t test was used to compare difference in mean values between the two groups. Chi-square test was used for categorical variables. Paired t-test has been used for within group analysis. For every outcome variable, results are presented as mean±SD (Standard Deviation), p value <0.05 was considered statistically significant. STATA 12.0 (STATA Corp, Houston, TX, USA) statistical software has been used for data analysis.

ReSULTS

The mean age of the patients was 66±9 and 66±7 years respectively, with mean duration of diabetes of 6±2 years in the HCQ group and mean of 6±3 years in the teneligliptin group. Mean body weight was 70±8 kg and 70±8 kg respectively in HCQ and teneligliptin group. Baseline HbA1c was 8.1±0.3 in the hydroxychloroquine group and 8.2±0.2 in the teneligliptin group. The patient's baseline characteristics was almost similar in both the groups (Table 1).

At 24 weeks there were statistically significant reduction in mean HbA1c in the hydroxychloroquine group (1.1±0.3) as compared to the teneligliptin group (0.82±0.3) (P≤0.001) (Table 1 and Figure 1). The mean FBG and PPBG was 169±18 mg/dl and 232±18 mg/dl respectively in the hydroxychloroquine group which was reduced to 121±15 mg/dl and 161±19 mg/dl at the end of 24 weeks. In the teneligliptin group, FBG and PPBG was 171±16 mg/dl and 239±21 mg/dl which reduced to 121±15 mg/dl and 161±19 mg/dl respectively in same period of time (p≤0.005) (Table 2). Comparisons of change in baseline to 24 weeks between hydroxychloroquine and teneligliptin groups was also statistically significant (≤0.001), which indicates the superiority of hydroxychloroquine in reducing glycaemic parameters.

Table 1. Patient characteristics at the beginning of the study

Characteristic	HCQ group (N=90)	Teneligliptin group (N=90)	p value
Age (years)	66±9	66±7	0.827
Weight (kg)	70±8	72±13	0.253
Gender (male/female)	54/36	47/43	0.531
Duration of diabetes (Years)	6±2	6±3	0.741
Family history of diabetes	69 (77%)	72 (80%)	0.983
HbA1c (%)	8.1±0.3	8.2±0.2	0.137
Fasting blood glucose (mg/dl)	169±18	171±16	0.213
Post Prandial Blood Glucose	232±18	239±21	0.134
Creatinine (mg/dl)	0.85±0.2	0.88±0.1	0.549
Presence of comorbidities			
Hypertension	74 (82%)	76 (84%)	0.437
Dyslipidemia	64 (71%)	61 (68%)	

Table 2. Changes in variables in the two groups after 6 months

Parameters	HCQ group (N=90)				Teneligliptin group (N= 90)				p value
	Baseline	24 Week	Δ Change	p value	Baseline	24 Week	Δ Change	p value	
FBG (mg/dl)	169±18	121±15	-48±17	<0.001	171±16	121±15	-50±15	<0.005	<0.001
PPBG (mg/dl)	232±18	161±19	-71±18	<0.001	239±21	161±19	-78±20	<0.005	<0.001
HbA1c (%)	8.1±0.3	7±0.3	-1.1±0.3	<0.001	8.2±0.2	7.38±0.3	-0.82±0.3	<0.001	<0.001

Table 3. Changes in variables to access safety and tolerability in the two groups after 3 months

Parameters	HCQ group (N=90)				Teneli group (N= 90)				p value
	Baseline	24 weeks	Δ Change	p value	Baseline	24 weeks	Δ Change	p value	
Weight (kg)	70±8	69±6	1±3	0.983	72±13	72±10	0±6	0.961	0.681
Sr. Cr (mg/dl)	0.85±0.2	0.84±0.2	0.01±0.02	0.934	0.88±0.1	0.89±0.1	+0.01±0.01	0.729	0.927

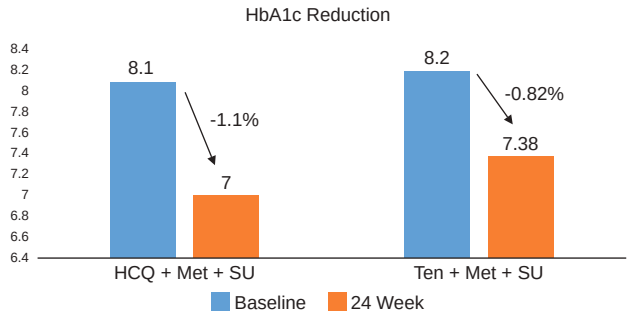

Figure 1. Change in HbA1c in two groups.

There was no statistically significant change in body weight of both the groups (Table 2). No marked changes in creatinine levels were found in patients in both the groups (Table 3).

There were no meaningful differences between groups in incidences of overall clinical adverse experiences or of those assessed as serious, drug-related, or leading to discontinuation. There were 4 incidences of hypoglycaemic events in the hydroxychloroquine group (4.4%) and 6 in the teneligliptin group (6.67%). No patients required medical assistance for hypoglycaemic events. There was no statistically significant change in body weight of both the group. No marked changes in creatinine levels were found in patients in both the groups.

In has been noted that in HCQ treated group there was a significant number of patients who achieved target glycaemic control (≤6.5%). Forty eight percent of patients have achieved HbA1c ≤6.5% in the HCQ treated group, compared to 29% with the teneligliptin treated group.

DISCUSSION

Type 2 diabetes is a major risk factor for developing both microvascular and macrovascular complications.[19] Systemic inflammation is reported to be a strong predictor of atherosclerosis.[20] The primary goal of treatment is to target glycaemic control by maintaining the HbA1c level near 6–7% in order to decrease the incidence of microvascular and macrovascular complications without predisposing patients to hypoglycaemia.[21] If diabetes remains uncontrolled with first-line therapy, medications including insulin, SU, thiazolidinediones (TZDs), gliptins, GLP-1 analogs or gliflozins may be employed.[22] The use of these traditional agents may be limited, however, because of several factors. Biguanides and TZDs improve insulin resistance, but do not address the progressive decline in beta-cell function. SUs can lose their effectiveness over time, while TZDs increase the risk of fracture and cardiac failure. Hence, new treatment options are sought. Hydroxychloroquine has been shown to reduce inflammatory markers in diabetes mellitus.[23, 24]

This study was performed to provide an assessment of the efficacy and tolerability of hydroxychloroquine at doses of 400 mg once daily as add on therapy in patients with type 2 diabetes with inadequate glycaemic control on metformin and sulfonylurea. Treatment with hydroxychloroquine provided clinically meaningful reductions in A1C, FBG, and PPBG compared with teneligliptin.

Overall assessment of safety demonstrated that both hydroxychloroquine and teneligliptin were well tolerated in this observational real-world efficacy and safety assessment study. No meaningful differences were found in the adverse experience profiles between

hydroxychloroquine and teneligliptin treatments. There was a very low incidence of hypoglycaemia with hydroxychloroquine that was similar to teneligliptin. Slightly higher, but not statistically significant, incidences of gastritis, constipation, and diarrhea were reported with hydroxychloroquine, but these events were generally mild or moderate, self-limited, and not temporally related to initiation of study medication. There were two cases of mild pigmentation with hydroxychloroquine therapy, but both patients have continued HCQ.

Pioglitazone and metformin are anti-diabetic drugs, and both are specifically reported to effectively improve insulin resistance.[25] Insulin resistance is also associated with the progression of atherosclerotic disease in a study of a Japanese population.[26] Pioglitazone has anti-atherogenic effects[27] by increasing adiponectin, which is derived from adipose tissue.[28] In a similar way, hydroxychloroquine has also demonstrated its effect on increasing adiponectin levels, and this possibly mediates the favourable effects on glucose metabolism.[29] The role of adiposity on the regulation of the inflammatory response is well known. Adipose tissue itself is a source of CRP and is also a major producer of interleukin-6, which is a key stimulator of CRP secretion. In obesity and type 2 diabetes, adipose tissue contains an increased number of resident macrophages and T cells, which interact closely with adipocytes to modulate the inflammatory response.[30] In this study, the mechanism underlying these anti-inflammatory effects has been attributed to the improvement of insulin resistance and favourable effect on glycaemic parameters were observed with hydroxychloroquine 400 mg.

Teneligliptin and hydroxychloroquine are two anti-diabetic drugs which were recently approved by DCGI (Drug Controller General of India) to treat type 2 diabetes. Both teneligliptin and hydroxychloroquine are available in India at economical prices which can be afforded by a patient who are financially unstable or belong to the middle-class.

The main rationale to conduct this study is to evaluate the efficacy and safety of two newly approved drugs among Indian type 2 diabetes patients. The result clearly demonstrates that hydroxychloroquine can offer tighter glycaemic control than teneligliptin in a real world set up.

Limitations

The present study has certain limitations, including the short duration of treatment and also small sample size. Prospective multicentre clinical trials with longer follow-up of subjects are warranted to confirm the results of the present study and to investigate long-term therapeutic effects of hydroxychloroquine in preventing disease progression in Indian subjects with T2DM.

CONCLUSIONS

Both hydroxychloroquine and teneligliptin-based treatments resulted in significant and improvements in metabolic parameters for different baseline HbA1c levels. Hydroxychloroquine treatment exhibited greater effectiveness in decreasing FBG, PPBG and HbA1c than teneligliptin in a real world setting. In conclusion, treatment with HCQ 400 mg OD for 24 weeks led to statistically significantly greater lowering of the HbA1c than teneligliptin 20 mg in this cohort of Indian Type 2 diabetes patients, although the difference is modest.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

Hyperthyroidism presenting as ST elevation Myocardial Infarction with Normal Coronaries – A Case Report

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Abstract

A 31-year-old male, apparently well, presented with typical chest pain. His ECG showed ST-elevation from V1-V4 and echocardiogram revealed anteroseptal wall hypokinesia with ejection fraction of 45%. Normal coronary arteries were seen on coronary angiogram. A thyroid function test showed elevated free T4 levels with suppressed thyroid stimulating hormone (TSH). Treatment with thionamides and beta-blockers improved symptoms. Upon review 4 months later he was well. Repeat echocardiogram showed good ejection fraction with no hypokinetic area.

Key words: thyrotoxicosis, Acute Myocardial Infarction (AMI), angina, Graves' disease, Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA)

INTRODUCTION

An acute myocardial infarction (AMI) can be triggered by multiple factors like increased oxygen demand, hyperlipidemia, hypercoagulable states, coronary vasospasm and cocaine abuse.[1] Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) is an increasingly recognised entity.[2] It is well known that hyperthyroidism is associated with heart disease, and rarely, can cause AMI.[3] The mechanism for this is not fully understood, although there have been many postulations.[1] We present an interesting case of a young man with newly diagnosed thyrotoxicosis secondary to Graves' disease presenting with AMI and normal coronaries.

CASe

A 31-year-old male with no prior medical illness presented to the Emergency Department with sudden onset of severe left-sided chest pain at rest, associated with palpitations, diaphoresis and dyspnea. Over the preceding month, he had palpitations, heat intolerance and lost 3 kg of weight. He denied use of illicit drugs. He is a smoker and works as a rubber tapper. Family history was non-contributory. On presentation, blood pressure was 133/86 mmHg, with heart rate of 137 beats per minute, regular with good volume. Cardiovascular and respiratory system examination were otherwise unremarkable. He had exophthalmos and a diffuse goitre measuring 9x6 cm, with no bruit. Electrocardiogram (ECG) showed sinus tachycardia with ST elevation in leads V1 to V4 (Figure 1). His complete blood count and renal profile were normal. Creatinine kinase-MB (CK-MB) done within 6 hours of presentation was normal; however, a Troponin level was not measured. Echocardiogram showed hypokinetic anteroseptal wall with ejection fraction 45%, normal valves, chamber sizes and ventricular dimensions with no evidence of left ventricular hypertrophy. He was treated for ST elevation myocardial infarction and thrombolysed with intravenous (IV) Streptokinase. He was subsequently started on aspirin, clopidogrel, fondaparinux, metoprolol and atorvastatin. Despite resolution of pain, there was minimal reduction of ST elevation with poor R wave progression from V2-V5. Coronary angiography done 3 days later showed completely normal coronary vessels with no stenosis or spasm. Thyroid function test (TFT) revealed TSH- <0.005 mIU/L (0.4-4.0) and FT4- 66 pmol/L (7.86-14.4 pmol/L). Neck ultrasound showed a diffusely enlarged thyroid gland with increased vascularity. Burch-Wartofsky score on presentation was 30. A clinical diagnosis of Graves' disease with thyrotoxicosis was made. TSH receptor antibodies were not done as it was not supported by the local lab. He was started on carbimazole 30 mg daily, gradually tapered over 4 months, and propranolol 40 mg twice daily while all other medications were discontinued. Upon review 4 months later, he was well with good effort tolerance. He was clinically and biochemically euthyroid. A repeat electrocardiogram (ECG) showed persistent T-wave inversions in leads V2 to V5 with poor R-wave progression (Figure 2). Repeat echocardiogram showed normal chambers with ejection fraction 53% and no hypokinetic area.

DISCUSSION

Myocardial infarction induced by thyrotoxicosis is rare with an incidence of 1.8% but is showing an upward trend[4] A subset of thyrotoxic patients can experience angina-like chest pain. Thyrotoxic angina is described as the following: (i) the presence of angina at rest, ii) rapidly progressive angina, (iii) cessation of angina with treatment of hyperthyroidism and (iv) the lack of typical clinical

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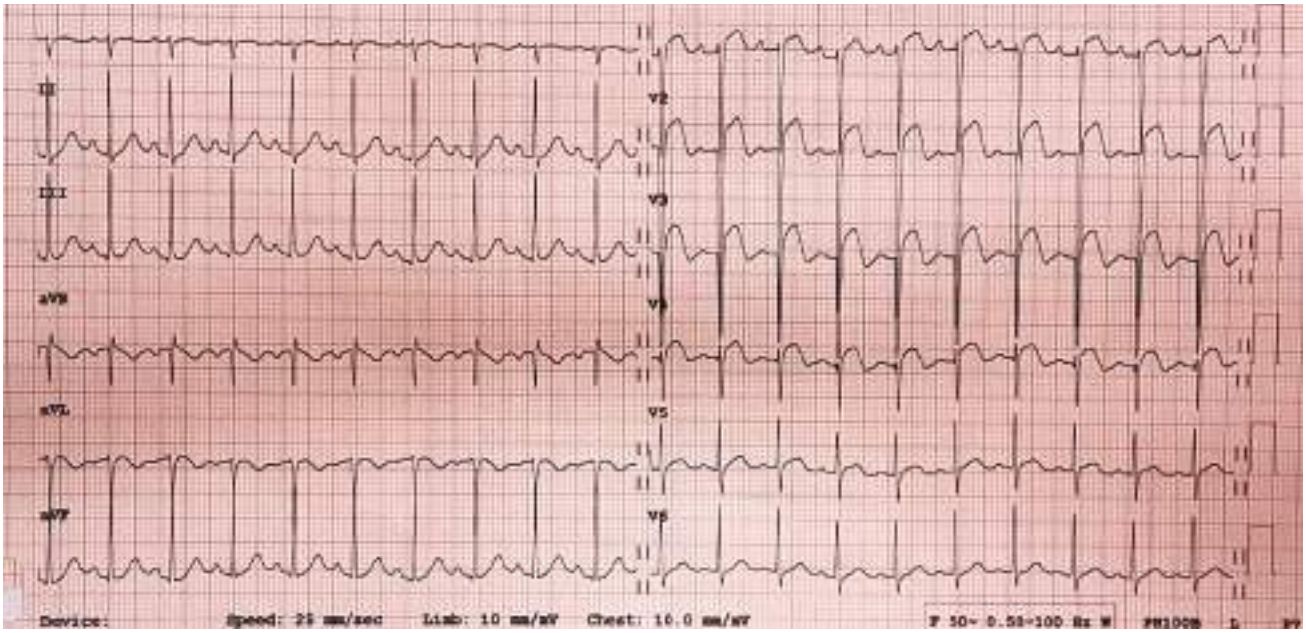

Figure 1. ECG upon arrival (March 2018).

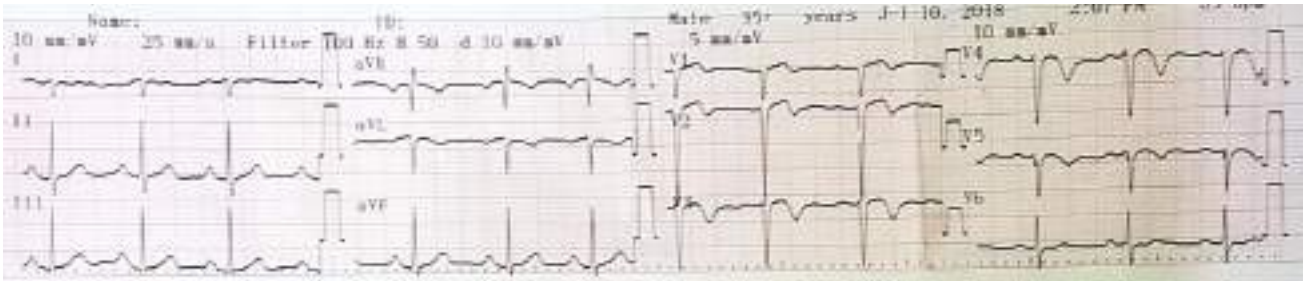

Figure 2. ECG upon review 4 months later (July 2018).

manifestations of hyperthyroidism upon presentation.[5] Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) is being increasingly recognised and has multiple potential underlying mechanisms.[2] The diagnosis of MINOCA requires: (i) clinical documentation of a myocardial infarct, (ii) exclusion of obstructive coronary arteries and (iii) no overt cause for the AMI presentation, such as cardiac trauma.[2]

The exact cause of acute myocardial infarction (AMI) in thyrotoxic patients with normal coronary arteries is unclear. There are several proposed mechanisms such as temporary major coronary artery occlusion, small vessel disease and increased myocardial oxygen demand.[1] There is evidence that thyrotoxicosis is directly associated with the presence of a prothrombotic state.[6] Higher levels of prothrombotic factors and lower levels of anticoagulative factors have been demonstrated among patients with a history of thyroid cancer receiving TSH-suppressive L-thyroxine therapy in comparison the same subjects in hypothyroid phase prior to radioiodine whole-body scanning procedure.[6] Homoncik et al., reported raised concentrations of von-Willibrand factor (vWF) and increased baseline platelet plug formation in patients with thyrotoxicosis which were corrected by treatment of thyrotoxicosis with thionamides.[7] Vasospastic angina secondary to transient coronary vasospasm occurs in up to 20% of hyperthyroid patients, yet is difficult to confirm.[8] Diagnosis is suggested by finding a reversible coronary artery stenosis on coronary angiography. However, the use of coronary angiography as a first diagnostic test in confirming this is not supported as iodine containing contrast agents used have the potential to induce thyrotoxicosis.[3,5] Possible mechanisms of thyrotoxicosis-induced vasospasm include enhanced coronary sensitivity to vasoconstrictors and reduced sensitivity to vasodilators.[3] Coronary vasospasm can also promote atherosclerosis by accelerating the formation of a thrombus and delaying fibrinolysis.[3] In a subgroup of females under 50 years old with documented coronary artery spasm, the incidence of hyperthyroidism was 29% and these subjects, like in our reported case, presented with severe myocardial ischemia.[9] Angina associated with coronary artery spasm among hyperthyroid patients resolve upon being rendered euthyroid.[9]

The documented aetiology of MINOCA include coronary artery spasm, microvascular dysfunction and thrombophilic states.[2] Although thyrotoxicosis has not been documented as a cause for MINOCA, the postulated mechanisms leading to thyrotoxicosis associated AMI is similar to some causes for MINOCA.

Our patient's coronary angiography did not demonstrate coronary vasospasm (Figure 3), possibly because it was done relatively late, after administration of nitrates and resolution of symptoms. Another postulate is that he had a clot occluding his coronary vessel which

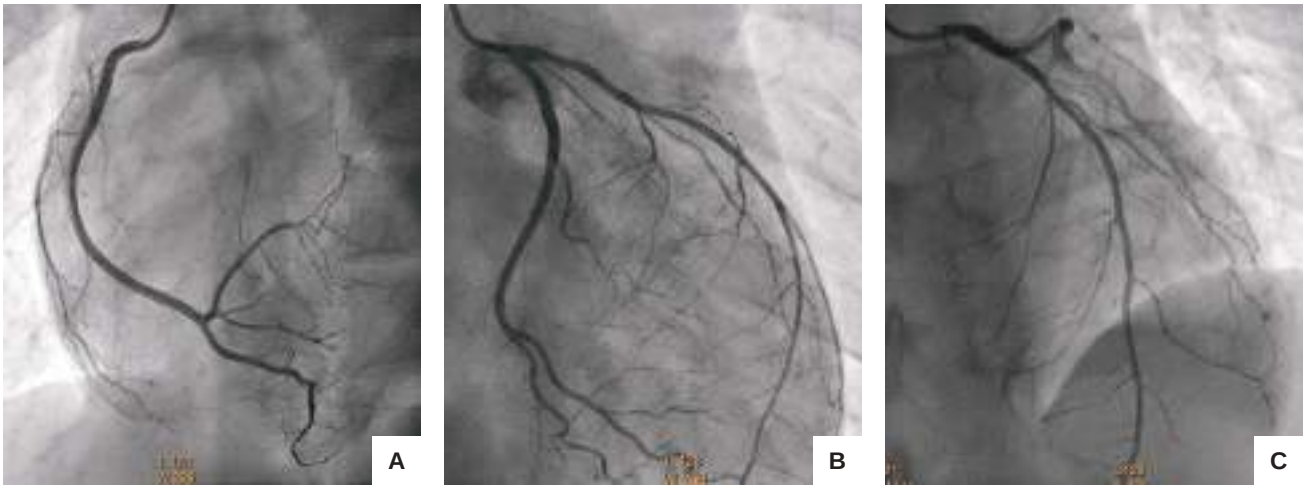

Figure 3. Coronary angiogram (March 2018) showing: **(A)** Left- Normal right coronary artery (RCA); **(B)** middle- Normal left circumflex artery (LCx); **(C)** Right- Normal left anterior descending artery (LAD).

was successfully thrombolysed with IV Streptokinase. Limitations of this case report includes unavailability of a Troponin test that is a more sensitive marker confirming myocardial damage. This could have had added value as his CK-MB value was normal. A cardiac MRI if done early may be able to aid diagnosis in confirming the cause of initial cardiomyopathy. However, this was not done as the service was not readily available at our centre.

CONCLUSION

Our case highlights that thyrotoxicosis can present as ST elevation myocardial infarction and may be a potential cause for MINOCA. A diagnosis of hyperthyroidism should be considered in a patient with little or no risk factors presenting with AMI.

Ethical Consideration
Authors certified that all efforts to secure patient consent have been exhausted to no avail. All information in the case report has been provided without mention of name and every effort has been taken to ensure anonymity. They have sought permission from the Head of the Department of Medicine of Hospital Raja Perempuan Zainab II (HRPZ II) to publish the case.

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

Author Disclosure
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CASE REPORT

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A Case of Retroperitoneal Liposarcoma Mimicking an Adrenocortical Carcinoma

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Abstract

An adrenal mass can be a diagnostic challenge as it is not easy to differentiate the adrenal glands from other adrenal pseudotumours with only radio-imaging. We report a 28-year-old patient who was diagnosed radiologically as an adrenal cortical carcinoma after he presented with abdominal pain and fullness. Biochemically, he demonstrated secondary hyperaldosteronism. Intra-operatively there was a huge mass, inferior to a normal right adrenal, which was histopathologically proven to be a dedifferentiated liposarcoma.

Key words: adrenal pseudotumour, dedifferentiated liposarcoma, histopathology

INTRODUCTION

The investigations of an adrenal mass include assessing its functionality and its potential to be malignant. Often large adrenal tumours (LATs) point to an adrenal cortical carcinoma, especially if patients present with features suggestive of hormonal excess. Preoperative investigations, such as radio-imaging, is integral in establishing a preliminary diagnosis, as well as to provide essential information in formulating a management plan. However, as the adrenals are bordered by various anatomical structures, at times adrenal pseudotumours may be misinterpreted as adrenal pathologies. A large adrenal pseudotumour >4 cm, might be interpreted as an adrenocortical carcinoma if the patient is hypertensive or exhibits hypercortisolism.

CASe

A 28-year-old male who was recently diagnosed as hypertensive for the past 1 year but not on treatment, presented with 1-month history of abdominal pain and fullness associated with nausea, vomiting, and significant weight loss in the preceding three months. Clinical examination revealed blood pressure ranging from 130-140/80-90 mmHg, with presence of a vague mass at the right lumbar region. There were no features suggestive of Cushing's syndrome or phaeochromocytoma. Abdomen ultrasound demonstrated a suprarenal mass measuring 13 cm x 12.5 cm x 14 cm. This was confirmed by a CT scan, which showed a right suprarenal mass, likely of adrenal origin, measuring 14 cm x 12 cm x 15 cm with compression of the inferior vena cava, right renal vein and right renal artery. Biochemically, there was evidence of secondary hyperaldosteronism with raised plasma renin activity and serum aldosterone, possibly due to compression of the renal vasculature by the mass. His serum electrolytes, DHEA-Sulphate, urine catecholamines and steroid profiles were normal (Table 1).

Table 1. Biochemical investigations results of the patient

Parameters	Results	Normal Range
Plasma renin activity	3.08	0.30 – 1.90
Serum aldosterone	325.1	41.71-208.9 pg/ml (supine) 67.40 – 335.1 pg/ml (upright)
DHEA-sulphate	10.44	0.44 – 13.4 µmol/L
24-hour urinary free epinephrine	19	<21 mcg/24 hours
24-hour urinary free norepinephrine	136	15-80 mcg/24 hours
24-hour urinary free dopamine	451	65-400 mcg/24 hours

A month later, he presented with abdominal pain and fullness, suggesting the possibility of an enlarging adrenal mass. Adrenal CT revealed an enlarged mass measuring 15.8 cm x 14.4 cm x 17.9 cm with local infiltration to the right kidney. There were hypodense areas within the tumour, representing areas of necrosis (Figure 1A and 1B).

Due to the rapid progression of the size of the tumour, a right adrenalectomy was performed. However, intraoperatively, a huge peritoneal mass (16 cm x 14 cm x 11cm) was noted inferior to the normal right adrenal gland, with a normal-looking right kidney (i.e., no evidence of tumour invasion). Both the tumour and right adrenal were removed (Figure 2A and 2B).

Histopathological examination of the tumour revealed a FNCLCC (Fédération Nationale des Centres de Lutte Centre Le Cancer) grade 2 dedifferentiated liposarcoma (Figure 3A and 3B). Sections of the tumour show a

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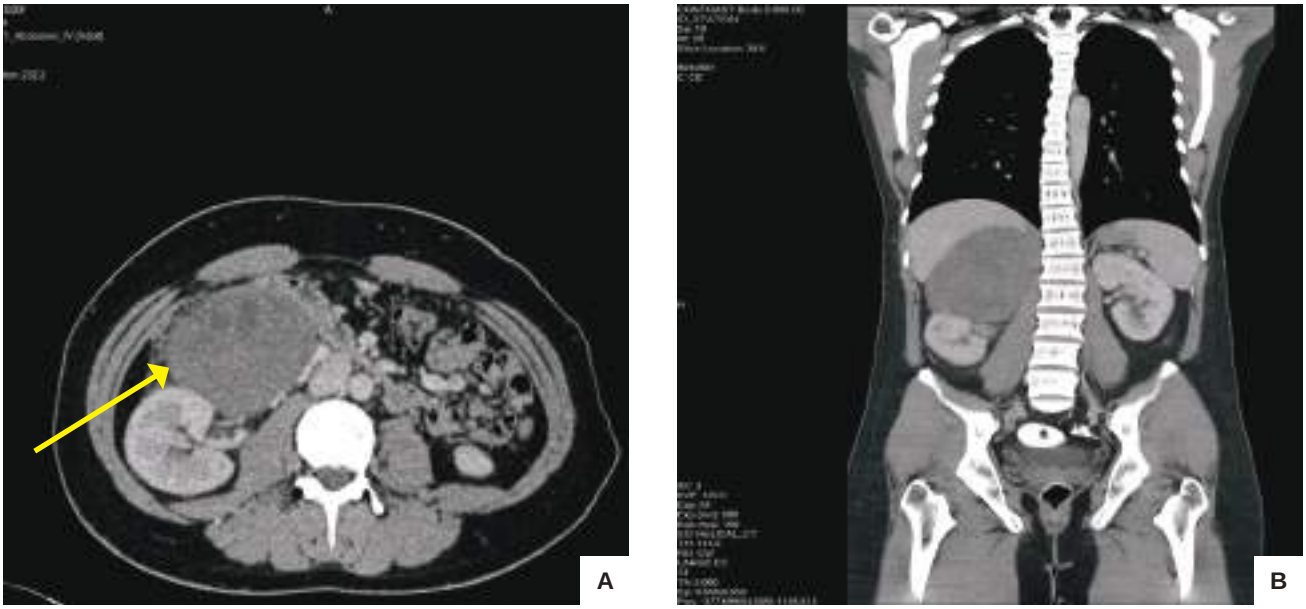

Figure 1. (A) Suprarenal mass with hypodense areas displacing the right kidney postero-inferiorly (CT Abdomen axial view); **(B)** CT Abdomen (coronal view).

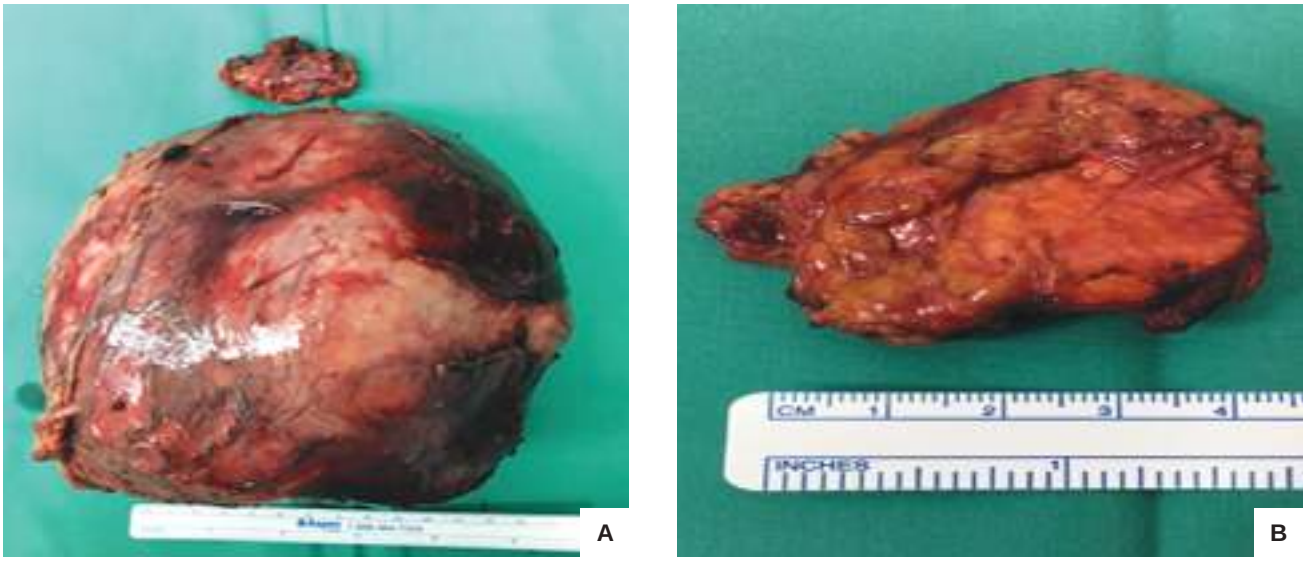

Figure 2. (A) Huge mass measuring 16 cm x 14 cm x 11 cm, weighing 1610.6 g, comparing to the normal right adrenal gland (4.0 cm x 3.5 cm x 1.3 cm); **(B)** Normal right adrenal measuring 4.0 cm x 3.5 cm x 1.3 cm.

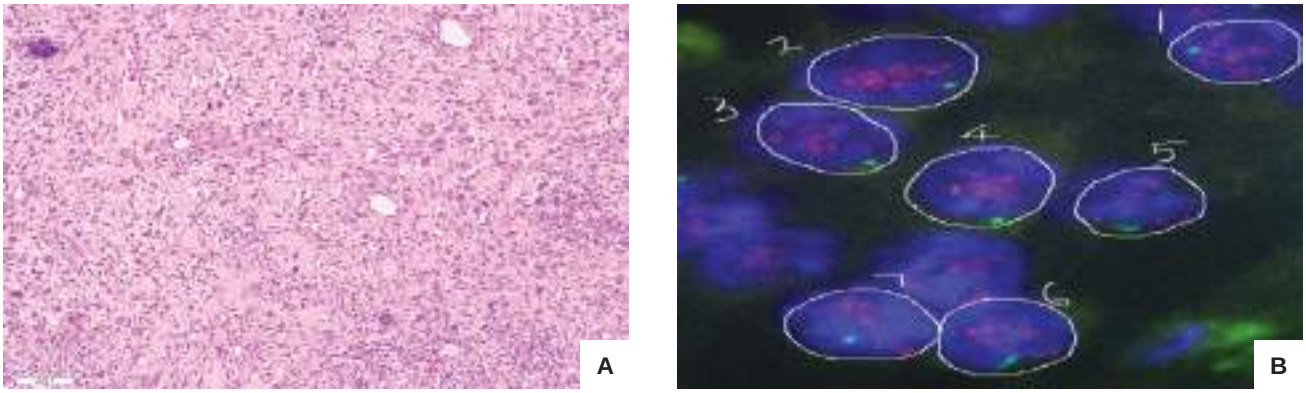

Figure 3. (A) Dedifferentiated area composed of diffuse sheets of pleomorphic cells displaying large irregular nuclei with vesicular chromatin, inconspicuous nucleoli and moderate eosinophilic cytoplasm. Numerous bizarre and multinucleated cells are seen (H&E, x40); **(B)** Fluorescence in situ hybridization (FISH) analysis for MDM2 gene using MDM2/CEP 12 probe (green signal) (VYSIS), shows many nuclei with amplified signals (red signal), i.e., consistent with MDM2 gene amplification.

fairly circumscribed tumour composed of diffuse sheets of pleomorphic cells displaying large irregular nuclei with vesicular chromatin, inconspicuous nucleoli, and moderate pale eosinophilic bubbly cytoplasm with indistinct borders. Numerous bizarre and multinucleated cells are seen with occasional mitoses (mitotic count of 4-5 mitoses/10 hpf). Sheets of atypical adipocytic cells and lipoblasts, were scattered collagen bundles, are seen throughout the high-grade component. There is tumour necrosis (<50%) and presence of a focus of chondroid differentiation.

Fluorescence in-situ hybridization (FISH) analysis for MDM2 gene were performed using Vysis MDM2/CEP 12 probe (Abbott Molecular, USA). There were many nuclei with amplified signals seen, consistent with MDM2 gene amplification.

Sections of the right adrenal gland show normal adrenal tissue. There is a clear demarcation between the tumour and residual adrenal tissue with clear margins from the tumour cells.

Postoperatively, the patient's blood pressure normalised without requiring any anti-hypertensive agents. He was subsequently referred to the oncology team for subsequent management.

DISCUSSION

Large adrenal tumours (LATs), defined as adrenal masses with the size of 6 cm or more, are often rare with the incidence of 8.6% to 38.6%.[1–3] The discovery of a LATs often indicates malignancies unless proven otherwise.[2] A study by Mege et al., in 2014 reported that 64% of their LATs patients had malignancies, with 44%, 27% and 21% of these patients having adrenocortical carcinomas, adrenal metastases and malignant phaeochromocytomas respectively.[4]

However, adrenal pseudotumours can sometimes be misinterpreted as LATS. Kerkhofs et al., identified several adrenal pseudotumours, which include adrenal lymphomas, liposarcomas, schwannomas, ganglioneuromas, haemangioma, angiomyolipoa, epitheliod angiosarcomas, leiomyosarcoma, and adrenal cysts.[5] There have been other reports of an accessory spleen or colon being misinterpreted as pseudotumours. In large tumours >4 cm, it may be difficult or even impossible to differentiate between adrenal tumours and pseudotumours, especially if they show features of hyperfunctional adrenals. If an adrenal mass is highly suspicious to be of malignant origin, then a radical surgical resection is of utmost importance for histopathological confirmation of the pathology.

Retroperitoneal liposarcomas (LPS) can be mistaken for an adrenal mass. Dedifferentiated liposarcomas (DDLPS), commonly found retroperitoneally, are the most frequent subtype, accounting almost 45% of all retroperitoneal soft tissue sarcomas.[6] The DDLPS are believed to often start off with a well-differentiated liposarcomas (WDLPS), usually a non-metastasizing tumour composed of matured adipocytes, which later dedifferentiate and metastasize, evolving into a more aggressive local disease with high metastatic potential.[7]

DDLPS have been proven to exhibit amplification of chromosome 12q13-15, involving the liposarcoma genesis oncogenes MDM2, HMGA2, CDK4.[8,9] The oncogenes MDM2 and CDK4 are responsible for the malignant tumour process.[10] MDM2 is essential for ubiquitination and degradation of the tumour suppressor gene p53; by inhibiting P53, apoptosis is decreased resulting inversely in increased cell survivals.[11,12] CDK4 allows the cell cycle to proceed unregulated by phosphorylating the Rb gene products.[13] On the contrary, amplication of other genes such as ASK1 and JUN results in inactivation of peroxisome proliferator-activated receptor (PPAR) gamma, hence inhibiting adipocytic differentiation in DDPLS.[10]

Histologically, DDLPS is characterized by the abrupt transition from WDLPS to a region of non-lipogenic sarcoma. Under the microscope, the dedifferentiated area appears as atypical non-lipogenic stromal cells with hyperchromatic nuclei scattered in fibrous septa. Ninety percent of DDLS arises de novo, while 10% occurs in recurrence. In recurrent tumours, dedifferentiation occurs in almost 20% of first time recurrences and 44% of second-time local recurrences, implying acquisition of additional aberrations within WDLS as it recurs.[14]

The risk of dedifferentiation is higher in deep-seated tumours, especially in the retroperitoneum and is probably a time-dependent phenomenon.[10]

Often, DDLS can be diagnosed easily through adrenal radio-imaging such as CT or MRI, with features often described as heterogenous, non-lipogenic with a region of abnormal-appearing fat.[15] In cases where histological examination is equivocal, immunohistochemical staining of MDM2 (sensitivity 95%, specificity 81%) and CDK4 (sensitivity 92%, specificity 95%), allows a definitive diagnosis of DDLPS.[16] The detection of MDM2 amplification and overexpression of MDM2 genes (100% of cases) and CDK4 (90% of cases) using FISH or quantitative PCR is highly specific for the diagnosis of DDLS.[10]

Treatment of primary retroperitoneal DDLS is surgery. Systemic therapy with chemotherapy or targeted agents should be considered if a surgical margin is not feasible or there is recurrence. Targeted therapies aimed at MDM2 and CDK4 oncogenes are still in clinical trials.[6] Prognosis is determined by local recurrences (40-60%), especially in the retroperitoneum, despite the low metastatic potential (15-20%). There is an overall rate of 41% of local recurrence. The overall mortality ranges from 28-40% at 5 years.[10,15] Retroperitoneal lesions have 100% local recurrence rate and almost invariably lead to death.

CONCLUSION

Presentation of an adrenal mass can pose a diagnostic challenge as it is difficult to differentiate an adrenal mass from other retroperitoneal masses (lymphomas, liposarcomas, ganglioneuromas, etc.) by using radio-imaging modalities due to the close proximities of various organs in a tight retroperitoneal space. Surgical resection is often necessary if the mass exhibits features suggestive of malignancy while a histopathological examination will provide a definite diagnosis. Retroperitoneal liposarcomas are often aggressive and may present to the endocrinologist

as an adrenocortical carcinoma. Identification of the MDM2 and CDK4 genes via immunohistochemical staining, qualitative PCR and FISH is diagnostic.

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

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CASE REPORT

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Methimazole-Induced Aplastic Anemia with Concomitant Hepatitis in a young Filipina with graves' Disease

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Abstract

A 34-year-old female Filipino with Graves' disease on methimazole came in due to fever, sore throat and jaundice. She was initially diagnosed with methimazole-induced agranulocytosis and drug-induced liver injury. She was treated with intravenous broad-spectrum antibiotic and granulocyte colony stimulating factor. On day 4 of admission, she developed pancytopenia and was managed as methimazole-induced aplastic anemia. She was started on steroid therapy and received 1 unit of packed red blood cell. The jaundice also increased, hence, she was given ursodeoxycholic acid. On day 9 of admission, with the consideration of "lineage steal phenomenon," biopsy was done and eltrombopag was started. Patient was discharged stable at 12th hospital day. This case presents 3 rare life-threatening complications of methimazole namely: agranulocytosis, aplastic anemia and hepatitis.

Key words: anemia, aplastic, agranulocytosis, methimazole, antithyroid agents

INTRODUCTION

Antithyroid drug (ATD) therapy, exemplified by methimazole and propylthiouracil are essential for the treatment of hyperthyroidism, together with surgery and radioactive iodine.[1] However, the use of ATDs is not without risks. Antithyroid drug-induced agranulocytosis, aplastic anemia and hepatotoxicity are uncommon but potentially serious adverse events reported to occur with patients on these agents.[2] The frequency of agranulocytosis is reported to be 0.18-0.55%.[3] To date, at least 36 cases of aplastic anemia (AA) due to antithyroid drugs have been published.[4] Simultaneous occurrence of both aplastic anemia and hepatotoxicity in the same patient is extremely rare.[5] In our review of literature, this is the first case in the Philippines to report a case of methimazole-induced agranulocytosis, aplastic anemia and hepatitis that occurred 28 days after starting ATD .

CASe

A 34-year-old female Filipino, presented with a 1-month history of loose bowel movement, palpitations, anterior neck mass and weight loss. Upon consultation with a family physician, she was noted to have a low TSH level (<0.005 mIU/l; normal: 0.270-4.20) and elevated FT4 (4.87 ng/dl; normal: 0.932-1.71). She was then diagnosed with Graves' disease and she was started on methimazole 20 mg three times a day.

On the 28th day of treatment, she presented with a 3-day history of fever, sore throat and jaundice. She was febrile at 39.2°C and tachycardic at 127 beats per minute, regularly regular; with icteric sclerae and lingual frenulum. The thyroid was enlarged (Grade 2 by WHO criteria), soft, non-tender, no bruit. She had enlarged tonsils with exudates. Complete blood count showed leucopenia at 0.58 x 10^9/L with absolute neutrophil count (ANC) of 58 cells/μL and thrombocytopenia at 126 x 10^9/L. Her total, direct and indirect bilirubin were elevated at 6.90 mg/dL; 4.03 mg/dL; and 2.86 mg/dL respectively. The ALT was slightly elevated at 78 mg/dL and AST was normal at 37 mg/dL. Repeat thyroid function test showed a normal FT4 and TSH.

The patient was managed as a case of methimazole-induced agranulocytosis with concomitant hepatotoxicity and was treated with broad-spectrum antibiotic (cefepime) along with subcutaneous injection of granulocyte colony stimulating factor (G-CSF) 250 mcg/day. Methimazole was withheld.

At day 4 of hospitalization, despite treatment with GCSF, a repeat peripheral blood count demonstrated significant pancytopenia, the working impression was revised to methimazole induced aplastic anemia and transfusion of one unit of PRBC and steroid therapy (prednisone 20 mg tablet twice a day) were initiated. During this time, our patient was also noted to be persistently febrile, and antibiotic was shifted to a broader spectrum (piperacillin tazobactam).

At day 5 of hospitalization, due to progression of leucopenia, GCSF therapy was then increased to 250 mcg two times a day. During this time, there was also progression of jaundice, total bilirubin level was also repeated and showed further increase. She was subsequently started on ursodeoxycholic acid 500 mg/tab twice a day.

Due to persistence of fever and pancytopenia despite 3 days of steroid therapy and piperacillin tazobactam, prednisone was discontinued due to possibility of progression of infection.

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At day 7 of hospitalization, patient was already afebrile with less jaundice but with persistent pancytopenia. Final blood culture and sensitivity results were negative. The antibiotic regimen was then shifted to ciprofloxacin and G-CSF 250 mcg was continued two times a day.

At day 9 of hospitalization, repeat peripheral blood count showed improvement of white blood cell count though hemoglobin and platelet count were persistently low. A "lineage steal phenomenon" was considered, and a bone marrow aspiration biopsy under local anesthesia demonstrated a moderately hypocellular bone marrow for age with non-evident granulocytes and myeloid series than erythroids and megakaryocytes. The G-CSF was then decreased to once a day and patient was started on eltrombopag 25 mg/tab once a day.

Three days into eltrombopag therapy, a repeat peripheral blood count showed improvement in hemoglobin and platelet levels and normalization of white blood cell count. Repeat total bilirubin also showed decreasing trend. Our patient was then discharged with eltrombopag as home medication.

The patient was noted to have a complete recovery of all cell lines after 1 week of eltrombopag therapy. She underwent radioactive iodine therapy 2 weeks after her discharge (Table 1).

DISCUSSION

Agranulocytosis, aplastic anemia and hepatotoxicity are rare, independent and potentially life-threatening adverse effects of antithyroid drugs, including methimazole.[6]

Agranulocytosis is defined as an absolute granulocyte count of less than 500 per microliter. Its frequency is reported to be 0.18-0.55% in those receiving ATDs and 0.35% in those receiving methimazole.[3] Aplastic anemia (AA) is defined as pancytopenia with bone marrow hypocellularity secondary to severe damage to the hematopoietic cell compartment. It is more rare than agranulocytosis and to date; at least 36 cases of aplastic anemia due to antithyroid drugs have been published[2] for carbimazole, 32 for methimazole and 2 for prophythiouracil. Previously, it was reported that agranulocytosis and aplastic anemia developed in patients administered with more than 40 mg/day methimazole and that the usual interval between most cases is within 2 to 3 months after the start of therapy;[7] however, both could develop regardless of the dosage and duration of methimazole administration, even after years of continuous or intermittent treatment.[2] The occurrence is usually sudden with fever and sore throat being the earliest symptoms.[8]

Cholestasis and hepatocellular injury are the 2 types of hepatic injury reported following treatment with methimazole or carbimazole. Cholestasis is more common than hepatocellular injury. Liver toxicity is rare with an estimated frequency of 0.1 to 0.2%.[2] It has been reported in both sexes, at any age, usually developing in patients with doses ≥30 mg daily and presenting anywhere from 3 days to 5 months after methimazole initiation.[2] The typical presenting symptoms are abdominal pain, scleral icterus and dark urine. For our patient, she presented with scleral icterus and dark urine without symptom of abdominal pain.

In this case, our patient was started with 60 mg per day of methimazole, and she presented with fever, sore throat and jaundice 28 days after initiation of methimazole. Her initial peripheral blood count showed leucopenia at 0.58 x 10^9/L with ANC of 58 cells/μL. Her total bilirubin level was elevated. She was managed as methimazole-induced agranulocytosis with concomitant hepatitis.

The pathogenic mechanisms of agranulocytosis and aplastic anemia as a result of the administration of methimazole are unclear; however, direct cytotoxic effects by methimazole or autoimmune humoral reaction against myeloid precursors have been suggested.[9] The contribution of genetics to these immunogenic abnormalities that underlie drug sensitivity has also been shown in several studies in different population such as Hong Kongers, Chinese, Taiwanese, Vietnamese and European Caucasians. Among these population, HLA-B*38:02 is consistently associated

Table 1. Laboratory data of this case during admission

	Day-0	Day-1	Day-3	Day-5	Day-6	Day-7	Day-9	Day-11
Hgb (g/L)	123	105	88	96	102	95	82	87
Ht (%)	36	31	26	28	29	27	24	26
WBC (10^9/L)	0.58	0.76	1.49	0.57	0.88	0.75	3.46	8.81
Neutro (%)	10	4	14	12	4	10	17	60
Lympho (%)	84	84	66	68	88	78	59	35
Monoc (%)	2	8	10	12	7	12	23	5
Eosino (%)	2	4	10	8	1		1	
PLT (10^9/L)	126	117	96	96	70	65	24	32
ANC	58	30.4	209	67.4	35	75	588	5,286

	Day-0	Day-3	Day-5	Day-9
ALT (N: 10-40 mg/dL)	78	31	22	
AST (N: 10-42 mg/dL)	37			
Total Bilirubin (N: 0.2-1.0 mg/dL)	6.90	13.94	19.57	5.76
Direct Bilirubin (N: 0-0.2 mg/dL)	4.03			
Indirect Bilirubin (N: 0.2-0.7 mg/dL)	2.86			
Albumin (N: 3.5-5.5 g/dL)			2.30	
Alk. Phos (N: 44-147 IU/L)			194.12	

with ATD-induced agranulocytosis in Asian population while HLA-B*27:05 is associated with this adverse event in Caucasian population.[10-14]

As all patients with antithyroid drug-induced aplastic anemia have concomitant agranulocytosis, it is probable that these two side effects have common pathogenic mechanisms. For our patient, pancytopenia was preceded by agranulocytosis and occurred thirty one days after the initiation of methimazole.

The underlying mechanism for hepatotoxicity is believed to be idiosyncratic or immunologic. Liver toxicity with methimazole/carbimazole is possibly dose-dependent.[9] Methimazole/carbimazole reactive metabolites like glyoxal cause cytotoxicity of hepatocytes via the formation of reactive oxygen species, lipid peroxidation, and mitochondrial injury.[15] Hepatotoxicity usually resolves in all patients after the ATD is discontinued at variable intervals. For this case, ursodeoxycholic acid was started with consideration of its benefit which is protection against cytotoxicity caused by toxic bile salts, stimulation of hepatobiliary secretion, antioxidant activity, enhancement in glutathione levels, and the inhibition of liver cell apoptosis.[16]

Treatment starts with the identification and immediate discontinuation of the causative agent to prevent further damage. Intravenous broad-spectrum antibiotics are the mainstay of treatment, initiated soon after blood, urine and other samples are cultured. Hospitalization is usually required to monitor development and administration of intravenous antibiotics.[17] For our patient, methimazole was immediately discontinued. Intravenous broad-spectrum antibiotics were initiated soon after blood culture was obtained. Patient was hospitalized and started on G-CSF 250 μg subcutaneously once daily, and subsequently increased to 250 ug twice daily.

The use of granulocyte colony stimulating factor (G-CSF) in ATD-induced agranulocytosis has been shown to reduce the time to hematologic recovery, duration of antibiotic therapy, length of hospitalization and global cost.[18] The prognosis is generally good, with life-threatening infections and multiple organ failure being the most common cause of death.[19] Previous studies have reported a 2-20% mortality rate in antithyroid drug-induced agranulocytosis.[19]

On the 7th day of hospitalization, patient was already afebrile and jaundice was decreasing though pancytopenia persisted. The duration of drug-induced agranulocytosis and aplastic anemia has been reported to range from 4 to 56 days.[18] There is extremely limited information regarding the treatment of pancytopenia. The prognosis of antithyroid drug-induced aplastic anemia is usually related to the degree of bone marrow hypoplasia and blood pancytopenia. Analysis of the 36 published cases, revealed an overall good prognosis, with a survival rate of more than 94%, approximately 90% of patients obtain partial or complete clinical and laboratory recovery within 9 to 35 days.[7] Only 2 antithyroid drug-induced aplastic anemia deaths have been published. Human recombinant colony-stimulating factors were reported to have been used in combination with high-dose glucocorticoid therapy with good result.[7] In cases of severe aplastic anemia, erythrocyte and platelet transfusion is required. Adjuvant therapies such as antithymocite globulin (ATG) in combination with cyclosporine have been used in a patient with methimazole-inducted aplastic anemia.[6]

On the 9th day of hospitalization, absolute granulocyte count improved; however, there was subsequent progression of anemia and thrombocytopenia, hence lineage steal phenomenon / stem cell steal phenomenon was considered. It is a concept that is proposed based on evidence in animals that megakaryocyte, myeloid and erythroid cell lineages share a common progenitor cell; and therefore, an increase in one precursor may lead the pluripotent stem cells to evolve toward one's lineage, resulting in a decreased number of other cell lineage precursors and subsequently, mature cells.[20,21]

The patient was then started on eltrombopag. Eltrombopag is a small-molecule-thrombopoietin (TPO) receptor agonist that interacts with human TPO receptor transmembrane domain of human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. It received FDA breakthrough treatment designation in February 2014 for patients with aplastic anemia for which immunosuppression has not been successful.[22] In 2017, the NIH made eltrombopag a standard of care in aplastic anemia.[23] It has been shown to produce a trilineage hematopoiesis in some patients with aplastic anemia, resulting in increased platelet counts, along with red and white blood cell.[24] In our patient, an improvement in hemoglobin, white blood cell and platelet was noted on day 3 of eltrombopag therapy.

In cases of ATD-induced agranulocytosis and aplastic anemia, surgery or radioactive iodine seems to be an effective alternative treatment option. In fact, radioactive iodine has a success rate of 88.8% after treatment.[8] Intake of other antithyroid drugs such as carbimazole and propylthiouracil may have a cross reaction in 15.2% of patients, and therefore is contraindicated.[3]

This case underscores the importance of timely detection and recognition of these rare but dangerous side effects associated with methimazole, as well as the institution of proper therapeutic management to prevent mortality and morbidity. Physicians prescribing this drug should be aware of these potential complications that can occur at any time irrespective of age, duration of use, and methimazole dose at the first or subsequent exposure. The dose of methimazole should be commensurate with the degree of thyrotoxicosis, and a recommendation for methimazole dosing can be found in the American Thyroid Association guidelines for the management of hyperthyroidism by Ross et al. In this case, with a free T4 of 4.87 ng/dL, a dose of 30 mg a day would be appropriate, rather than 60 mg a day which was prescribed.[25] This is also why patient education at the time of methimazole initiation must not be underestimated and structured programs should be implemented. Patients should be routinely educated about the symptoms associated with these side effects and advised to immediately seek medical attention should they experience such symptoms. For patients who present with neutropenia, the offending agent should be promptly discontinued and all ATDs subsequently avoided.

CONCLUSION

Antithyroid drugs, specifically methimazole, is the first line therapy for hyperthyroidism but its use is not without any risk. Rare and life-threatening complications (<1%) include agranulocytosis, aplastic anemia and hepatitis. These complications usually occur within 2 to 3 months of therapy and they can occur with any dose of methimazole but is more frequent with larger doses (more than 40 mg/day). In this case, the dose of methimazole prescribed to the patient was probably excessive. Immediate discontinuation of the drug should be done once complications are identified. Intravenous broad-spectrum antibiotics are the mainstay of treatment for agranulocytosis. Administration of G-CSF has been shown to reduce time to hematologic recovery, duration of antibiotic therapy, length of hospitalization and cost. Though treatment with eltrombopag for drug-induced aplastic anemia is less clear, it was considered because the patient was refractory to the administration of G-CSF, and it has proven its benefit in this case.

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

Statement of Authorship
All certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

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guillain–Barré Syndrome developing in a patient with graves' Disease

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Abstract

Graves' disease (GD) and Guillain-Barré syndrome (GBS) are both autoimmune disorders and are triggered by interactions between genetic and environmental factors. GBS in patients who suffer from other autoimmune diseases is rarely reported, and the development of atypical GBS with cranial nerve involvement in a patient with GD has never been previously reported. Herein, we report a patient with GD and a rare form of pharyngo-cervico-brachial variety of GBS.

Key words: Graves' disease, Guillain-Barré syndrome, pharyngo–cervico–brachial variety

INTRODUCTION

Graves' disease (GD) is a disorder with three major manifestations: hyperthyroidism with diffuse goitre, ophthalmopathy and dermopathy.[1] The homeostatic mechanism that normally adjusts hormone secretion to meet the needs of peripheral tissue is disrupted due to immune reactivity. Autoantibodies directed to the TSH receptor (TRAb), thyroid peroxidase (TPO), and thyroglobulin (TG) are strongly associated with GD.[2] Among them TRAb is the stimulating antibody. Thus, while the basic cause of Graves' disease is not well understood, an immunoglobulin or a family of immunoglobulins directed against the TSH receptor mediates the thyroid stimulation and is also responsible for the related connective tissue manifestations of GD.

Guillain-Barré syndrome (GBS) is typically characterized by symmetric ascending weakness, predominantly proximal than distal, with hyporeflexia or areflexia without sensory or sphincter involvements. Sometimes cranial nerves and respiratory muscles are also involved. The illness progresses to its nadir within 4 weeks. Cerebrospinal fluid (CFS) study shows "albumino-cytologic dissociation" in 90% of cases.[3] It is an acute inflammatory demyelinating polyneuropathy with evidence of the immune attack directed at peripheral myelin sheath with secondary axon loss.[3] Various atypical forms of GBS have been described,[4] one of which is the pharyngo-cervico-brachial variety which is very rare. This particular variant has not been reported in previous literature in association with GD.

CASe

FB, a 35-year-old Indian female, presented with a gradually enlarging goitre for the past 1 year accompanied by palpitations, tremor and weight loss. She also admitted heat intolerance, increased appetite, sleeplessness and amenorrhea for 4 months. However, she did not complain of any visual disturbance or hoarseness of voice and did not consult any physician for her complaints. With this background, the patient developed sudden onset of dysarthria with nasal intonation of speech and nasal regurgitation of liquids about 2 weeks before presentation. She denied any weakness of limbs and sphincter disturbances. There was no history of visual disturbances, other cranial nerve involvement, headache, vomiting, fever, skin rash or recent vaccination. No history of diurnal variation of symptoms was found.

She looked anxious and restless. She was found to be 146 cm in height, 38 kg in weight and had a regular pulse of 128/min. We also observed fine postural tremor, staring look, lid-lag and lid retraction, although exophthalmos and dermopathy were absent. The thyroid gland was diffusely enlarged (Grade 2), soft to feel with a bruit. Neurological examination revealed bulbar palsy with involvement of 9th and 10th cranial nerves. There was mild weakness of neck flexors (IV/V) and proximal muscles of upper limbs (IV/V). Deep tendon reflexes were normal in lower limbs, but hypo-reflexic in upper limbs.

Investigations revealed Hb of 12.6 gm% TLC 7500/cumm with normal differential counts, fasting plasma glucose 94 (70-99 mg/dl), urea 19 (7 to 20 mg/dl) and creatinine 0.6 (0.6 to 1.2 mg/dL). Her thyroid profile showed T3 2.6 (0.80-1.8 ng/ml), T4 19.2 (4.6-12 ug/dl) and TSH <0.1 (0.45-4.12 mIU/ml), while Tc-99 m scan indicated increased and uniform uptake. Her anti-TSH receptor antibody (TRAb) and Anti-TPO antibody were also strongly positive and suggestive of Graves' disease.

Magnetic Resonance Imaging (MRI) of the brain was normal. Electrophysiological studies showed only ill-persistent "F" waves in upper limbs, suggestive of demyelination of proximal region. Repetitive nerve

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stimulation test (RNST) was normal. CSF study showed protein level of 155mg/dl with normal glucose values and cell count (8 cell/ml- all lymphocytes) – so called "albumino-cytological dissociation". All these findings were suggestive of atypical variety of GBS – the rare "pharyngo- cervico- brachial" variety.

Fortunately, there was no further progression of weakness, dysarthria, nasal intonation of speech and the patient improved over the next 4 weeks without any specific therapy. Her GD was treated with an antithyroid drug. Methimazole was started with 20 mg dose and was followed by thyroid function, blood counts and liver function tests every 2 months. She was scrupulously alerted to stop the medication if there were symptoms suggestive of agranulocytosis or hepatic injury.

She became euthyroid in the next 6 months and the methimazole dose was reduced to a maintenance dose of 5 mg daily. The neurological symptoms were most severe during the initial presentation, progressively improving on follow up and almost complete recovery occurred over next 4 weeks with improvement of thyroid function but before the normalisation of FT4 level. She was not treated with intravenous immunoglobulin (IVIG) as her neurological abnormalities were improving day-by-day, and also because she could not afford the cost of this highly priced therapy.

DISCUSSION

The case presented is characterized by an association between GD and GBS. GD is the major immunologically mediated form of hyperthyroidism and multiple factors contribute to the etiology of GD, including a host of genetic as well as environmental factors. It is a slowly progressive disease that involves the activation and recruitment of TSH receptor-specific T and B cells. This activation eventually results in the production of stimulatory antibodies (TRAb) directed against the TSH receptors on the thyroid follicular cells and stimulate thyroid hormone production.[2] Increased incidence of GD among members of a family indicates that genetic factors might also play an important role. The risk of developing the disease is higher among individuals with a major histocompatibility complex (MHC) class-II haplotype of HLA-B8, HLA-DR3 or with DQA1*0501 haplotype and in contrast, the expression of HLA DR β1*07 appears to confer protection. As with other autoimmune diseases, environmental factors have also been suspected in the etiology of GD. There are a number of potential mechanisms by which an environmental agent could trigger an autoimmune response and molecular mimicry is one of the commonly invoked mechanisms for the induction of autoimmunity. The bacteria, *Y. enterocolitica* has been postulated to play a role in the induction of GD via molecular mimicry.[2] Strongly positive TRAb and TPO antibody in our patient confirms the diagnosis of GD but we could not check HLA type in our medical set-up. She did not have any history (fever, vomiting, diarrhea, etc.) suggestive of recent *Y. enterocolitica* infection.

GBS, an acute inflammatory demyelinating polyneuropathy, is a disorder of the peripheral nervous system. One of the hallmarks of the pathogenesis is a significantly elevated cerebrospinal fluid (CSF) protein level. It was estimated 155 mg/dl in our subject as against 20-40 mg/dl among normal subjects. This elevated CSF protein was not associated with any rise in cell count and 8 cells/ml was well within normal reference range of 0-10 cells/ml. A non-specific rise in total CSF protein concentration is because of protein leakage from blood through the blood-nerve barrier.[5] GBS is thought to be associated with autoimmune response against neuro-specific molecules. Autoantibodies directed against cell adhesion proteins localized at Ranvier's nodes have been suggested as a possible target, but no reliable corresponding autoantibodies have been found. Proteome analysis suggests bacteria and/or virus infections as possible autoimmune triggers as GBS patients are more immunopositive with polyinfections. Recently, it has been suggested that the primary peripheral nervous system damage is being initiated as an innate immunity-associated local inflammation following neurotropic viruses egress, and the autoantibody production is a complementary secondary process.[5] However, we did not find any suggestive history of recent viral or bacterial infection in our subject.

Transient multiple lower cranial nerve palsy, mild neck flexors and proximal upper limb weakness along with ill-persistent "F" waves in upper limbs and albumino–cytologic dissociation suggest atypical variety of GBS – the pharyngo–cervico–brachial variety. There is no single serological marker for this variety of GBS, although sometimes it is associated with Ig anti-ganglioside antibody (anti-GM1 and anti-GT1A).[5] Occasionally this variety overlaps with Miller- Fisher syndrome, where ophthalmoparesis is also seen along with ataxia. Miller-Fisher syndrome is associated with anti GQ1 antibody and the above two antibodies often cross-react with each other.[6]

Although GD and GBS are autoimmune disorders, simultaneous occurrence is a rarity. The exact mechanism of this association is not well understood but the autoimmunity is the leading cause of development of both the diseases. After evaluation of literature, we found 3 possible explanations for simultaneous presentation of GD and GBS (Figure 1). First, the plasma membranes of both thyrocytes and neuronal cells are rich in gangliosides.[7] The gangliosides may cause production of autoantibodies leading to GBS and certain neuropathies. The pathophysiological mechanism in our patient, may be the consequence of an immunological interaction of autoantibodies against thyrocytes and also neuronal cells. Second, circulating form of intercellular adhesion molecule (ICAM) is significantly elevated in certain autoimmune diseases.[8] High serum levels of ICAM- 1 is associated with autoimmune thyroid disease, both GD and Hashimoto's disease.[9] Interleukin -17 and ICAM-1 polymorphisms have significant association with GBS and their enhanced expressions have possible role in GBS development.[10] However, circulating form of ICAM is present in normal persons; and elevated levels in certain immune mediated diseases is not necessarily pathogenic and may be nonspecific markers of immune dysregulation. Third, in the backdrop of susceptible genetic background, environmental factors such as bacteria and/or viruses are often partially accountable for

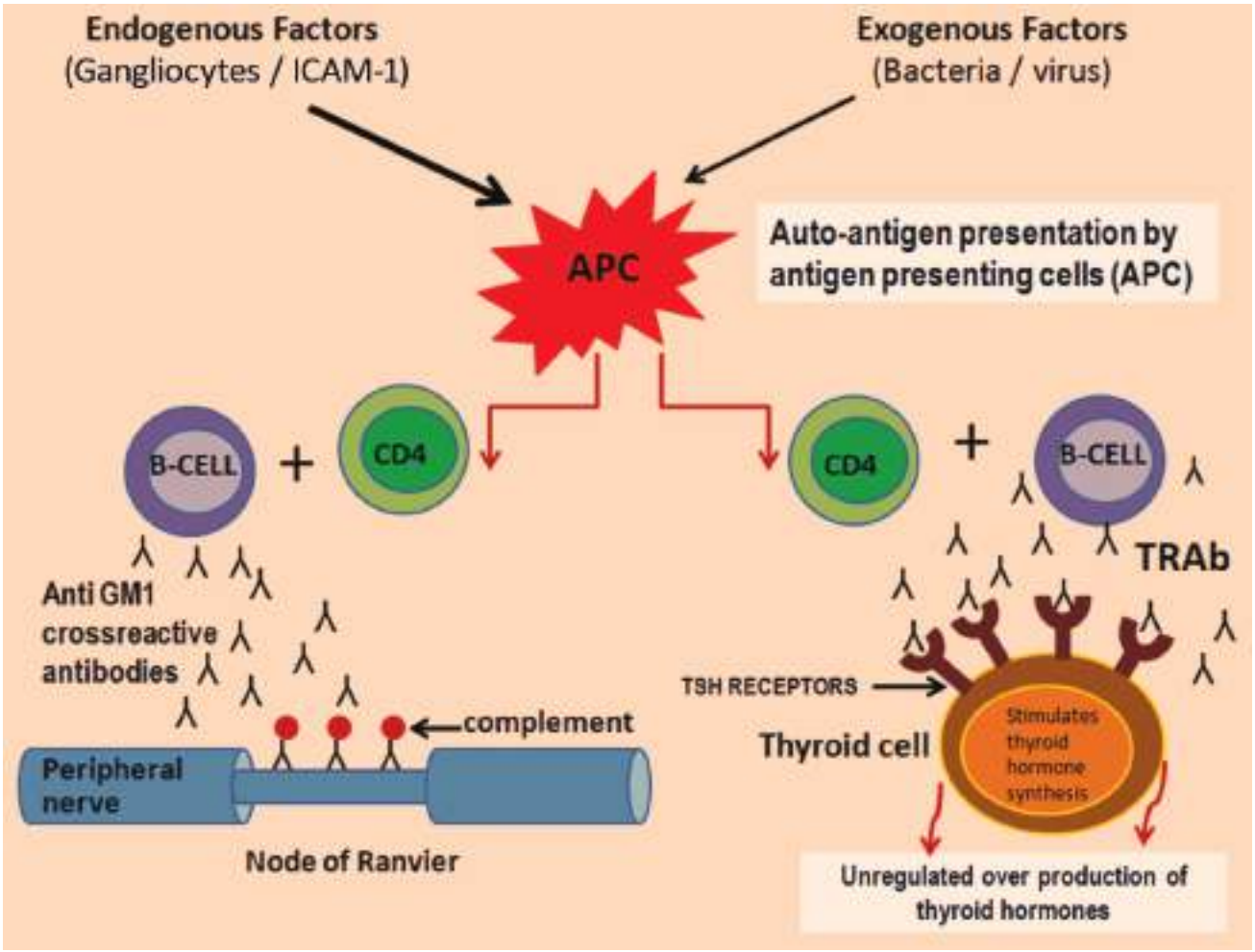

Figure 1. Molecular mechanisms of simultaneous presentation of GD and GBS.

the development of autoimmune diseases. In GD, *Yersinia*-derived T cell superantigens and B cell mitogens might act independently or in combination to activate T cells and/or B cells, resulting in preferential expansion of B cells recognizing cross-reactive epitopes on TSHR and *Yersinia*.[2] On the other hand, *Campylobacter jejuni*, Epstein-Barr virus, Cytomegalovirus, Zika virus and *Mycoplasma pneumoniae* are thought to be able to trigger GBS. The antibodies to these infective agents have an affinity for GM1 and GT1A gangliosides, which are located in the paranodal areas and the nodes of Ranvier in peripheral nerves and molecular mimicry mechanisms and cytokine stimulation are implicated in the pathogenesis of GBS.[5] Though the infective agents involved in the pathogenesis of GD and GBS are different, a common infective aetiology may be a possible explanation for simultaneous occurrence of GD and GBS.

Lastly, it is important to note that with the rise in thyroid hormone levels the frequency and severity of GBS also increases.[11] Further investigation into similar cases could reveal the relationship of these autoimmune diseases. GBS, provoked by antecedent infection (postinfectious GBS), has been reported in patient who suffered from methimazole-induced agranulocytosis with GD.[12] However, our subject was newly diagnosed and was not treated with any antithyroid drug at the time of presentation. In this clinical case, the concomitant presence of 2 rarely associated autoimmune disorders is demonstrated. We know the limitations of the report of our case such as not having measured anti-ganglioside antibodies and serum level of ICAM and the inability to demonstrate a common infective aetiology of the case. Despite this, it is the first case described in literature that associates the pharyngo–cervico–brachial variety of GBS with GD.

CONCLUSION

Association of GBS with one or other autoimmune diseases has been reported rarely. GBS and GD apparently have a common autoimmune pathophysiology. In the clinical case described above, the concomitant presentation of pharyngo–cervico–brachial variety of GBS with GD is a rare clinical situation.

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

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

Author Disclosure
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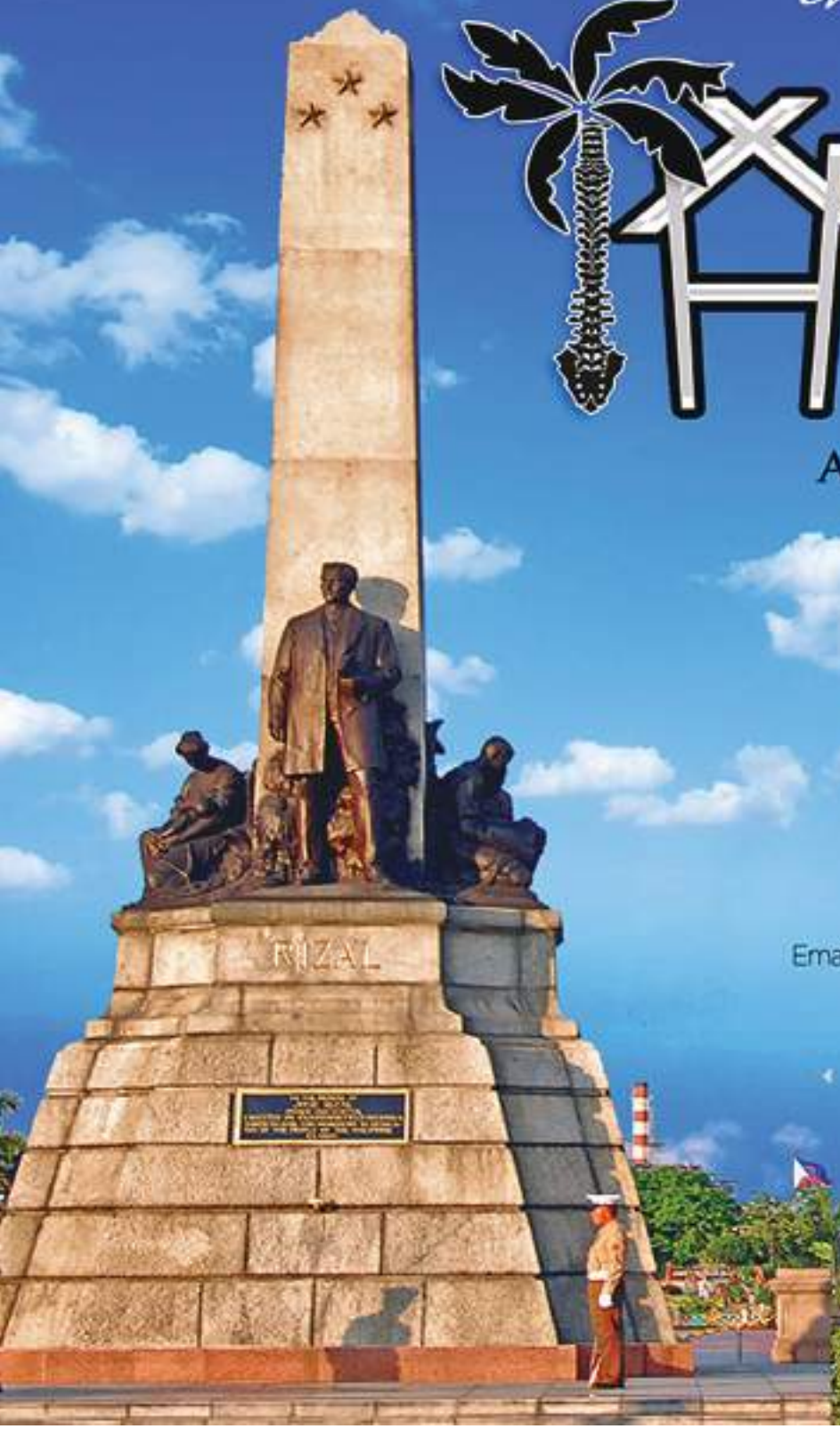

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5. If appropriate, information should be provided on institutional review board/ethics committee approval.
6. Acknowledgments to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

References

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

Journal Article

Padua FR, Paspe MG. Antinuclear antibody in the rheumatic and non-rheumatic diseases among Filipinos. Acta Med Philippina. 1990; 26(2):81-85.

One to Six Authors (Commentary, Online)

Krause RM. The origin of plagues: old and new. Science. 1992;257:1073-1078.

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

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

More than Six Authors

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

Authors Representing a Group

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

Book

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

World Wide Web

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

Tables

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

Figures and Graphs

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

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1. Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as.jpeg or.gif files).
2. For photomicrographs, the stain used (e.g., H&E) and magnification (e.g., X400) should be included in the description.
3. Computer-generated illustrations which are not suited for reproduction should be professionally redrawn or printed on good quality laser printers. Photocopies are not acceptable.
4. All letterings for illustration should be done professionally and should be of adequate size to retain even after size reduction.
5. Figure legends should be numbered sequentially, typed double-spaced on a separate sheet of paper. Give the meaning of all symbols and abbreviations used in the figure.
6. Up to a maximum of five (5) illustrations/photographs are allowed.

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

PROCESS

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

EDITORIAL OFFICE CONTACT INFORMATION:

Journal of the ASEAN Federation of Endocrine Societies
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ARTICLe TyPeS

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

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

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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 g rand 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
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e ditorials
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.

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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.

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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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Abstract	☐ Provide an abstract conforming with the format ☐ Structured for Original Articles: Objective/s, Methodology, Results, Conclusion ☐ Unstructured for Case Reports and Feature Articles
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Journal of the
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Author Form

COMPLETE TITLE OF MANUSCRIPT

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

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- ☐ (3) that we are all responsible for the final approval of the version to be published; AND
- ☐ (4) we all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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Other: Anything not covered under the previous three boxes
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4. Are you the corresponding author? ☐ Yes ☐ No

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

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MEMS ANNUAL CONGRESS

MAC10 2019

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Malaysian Endocrine & Metabolic Society

Pre-Congress: 18 July 2019 | Congress: 19 - 21 July 2019
Hilton & Le Méridien Kuala Lumpur, Malaysia

SIMPLIFYING THE COMPLEXITY OF ENDOCRINOLOGY

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Sengkang General Hospital, Singapore

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Singapore General Hospital, Singapore

CONGRESS HIGHLIGHT

- **Adolescent & Puberty** – Too late or too early? To stop or let it be?
- **Minding Your Pituitary** – Functioning & Non-Functioning Tumours, Hypophysitis
- **Balancing the Adrenal** – Steroid disorders, Adrenal hypertension, CAH
- **Unbreak Your Bones** – Osteoporosis, Metabolic Bone Disease
- **Wings of the Thyroid** – Thyroid nodules, Subclinical disease
- **Combating Obesity** – Nutritional & Therapeutics
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PRE-CONGRESS *Masterclass in Pheochromocytoma, Paraganglioma and Neuroendocrine Tumors*

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MASTERCLASS IN PHEOCHROMOCYTOMA, PARAGANGLIOMA AND NEUROENDOCRINE TUMOURS

18th July 2019, Le Meridien Kuala Lumpur

OBJECTIVE

- To improve the understanding of epidemiology, genetics and the role of various imaging modalities in pheochromocytoma, paraganglioma and neuroendocrine tumours (NETs)
- To provide the latest updates on the investigations and multimodal treatment options for pheochromocytoma, paraganglioma and NETs

WHO SHOULD ATTEND

Specialist / Trainee / General Physician / Paediatrician/ Medical Officer / Allied Health Professionals in the following specialties: Endocrinology, Oncology, Nuclear Medicine, Radiology, Pathology

PROGRAMME / TOPIC

7:45am	Registration
8:15am	**Welcome Speech & Overview of Pheochromocytoma in Malaysia** ***Zanariah Hussein***
8:30am	**The Influence of Genotype on the Phenotype of Patients with Pheochromocytoma & Paraganglioma** ***Leilani Mercado-Asis***
9:10am	**Understanding the Link between Genotype and Molecular Imaging Phenotype in Pheochromocytoma & Paraganglioma** ***Rodney Hicks***
9:50am	**Advances in Molecular-Targeted Therapy in Pheochromocytoma and Paraganglioma: Impact on Treatment Decision - How Do We Choose?** ***Karel Pacak***
10:30am	Tea Break
11:00am	**New Horizon in the Management of Malignant Pheochromocytoma - Where Do We Stand?** ***Karel Pacak***
11:40am	**Difficult Case Discussion** Case 1 : *Pelvic Paraganglioma with bone metastasis* Case 2 : *Metastatic paraganglioma/pheochromocytoma* Case 3 : *Bilateral Pheo and VHL: Can It Be More Complicated?*
1:00pm	Lunch
2:10pm	**Pathology of NET in 2019** ***Looi Lai Meng***
2:40pm	**Clinical, Radiologic and Biologic Markers - Are They Really Useful in Determining Prognosis in GEP NET?** ***Zanariah Hussein***
3:10pm	**The role of endoscopy and EUS in GEP - NET** ***Sharmila A/P Sachithanandan***
3:40pm	Tea Break
4:00pm	**Systemic Therapy in NET: Current Options And Challenges** ***Rodney Hicks***
4:30pm	**Difficult Case Discussion** Case 1 : *Refractory diarrhoea in VIPOMA* Case 2 : *Metastatic Non-functioning NET*
5:10pm	End of Programme

REGISTRATION FEES

CATEGORY	Early Bird Fee (by 30th April 2019)	Standard Fee
MEMS member / Endo Trainee	RM 180	RM 220
Medical Professional	RM 320	RM 360
International delegate	USD 160	USD 180

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1. The ADVANCE Collaborative group. N Eng J Med 2008; 358: 2560-2572. 2. Perkovic V et al. Kidney Int. 2013 Jan. Advance Online Publication. 3. Turnbull FM et al. Diabetologia (2009) 52: 2288-2298. 4. Sawada T et al. Metabolism Clinical and Experimental 57 (2008) 1038-1045.

CONFIGURATION: Diamicron MR 60 mg, modified release tablet containing 60 mg of gliclazide, contains lactose as an excipient. INDICATION: Non-insulin-dependent diabetes (type II) in adults, in association with dietary measures and with exercise, when these measures alone are not sufficient. DOSAGE AND ADMINISTRATION: One half to 2 tablets per day i.e. from 30 to 120 mg taken orally as a single intake at breakfast time, including in elderly patients and those with mild to moderate renal insufficiency with careful patient monitoring. One tablet of Diamicron MR 60 mg is equivalent to 2 tablets of Diamicron MR 30 mg. The bioavailability of Diamicron MR 60 mg enables flexibility of dosing to be achieved. In patients at risk of hypoglycemia, daily starting dose of 30 mg is recommended. Combination with other antidiabetics: Diamicron MR 60 mg can be given in combination with biguanides, alpha-glucosidase inhibitors or insulin (under close medical supervision). CONTRAINDICATIONS: Hypersensitivity to gliclazide or to any of the excipients, other sulfonylureas or sulphonamides, type 1 diabetes, diabetic pre-coma and coma, diabetic ketoacidosis, severe renal or hepatic insufficiency (in these cases the use of insulin is recommended), treatment with miconazole (see interactions section), lactation (see fertility, pregnancy and lactation section). WARNINGS: Hypoglycemia may occur with all sulfonylurea drugs, in cases of accidental overdose, when calorie or glucose intake is deficient, following prolonged or strenuous exercise, and in patients with severe hepatic or renal impairment. Hospitalization and glucose administration for several days may be necessary. Patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels. To be prescribed only in patients with regular food intake. Use with caution in patients with G6PD deficiency. Excipient contains lactose. INTERACTIONS: Risk of hypoglycemia - contraindicated: miconazole; not recommended: phenylbutazone, alcohol; use with caution: other antidiabetic agents, beta-blockers, fluconazole, ACE inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, clarithromycin, NSAIDs. Risk of hyperglycemia - not recommended: danazol; use with caution: chlorpromazine at high doses, glucocorticoids, strontium, salbutamol, terbutaline, Saint John's Wort (hypericum perforatum) preparations. Risk of dysglycemia - use with caution: fluoroquinolones. Potentiation of anticoagulant therapy (eg, warfarin), adjustment of the anticoagulant may be necessary. PREGNANCY AND BREASTFEEDING: Pregnancy: Change to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered. Lactation: Contraindicated. DRIVING & USE OF MACHINES: Possible symptoms of hypoglycemia to be taken into account especially at the beginning of the treatment. UNDESIRABLE EFFECTS: Hypoglycemia, abdominal pain, nausea, vomiting, dyspepsia, diarrhea, constipation. Rare: changes in hematology generally reversible (anemia, leukopenia, thrombocytopenia, granulocytopenia). Raised hepatic enzymes levels (AST, ALT, alkaline phosphatase); hepatitis (isolated reports). If cholestatic jaundice: discontinuation of treatment. Transient mixed disturbances at start of treatment. More rarely rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS). As for other sulfonylureas, observed cases of erythrocytopenia, agranulocytosis, hemolytic anemia, pancytopenia, allergic vasculitis, hyponatremia, elevated liver enzymes, impairment of liver function (cholestasis, jaundice) and hepatitis which led to life-threatening liver failure in isolated cases. OVERDOSE: Possible severe hypoglycemia requiring urgent IV glucose, immediate hospitalization and monitoring. PRESENTATION: Diamicron MR 60 mg is a sulfonylurea reducing blood glucose levels by stimulating insulin secretion from beta cells in the islets of Langerhans, thereby restoring the first peak of insulin secretion and increasing the second phase of insulin secretion in response to a meal or intake of glucose. Independent hemovascular properties. PRESENTATION: Box of 60 tablets of Diamicron MR 60 mg in blister. Store at temperatures not exceeding 30°C. Reach, Drugs, Devices & Cosmetic Act prohibits dispensing without prescription. For suspected adverse drug reaction, report to FDA at www.fda.gov.ph.

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