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Diabetes Clinical Practice Guidelines

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The Journal of the ASEAN Federation of Endocrine Societies (JAFES) is a peer-reviewed, English language, medical and health science journal that is published two times a year by the ASEAN Federation of Endocrine Societies. It shall serve as the endocrine window between the ASEAN region and the world, featuring original papers and publishing key findings from specialists and experts of endocrinology. Its editorial policies are aligned with the policies of the International Committee of Medical Journal Editors (www.icmje.org). Authors may include members and non-members of the AFES.

JAFES welcomes manuscripts on all aspects of endocrinology and metabolism in the form of original articles, review articles, case reports, feature articles (clinical case seminars, clinical practice guidelines and book reviews), editorials, letters to the Editor, brief communications and special announcements.

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Journal of the ASEAN Federation of Endocrine Societies
Unit 1701, 17th Floor, Medical Plaza Ortigas, San Miguel Avenue,
Ortigas Center, Pasig City, Philippines 1605
Editorial Assistant: Amado O. Tandoc III, MD
Telefax number: (+632)6373162
E-mail: JAFES@Asia.com

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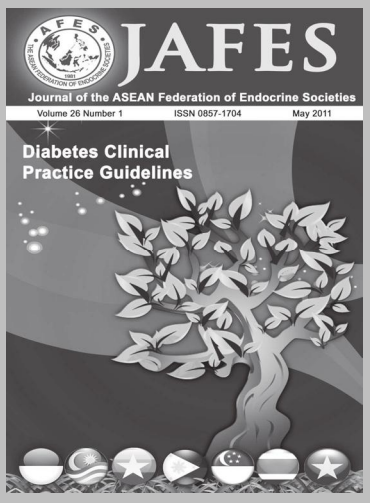

ABOUT THE COVER

Cover Design by: **Mia C. Fojas**
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A tree has always been a symbol of family, a common root spreading out into our rich soil, our cultural heritage that is distinctly Southeast Asian.

The tree trunk is a symbol of strength and unity, and the leaves and fruits stand for our scientific contribution to the world.

A tree is also a symbol of life. Its leaves reaching out into the sun, soaking in the warmth.

We are physician scientists reaching out to the world seeking answers to our questions on how to improve the life of our patients and countrymen.

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VOL. 26 NO. 1 MAY 2011

ASEAN Federation of Endocrine Societies (AFES): 1981-2011
Renewing Our Commitment to the ASEAN Region after 30 Years

Elizabeth Paz-Pacheco and Roberto C. Mirasol

Past Presidents, Philippine Society of Endocrinology and Metabolism (PSEM)

The year 1963 marked a very special time in the Federation's history. PSEM, then in its second year of existence, hosted the 3rd Asia-Oceania Congress of Endocrinology in Manila, where about 200 participants from 11 countries gathered. It was in this meeting that the idea of a Federation of Endocrine Societies in the Region was adopted.[1]

It took several years for this idea to re-emerge in July 1979. The opportunity to meet the various physicians arose during the 14th Singapore-Malaysia Congress of Medicine. Prof. Lim Pin of Singapore convened a meeting of endocrinologists from the ASEAN region on July 22, 1979. Preliminary inquiries had elicited strong interest from all the national endocrine societies to participate in this regional professional and academic enterprise. A management committee was formed to explore the idea. This committee consisted of Dr. Syafril Syabuddin (Indonesia), Prof. Mustaffa Embong (Malaysia), with Prof. Lim Pin (Singapore) as Chairman and Dr. Peter P.B. Yeo (Singapore) as Secretary.[2]

In 1980, Prof. Thanpuying Srichita C. Bunnag of Thailand had the opportunity to meet with her colleagues, Prof. Utoyo Sukaton of Indonesia, Prof. B.E. Mustaffa of Malaysia, Prof. Augusto D. Litonjua of the Philippines and Prof. Peter P.B. Yeo of Singapore on several occasions concerning the effort of attracting more physicians to be interested in the field of Endocrinology. There was, as expected, unanimous agreement and strong endorsement for the formation of an ASEAN association of endocrinologists. At that meeting, Prof. Mustaffa Embong was nominated as Chairman of the Steering Committee while Prof. Augusto D. Litonjua volunteered to undertake the task of drafting a constitution for the Association. They also agreed to organize an ASEAN endocrinology conference on a regular basis to promote exchange of knowledge and closer cooperation among endocrinologists in the region. The conference was to be held every two years. They also unanimously agreed that the first conference would be held in Indonesia in the following year (1981), so that Prof. Utoyo Sukaton—in deference to his being the most senior member in the group—would be elected the first president of the ASEAN Federation of Endocrine Societies (AFES).[3] After a lengthy discussion of benefits and risks, the Association of South East Asian Nations (ASEAN) Federation of Endocrine Societies (AFES) was finally established and officially formed during a meeting at the Merlin Hotel in Kuala Lumpur, Malaysia. The Executive Committee was composed of two representatives from each component endocrine society.[4]

The draft constitution of AFES prepared by Prof. Augusto D. Litonjua was adopted and endorsed by representatives of member societies from the five ASEAN countries.[3] The 1st AFES Convention and signing of the AFES constitution was held in November 27 to 28, 1981, in Jogjakarta, Indonesia, beneath the shadows of the great Asian temple in Borobodur.[5] The theme of the 1st Congress was *ASEAN Diabetes Update '81*.[6] The five component societies that signed the constitution were: The Indonesian Society of Endocrinology headed by Prof. Utoyo Sukaton and Dr. Slamet Suyano; the Malaysian Endocrine and Metabolic Society represented by Assoc. Prof. Dr. Mustaffa Embong; the Philippine Society of Endocrinology and Metabolism represented by Prof. Augusto D. Litonjua; the Endocrine and Metabolic Society of Singapore represented by Assoc. Prof. Dr. Peter P.B. Yeo; and the Endocrine Society of Thailand headed by Prof. S.C. Bunnag and Dr. Yong Uahwatanasakul. It was agreed that the Secretariat of the Federation shall be based in a country determined by the Executive Committee, which was to be reassigned every two years.

The first Executive Committee meeting of the Federation was held in conjunction with the Federation's first scientific meeting. Prof. Utoyo Sukaton of Indonesia was the first President of the AFES and organized the first AFES Congress. The Secretary was Dr. Slamet Suyono. It was the first opportunity among member nations to share and exchange knowledge in the field of Endocrinology. Since then, the AFES has been held every two years, with the host country being rotated according to alphabetical order.[4] The Journal of the ASEAN Federation of Endocrine Societies (JAFES) was subsequently initiated and circulated to all members of each nation's society, with Prof. Mustaffa Embong serving as its initial Editor-in-Chief.

After the very successful inaugural year of the Federation, the seat of office of the Executive Committee was transferred to Thailand. The 2nd AFES Congress and the Pre-Federation Course themed *Diabetes Mellitus in General Medicine* were held on November 26 to 29, 1983, at the Bangkok Palace Hotel as part of the bicentennial celebration of Bangkok, the capital of Thailand. The course was under the auspices of the Joslin Diabetes Center,

THE ASEAN FEDERATION OF ENDOCRINE SOCIETIES CONSTITUTION

1. NAME

The name of the Association shall be the ASEAN (Association of South East Asian Nations) Federation of Endocrine Societies, which consists of:

i. The Indonesian Society of Endocrinology (PERKENI)
ii. Malaysian Endocrine and Metabolic Society, MEMS
iii. Philippine Society of Endocrinology and Metabolic, Incorporated (PSEM)
iv. The Endocrine and Metabolic Society of Singapore (EMSS)
v. The Endocrine Society of Thailand (EST)
vi. Myanmar Society of Endocrinology and Metabolism (MSEM)

2. PLACE OF BUSINESS

The Secretariat shall be based in a country to be determined by the Executive Committee every two years.

3. OBJECTIVE

The objects of the Federation shall be:

a. To promote and coordinate activities among the component endocrine societies.
b. To advance the knowledge and practice medicine in the field of endocrinology and metabolism in the member countries.
c. To promote research in endocrinology and metabolism, emphasizing on regional problems.
d. To organize regular scientific meetings and practical demonstration on subjects relating to endocrinology and metabolism.
e. To acquire, establish, print and publish books, magazines, periodicals, leaflets or other literary or scientific works that the Federation may think desirable for the promotion of its objectives.
f. To receive cash or bonds or share certificates from any person or group so disposed, on behalf of the Federation, and also to borrow or raise money to invest and deal with money so derived for the purpose of enhancing the study and research in endocrine and metabolic diseases.

4. MEMBERSHIP

Membership shall be of two kinds:

a. **Ordinary Members**

Members of component endocrine societies shall automatically be members of the Federation. Their privileges are to attend meetings, receive publications and to be eligible to hold office in the Federation.

b. **Honorary Members**

Distinguished persons who have rendered notable service to the Federation or to the advancement of endocrinology and metabolism, may on the recommendation of a member of the Executive Committee be elected honorary members by a simple majority at the executive committee meeting. They will be permitted to attend all general and scientific meetings organized by the Federation and to receive publications of the Federation.

5. SUBSCRIPTION

There shall be no collection of the subscription fee. The National Society of the country in which the Secretariat is based will bear administrative expenses during that period.

6. EXECUTIVE COMMITTEE

a. The governing body of the Federation shall be the Executive Committee.
b. The Executive Committee shall consist of two members nominated by each of the member societies from whom will be elected a President and an Honorary Secretary.
c. The President shall act as chairman at all committee meetings. In his or her absence, the Executive Committee shall elect an acting chairman.
d. The Honorary Secretary shall keep all records of the Federation and shall be responsible for their correctness. During the period of office, he shall supervise the overall administration of the Federation and will keep minutes of all committee meetings. He or she shall be responsible for all official correspondence related to the Federation.
e. In the interval between biennial meetings, the Executive Committee shall exercise management and discretion in the business and conduct of the affairs of the Federation.
f. Minutes shall be kept of all meetings of the Executive Committee.
g. The quorum at meetings of the Executive Committee shall be at least one representative from each component society.
h. The biennial meeting shall be held at a place and time as determined by the Executive Committee.

7. PROHIBITION

The Federation shall not indulge in any political activity or allow its funds and/or premises to be used for political purposes.

8. INTERPRETATION

In the event of any question or matter arising out of any point which is not expressly provided for in the constitution, the Executive Committee shall have power to use its own discretion and whose decision shall be final and binding on all members of the Federation unless and until countermanded by a resolution of a general meeting.

9. DISSOLUTION

The Federation shall not be dissolved except with the consent of not less than two-thirds of the Executive Committee members expressed in person or by proxy at a meeting convened for this purpose or by postal vote.

1st Announcement

MAC 3

MEMS Annual Congress

19th to 22th May 2011,
KUALA LUMPUR

in conjunction with MEMS 30th Anniversary Celebration & Postgraduate Endocrine Course

Hormonal integrity: from womb to tomb

The Royale Chulan Hotel Kuala Lumpur

30th Anniversary 1981-2011

MEMS
Established 1981
Malaysian Endocrine & Metabolic Society

Pre-Congress Workshops

- Molecular endocrinology for novices
- Grand rounds in pediatric endocrinology
- Imaging and interventional radiology in endocrinology

Congress Highlights

Plenaries	:	The future of islet cell transplantation
		Controversies in treatment of male hypogonadism
		Sexual ambiguity : transition from childhood to adulthood
		Obesity in Malaysia : are we heading for disaster ?
		Growth hormone replacement: Malaysian CPG
Symposia	:	Adrenal and pituitary disorders
		Thyroid disorders
		Calcium and bone metabolism
		Human sexuality & reproductive medicine
		Transition endocrinology
		Life Sciences
Debate	:	Metformin failure ; what should be the next choice ?
Competition	:	Oral & Poster presentations
Social activities	:	30th Anniversary Dinner
MEMS Jogathon	:	"Run TOGETHER for HEALTH"

Secretariat

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The Indonesian Society of Endocrinology's Summary Article of Diabetes Mellitus National Clinical Practice Guidelines

Ahmad Rudianto[1], Pradana Soewondo[2], Sarwono Waspadji[2], Em Yunir[2], Dyah Purnamasari[2]
on behalf of the Indonesian Society of Endocrinologists (ISE)

[1]*Department of Internal Medicine, Faculty of Medicine, Brawijaya University, Malang, Indonesia*
[2]*Division of Endocrinology, Department of Internal Medicine,*
Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Introduction

Various epidemiological studies indicate increased incidence and prevalence rates of type 2 Diabetes Mellitus (DM) worldwide. Research in various areas in Indonesia in the 1980s indicated that the distribution of type 2 diabetes prevalence was 6.1% obtained in Manado. A study in Jakarta, the capital city of Indonesia, reported a steep rise in the prevalence of DM from 1.7% in 1982, 5.7% in 1993 to 12.8% in 2001.

The Central Bureau of Statistics Indonesia (2003) estimated that the number of adult population over 20 years old is approximately 133 million. Based on the prevalence of DM in urban (14.7%) and rural (7.2%) areas , it was predicted that by the year 2003, there shall be 8.2 million and 5.5 million people with DM in urban and rural areas, respectively. A study by the Health Research Association of the Ministry of Health in 2007, showed that the prevalence of DM in urban areas in Indonesia among 15 years old and above was 5.7%. The lowest and highest prevalence rates were 1.7% in Papua and 11.1% in North Maluku and West Kalimantan. The prevalence of impaired glucose tolerance (IGT) ranged from 4.0% in Jambi Province to 21.8% in West Papua Province.

Diabetes mellitus is a chronic disease. In addition to doctors, nurses, nutritionists and other health personnel, the role of patients and family members is very important. Education of patients and their families will provide further understanding about the course of the disease, prevention, complications, and likewise increase their participation in the management of DM.

To provide proper management and reduce the incidence of chronic complications, a standard guideline for managing DM is needed. Completion and periodic revision of standards of care should be ongoing and tailored to the latest scientific advances, to obtain maximum benefits for persons with diabetes.

This guideline contains the fourth revised consensus of "The Management and Prevention of DM in Indonesia." The latest revision was based on the agreement of diabetes experts in Indonesia which was initiated by the PB Perkeni (*Indonesian Society of Endocrinology*, ISE) meeting in Jakarta. The consensus has already been revised several times, from 1998, 2002, 2006 to 2010.

Definition

According to the American Diabetes Association (ADA) 2010, diabetes mellitus is a group of metabolic diseases with characteristic hyperglycemia that occurs because of abnormalities of insulin secretion, insulin resistance or both.

Classification

The classification of DM can be seen in Table 1.

Table 1. Classification of DM

Type 1	Beta cell destruction, usually leading to absolute insulin d eficiency Autoimmune Idiopathic
Type 2	Varied, ranging from dominant insulin resistance accompanied by relative insulin deficiency to predominantly insulin secretory defect with insulin resistance
Other types	Genetic defect of beta cell function Genetic defect of insulin Exocrine pancreatic disease Endocrinopathy Because the drug or chemical substance Infection Rare immunological causes Other genetic syndromes associated with DM
Gestational DM	Any degree of glucose intolerance with onset or first recognition during pregnancy

Diagnosis

Diabetes mellitus is diagnosed by venous blood glucose examination, which uses an enzymatic method. For monitoring the adequacy of treatment, capillary blood glucose (CBG) examination with a glucometer can be used.

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Corresponding author: Dyah Purnamasari, SpPD
Division of Endocrinology, Department of Internal Medicine,
Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital,
Jakarta, Indonesia
E-mail: dyah_p_irawan@yahoo.com

Diagnosis of DM

If there are classic symptoms (polyuria, polyphagia, polydipsia and weight loss with unknown etiology), then random blood glucose ≥200 mg/dL or fasting plasma glucose ≥126 mg/dL are sufficient to diagnose diabetes. If there are no classic symptoms, we need two abnormal blood glucose level results.

Although the oral glucose tolerance test (OGTT) by 75 g glucose load is more sensitive and specific than fasting plasma glucose checks, it has some limitations. It is difficult to perform repeatedly and is very rarely done in practice. If the OGTT results do not meet the diagnosis of diabetes, depending on the results obtained, it can be classified into either impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or the combination of both (IGT-IFG).

1. IGT: IGT is established when the 2 hour post loading plasma glucose ranges from 140 to 199 mg/dL (7.8 to 11.0 mmol/L) and the fasting plasma glucose is < 100 mg/dL (5.6 mmol/L).
2. IFG: IFG is established when the 2 hour post loading plasma glucose is <140 mg/dL (7.8 mmol/L) and the fasting plasma glucose ranges from 100 to 126 mg/dL (5.6 to 6.9 mmol/L).
3. IGT-IFG: IGT-IFG is established when the 2 hour post loading plasma glucose ranges from 140 to 199 mg/dL (7.8 to 11.0 mmol/L) and the fasting plasma glucose ranges from 100 to 126 mg/dL (5.6 to 6.9 mmol/L).

Criteria for diagnosis of DM can be seen in Table 2.

Table 2. Criteria for diagnosis of DM

1. Classic symptoms of DM + random blood glucose ≥200 mg/dL (11.1 mmol/L)
   Random blood glucose is the result of examination at any time in a day regardless of the time of the last meal.
   Or
2. Classic symptoms of DM
   +
   Fasting blood glucose level ≥126 mg/dL (7.0 mmol/L)
   Fasting is defined as the condition when patients do not obtain extra calories for at least 8 hours
   Or
3. The 2 hours post loading plasma glucose ≥200 mg/dL (11.1 mmol/L)
   OGTT is performed according to WHO standard, using 75 g anhydrous glucose load which is dissolved into the water

ADA 2010 had also recommended using A1C ≥ 6.5% as part of diabetes diagnostic criteria. The diagnostic test should be performed using a method certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay.

The preparation of OGTT is based on WHO guidelines (1994) as described below:

- Three days before the examination, the subject may keep his daily eating habits (with enough carbohydrates) and usual physical activities
- Fasting for at least 8 hours (starting the night) before the examination. Plain water may be allowed
- Collect blood sample for fasting blood glucose examination
- Give 75 grams of anhydrous glucose (adults), or 1.75 g/kg (children), dissolved in 250 mL of water and drink within 5 minutes
- Fasting for 2 hours after ingestion of glucose load.
- Collect blood sample for 2 hour post loading blood glucose examination
- During the OGTT procedure, the subject must remain at rest and must not smoke

Screening

Screening is conducted on those who have diabetes risks, but do not show any symptoms of DM. Screening seeks to capture undiagnosed DM or prediabetes so it can be managed earlier and more appropriately.

Mass screening is not recommended considering the costs, which are generally not followed by action plan for those who were found to have abnormal results.

Standard values of random blood glucose and fasting blood glucose for screening and diagnosis of DM can be seen in Table 3.

Table 3. Standard values of random blood glucose and fasting blood glucose for screening and diagnosis of DM (mg/dL)

		Non DM	Uncertain DM	DM
Random blood glucose level (mg/dL)	Venous plasma	<100	100 – 199	≥200
Fasting blood glucose level (mg/dL)	Venous plasma	<100	100 – 125	≥126

Notes: For high-risk groups which show no abnormal results, the test should be done every year. For those aged > 45 years without other risk factors, screening can be done every 3 years. The diagnostic procedure for DM can be seen in Figure 1.

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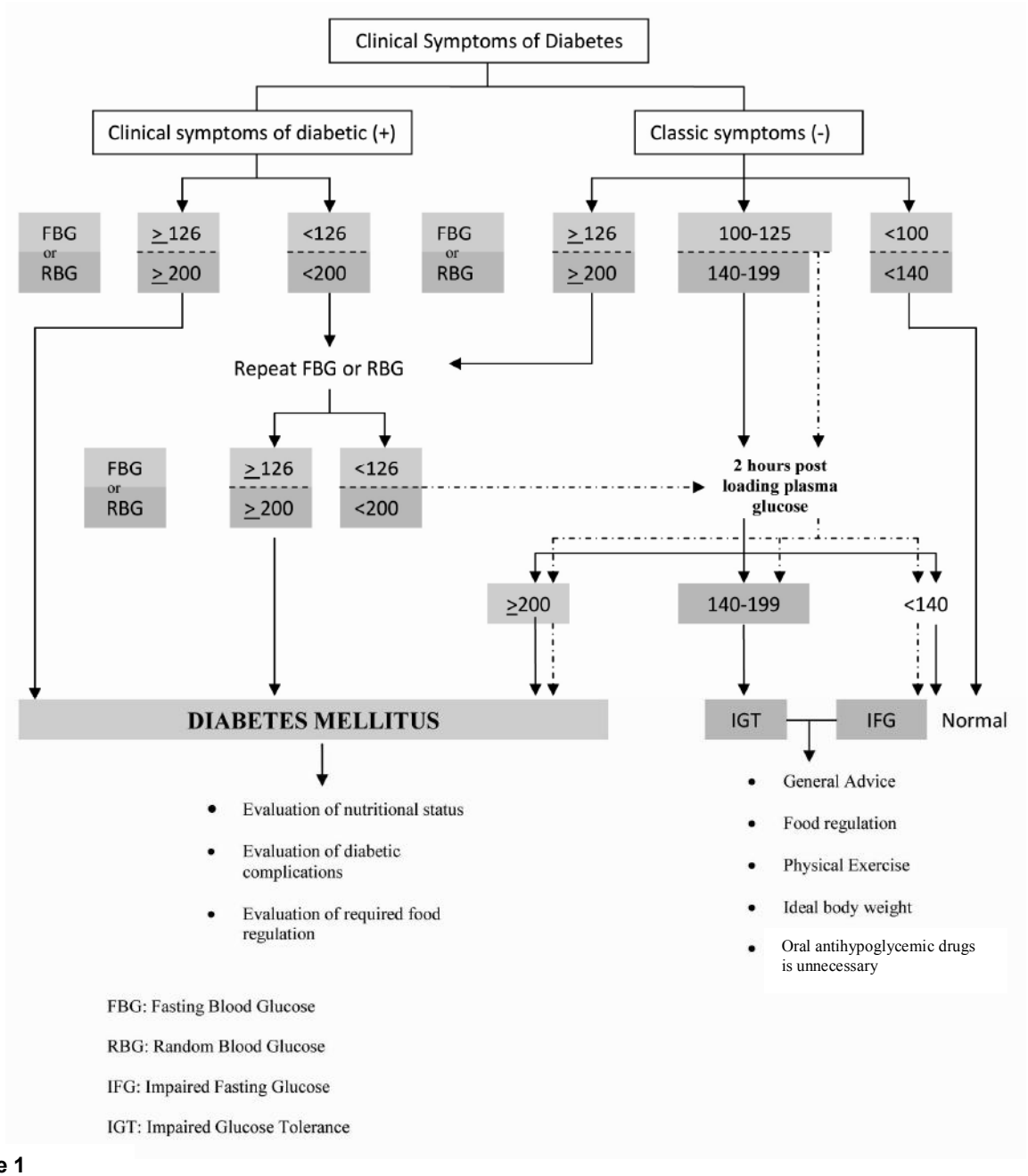

Figure 1

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FEATURE ARTICLE

A Summary of the Malaysian Clinical Practice Guidelines: Management of Type 2 Diabetes Mellitus (4th Edition) 2009

Feisul Idzwan Mustapha[1], Rohana Abdul Ghani[2], Alexander Tan[3],
Wan Mohd Izani Wan Mohamed[4], Winnie Chee Siew Swee[5]
on behalf of the CPG Secretariat, Health Technology Assessment Section,
Medical Development Division, Ministry of Health, Malaysia

[1]*Disease Control Division (NCD Section), Ministry of Health, Malaysia*
[2]*Faculty of Medicine, National University of Malaysia*
[3]*Faculty of Medicine, University of Malaya*
[4]*Faculty of Medicine, University of Science, Malaysia*
[5]*International Medical University, Malaysia*

Introduction

There were three previous Clinical Practice Guidelines (CPG) on the Management of Type 2 Diabetes Mellitus, the 1st edition published in 1992, followed by the 2nd edition (1996) and the 3rd edition (2004). This 4th edition was deemed necessary due to the tremendous body of new evidence that has become available in the last 4 to 5 years that has major impact on the management of Type 2 Diabetes, including new targets for control, new classes of pharmacological agents targeting novel pathways, as well as major outcome studies.

The main objective of this guideline is to provide evidence-based recommendations to assist health care providers in the identification, diagnosis and management of people with type 2 diabetes mellitus (T2DM). It seeks to answer four main clinical questions i.e., (i) How can diabetes be prevented? (ii) How to screen for glucose intolerance? (iii) How is diabetes diagnosed? and (iv) How can people with diabetes be managed?

This guideline is divided into six main sections as follows: Section 1 - Diabetes: The Disease; Section 2 - Screening and Diagnosis; Section 3 - Management of Type 2 Diabetes Mellitus; Section 4 - Metabolic Syndrome; Section 5 - Management of Chronic Complications; and lastly, Section 6 - Prevention of Type 2 Diabetes Mellitus. In addition, the appendices contain the following information (i) carbohydrate content of common Malaysian foods; (ii) glycaemic index of foods; (iii) examples of physical activity; (iv) food exchange list; (v) the 5-item version of the International Index of Erectile Function; (vi) dosage of anti-diabetic agents in renal failure; and lastly (vii) clinical monitoring protocol.

Guideline Development

In Malaysia, the development of clinical practice guidelines is coordinated by the CPG Secretariat, Health Technology Assessment Section, Medical Development Division, Ministry of Health (MOH). Malaysia already has in place standard operating procedures (SOPs) for the development of new CPGs or the revision of existing CPGs. For this guideline, the Guideline Development Task Force was formed in 2008, consisting of endocrinologists, a nephrologist, an ophthalmologist, two family medicine specialists, a general physician, a neurologist, a paediatric endocrinologist, two public health specialists, a dietician and a diabetic nurse educator.

The clinical questions were divided into major subgroups and members of the CPG Task Force were assigned individual topics within these subgroups. Literature search was carried out on PUBMED, Medline, Cochrane Databases of Systemic Reviews, and via the OVID search engine. References were also made on existing guidelines on the management of Type 2 diabetes, including American Diabetes Association (ADA) Position Statement on Standards of Medical Care in Diabetes 2008; American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus 2007; International Diabetes Federation (IDF) Global Guideline for Type 2 Diabetes 2005; American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Management of Hyperglycaemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy 2006; Malaysian CPG on Management of Obesity 2004; Canadian Clinical Practice Guidelines 2003; and Medical Nutrition Therapy Guidelines for Type 2 Diabetes, Malaysian Dietitian Association 2005.

All literature retrieved were critically appraised, presented and discussed during group meetings. The articles were graded using the criteria used by the United States/Canadian Preventive Services Task Force, while the grading of recommendation in this guideline was modified from the Scottish Intercollegiate Guidelines

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Corresponding author: Feisul Idzwan Mustapha, MD
Disease Control Division (NCD Section), Ministry of Health, Malaysia,
Level 6, Block E10, Parcel E, 62590 Putrajaya, Malaysia
Email: dr.feisul@moh.gov.my

Network (SIGN). All statements and recommendations formulated were agreed by the CPG Task Force members. Where the evidence was insufficient, the recommendations were derived by group consensus.

The draft guideline was submitted to external reviewers consisting of senior consultants of various relevant specialties. In addition, the draft guideline was also posted on the MOH website for comments and feedback. Finally in May 2009, the final guideline received the approval of the Health Technology Assessment and Clinical Practice Guidelines Council, MOH. It was officially launched by the Director General of Health Malaysia in Putrajaya, Malaysia in August 2009.

Screening and Diagnosis

The guideline recommendations on screening are divided into four main categories: (i) for symptomatic individuals; (ii) asymptomatic adults; (iii) pregnant women; and (iv) children and adolescents. The indications for screening are consistent with current international guidelines and were mostly adapted from ADA recommendations.[1] One major exception is the age cut-off point of 30 years for screening in the general population. The decision was based on the results of the Third National Health and Morbidity Survey (NMHS III) 2006,[2] which showed a sharp increase in age-specific prevalence after the age of 30 years. (Figure 1)

The screening algorithm for symptomatic individuals is shown in Figure 2, while for asymptomatic individuals in Figure 3. Screening for diabetes using fasting plasma glucose (FPG) should be performed annually in those with risk factors and those ≥30 years. For children and adolescents at risk of developing diabetes, screening every 2 years should be initiated at 10 years old or at onset of puberty if puberty occurs at a younger age. In addition, more frequent or earlier testing with either a FPG or 2-hour plasma glucose in a 75g oral glucose tolerance test (OGTT) should be considered in people with additional risk factors for diabetes. For diagnosis using OGTT, Malaysia used 6.1 mmol/L as the cut-off point at 0-hour, instead of ADA's 5.6 mmol/L (Table 1), consistent with IDF recommendations.[3]

Management of Type 2 Diabetes Mellitus

The CPG Task Force has created a unique treatment algorithm for Malaysia for the management of T2DM in relation to diagnosis and glycaemic targets. (Figure 4) The initial treatment regime is determined by the HbA_{1c} level at diagnosis. However, taking into account that the coverage of HbA_{1c} testing in Malaysia is not universal, particularly within the public health sector where over 70% of diabetes patients are on active follow-up, the CPG Task Force also included the corresponding fasting plasma glucose levels as well. The treatment targets are modified from the IDF Western Pacific Region (IDF-WPR) Type 2 Diabetes Practical Targets and Treatment as shown in Table 2.[3] In particular, the CPG Task Force has adopted HbA_{1c} of <6.5% as optimum glycaemic control**.** Targets for control are applicable for all age groups. However, in patients with co-morbidities or elderly patients, targets should be individualised.

Table 1. Values for Oral Glucose Tolerance Test (OGTT)

OGTT Plasma Glucose Values (mmol/L)		
Category	**0-hour**	**2-hour**
Normal	< 6.1*	< 7.8
Impaired Fasting Glucose	6.1* – 6.9	-
Impaire Glucose Tolerance	-	7.8 – 11.0
Diabetes Mellitus	≥ 7.0	≥ 11.1

** ADA uses 5.6 mmol/L*

Table 2. Treatment Targets

	Levels
Glycaemic Control*	
Fasting	4.4 – 6.1 mmol/L
Non-fasting	4.4 – 8.0 mmol/L
HbA_{1c}	<6.5 %
Lipids	
Triglycerides	≤1.7 mmol/L
HDL cholesterol	≥1.1 mmol/L
LDL cholesterol	≤2.6 mmol/L[#]
Exercise	150 mins/week
Blood Pressure	
Normal Renal Function	≤130/80 mmHg[§]
Renal Impairment/Gross Proteinuria	≤125/75 mmHg

** Glycaemic target should be individualised to minimize risk of hypoglycaemia.*
[#] In Individuals with overt CVD, LDL cholesterol target is <1.8 mmol/L
[§] In children and adolescents, blood pressure should be <95th percentile for age and sex

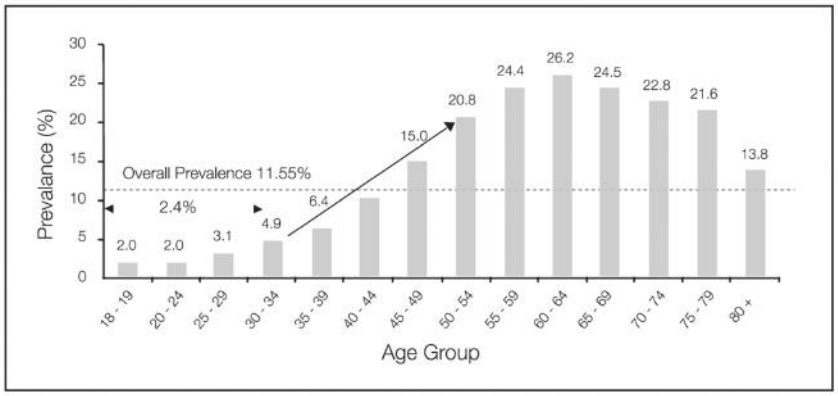

Figure 1. Prevalence of diabetes in Malaysia by age group, 2006

All T2DM patients are started on pharmacological treatment. As first-line therapy, metformin is the preferred choice; however other oral anti-diabetic (OAD) agents are acceptable alternatives. The algorithm also specifically states that sulphonylureas should preferably not be used as first-line. Second-line therapy after metformin is open to all classes of drugs. The CPG included references to five classes of OAD which are (i) α-glucosidase inhibitors; (ii) biguanides; (iii) dipeptidyl peptidase-4 inhibitors; (iv) insulin secretagogues; and (v) thiazolidinediones. When indicated, start with a minimal dose of OAD agent, while re-emphasising diet and physical activity. An appropriate duration of time (2 to 16 weeks, depending on the OAD agent used) between increments are given to allow achievement of steady state blood glucose control.

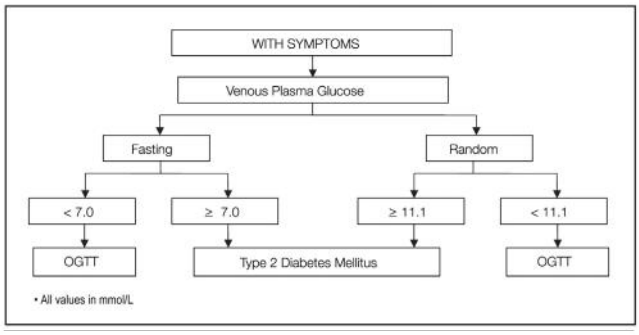

Figure 2. Screening algorithm for symptomatic individuals

Insulin may be used as initial therapy in T2DM particularly in marked hyperglycaemia or if targets have not been reached despite optimal OAD therapy. The CPG recommends starting with either pre-bed intermediate-acting, or pre-bed long-acting insulin or pre-dinner premixed insulin. The 'fix the fasting first' principle is applied in optimising the insulin dose. In children and adolescents, long-acting or intermediate-acting insulin may be added at a dose of 0.5u/kg at bed-time. In addition, short-term insulin therapy should be considered in (i) acute illness, surgery, stress and emergencies; (ii) pregnancy; (iii) breast-feeding; and (iv) severe metabolic decompensation. Upon diagnosis, all patients are advised on lifestyle modification, medication and patient education to encourage self-care. It is recommended that all individuals with diabetes receive diet counseling by a dietitian. Diet counseling should be individualised according to nutrient needs, severity of disease, cultural preferences and willingness to change. The primary strategy recommended is monitoring of carbohydrate intake by carbohydrate exchanges. Total carbohydrate intake should be consistent and evenly distributed throughout the day with regular meal timings and synchronised with medication time actions. Glycemic index (GI) may be used to guide food choices while keeping to calories and carbohydrate prescription. Excessive intake of sucrose is discouraged as it may lead to weight gain and sucrose intake must be counted as part of the total carbohydrate allowance for the day. Artificial sweeteners such as aspartame are allowed. Other dietary recommendations include reducing saturated fat and cholesterol intake and limiting sodium intake.[4]

For physical activity, it is recommended that individuals should exercise 5 days a week and brisk walking is recommended for all. The duration of exercise should be at least 150 mins/week of moderate intensity activities. For overweight and obese individuals, physical activity should gradually be increased to 60 to 90 minutes per day for long term weight loss. Any increase in daily energy expenditure such as gardening, walking up stairs, or washing the car is beneficial.

Management of T2DM in Pregnancy

The recommendations for this section are mostly adapted from the National Institute for Health and Clinical Excellence (NICE), Diabetes in Pregnancy.[5] The CPG emphasises on pre-pregnancy euglycaemia with early referral to physician or endocrinologist, counselling and target HbA_{1c}<6.5% with insulin therapy if necessary. The

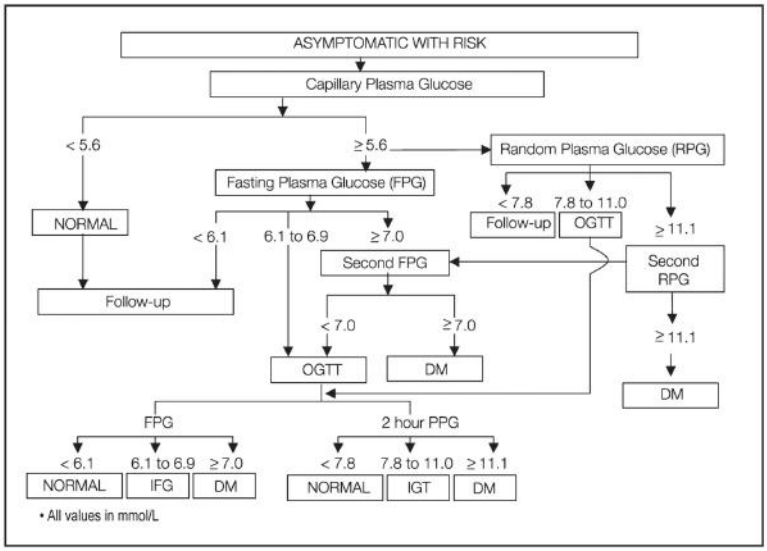

Figure 3. Screening algorithm for asymptomatic individuals

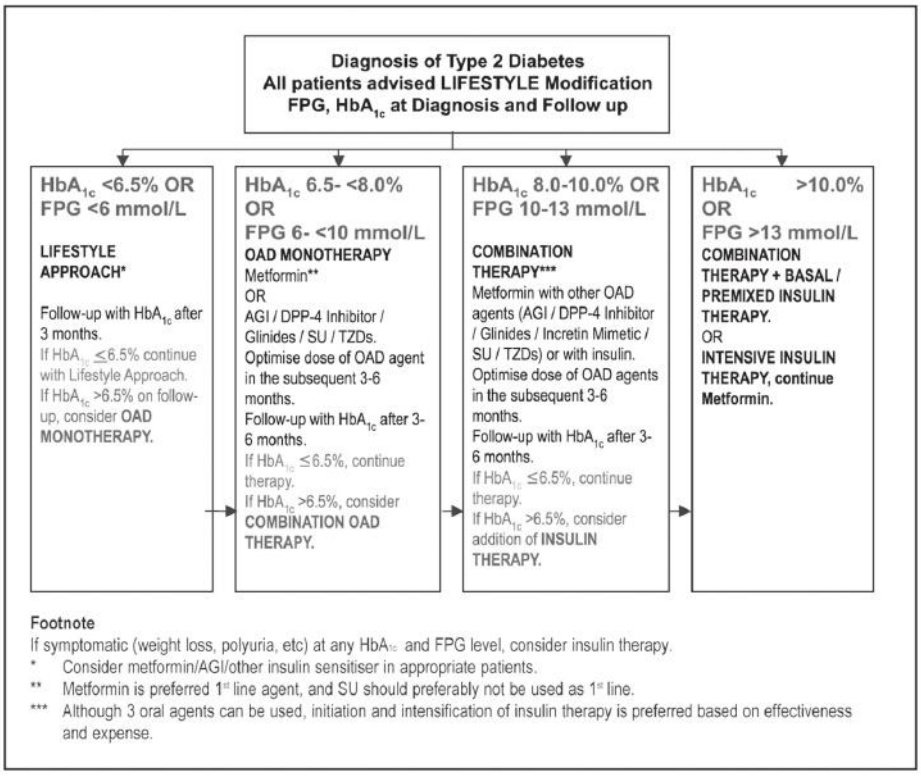

Figure 4. Treatment algorithm

glycaemic targets during pregnancy are shown in Table 3, with individualised monitoring recommended as follows:

- Diet therapy: pre-breakfast,1 hour post prandial glucose (PPG) levels (weekly to fortnightly);
- Insulin therapy: pre-meals and pre-bed glucose levels (weekly to fortnightly). Test PPG after pre-meal targets are achieved.
- HbA1c (4 to 6 weekly)

Table 3. Glycaemic Targets During Pregnancy

Timing Glucose Level (mmol/L)	
Pre-breakfast	3.5 – 5.9
Pre-prandial	3.5 – 5.9
1-hour post prandial	< 7.8
2-hour post prandial	4.4 – 6.7
0200 – 0400 hours	> 3.9

All insulin including rapid acting insulin is safe. Metformin and glibenclamide are not recommended during pregnancy. In addition, Glucose-Insulin-Potassium (GIK) regimen can be used during delivery or caesarean section. During post-partum period, insulin dosage must be reduced as insulin requirement drops immediately after delivery by 60-75%. For breast-feeding patients insulin therapy should be continued at a lower dose if necessary. In non-breast-feeding patients, OAD agents can be continued.

Hypertension and T2DM

The CPG recommends initiation of treatment in diabetics with blood pressure (BP) >130/80 mmHg and they should be screened for proteinuria or microalbuminuria.[6] Tight BP control (<130/80 mmHg) should take precedence over the class of anti-hypertensive drug used. In the presence of proteinuria of >1g/24 hours, the target BP is ≤125/75 mmHg. The treatment of hypertension in diabetes is recommended based on the Malaysian Clinical Practice Guidelines for the Management of Hypertension 2008.[7] This includes dietary counselling targeting optimal body weight and dietary sodium restriction.

Angiotensin converting enzyme inhibitors (ACEI) are the drug of choice for patients with diabetes, both with and without microalbuminuria or proteinuria, with angiotensin receptor blocker (ARBs) recommended for ACEI intolerant patients. Diuretics, calcium channel blockers (CCBs), beta-blockers and peripheral alpha blockers may be used as add-on therapy. A table which illustrates the choice of anti-hypertensive drugs in diabetes patients with concomitant conditions, adapted from the Malaysian Hypertension CPG is also included in the guideline.[7]

Dyslipidaemia and T2DM

The guideline emphasises LDL-C as the primary target. Without overt CVD patients >40 years old should be treated with a statin regardless of baseline LDL cholesterol levels. With overt CVD, all patients should be treated with a statin to a target LDL-C of 1.8mmol/L. The secondary targets are non-HDL-C, HDL-C and TG. The recommended medications are as follows:

- Lower LDL-C: Statin
- Increase HDL-C: Fibrate +/- Nicotinic Acid
- Lower TG: Fibrate +/- Statin

- Combined Hyperlipidaemia: Statins +/- Fibrate or Resin +Fibrate or Nicotinic Acid

Statin therapy is contraindicated in pregnancy. In children and adolescents lipid lowering medications should only be initiated in those >10 years old.

Metabolic Syndrome

The CPG recognises the metabolic syndrome based on the IDF definition, which includes central obesity (waist circumference of 90 cm for men and 80 cm for women) plus any two of the following: (i) raised TG level >1.7 mmol/L; (ii) low HDL-C (<1.0 mmol/L in men and <1.3 mmol/L in women); (iii) high BP ≥130/85 mm Hg; (iv) raised FPG ≥5.6 mmol/L or previously diagnosed T2DM.

The main aim of therapy is to reduce the risk of cardiovascular disease and the development of T2DM. Management includes lifestyle modification with pharmacological treatment of the individual components of the syndrome to target values as shown in Table 2. The recommended optimal weight loss is 1 to 2 kg/month in adults. The recommended anti-obesity agents in diabetics include orlistat and sibutramine. Bariatric surgery may be an option in patients with BMI >35 kg/m^2. Anti-obesity agents and bariatric surgery are not recommended in children.

Management of Chronic Complications

People with T2DM should be screened for complications at diagnosis and thereafter at yearly intervals. The screening schedule is shown in Table 4. Achieving as well as maintaining tight glycaemic and blood pressure control is reiterated repeatedly for prevention of complications.

For retinopathy, health care professionals should refer patients to an ophthalmologist for (i) unexplained poor vision; (ii) diabetic retinopathy greater than occasional microaneurysms; and (iii) macular oedema or hard exudates within the macula. Urgent referral is required if there is (i) sudden visual deterioration; (ii) new vessels on fundoscopy; (iii) rubeosisiridis; (iv) vitreous haemorrhage; and (v) retinal detachment.

Annual screening for microalbuminuria is advocated as essential. Microalbuminuria is defined as a urinary albumin:creatinine ratio (ACR) >2.5 mg/mmol in men and >3.5 mg/mmol in women, or a urinary albumin concentration >20mg/l. Screening can be done initially with conventional dipstick on an early morning urine specimen if urine dipstick for proteinuria is negative. Two further tests within 3 to 6 months is required to confirm a positive microalbuminuria. In patients with proteinuria of >1 gram a day, the target BP is ≤125/75 mmHg. ACEI or ARB should be started unless contraindicated. Referral to a nephrologist should be made if (i) serum creatinine >200 μmol/L; (ii) haematuria; (iii) nephritic syndrome; (iv) absence of retinopathy (where the diagnosis of diabetic nephropathy may be in doubt); (v) difficult to control blood pressure; and (vi) worsening renal function.

Table 4. Schedule for Screening for Complications

Test	Initial visit	Follow-up visit	Quarterly visit	Annual visit
Eye: visual acuity & funduscopy	✓			✓
Feet: pulses & neuropathy	✓		✓	✓
Weight	✓	✓	✓	✓
BMI	✓			✓
Blood pressure	✓	✓	✓	✓
Blood glucose	✓	✓	✓	✓
HbA_{1c}	✓		✓	✓
Cholesterol/HDL cholesterol	✓		★	✓
Triglycerides	✓		★	✓
Albuminuria*	✓		★	✓
Creatinine/BUN	✓		★	✓
ECG	✓			✓
Urine microscopy	✓			✓

✓ Conduct test
★ Conduct test if abnormal first visit
* Microalbuminuria if resources are available

Diabetic peripheral neuropathy may be diagnosed by 10-g monofilament pressure sensation, 128 Hz tuning fork, ankle jerks (deep tendon reflexes) and pin prick test. Medical treatment for sensory symptoms of painful peripheral neuropathy includes: gabapentin, lamotrigine, carbamazepine or amitriptyline.

To reduce the risk of coronary heart disease (CHD), patients with atypical symptoms or who are asymptomatic should be screened using a resting ECG and by applying an established cardiovascular risk assessment tool such as Framingham Risk Score or UKPDS Risk Engine.[8,9] Patients with an abnormal resting ECG or those having high risk should be referred to a cardiologist for further evaluation. Primary prevention with low dose aspirin is not generally recommended unless patients have high risk of developing CHD based on the Framingham Risk Assessment Score (>10% risk over a 10 year period).

All adult male T2DM patients over the age of 40 should be asked about erectile dysfunction (ED) and screened for ED by using the International Index of Erectile Function (IIEF) questionnaire. Medications which cause ED should be avoided if possible. Phosphodiesterase-5 (PDE-5) inhibitors can be used to treat ED in patients without contraindications. Urology referral may be necessary for those not responding; or for those with contraindications to PDE-5 inhibitors.

Prevention of Diabetes

In addition to lifestyle modification to decrease the risk of conversion of IFG or IGT to frank T2DM, metformin should be considered as off-label use for those at very high risk (combined IFG and IGT plus other risk factors) or for those who fail lifestyle therapy after 6 months. The use of other agents like ACEIs, ARBs and statins are not

recommended solely for the purpose of primary prevention.

For prevention of diabetes, weight loss (5-10% of initial body weight), regular physical activity (150 min/week), with dietary strategies including reduced calories and behavior modification are recommended. A high fibre diet (20-30g/day with 5 to 7 servings/day) consisting of vegetables, fruits, legumes and whole grains is encouraged.[4]

Dissemination of Information

To support the dissemination of the recommendations contained in the CPG, the CPG Task Force also developed and published two supporting documents. The first document is the 'Quick Reference for Health Care Providers,' an 8-page pocket-size booklet which provides key messages and a summary of the main recommendations in the CPG Management of T2DM (4th edition) 2009. The main objective of this booklet is to provide an easy and quick reference for doctors, assistant medical officers and nurses involved in the management of T2DM patients, particularly at the primary care level.

The second document published is the 'Training Module for Health Care Providers.' This is a comprehensive document which also includes a CD containing powerpoint presentations of the various topics contained in the T2DM CPG together with relevant case studies. The main objective of this document is to provide a standardised training package to assist trainers in conducting training to disseminate the recommendations contained in the CPG to all health care providers involved in the management of T2DM particularly at the primary care level.

The CPG Task Force also undertook a series of training-of-trainers (TOT) workshops held in five different regions throughout Malaysia which was held from October 2009 until January 2010. A total 169 family medicine specialists, physicians and medical officers from various MOH health care facilities underwent this 2-full day training, which was conducted mostly by members of the CPG Task Force. The Training Module developed was used as the training material during the TOT and subsequent echo trainings held at the state, district and hospital level throughout 2010.

Summary

Publication of the T2DM CPG was only the first step in the process of disseminating the latest recommendations to further improve the quality of care of T2DM patients. It is an important tool, but it will only prove useful if health care providers are aware of its existence, have easy access, ease of retrieving the required information and have the opportunity to undergo training on the practical aspects of implementation. All of the documents mentioned in this article were printed and distributed throughout Malaysia. They are also downloadable in pdf format from the MOH website, together with the powerpoint slides for the Training Module.

For the public primary health care facilities, Malaysia has in place an audit mechanism called the 'Diabetes Clinical Audit,' together with a National Quality Assurance (QA) Program entitled 'Quality of Diabetes Care at MOH Health Care Facilities: Glycaemic Control' which are implemented in all MOH health clinics throughout Malaysia involved in the management of T2DM patients since 2009. For the QA program, the current set optimum standard is ≥30% of T2DM patients achieving HbA_{1c}<6.5% for each health clinic. Compliance to the current T2DM CPG forms part of the shortfall in quality (SIQ) investigation within the QA program. Over the coming years, the CPG Task Force hopes to see a positive impact of the implementation of the recommendations contained in the CPG.

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The full document is available at the Malaysia Ministry of Health website at http://www.moh.gov.my/v/ed.

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JAFES Journal of the ASEAN Federation of Endocrine Societies

FEATURE ARTICLE

A Summary of the Philippines UNITE for Diabetes Clinical Practice Guidelines for the Diagnosis and Management of Diabetes (Part I: Screening and Diagnosis of DM)

Cecilia Jimeno [1] on behalf of the Technical Review Committee of the UNITE for DM Clinical Practice Guidelines on the Diagnosis and Management of Diabetes

[1]*University of the Philippines College of Medicine*

Introduction

Clinical practice guidelines are systematically developed statements intended to assist practitioners and patients in making decisions about appropriate health care.[1] They are user-friendly statements that bring together the best external evidence (research) and clinical experience for rational decision-making about specific health problems. These recommendations are intended to improve the quality of medical care delivered by doctors or groups of doctors, leading to better outcomes such as disease prevention, prevention of complications, and an overall improvement in the quality and quantity of life of patients. For guidelines to be able to achieve these objectives they must ideally be evidence-based; adapted to the local setting; incorporate patients' values in decision-making; and in a developing country like the Philippines, consider issues of equity.

The Philippine Practice Guidelines on the Diagnosis and Management of Diabetes Mellitus is a pilot project of the UNITE FOR DM organization, a coalition of organizations caring for individuals with diabetes mellitus. This coalition is made up of the following organizations: The Diabetes Philippines (formerly The Philippine Diabetes Association); the Institute for Studies on Diabetes Foundation, Inc (ISDFI); the Philippine Society for Endocrinology and Metabolism (PSEM); and the Philippine Center for Diabetes Education Foundation (PCDEF). The objective of this project is to develop clinical practice guidelines on the screening, diagnosis and management of diabetes which reflect the current best evidence and which incorporate local data into the recommendations, in view of aiding clinical decision making for the benefit of the Filipino patient.

This guideline is a response to the call of the International Diabetes Federation (IDF) for concerted efforts worldwide to develop systematic initiatives to halt the progression of diabetes and its complications. The global projection for diabetes is an increase in total number from 246 million diabetics in 2007 to 380 million or 55 percent increase in prevalence by the year 2025.[2] In the Philippines, the national prevalence was predicted to be 7.9% 08.

For the last 10 years, the prevalence of diabetes mellitus in the Philippines according to the National Nutrition and Health Survey is as follows:[3]

	1998	2003	2008
FBS > 125	3.9	3.4	4.8
DM based on history	---	2.6	4.0
FBS or OGTT or History	---	4.6	7.1

Adding on those who have pre-diabetes (impaired fasting glucose or impaired glucose tolerance), this figure is likely to exceed 10percent. In simple terms, one out of every 10 Filipinos could potentially have diabetes mellitus or prediabetes.

Summary of the Methodology for Guideline Development

The main focus of the Philippine guidelines is the outpatient management of adult patients with Type 2 diabetes mellitus. Type 1 diabetes was also briefly discussed in relation to screening and diagnosis, but management will not be addressed as this group of patients are typically under subspecialty care. The management of diabetes in children will also not be included. Finally, guidelines on the inpatient management of diabetes mellitus will not be discussed in this document, but will be developed in future clinical practice guidelines.

The guideline statements will cover 4 general areas: (1) screening and diagnosis of diabetes; (2) follow-up care and screening for complications; (3) prevention and treatment of diabetes and (4) gestational diabetes. This synopsis will only cover the first section of the practice guideline, which has already been presented and approved by stakeholders.

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Corresponding author: Cecilia A. Jimeno, MD
Associate Professor, University of the Philippines College of Medicine, Department of Pharmacology
Clinical Associate Professor, UPCM Philippine General Hospital, Department of Medicine, Section of Endocrinology, Diabetes and Metabolism
Associate Professor, Ateneo School of Medicine and Public Health
E-mail: ceciledoc@yahoo.com

These guidelines are intended for all physicians who are caring for patients with diabetes including diabetologists, endocrinologists, general practitioners, family physicians and general internists, as well as for medical students, resident trainees of internal medicine or family medicine, and endocrine or diabetology fellows-in-training.

This CPG used two main methods for guideline development: (1) guideline adaptation using the ADAPTE process, and (2) de novo development of guideline statements whenever there are no guidelines on certain issues. The latter is the strategy used for developing statements regarding the use of alternative methods for diagnosis of diabetes, and the use of herbal medications or nutraceuticals for the treatment of diabetes mellitus.

The rationale for using the ADAPTE process is to take advantage of existing guidelines and reduce duplication of effort, thereby shortening the amount of time needed for guideline generation.[4] The full methodology of the ADAPTE process is available at the website www.adapte.org.

The UNITE for DM CPG used the Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009 version) for grading the levels of evidence and strength of recommendations.[5] Briefly, the levels of evidence are graded according to Arabic numerals 1-5, considering the hierarchy of literature (e.g. for questions of therapeutic efficacy, randomized controlled trials are ranked higher than non-blinded or non-randomized trials or observational studies). The strength of the recommendation is indicated by the letters A to D, with A being the strongest recommendation based on consistent level 1 studies; Grade B strength is derived from consistent level 2 or 3 studies or extrapolations from level 1 studies; Grade C strength is from level 4 studies or extrapolations from level 2 or 3 studies; and Grade D is based on level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Summary of the Recommendations

The following are the clinical practice guideline recommendations for the screening and diagnosis of diabetes in the Philippines:

Issue 1. Classification of Diabetes: How is diabetes classified?

Diabetes mellitus is classified into 4 clinical types according to etiology:

- Type 1 diabetes mellitus (formerly insulin dependent diabetes mellitus or juvenile diabetes mellitus): results from autoimmune beta-cell destruction, leading to absolute insulin deficiency
- Type 2 diabetes mellitus (formerly non-insulin dependent diabetes mellitus or adult-onset DM): results from a progressive insulin secretory defect in the background of insulin resistance
- Gestational diabetes mellitus (GDM): diabetes first diagnosed during pregnancy
- Secondary diabetes: e.g., genetic defects in beta cell function or insulin action, diabetes of the exocrine pancreas (pancreatitis, cystic fibrosis), drug- or chemical-induced diabetes (such as from the treatment of AIDS, after organ transplantation, glucocorticoids), other endocrine diseases (Cushing's syndrome, hyperthyroidism)

Screening and Testing for Diabetes in Asymptomatic Individuals

Issue 2: Should universal screening be done and how should screening be done?

Statement 2.1 All individuals being seen at any physician's clinic or by any health care provider should be evaluated annually for risk factors for type 2 diabetes and pre-diabetes. (Table 1) [Grade D, Level 5]

Statement 2.2 Universal screening using laboratory tests is not recommended, as it would identify very few individuals who are at risk. [Grade D, Consensus]

Issue 3.1: Who should undergo laboratory testing for diabetes/pre-diabetes?

Laboratory testing for diabetes and pre-diabetes is recommended for individuals with any of the risk factors for Type 2 diabetes mellitus. (Table 1) [Level 3-4, Grade B]

Table 1. Demographic and Clinical Risk Factors for Type 2 DM

- Testing should be considered in all adults ≥ 40 years old
- Consider earlier testing if with at least one other risk factor as follows:
  - History of IGT or IFG
  - History of GDM or delivery of a baby weighing 8 lbs or above
  - Polycystic ovary syndrome (PCOS)
  - Overweight: Body Mass Index (BMI)^2 of ≥ 23 kg/m^2 or Obese: BMI of ≥ 25 kg/m^2, or
  - Waist circumference ≥ 80 cm (females) and ≥ 90 cm (males), or Waist-hip ratio (WHR) of ≥ 1 for males and ≥ 0.85 for females
  - First degree relative with Type 2 diabetes
  - Sedentary lifestyle
  - Hypertension (BP ≥ 140/90 mm Hg)
  - Diagnosis or history of any vascular diseases including stroke, peripheral arterial occlusive disease, coronary artery disease
  - Acanthosis nigricans
  - Schizophrenia
  - Serum HDL < 35 mg/dL (0.9 mmol/L) and/or
  - Serum Triglycerides > 250 mg/dL (2.82 mmol/L)

Issue 3.2 In what setting/s should testing for diabetes be done?

- *Because of the need for follow-up and discussion of abnormal results with qualified health care professionals (nurse, diabetes educator, physician), testing should ideally be carried out within the health care setting (clinics, hospitals, local health centers). [Level 3, Grade B]*
- *Testing at any setting should be supervised by a qualified health care professional. [Level 5, Grade D]*

Issue 3.3 If initial test(s) are negative for diabetes, when should repeat testing bedone?

- *Repeat testing should ideally be done annually. [Level 5, Grade D]*

Screening and Diagnosis of Diabetes in Children

Issue 4.1 Should screening be done for Type 1 diabetes mellitus?

Screening for Type 1 DM is NOT recommended at the moment for the following reasons:

a. The disease is of low prevalence although an increasing trend is observed. The exact prevalence/incidence has yet to be established. Screening using serologic markers is not readily available and expensive, so that screening is not cost-effective.

b. Since clinical trials for interventions to prevent or delay Type 1 diabetes have not been proven effective, screening for Type 1 diabetes is NOT recommended.

Issue 4.2 Should screening for Type 2 DM be done in children?

Screening for prediabetes and Type 2 DM is recommended among asymptomatic children commencing at age 10 years or at onset of puberty, if puberty occurs at a younger age (ADA) with the following risk factors: [Grade C, Level 4]

- Overweight (BMI > 85th percentile for age and sex, weight –for-height > 85th percentile, or weight > 120percent of ideal for height) OR
- Obese: BMI >95th centile or ≥ +2SD (WHO criteria)
- Plus any (two) of the following risk factors
  - Family history (especially parents and grandparents) of Type 2 DM
  - Signs of insulin resistance (Acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small for gestational age birth weight)
  - Maternal history of diabetes or GDM during the child's gestation

Diagnosis of Diabetes

Issue 5.1 What tests and criteria should be used to diagnose diabetes?

The diagnosis of diabetes mellitus can be made based on any of the following criteria: [Level 2, Grade B]*

1. Plasma glucose ≥ 126 mg/dl (7.0 mmol/L) after an overnight fast. Fasting is defined as no caloric intake for at least 8 hours up to a maximum of 14 hours.
2. Two-hour plasma glucose ≥ 200 mg/dl (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water after an overnight fast of between 8 and 14 hours.
3. A random plasma glucose ≥ 200 mg/dl (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia (weight loss, polyuria, polyphagia, polydipsia) or with signs and symptoms of hyperglycemic crisis.

*Among ASYMPTOMATIC individuals with positive results, any of the three tests should be REPEATED within two weeks for confirmation. [Level 4, Grade C]

Issue 5.2 Who should undergo OGTT as the preferred initial test for screening for diabetes?

A 75-gram OGTT is preferred as the first test in the following individuals who have:[(Level 3, Grade B]

1. A previous FBS showing Impaired Fasting Glucose (100 to 125 mg/dL or 5.6 to 6.9 mmol/L)
2. Previous diagnosis of Cardiovascular Disease (Coronary Artery Disease, Stroke, Peripheral Arteriovascular Disease) or who are at high risk for cardiovascular disease.
3. A diagnosis of Metabolic Syndrome

Issue 5.3 Can other laboratory tests be used for the diagnosis of diabetes?

Issue 5.3.1. At present, we cannot recommend the routine use of the following tests for the diagnosis of diabetes: HBA1c, capillary blood glucose and fructosamine. [Level 3, Grade C] However, if a result is available upon consultation due to prior testing, it should be interpreted with caution and should be confirmed by any of the three tests that are considered standard: Fasting Plasma Glucose, Oral Glucose Tolerance Test or Random Plasma Glucose. [Level 2, Grade B].

The HbA1c is currently not yet recommended as a diagnostic test for diabetes mellitus in the Philippines due to unavailability in many areas of the country and the lack of standardization of the test in our setting.

Recommendation 5.3.2: The use of routine urinalysis (for urine glucose) and plasma insulin are NOT recommended for the diagnosis of diabetes. [Level 3, Grade B]

Issue 5.4: What criteria can be used to diagnose prediabetes?

The criteria for prediabetes are:

1. *Impaired Fasting Glucose defined as FBS of 100 mg/dl (5.6 mmol/L) up to 125 mg/dl (6.9 mmol/L) [Level 2, Grade B]*
2. *Impaired Glucose Tolerance defined as a 2-hr blood sugar in the 75-gm OGTT ≥ 140 mg/dl (7.7mmol/L) up to 199 mg/dl (11.0 mmol/L) [Level 2, Grade B]*

Issue 5.5 What are the criteria for normal blood sugar?

Normal blood is sugar is defined as: (1) An FBS < 100 mg/dL (5.6 mmol/L), or (2) Random/casual blood glucose < 140 mg/dl (7.7mmol/L), or (3) 2-hr blood sugar in the 75gm OGTT < 140 mg/dl (7.7mmol/L) [Level 2, Grade B].

Issue 5.6: If initial test(s) are negative for diabetes, when should the tests be repeated?

Repeat testing should ideally be done annually. [Level 5, Grade D]

Gestational Diabetes: Screening and Diagnosis of Diabetes in Pregnant Women

Issue 6.1 For pregnant women, HOW should screening be done?

All pregnant women should be evaluated at the ***first prenatal visit*** *for risk factors for diabetes [Level 5, Grade E]. These risk factors include: age ≥ 25 years old; overweight or obese before pregnancy; history of abnormal glucose metabolism; history of poor obstetric outcome (abnormal glucose tolerance, macrosomia [>8 lbs], congenital malformations, recurrent abortions, unexplained intrauterine death); family history of diabetes (first-degree relative); intake of drugs affecting carbohydrate metabolism, i.e. steroids; and glucosuria.*

Risk evaluation is done to determine the urgency for doing screening laboratory tests; those with any of the risk factors are considered to be high risk and must undergo laboratory testing as soon as possible.

Issue 6.2 Timing of Laboratory Testing

Routine testing for gestational diabetes mellitus (GDM) is recommended at 24-28 weeks age of gestation [Grade A]. High-risk women should be screened at the soonest possible time [Grade B].

Issue 6.3 Which tests should be used to screen pregnant women for GDM?

An oral glucose tolerance test (OGTT), preferably the 75-g OGTT, should be used to screen for gestational diabetes [Level 3, Grade B].

Issue 6.4 What criteria should be used to interpret the 75-g OGTT?

The criteria put forth by the International Association of Diabetes & Pregnancy Study Group (IADPSG) will be used to interpret the 75-g OGTT [Level 3, Grade B].

There are several ways by which the 75-g OGTT has been used to diagnose gestational diabetes (Table 3). The IADPSG recommendations have the advantage of having been based on an analysis of the HAPO study[6] results which enrolled an "ethnically diverse cohort of ~25,000 women in the third trimester of gestation." Blood glucose levels at which odds ratios for specific outcomes reached predefined values were used to determine the recommended thresholds.

Table 2. Interpreting the 75-g OGTT results

75-g OGTT	Threshold(s) for diagnosing gestational diabetes (mg/dl)		
	IADPSG*	ADA**	ASGODIP & DIPSI
FBS	92	95	NA
1-hour	180	180	NA
2-hour	153	155	140
3-hour	NA	140	NA

* *Any one value meeting threshold is considered gestational diabetes.*
** *Two values must meet thresholds to be considered gestational diabetes.*

6.5 Can we use other tests to screen pregnant women for diabetes?

The following tests should NOT be used for the diagnosis of diabetes in pregnancy: Capillary Blood Glucose, FBS, RBS, HbA1c, fructosamine, urine glucose. However, if patients already have FBS or RBS at the time of consultation, thresholds for DM will be the same as non-pregnant individuals. Those with glucosuria, elevated CBG or HbA1c should undergo OGTT. [Grade D, Level 4-5]

Issue 6.6 FOLLOW-UP. How should we follow up women who develop diabetes during pregnancy?

6.6.1 Postpartum recommendation. A 75-gram oral glucose tolerance test should be done 6–12 weeks after delivery in women with GDM who did not have diabetes immediately postpartum. [Grade D, Level 4-5]

6.6.2 An FBS or RBS is not recommended for the long term follow-up and reclassification of women with previous GDM. However, if patients already have FBS or RBS at the time of consultation, thresholds for DM will be the same as non-pregnant individuals. [Grade D, Level 4-5]

6.6.3. Women with previous GDM should also undergo screening for other cardiovascular risk factors and components of the metabolic syndrome. [Grade D, Level 4-5]

Recommendations

Clinical practice guidelines are tools to improve the quality of patient care. In order for clinical practice guidelines to achieve its objectives, it must be well disseminated to the end-users. Its acceptability, compliance and eventual impact on health outcomes must be assessed. It must also reflect current best evidence. Hence, a system for updating practice guidelines to incorporate new findings from researches must be developed and incorporated into the methodology of the guideline.

Finally, physicians must realize that guidelines are meant to enlighten the way they practice and are not intended to replace sound clinical judgment. Decisions about the care of patients must be individualized in the context of unique or specific clinical circumstances that may be encountered in daily practice.

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Composition of the Technical Review Committee of the UNITE for Diabetes Clinical Practice Guidelines for the Diagnosis and Management of Diabetes: Cecilia A. Jimeno, M.D. (Head), Members: Lorna Abad, M.D., Aimee Andag-Silva, M.D., Elaine Cunanan, M.D., Richard Elwynn Fernando, M.D., Mia Fojas, M.D., Iris Thiele Isip-Tan, M.D., Leilani Mercado-Asis , M.D.

Administrative Panel for the UNITE for Diabetes CPG: Dr. Maria Honolina Gomez (PCDEF), Dr. Gabriel V. Jasul, Jr (PSEM), Dr. Leorino M. Sobrepeña (ISDF), Dr. Tommy Ty Willing (Diabetes Philippines)

Composition of the Consensus Panel of Stakeholders for the UNITE for Diabetes CPG:

1. Diabetes Philippines: Susan Yu-Gan, M.D., Sanirose S. Orbeta, MSRD, Joy C. Fontanilla, M.D.
2. Diabetes Center (Philippine Center for Diabetes Education Foundation): Jose Carlos Miranda, M.D., Jimmy Aragon, M.D., Augusto Litonjua, M.D., Carolyn Narvacan-Montano, M.D.

3. Institute for Studies on Diabetes Foundation, Inc (ISDFI): Grace K. delos Santos, M.D., Rima Tan, M.D., Ernesto Ang, M.D.
4. Philippine Society for Endocrinology and Metabolism (PSEM): Nemencio A. Nicodemus Jr, M.D., Laura Trajano-Acampado, M.D., Bien J. Matawaran, M.D.
5. Philippine Association of Diabetes Educators (PADE): Francis Pasaporte, M.D., Ronaldo Toledo, M.D.
6. Philippine Society for Pediatric Metabolism & Endocrinology (PSPME) and Philippine Pediatric Society: Susan Padilla-Campos, M.D.
7. American Association for Clinical Endocrinology (AACE), Phil Chapter: Yvette Amante, M.D., Jose Carlos Miranda, M.D.
8. Association of Diabetes Nurse Educators Philippines (ADNEP): Leyden F. Florido, RN, MAN
9. Association of Municipal Health Officers of the Philippines (AMHOP): Leonardo Afable Jr, M.D.
10. (Philippine) Food and Drug Authority (FDA)
11. Department of Education (DepEd): Minda U. Meimban, M.D.
12. Department of Health (DOH): Ma. Elizabeth I. Caluag, M.D., Ma. Elizabeth I. Caluag, M.D.
13. Food and Nutrition Research Institute (FNRI): Charmaine A. Duante, RMT
14. Lay representatives of diabetic patients: Helena Reginaldo, Marlene Rose Lim
15. Nutritionists and Dietitians Association of the Philippines (NDAP): Nieves Serra, RND
16. Philippine Academy of Family Physicians (PAFP): Alex J.B. Alip Jr., M.D.
17. Philippine Association of Medical technologists (PAMET): Leila M. Florento, RMT, PhD
18. Philippine College of Occupational Medicine (PCOM): Rustico Jimenez, M.D.
19. Philippine College of Physicians
20. Philippine Heart Association (PHA): Jose Antonio Bautista, M.D.
21. Philippine Health Insurance Corporation (PhilHealth) (NON-VOTING): Shirley Domingo, M.D.
22. Philippine Lipid and Atherosclerosis Society (PLAS): Abdias V. Aquino, M.D
23. Philippine Medical Association (PMA): Arthur Catli, M.D.
24. Philippine Obstetrics and Gynecology Society (POGS)
25. Philippine Society of Hypertension (PSH): Abdias V. Aquino, M.D. and Norbert Lingling Uy, M.D
26. Philippine Society of Nephrology (PSN): Benjamin Balmores Jr., M.D.

The full document is available at the PSEM website http://www.endo-society.org.ph and the Philippine Diabetes Association website http://www.diabetesphil.org.

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FEATURE ARTICLE

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The Diabetes Mellitus Clinical Practice Guidelines of Singapore – Looking Back and Ahead

Foo Joo Pin,[1] Richard Chen,[1] Lim Su Chi[2] and Goh Su Yen[3]"
on behalf of the Singapore Clinical Practice Guidelines Writing Group

[1] *Department of Endocrinology, Changi General Hospital*
[2]*Department of Medicine, Khoo Teck Puat Hospital*
[3]*Department of Endocrinology, Singapore General Hospital*

The Singapore clinical practice guidelines (CPG) on diabetes mellitus were first drawn up in 1999. The main aim of the guidelines was to help physicians make sound clinical decisions on the management of diabetes mellitus by presenting up-to-date information on diagnosis, classification, treatment, outcomes and follow-up. The guidelines contained detailed recommendations on many aspects of diabetes care including the screening and diagnosis of diabetes, classification of diabetes, lifestyle modifications, pharmacotherapy, management of diabetic complications, and treatment of associated metabolic disorders. Diabetes management in special populations including children and adolescents, and pregnant women, were also detailed. The CPG was last revised in 2006. Since then, there has been a phenomenal rate of development of knowledge and an explosion of data challenging many traditional notions of diabetes. Therefore, a new working committee has been set up to update the Singapore diabetes mellitus CPG targeted for publication in 2012. In this manuscript, we aim to discuss briefly selected key issues that are likely to be extensively reviewed in our next CPG.

The Diagnosis of Diabetes Mellitus

The 2006 guidelines endorsed the long-held diagnostic criteria of diabetes: random glucose ≥ 11.1 mmol/L (in the presence of symptoms), fasting plasma glucose (FPG) ≥ 7.0 mmol/L and 2-hour post-load plasma glucose (2HPG) in an oral glucose tolerance test (OGTT) of ≥ 11.1 mmol/L.

Recently, the American Diabetes Association (ADA) included the use of glycated hemoglobin (HbA_{1C}) threshold ≥ 6.5% to diagnose diabetes.[1] Epidemiological studies have demonstrated a relationship between risk of retinopathy and HbA_{1C}, similar to FPG and 2 HPG. The convenience of performing HbA_{1C} testing without the need for fasting, and purported reduced day-to-day fluctuations related to stress and illnesses, lend further support to utilizing HbA_{1C} as a diagnostic test. There are, however, some legitimate concerns. These include limited availability or standardization of the test, especially in developing countries; higher cost; systematic differences dependent on ethnicity[2]; and the effect of anemia and hemoglobinopathies on HbA_{1C}. Currently, most of the laboratories in Singapore perform HbA_{1C} certified by the National Glycohemoglobin Standardization Program (NGSP), standardized to the Diabetes Control and Complications Trial (DCCT) reference assay. The test is also widely available in Singapore. It is anticipated that the use of HbA_{1C} as a diagnostic test for diabetes will be carefully considered.

Glycemic Targets and Assessment

The 2006 guidelines described glycemic targets of HbA_{1C} 4.5 to 6.4% as "ideal," 6.5 to 7.0% as "optimal," 7.1 to 8.0% as "suboptimal," and > 8.0% as "unacceptable." The recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial and the Veterans Affairs Diabetes Trial (VADT) have challenged existing paradigms.[3-5] These trials were designed to study the effects of intensive (aiming to achieve near-euglycemia) versus conventional therapy on cardiovascular outcomes in subjects with longstanding type 2 diabetes. Within the period of follow up—although these three trials demonstrated varying degrees of benefit, albeit modest, on the onset or progression of microvascular outcomes—none showed any benefit of intensive control with regard to macrovascular outcomes. Moreover, results from ACCORD showed a significant increase in total (hazard ratio 1.22) and cardiovascular (hazard ratio 1.35) mortality with intensive therapy. These results were in contrast to the findings of the United Kingdom Prospective Diabetes Study (UKPDS), which demonstrated consistent benefits in both microvascular and macrovascular outcomes in

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Corresponding author: Lim Su Chi, MD, PhD
Khoo Teck Puat Hospital - Alexandra Health
90 Yishun Central, Singapore 768828
E-Mail: lim.su.chi@alexandrahealth.com.sg

intensively treated patients on long term follow up.[6] Some reconciliation of inconsistent findings from these clinical trials may be possible upon consideration of the known pathophysiology of diabetes and its vascular complications. For instance, the patient profile of UKPDS, consisting mainly of newly diagnosed diabetics, was different from the longstanding diabetic population of ADVANCE, ACCORD and VADT. This suggests that glycemic targets should be individualized based on age, duration of diabetes, and the presence of advanced vascular disease, amongst other factors.

Assessment of glycemic control utilizing traditional methods, including glycated hemoglobin and self monitoring of blood glucose (SMBG), were included in the 2006 guidelines. Recent advances in newer technology, particularly continuous blood glucose monitoring (CGM), and new data demonstrating its benefits in further improving glycemic control while limiting hypoglycemia, have supported the role of CGM in the management of type 1 diabetics on intensive insulin therapy.[7] The next revision of the guidelines should perhaps incorporate these evolving technologies, which may serve an ancillary role in the management of diabetes.

Therapeutic Options and Treatment Algorithm for Diabetes

The long term safety of anti-hyperglycemic agents—thiazolidinediones (TZDs) in particular (primarily relating to rosiglitazone)—has been the subject of intense discussion. Rosiglitazone was found to be associated with a significant increase in the risk of myocardial infarction and an increased risk of death from cardiovascular causes as reported by Nissen et al in 2007.[8] The 2008 ADA and the European Association for the Study of Diabetes (EASD) consensus algorithm recommended against the use of rosiglitazone, owing to safety concerns and the availability of alternative therapies (pioglitazone in particular), which seemed not to share the same concerns. In 2010, the European Medicines Agency suspended sales of rosiglitazone. In the same year, the United States Food and Drug Administration (FDA) restricted its use to patients with type 2 diabetes who cannot achieve adequate glycemic control with other medications. Back in the 2006 guidelines, TZDs had an integral role as an oral therapeutic option for type 2 diabetes. Rosiglitazone was the only TZD available in Singapore at that time. Although rosiglitazone is still available in Singapore, it is unlikely to continue to play a major role as a therapeutic option for type 2 diabetes owing to its safety concerns. The other available TZD, pioglitazone, has its own share of issues including concerns with heart failure, fracture risk and, lately, bladder tumors.[9] Therefore, the therapeutic placement of TZDs will be reviewed.

The other controversy, which has gathered significant attention in recent years, is with the insulin analog insulin glargine and mitogenicity. In an observational cohort study published in 2009, Hemkens et al reported that cancer incidence in patients on glargine was higher than expected, than in patients on human insulin.[10] Other epidemiological data largely demonstrated no causal relationship between insulin glargine and cancer risk.[11,12] Some remain concerned because glargine has a higher affinity for insulin-like growth factor-1 (IGF-1) receptor compared to human insulin, which theoretically could alter mitogenic activity. There is, to date, insufficient evidence to make a recommendation against glargine. Therefore, the epidemiological observation only generates some hypotheses but is unable to establish causation. The CPG committee will carefully consider this issue.

While some therapeutic agents have been under scrutiny for their safety concerns, there have been several new classes of therapeutic agents that may play increasingly important roles in the management of diabetes. These include incretin-based treatment, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs. These agents have gained increased use in part due to their favorable effect on weight and their postulated beneficial effect on beta-cell function in animal studies.[13,14] The ADA and EASD consensus algorithm for the initiation and adjustment of therapy in 2008 endorsed the use of incretin-based therapeutic agents as an add-on to metformin, specifically when avoidance of hypoglycemia and weight loss are desirable.[15]

Novel technology and techniques have added new options to the treatment armamentarium for diabetes over the years. Insulin pump therapy has evolved to become an established form of intensive insulin therapy in type 1 diabetics. Studies exploring the utility of insulin pump therapy in type 2 diabetic patients have been steadily increasing.[16,17] The advent of bariatric surgery as a possible option in the treatment of diabetes has presented a provocative challenge to the usual concepts in diabetes treatment.[18] With the emergence of newer therapeutic options and novel concepts on diabetes care, a paradigm shift in the management algorithm of diabetes will be one of the key issues in our next CPG.

Management of Diabetic Complications

The management of diabetic microvascular complications, including diabetic nephropathy and eye complications, was well highlighted in the 2006 guidelines. The recommended use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in the treatment of microalbuminuria or overt nephropathy is established practice applicable even to this day. Over the years, several trials have demonstrated additional albuminuria-lowering benefits with dual blockade of the renin-angiotensin system (RAS) using both ACE inhibitors and ARBs.[19,20] With dual blockade, studies showing better long-term renal and cardiovascular outcomes are still lacking, and an increased risk of hyperkalemia has also been described. Nevertheless, dual

blockade remains a viable option should patients have persistently significant proteinuria despite optimization of a single RAS-blocking agent. Furthermore, the direct renin inhibitor aliskiren has been approved by FDA for the treatment of hypertension since 2007. Although its role in the prevention of progression of diabetic nephropathy is unknown, data demonstrating its albuminuria-lowering properties has been promising.[21] Studies also demonstrating additive proteinuria-lowering benefits with the use of spironolactone, an aldosterone antagonist, have been mounting.[22,23] These additional agents offer a wider range of options in the management of diabetic nephropathy and should be addressed in the next revision to the Singapore guidelines.

Screening for diabetic retinopathy, and management of systemic risk factors for prevention of progression of diabetic retinopathy (including glycemic control, blood pressure control and treatment of hyperlipidemia), were well-detailed in the 2006 guidelines. Intensive diabetes management achieving near normoglycemia has been shown to prevent or delay the onset and progression of retinopathy.[24] Lowering of blood pressure is also well established in reducing the progression of retinopathy.[25] However, the role of treatment of hyperlipidemia has not clearly been linked to retardation of progression of retinopathy. In recent years, a reduced need for laser treatment for diabetic retinopathy was demonstrated in patients treated with fenofibrate.[26] Retardation of progression of diabetic retinopathy with fenofibrate was also observed in the ACCORD Eye Study.[27] Further data confirming the benefits of fibrates in primary prevention and progression of retinopathy are highly anticipated and will undoubtedly have an impact on the management of dyslipidemia in the near future.

Diabetes in Special Populations – Diabetes in Pregnancy

The 2006 guidelines included recommendations on the management of women with pre-gestational and gestational diabetes mellitus (GDM). Guidelines on screening for, and detection of, gestational diabetes; glycemic control; and intrapartum and postnatal management; were highlighted. Traditionally, the term "gestational diabetes" was used to define women with onset or first recognition of abnormal glucose tolerance during pregnancy. With the continuing rise in incidence of diabetic patients presenting at an earlier age, it is inevitable to see an increasing trend of patients with diabetes during pregnancy. Diabetes may even antedate pregnancy. With the advent of data from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the ADA have recently revised guidelines on the diagnosis and classification of diabetes in pregnancy. The classification of "overt diabetes" has been proposed for diabetes detected on initial antenatal visit using the standard diagnostic test. Revised 75-gram OGTT criteria for diagnosis of GDM using any one positive criterion (fasting glucose ≥ 5.1 mmol/L, 1-hour post-load glucose ≥ 10.0 mmol/L or 2-hour post-load glucose ≥ 8.5 mmol/L) has been endorsed.[28] Besides changes to the diagnostic criteria, data demonstrating the safety of oral hypoglycemic agents in pregnancy, particularly metformin and glibenclamide, have been increasing in recent years.[29,30] The use of the rapid-acting insulin analogs, lispro and aspart, has also been shown to have acceptable safety profiles and minimal transfer across the placenta, without evidence of teratogenesis.[31,32] Guidelines on glycemic targets including premeal capillary glucose, peak post-prandial glucose and HbA1C targets for pre-existing type 1 or 2 diabetic women who become pregnant have been updated recently.[33] The relevance and adoptability of these changes will be considered by the new CPG committee.

Conclusion

In the few years since the last revision to the Singapore diabetes CPG in 2006, there has been an astounding avalanche of data challenging traditional notions and bringing new perspectives to diabetes. It is timely that the guidelines be updated to reflect the latest developments and consensus in diabetes care. The challenge lies in adapting this considerable body of data and recommendations to the local setting, making them relevant to local practitioners. Diabetes is a rapidly developing field where exciting new information continues to challenge old practices. We look forward to the next revision to the Singapore Diabetes Mellitus CPG and hope that it will continue to enormously assist our local practitioners in enhancing their care for the diabetic population of Singapore.

The full article of the 2006 Guidelines is no longer available at the Singapore Ministry of Health website as it is currently under review.

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EDITORIAL

Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: *Country Initiatives for Collectively Enhanced Diabetes Care in the Region*

Elizabeth Paz-Pacheco

The prevalence of diabetes in the region is clearly increasing, and so is the burden of this chronic disease and its complications. The Philippines reports a true prevalence of about 7.2% among adults aged 20 years and older in 2008[1]; in the 2010 International Diabetes Federation Diabetes Atlas, Indonesia, Malaysia and Singapore report 4.6%, 10.9% and 12.7% prevalence rates, respectively.[2] These rates are consistent with global estimates, and considering the increasing populations in these countries, the absolute numbers are certainly staggering.

Through improvement in diabetes care, diabetes complications can be prevented or delayed. Various strategies at early screening, diagnosis, and appropriate interventions have demonstrated improved outcomes in several populations.

However, the practice of diabetes care is far from uniform and optimal in most of the developing countries in the ASEAN region. Specialized care is mostly confined to city centers, with minimal reach to financially challenged underserved communities. Efforts to enhance and increase access to quality care are therefore imperative. Such efforts include the development and deployment of Clinical Practice Guidelines (or CPGs).

CPGs provide recommendations to define standards of care. When properly developed and deployed, CPGs are expected to provide the best possible care to the greater majority of the population.

This issue features CPGs for diabetes of the AFES countries, with reports from Indonesia, Malaysia, Philippines, and Singapore. These four DM CPGs vary in their scope. The Indonesian and Philippine CPGs focus on classification, screening, and diagnosis, while the Malaysian and Singaporean CPGs provide further recommendations to include management of diabetes and its complications.

The CPG for Indonesia was based on an expert consensus; with several revisions, the current report was completed in 2010. It represents a simplified set of guidelines for screening and diagnosis of prediabetes and diabetes, derived from guidelines set by US diabetes organizations. Mass screening is not recommended; screening is directed to high-risk patient groups.

The CPG for the Philippines is a summary of the output of the multi-organization umbrella Philippine UNITE for DM, in response to the call of the International Diabetes Federation (IDF), focusing on outpatient care for adult Type 2 DM. It has utilized a well-developed guideline adaptation system, supplemented by de novo development for aspects where there were no guidelines. It reflects current evidence, mostly derived from Northern American data. It intends to provide physicians with a guide and does not mean to replace individual clinical judgment.

The CPG for Singapore is a comprehensive report involving various aspects of diabetes care including management of diabetes, its complications and associated metabolic disorders. With the tremendous amount of new data, a need for updating is recognized and a new working committee is being set up to update the current CPG, with possible re-publication in 2012. The use of HbA1c for the diagnosis of diabetes, as recommended by the American Diabetes Association, is carefully being considered. Relevant statements on therapeutic options are discussed, including the use of thiazolidinediones and insulin glargine. The Singapore CPG also provides an insight into the use of the newer agents such as DPP IV inhibitors and GLP-1 analogs.

The CPG for Malaysia is likewise recently updated (2009) to accommodate new evidences. This set of guidelines covers many aspects of the diagnosis and treatment of diabetes. In addition, it describes country specific information, such as carbohydrate content of common Malaysian foods. Application of local results particularly from their Malaysian National Health and Morbidity Survey provided inputs on the decision for diabetes screening cut-offs. This set of guidelines was printed and distributed through the Ministry of Health with downloadable PowerPoint slides for the training modules. Evaluation programs have been instituted to provide an audit mechanism for the use of the CPG.

What is the value of these CPGs for the region?

Delineation of CPGs is the first step in determining a set of guidelines for diabetes care that is specific and applicable to each country. Presently, data resource is generally derived from international guidelines, as these are generally well-established and evidence-based. International guidelines frequently become the main

source of evidence, due to the paucity of national, or regional, studies.

To realize its goals, every CPG needs to be properly deployed to all end-users and its utility for improving diabetes care needs to be properly confirmed. In addition, it is critical to find a balance between what may be deemed to be minimum recommendation and what the department of health and its regulating agencies may impose to elevate the level of care. Challenges to the success of CPGs include the monitoring of appropriate use in all concerned populations. As a further step, research needs to be advanced to determine whether national guidelines derived from international guidelines prove to be adequate. There is a critical need to validate their correct application to developing countries. As diabetes is a heterogeneous disease, there is a need for better understanding of the etiopathogenesis of diabetes in various ethnic populations, with their respective dietary and lifestyle patterns.

The challenge to AFES is to stimulate discussion on these critical issues with parallel efforts and collective contributions from experts in the region. Particular issues such as country specific diets, popular physical activity practices, and the role of popular use of herbal supplements and alternative treatments have to be addressed. More public health strategies from both government and non-governmental organizations need to be pursued.

Discussion among AFES colleagues shall help advance the status of diabetes care not only individually among the member countries but collectively in the region. All this while, individual country-specific challenges and difficulties need to be identified as these will present as barriers to the true success of national CPGs. Coordination of country initiatives is the key to CPGs for a collectively enhanced diabetes care in the region.

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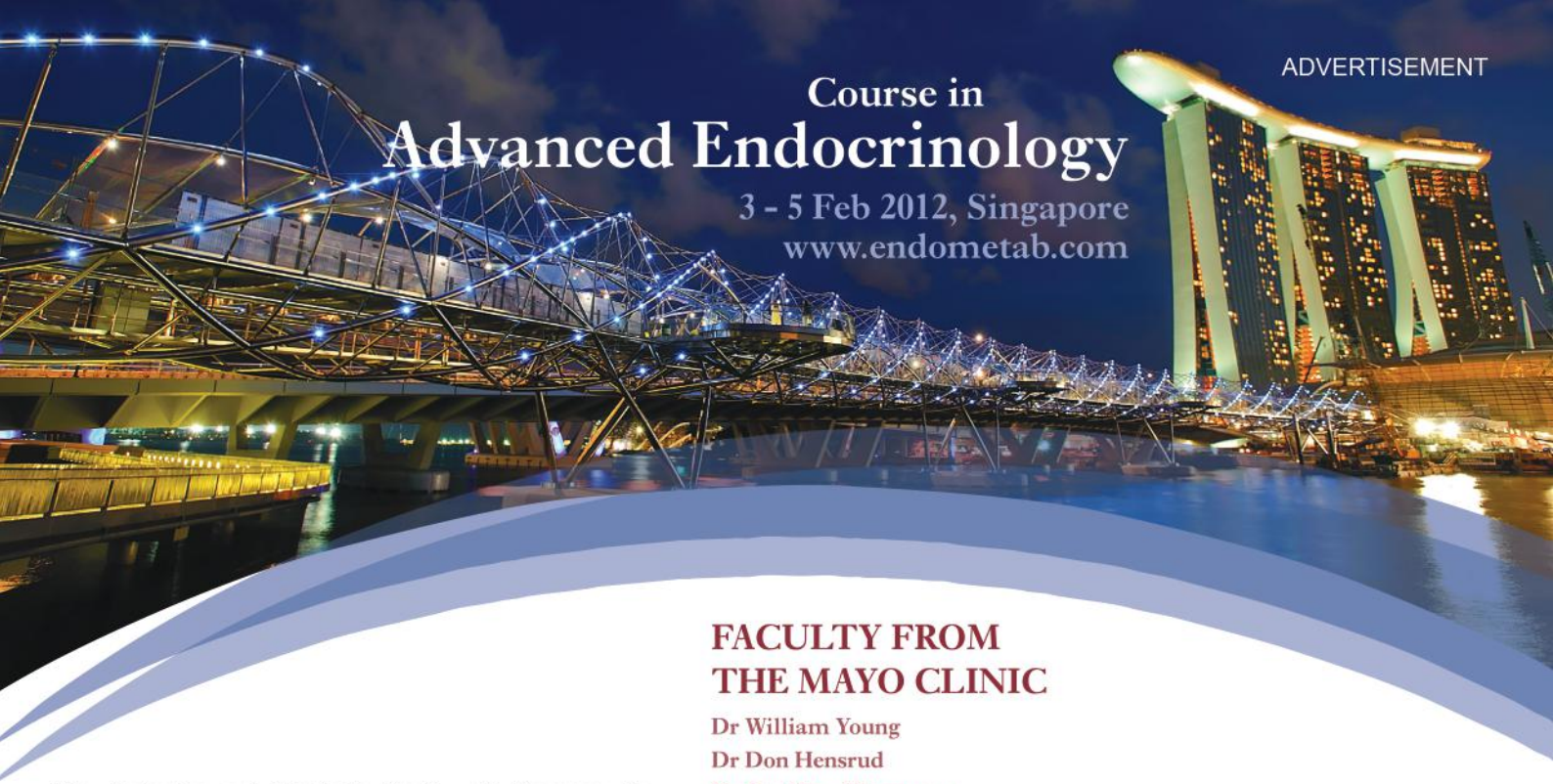

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ORIGINAL ARTICLE

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The Uncoupling Protein 2 Ala55val Polymorphism is Associated with Diabetes Mellitus in a Balinese Population

Made Ratna Saraswati[1*], Ketut Suastika[1], Safarina G. Malik[2], Herawati Sudoyo[2]

[1]*Endocrinology and Metabolism Division, Department of Internal Medicine, Faculty of Medicine Udayana University / Sanglah Hospital*
[2]*Eijkman Institute for Molecular Biology, Jl. Diponegoro 69, Jakarta, Indonesia*

Abstract

Background. The activity of uncoupling proteins have been reported to be associated with obesity and energy metabolism, and it is hypothesized that sequence variation in this gene might contribute to the pathogenesis of type 2 diabetes mellitus.

Objective. To investigate the association of the UCP2 Ala55Val polymorphism with blood glucose level and anthropometric status.

Methods. In a cross sectional study, 287 participants (179 male; 108 female) from Legian Village, Kuta, Bali, were enrolled. The UCP2 Ala55Val (C544T) polymorphism was detected by PCR-RFLP method. Fasting and 2 hours postprandial blood glucose were measured. Anthropometric status including body mass index (BMI) and waist circumference were taken. Analysis of variance (ANOVA) was used to test the equality of continuous variables. To compare categorical variables, a chi-square test was employed.

Results. The genotype frequency of the C/C (Ala/Ala), C/T (Ala/Val), and T/T (Val/Val) are 44.9%, 45.6%, and 9.4%, respectively. The minor allele frequency of the T (Val) allele is 32%. Individuals with the T/T (Val/Val) genotype have higher incidence of diabetes mellitus than those with the C/C (Ala/Ala) or C/T (Ala/Val) genotypes: 18.5%, 7.03%, and 6.92%, respectively (p=0.038). No significant associations were observed between Ala55Val polymorphism and obesity based on BMI and waist circumference determination.

Conclusion. The UCP2 Ala55Val polymorphism was associated with diabetes mellitus in a Balinese population of Legian Village, Kuta, Bali. No significant association was observed between Ala55Val polymorphism and obesity.

Keywords: UCP2Ala55Val, diabetes mellitus, obesity

Introduction

The investigation of heritable susceptibility to disease is an effort to associate disease phenotype with underlying genotype. Significant technological advances for identification of single-nucleotide polymorphisms (SNPs) have further strengthened research methodologies for genetic analysis. Association studies are the most widely used for identifying susceptibility gene(s) to advances in understanding the pathophysiology of disease. The simplest sort of association study count the frequency of each allele at a polymorphic marker and association exists when the allele frequencies differ between subject with disease and subject without disease.[1]

Uncoupling proteins (UCPs) are mitochondrial transporters present in the inner membrane of mitochondria. They are found in all mammals and in plants. They belong to the family of anion mitochondrial carriers including adenine nucleotide transporters. Uncoupling proteins (UCPs) reduce adenosine triphosphate (ATP) generation by separating oxidative phosphorylation from ATP production, and the energy is released as heat. The protein carrier catalyzes the regulated movement of protons across the mitochondrial inner membrane in brown adipose tissue, generating heat, and is therefore called UCP. The term "uncoupling protein," was originally used for UCP1 that resides on chromosome 4q31, which is uniquely present in mitochondria of brown adipocytes, the thermogenic cells

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Corresponding author: Made Ratna Saraswati, MD
Endocrinology and Metabolism Division, Department of Internal Medicine,
Faculty of Medicine Udayana University/Sanglah Hospital
Tel: +62 361 246274
Fax: +62 361 235982
E-mail: dragnusratna@yahoo.com

that maintain body temperature in small rodents. UCP2, ubiquitous and highly expressed in the lymphoid system, macrophages, and pancreatic islets, was discovered in 1997. However, definitive understanding of its function has so far eluded investigators. Potential role include regulating fat metabolism directly and indirectly via effects on insulin secretion. UCP3 is mainly expressed in skeletal muscles. The activities of UCPs have been reported to be associated with obesity and energy metabolism. In comparison to the established uncoupling and thermogenic activities, UCP1, UCP2, and UCP3 appear to be involved in the limitation of free radical levels in cells rather than in physiological uncoupling and thermogenesis. Moreover, UCP2 is a regulator of insulin secretion and UCP3 is involved in fatty acid metabolism. UCP2 and UCP3 were both mapped to chromosome 11q13 in humans.[2-4]

The mitochondrial uncoupling protein-2 (UCP-2) has been proposed to be involved in the regulation of energy balance. Several reports have shown that deficiency of UCP-2 gene expression has been observed in obesity, a disorder that is associated with disturbed energy homeostasis.[5-7] UCP2 was reported to be associated with childhood-onset obesity in African American, Asian, and Caucasian children.[8]

The onset of type 2 diabetes mellitus is preceded by obesity, insulin resistance, and impaired beta-cell function. UCP2 is expressed in a wide range of tissues including pancreatic cells, and several recent findings emphasize the hypothesis that sequence variation in this gene might contribute to the pathogenesis of type 2 diabetes mellitus. Work in transgenic mice suggests that increased expression of UCP2 decreases glucose-stimulated insulin secretion, thus impairs glucose homeostasis and increases the risk of diabetes mellitus.[9] Support for the hypothesis that UCP2 is a negative regulator of insulin secretion comes from investigations using UCP2 -/- mice that showed increased circulating insulin concentrations concomitant with reduced blood glucose in the fed state.[10]

In this study, we investigated the frequency of the homozygote C/C (Ala/Ala), heterozygote C/T (Ala/Val), and homozygote T/T (Val/Val). We also looked for the association of the commonly observed UCP2 Ala55Val polymorphism with blood glucose level and anthropometric status.

Subjects and Methods

A cross sectional study was conducted in Legian Village, Kuta, Bali. Subjects (aged 18 years old or more) were recruited from this village by stratified random sampling, and 287 (179 males, 108 females) participants were enrolled with informed consent (with the approval of the Faculty of Medicine Ethic Committee, Udayana University, and the Eijkman Institute Research Ethics Commission). Fasting and 2 hour - postprandial blood glucose were measured. Anthropometric status, included height, weight, and waist circumference (WC). Body mass index (BMI) was calculated as weight in kg divided by (height)^2 in m^2. Classification of weight by BMI and abdominal obesity by WC are determined according to the Asia-Pacific perspective redefining obesity in adult Asians.[11] BMI classification was as follows: underweight (< 18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight at risk (BMI 23-24.9 kg/m^2), obese I (BMI 25-29.9 kg/m^2), and obese II (BMI ≥ 30 kg/m^2), while the criteria for abdominal obesity were WC ≥ 90cm in male and WC ≥ 80cm in female.

DNA samples for genomic DNA analysis were isolated from Guthrie Cards using Chelex-100 protocol, as previously described.[12] The UCP2 Ala55Val (C164T) polymorphism was detected by PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method, as described previously.[13] Briefly, a 198 bp fragment of UCP2 exon 4 was PCR amplified using a pair of primer, 5'-CTGGAGTCTCGATGGTGTCTAC-3'(forward)and5'-CACCGCGGTACTGGGCGTTG-3' (reverse). This primer pair possessed mismatch bases to introduce a *Hin*cII site, which is used to digest the PCR fragment. The digested product was then separated on 3% agarose gel electrophoresis. The Val/Val genotype was detected by the presence of *Hin*cII site, resulting in 179 bp and 19 bp fragments.

The equality of continuous variables was tested by using the analysis of variance (ANOVA). Comparison of categorical variables was examined by employing the chi-square test.

Results and Discussion

Of the 287 participants enrolled, the mean age was found to be 46.6 ± 9.9 (range: 20 – 83) years. Three genotypes of UCP2 Ala55Val were found in the population of Legian Village, Kuta, Bali: Ala/Ala (C/C), Ala/Val (C/T), and Val/Val (T/T). The representative of the PCR-RFLP results are shown in Fig. 1A. Genotype frequency of the homozygote C/C (Ala/Ala), heterozygote C/T (Ala/Val), and homozygote T/T (Val/Val) are 44.9% (129/287), 45.6% (131/287), and 9.4% (27/287), respectively (Fig. 1B). Allele frequency of the C (Ala) allele in this population is 68%, whereas the T (Val) allele is 32% (Fig. 1C).

The characteristics of the study subjects based on the genotypes of UCP2 Ala55Val are summarized in Table 1. The mean BMI, waist circumference, fasting blood glucose, and 2 hour - postprandial blood glucose are 25.8 ± 4.9, 88.5 ± 10.7, 98.1± 36.7, 109.8 ± 56.1, respectively.

Indication of higher fasting and 2 hour - postprandial blood glucose were observed in T/T (Val/Val) genotype, as compared with the C/T (Ala/Val) or C/C (Ala/Ala) genotypes (103.0mg/dL, 98.1mg/dL, and 97.1mg/dL for fasting blood glucose; 115.9mg/dL, 109.5mg/dL,

108.9mg/dL for 2 hour - postprandial) (Table 1). However, the differences between these genotypes were not significant (Fig. 2).

We then determined type 2 diabetes mellitus based on the levels of fasting and 2 hour - postprandial blood glucose. Individuals with BMI >25 kg/m^2 were considered obese, while male with WC ≥ 90cm or female with WC ≥ 80cm were included in the abdominal obesity group. We found that those with the T/T (Val/Val) genotype have a higher incidence of diabetes mellitus than those with the C/C (Ala/Ala) or C/T (Ala/Val) genotypes: 18.51%, 7.03%, and 6.92%, respectively (p=0.038) (Table 2). No significant associations were observed between Ala55Val polymorphism and obesity based on BMI or abdominal obesity based on WC determination (Table 2).

We have studied the association of UCP2 Ala55Val polymorphism with diabetes mellitus in the population of Legian Village, Kuta, Bali. Legian Village is a famous tourist destination in Bali. Being a tourist destination, this village has many hotels and restaurants serving local and western food, including fast food restaurants. Although the price of this western food is usually higher than local food, it has become familiar since tourism improves the economic lives of the people. This population has been chosen based on several considerations : first, they have been exposed to Westernization for more than two decades, and second, increased incidence of diabetes mellitus and obesity has been observed. Therefore this particular population would be a good model for an association study of genetic variation and disease. Association of the commonly observed UCP2 Ala55Val polymorphism with diabetes mellitus and impaired fasting glucose (IFG) among 3684 participants in the Coronary Artery Risk Development in Young Adults (CARDIA) study has been reported.[14] In this study the Val/Val (VV) genotype had a higher incidence of diabetes than those having the Ala/Ala (AA) genotype (5.8% vs 3.3%; p=0.02).[14], which is in line with our result (18.51% in Val/Val genotype vs 7.03% in Ala/Ala genotype vs p=0.038).

The effects of UCP2 variants, including the Ala55Val, on BMI and T2DM, as well as on insulin secretion in relation to family-specific factors, have been confirmed in various studies which include a case-control population study, a family-based association study, and a metabolic study of

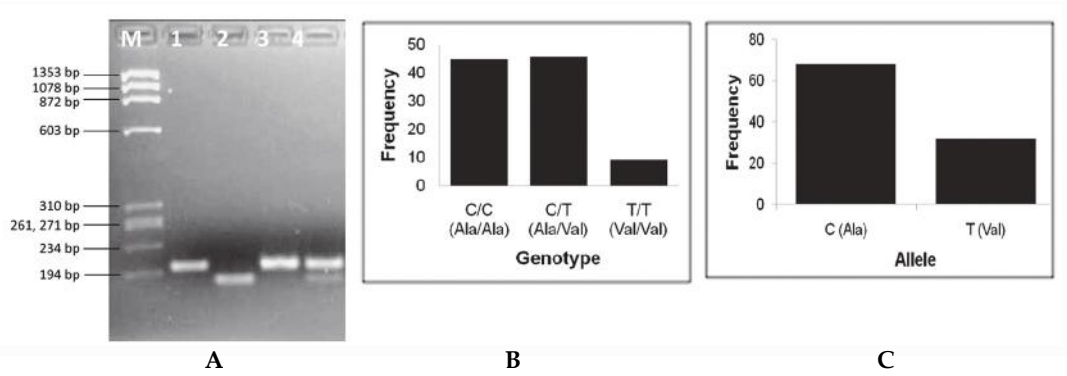

Figure 1. UCP2 Ala55Val detection and frequency. A. UCP2 Ala55Val (C164T) polymorphism was detected by PCR-RFLP method.[12] The digested fragments were electrophoresed in a 3% agarose gel at 80 Volt for 1.5 hours, and visualized under UV light. M: DNA marker (ϕX174 RF/*Hae*III), lane 1: PCR fragment (uncut DNA), lane 2: Val55 homozygote, lane 3: Ala55Val heterozygotes, lane 4: Ala55 homozygote. B. Genotype frequencies of C/C (Ala/Ala; 44.9%), C/T (Ala/Val; 45.6%), and T/T (Val/Val; 9.4%). C. Frequency of major C (Ala; 68%) and minor T (Val; 32%) alleles.

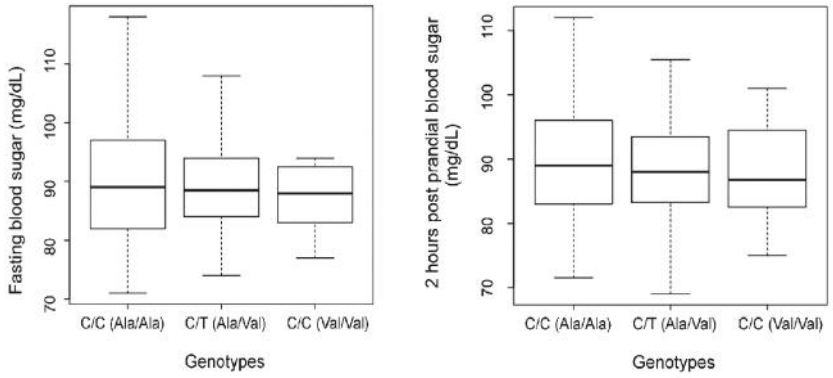

Figure 2. Distribution of fasting and 2 hour - postprandial blood glucose levels based on genotypes of UCP2 Ala55Val. Fasting (left panel) and 2 hour postprandial (right panel) blood glucose levels were plotted against genotypes. The 25 and 75 percentile coverage is indicated by the boxes, while the error bars indicate 10 and 90 percentile points. The horizontal line within the box is the median.

Table 1. Characteristics of study subjects grouped by UCP2 Ala55Val genotype

	C/C (Ala/Ala)	C/T (Ala/Val)	T/T (Val/Val)	Total
n = 287	*n* = 129	*n* = 131	*n* = 27	
Male : female (%)	61 : 39	66 : 34	52 : 48	62 : 38
Age	45.0 ± 9.9	46.2 ± 9.5	50.2 ±11.6	46.0 ± 9.9
Body weight (kg)	66.3 ± 13.5	70.0 ± 13.6	66.3 ±11.9	68.0 ± 13.5
Height (cm)	162.0 ± 8.6	162.4 ± 10.9	162.1 ± 7.7	162.2 ± 9.7
BMI (kg/m^2)	25.1 ±4.1	26.7 ± 5.6	25.1 ± 3.8	25.8 ± 4.9
WC (cm)	87.1 ±10.3	90.1 ± 11.0	87.9 ± 10.4	88.5 ± 10.7
FBS (mg/dL)	97.1± 29.5	98.1 ± 40.9	103.0 ± 46.3	98.1± 36.7
2 h PPBS (mg/dL)	108.9 ± 42.1	109.5 ± 64.2	115.9 ± 73.9	109.8 ± 56.1

Notes: BMI= body mass index, WC= waist circumference, FBS= Fasting blood glucose level, 2 h PPBS= 2 hours postprandial blood glucose level

Table 2. Prevalence of diabetes mellitus, obesity, and abdominal obesity grouped by UCP2 Ala55Val genotypes

	C/C (Ala/Ala)	C/T (Ala/Val)	T/T (Val/Val)	Total	*p*
Diabetes mellitus, n (%)	9 (7.03)	9 (6.92),	5 (18.51)	23 (8.07)	0.038*
Obesity, n (%)	88 (68.21)	103 (79.2)	19 (70.3)	210 (73.42)	0.124
Abdominal obesity, n (%)	75 (58.13)	84 (65.11)	15 (55.55)	174 (61.05)	0.428

*Notes: Obesity was determined based on BMI > 25 kg/m^2, abdominal obesity was determined based on WC ≥ 90cm in male and WC ≥ 80cm in female.[11] * Statistically significant, BMI= body mass index, WC= waist circumference*

individuals whose insulin sensitivity and secretory patterns were reported.[9] In a Taiwan community UCP2 Ala55Val variant was reported to be associated with obesity and also with increased insulin concentration that may lead to insulin resistance.[15] However, although the prevalence of obesity (73.42%) and abdominal obesity (61.03%) were found to be high in this study, no association was observed between the UCP2 Ala55Val polymorphism and obesity (high BMI) or abdominal obesity (high WC).

There are many risk factors that have been reported to be associated with obesity, and genetic variations are among them. Therefore, it is possible that the high prevalence of obesity and abdominal obesity observed in the population of Legian village, Kuta, was associated with other genetic factors, such as the beta adrenergic receptor (ADRB) gene polymorphisms. Further study is needed to explore the possibility of the involvement of genetic variations as risk factor for obesity in this population.

Conclusion

The UCP2 Ala55Val polymorphism was associated with diabetes in the population of Legian village, Kuta, Bali. However, there was no significant association observed between Ala55Val polymorphism and obesity based on BMI or abdominal obesity based on WC determination.

Acknowledgement

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Borobodur, the great Buddhist stupa, stands in sacred tranquility at Kedu Plain, in Java, Indonesia.
Photograph courtesy of Dr. Dyah Purnamasari.

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ORIGINAL ARTICLE

The Diagnostic Accuracy of Ultrasound Guided Fine-Needle Aspiration Biopsy and Intraoperative Frozen Section Examination in Nodular Thyroid Disease

James K. Young,[1] Cherrie Gail Lumapas-Gonzalez,[1] Roberto C. Mirasol[2]

[1]*Section of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, St. Luke's Medical Center, Philippines*
[2]*Section of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, St. Luke's Medical Center and Section of Endocrinology, Manila Doctors' Hospital*

Abstract

Objectives. To determine the diagnostic accuracy of combined ultrasound-guided fine needle aspiration biopsy (USG-FNAB) and intraoperative frozen section examinationin (FSE) in diagnosing malignant thyroid nodules.

Methodology. Retrospective review of patients undergoing thyroidectomy with intraoperative frozen section examination following ultrasound guided fine-needle aspiration biopsy. Sensitivity, specificity, positive and negative predictive values and accuracy were calculated with respect to final histology.

Results. A total of 2,239 nodules were subjected to USG-FNAB at the Diabetes, Thyroid and Endocrine Center, St. Luke's Medical Center between January 2007 and December 2009. Two hundred fifty-one nodules were surgically excised following USG-FNAB. Frozen section examinations were taken from 90 of 251 nodules. The USG-FNAB yielded 90.3% (n=1,721) adequate specimens and 9.7% (n=185) inadequate specimens. The histologic examination of the 251 surgically excised nodules revealed 182 (73%) benign and 69 (27%) malignant nodules. The sensitivity, specificity, positive and negative predictive values and accuracy rate of USG-FNAB cytology are 70.3%, 92.8%, 76.5%, 90.4% and 87.2%, respectively. The diagnosis by frozen section was benign in 56 cases (62%), malignant in 10 cases (11%) and deferred in 24 cases (27%). By FSE, the sensitivity, specificity, positive and negative predictive values and accuracy rate are 83.3%, 100%, 100%, 96.4% and 96.7%, respectively. A diagnostic accuracy of up to 97.2% was achieved when USG-FNAB and FSE were combined and when their findings were concordant. When USG-FNAB and FSE diagnoses were discordant, the FSE showed superior accuracy (83.3%) than cytology (16.7%). In the group of nodules with indeterminate or inadequate cytology, the diagnostic accuracy of frozen section is 100%.

Conclusion. Ultrasound guided fine-needle aspiration biopsy is an accurate preoperative test for the evaluation of nodular thyroid disease. It helps to distinguish malignant from benign lesions. The intraoperative frozen section is a valuable test for confirming the cytologic diagnosis. It is especially important in identifying malignant thyroid nodule in cases with indeterminate cytology. The combination of USG-FNAB and FSE greatly improves the accuracy rate in thyroid cancer detection.

Keywords: fine-needle aspiration biopsy; frozen section; diagnostic accuracy, thyroid nodules; thyroid neoplasm

Introduction

Thyroid nodules are commonly encountered problems in endocrine practice. In the past, its reported prevalence range from 3.2% to 4.2% in the Framingham and Wickham studies. [1] At present, the prevalence of clinically apparent thyroid nodules range from 4% to 7%[2] and it escalated to 49.5% based on autopsy series[1-3] and 10-55% with the use of ultrasonography.[3] The clinical presentation of these lesions may range from small, asymptomatic, solitary nodules to large, symptomatic nodules. Benign thyroid disease is extremely common compared to a small proportion of malignant neoplasms. [3-4] It is, therefore, important to identify this malignant thyroid nodule, which occurs in 4-5% of the thyroid nodules,[4-5] so that immediate surgical intervention can be instituted.

Thyroid cancer is the most common endocrine malignancy and accounts for majority of endocrine related deaths each year. In the Philippines, thyroid cancer is the 9th most common cancer for both sexes and it is the 6th leading cancer site among females and 15th among males.[6] Worldwide, the incidence of thyroid cancer is estimated between 5 and 8 cases per 10,000 inhabitants per year and its incidence increases faster than any other known malignancies having a rate of 3.8% per year.[7]

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Corresponding author: James K. Young, MD
Diabetes, Thyroid and Endocrine Center,12th Floor Cathedral Heights Building Complex, St. Luke's Medical Center, QC
Tel: 723-0101 loc 5210
E-mail: jameskyoung@doctor.com

Recent consensus guidelines recommend that thyroid nodules greater than 1 cm and subcentimetric nodules with suspicious sonographic features should undergo fine needle aspiration biopsy. [8-9] Ultrasound guided fine-needle aspiration biopsy (FNAB) is a clinical technique used to obtain cells, tissue, and/or fluid through a thin needle for the purpose of diagnosis and management of thyroid masses.[10-11] The procedure is done under sonographic guidance. It is currently the least invasive, most accurate and safe method to identify high-risk or malignant lesion within the thyroid gland. [10-12] The routine use of FNAB has decreased the number of patients treated surgically for benign thyroid nodules while it increased the diagnosis of malignancy in resected nodules. Before the advent of FNAB, intraoperative frozen section (FS) had a definite role in selecting appropriate surgical therapy by accurately differentiating papillary carcinoma from nodular hyperplasia. While FNAB is an effective triage tool in selecting patients requiring surgical intervention, FS is useful in determining the extent of thyroidectomy. Moreover, FS is valuable in reducing the need for completion thyroidectomy in patients with negative or non-diagnostic FNAB cytology whose clinical factors suggest malignant thyroid disease.[13] In our institution, patients are selected for surgery on the basis of three cytologic diagnoses: follicular neoplasm, suspicious for papillary carcinoma and positive for malignancy (papillary carcinoma, medullary thyroid carcinoma and anaplastic carcinoma). Patients positive for papillary carcinoma are subjected to total thyroidectomy while those with diagnosis of follicular neoplasm or suspicious for carcinoma undergo a lobectomy and depending on the frozen section and other intra-operative findings, a completion thyroidectomy is done within the same procedure. The routine use of FS for confirmation or clarification of preoperative FNAB cytology is still debatable and its use is justified when the diagnosis will alter the course of further surgery.

Objectives

The main objective of this study is to determine the diagnostic accuracy of combined ultrasound-guided fine needle aspiration biopsy (USG-FNAB) and intraoperative frozen section examination in (FSE) in diagnosing malignant thyroid nodules. We also aimed to determine the accuracy of USG-FNAB and intraoperative FSE when used alone in detecting nodular thyroid neoplasm, compare which diagnostic test (USG-FNAB versus FSE) detects nodular thyroid malignancy in discordant findings, and determine the accuracy of FSE in detecting nodular thyroid malignancy in indeterminate USG-FNAB cytology.

Materials and Methods

We retrospectively analyzed the medical charts of 1,737 consecutive patients who underwent USG-FNAB at the Diabetes, Thyroid and Endocrine Center, St. Luke's Medical Center. A total of 2,239 nodules were biopsied during the period of January 2007 to December 2009. All patients who underwent biopsy signed an informed consent. All USG-FNAB were performed in the same room, with the same USG equipment (Sonosite Micromaxx) and the same biopsy tray setup. There were no biopsy related complications in our study cohort. Specimens were submitted for analysis at the Institute of Pathology of St. Luke's Medical Center.

Each thyroid nodule is considered a case. Thyroid nodules that underwent USG-FNAB and were removed by thyroidectomy with intraoperative frozen section examination were included in the data analysis. Information on demographic data of the study population, ultrasound findings and the cytologic, FSE and histologic reports were abstracted after a review of patient's medical record and pathology report.

Each USG-FNAB cytology result was retrospectively classified for study purposes into one of the four categories: **benign cytology** is one in which the result indicates a non-malignant condition and includes nodular goiter, thyroiditis, colloid nodule and other benign conditions. **Malignant cytology** is one in which the result indicates the presence of cancer and may include papillary, anaplastic and medullary thyroid carcinoma. **Indeterminate cytology** is one in which specimens show hypercellularity and a pattern suggestive of follicular- or Hurthle-cell neoplasm or atypical features suggestive of, but not diagnostic for, malignancy. **Inadequate specimen** is one in which cytologic diagnosis is not possible due to paucity of thyrocytes.

Each intraoperative FSE result was also retrospectively classified into one of the three categories: **benign FSE** is one in which the pathology result indicate a non-malignant condition. **Malignant FSE** is one in which the pathology report indicated the presence of carcinoma. **Deferred FSE** is one in which follicular neoplasm or "Hurthle cell tumor" was reported. The foregoing diagnosis may either be benign or malignant lesion and histology demonstrating vascular and/or capsular invasion are required to confirm the presence of malignant conditions.

The accuracy of USG-FNAB and FSE was assessed by comparing the initial cytology and pathology reports with the final histopathology report. This comparison was used to calculate the values of the test. Histopathology examination is the gold standard in the diagnosis of thyroid cancer. The histologic result was classified into one of the two categories, namely, **malignant** when histology indicates the presence of cancer (papillary, anaplastic, medullary, follicular thyroid carcinoma) and **benign** when histology indicates a benign condition (follicular adenoma, Hurthle cell adenoma, thyroiditis and other benign findings).

Statistical Analysis

To assess the accuracy of USG-FNAB and intraoperative FSE the following were analyzed: (1) sensitivity (Sen), the proportion of patients with malignant thyroid disease and positive cytologic findings; (2) specificity (Sp), the proportion of patients without malignant thyroid disease and negative cytologic findings; (3) positive predictive value (PPV), proportion of patients with malignant thyroid disease and positive cytologic findings; (4) negative predictive value (NPV), proportion of patients not having malignant thyroid disease and with a negative cytologic finding; (5) false positive rate (FPR), proportion of patients with malignant FNAB or FSE who are found to have benign histology findings; (6) false negative rate, proportion of patients with benign FNAB or FSE who were confirmed to have malignant histology findings; and (7) accuracy rate (AR), proportion of correct results (true positive and true negative) in relation to all cases studied.

Results

Majority of our population consisted of females with a ratio of 7:1 and the median age is 46 yrs old (range 14-88 yrs old). The average number of FNAB was 1.3 per nodule (range 1-3). Among the 2,239 nodules, 1,721 (90.3%) yielded adequate specimens that include benign cytology in 64.4 %(765 with nodular goiter, 662 with colloid goiter, 83 with thyroiditis) and malignant cytology in 3% (65 with papillary thyroid carcinoma and 3 with malignant neoplasm). In the group with inadequate specimen, 64% (n=333) were cystic nodules. The rate of inadequate specimen was 9.7% after excluding cystic nodules.

Accuracy of USG-FNAB in the diagnosis of malignancy

In 2,239 biopsied cases, 251 nodules (11%) were surgically excised. Primary thyroid surgery consisted of either total thyroidectomy, unilateral thyroid lobectomy, isthmusectomy or subtotal thyroidectomy. The final histologic diagnosis was obtained from the paraffin embedded specimens.

Histologic examination of excised nodules showed 182 benign (72%) and 69 malignant (28%) lesions. Table 1 shows the correlation of USG-FNAB with definitive histologic diagnosis.

The FNA cytology indicated a benign diagnosis in 114 cases and was correct in 103 of the cases (90.4%). Among the nodules with benign cytology, 11 were found to have carcinoma on histology giving a 9.6% false negative rate. Five of the false negative cases were papillary microcarcinoma. The preoperative FNA cytology also indicated a malignant diagnosis in 34 cases, however, a malignant histology finding was noted in only 26 of the cases (76.5%). Of these nodules, 8 were found to have a benign lesion on histology resulting in a 23.5% false positive rate. The sensitivity, specificity, positive predictive value and negative predictive value are 70.3%, 92.8%, 76.5%, 90.4%, respectively. The overall accuracy rate of USG-FNAB is 87.2% for diagnosing malignant thyroid nodules.

In 74 cases, an indeterminate diagnosis was made and only 36.5% were correctly diagnosed as malignant nodules on histology. Twenty-two cases of the malignant nodules were papillary thyroid carcinoma, and of these 6 were follicular variant of papillary thyroid carcinoma. FNA cytology was inadequate for diagnosis in 29 nodules and the final histology was benign in 83%. The yield of carcinoma when USG-FNAB is applied preoperatively is 28% and the test identified malignancies in 26 nodules preoperatively (37.7%).

Accuracy of Intraoperative Frozen-Section Examination in the diagnosis of thyroid malignancy

Among the 251 nodules that were excised, 36% had intraoperative frozen section examination (n=90). Histologic examination showed 72 benign lesions (78%) and 18 malignant lesions (22%). Table 2 shows the correlation of FSE with definitive histologic diagnosis.

Among the 56 nodules with a benign diagnosis, the FSE was correct in 96.4% of the cases (n=54). Two nodules were found to have carcinoma on final histology giving a 3.6% false negative rate. In 10 nodules, the FSE and final histopathology both showed malignancy. The sensitivity,

Table 1. Distribution of Cases According to the Results of the Fine Needle Aspiration Biopsy Cytology and Final (Definitive) Histopathology Diagnosis

Fine needle aspiration biopsy	Histology (n= 251)										
	Benign lesion					Malignant lesion					
	NG (n=152)	FA (n=17)	HA (n=5)	LT (n=8)	subtotal	PTC (n=60)	FTC (n=5)	HC (n=3)	MTC (n=1)	subtotal	Total
Benign (n=114)	90	7	1	5	103	9	1	1	0	11	114
Malignant (n= 34)	8	0	0	0	8	25	0	0	1	26	34
Indeterminate (n=74)	32	8	4	3	47	22	3	2	0	27	74
Inadequate (n= 29)	22	2	0	0	24	4	1	0	0	5	29
Totals					182					69	251

NG, nodular goiter; FA, follicular adenoma; Hurthle cell adenoma; LT, lymphocytic thyroiditis; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HC, Hurthle cell carcinoma; MTC, medullary thyroid carcinoma

SENSITIVITY 70.3% SPECIFICITY 92.8% PPV 76.5% NPV 90.4%

Table 2. Distribution of Cases According to the Results of the FSE Cytology and the Final Histopathology Diagnosis

Frozen section examination	Histology (n= 90)										
	Benign lesion					Malignant lesion					
	NG (n=57)	FA (n= 10)	HA (n=3)	LT (n=2)	subtotal	PTC (n=16)	FTC (n=1)	HC (n=1)	MTC (n=0)	subtotal	totals
Benign	51	0	1	2	54	2	0	0	0	2	56
Malignant	0	0	0	0	0	10	0	0	0	10	10
Deferred *(n=24)*	6	10	2	0	18	4	1	1	0	6	6
totals					72					18	90

NG, nodular goiter; FA, follicular adenoma; Hurthle cell adenoma; LT, lymphocytic thyroiditis; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HC, Hurthle cell carcinoma; MTC, medullary thyroid carcinoma

SENSITIVITY 83.3% SPECIFICITY 100% PPV 100% NPV 96.4%

specificity, positive and negative predictive values and accuracy rate of FSE in diagnosing malignant thyroid nodules are 83.3%, 100%, 100%, 96.4% and 96.7%, respectively. In 24 cases, a deferred intraoperative FSE diagnosis was made and the definitive histology was benign in 75% of the nodules (n=18). The yield of carcinoma when FSE is applied intraoperatively is 22% and the test identified malignancies in 100% of the cases.

Accuracy of combined USG-FNAB and FSE in the diagnosis of thyroid malignancy

The correlation of combined USG-FNAB and FSE with final histology is shown in Table 3. The accuracy of combined USG-FNAB and FSE is shown in Table 4.

In the group with concordant USG-FNAB and intraoperative FSE findings (B/B and M/M), there were 5 nodules diagnosed as malignant by FNAB/FSE and in the final histology. Twenty-nine nodules initially diagnosed as benign by FNAB/FSE, had the same final histology. One nodule diagnosed as benign on FNAB/FSE was malignant on histology causing a 5% false negative rate. There was no false positive in the result. The sensitivity, specificity and accuracy rate in diagnosing thyroid malignancy are 83.3%, 100% and 97.1%.

In the group with discordant USG-FNAB and intraoperative FSE findings (B/M, M/B), there were 3 nodules with benign preoperative cytology were diagnosed as malignant on FSE and histology. Two nodules with malignant preoperative cytology were diagnosed as benign on FSE and histology. When the USG-FNAB and FSE were discordant, diagnostic accuracy of FSE was significantly better than the USG-FNAB: 83.3% versus 16.7%, respectively.

Diagnostic accuracy of FSE in diagnosing thyroid malignancy in FNAB with Indeterminate and Inadequate cytology

In the group of nodules with indeterminate and inadequate preoperative cytology but with diagnostic FSE result (InD/B, InD/M,InAd/B, InAd/M), the sensitivity, specificity and diagnostic accuracy of FSE diagnosing thyroid malignancy are 100%. Of the 39 nodules with indeterminate cytology, there were 20 benign nodules (51%) and 2 malignant nodules (5%) on histology that were correctly diagnosed by FSE. Among the nodules labeled as inadequate cytologic specimen, 90% (9 out of 10) were benign on FSE and final histology.

Discussion

Since the introduction of FNAB of thyroid nodules, there has been a reduction in the number of patients undergoing surgery for benign thyroid nodules and an increase in the prevalence of malignancy in pathologic thyroid specimens. While FNAB is useful as a diagnostic tool in selecting patients for thyroidectomy, the application of intraoperative frozen section has been a useful guide to formulate the optimal surgical plan. We have presented the results of an in-depth analysis of the utility of ultrasound guided fine-needle aspiration biopsy and frozen section examination in the management of nodular thyroid disease at St. Luke's Medical Center.

We evaluated the adequacy of our USG-FNAB in a large series of 2,239 consecutive cases and compared the results of USG-FNAB and FSE with the post-operative findings in thyroidectomy cases. In our study, the adequacy rate of USG-FNAB is 90.3%. Worldwide, the adequacy rate of FNAB ranges from 70-100% and our result is comparable to published studies.[14-22] The rate of malignant, indeterminate and benign cytodiagnosis are 3.3%, 11% and 76%. In most institutions, the range of malignant, indeterminate and benign cytodiagnosis are 5-38%, 11-42% and 22-65%, respectively.[13-22] The rate of inadequate FNAB specimen after excluding cystic thyroid nodules is 9.7% comparing to 5-29%[14-22] from the previous series. The inadequacy rate in our series may be due to the significant number of aspirated complex thyroid nodules wherein there is usually a paucity of thyrocyte numbers in the biopsied sample.

Table 3. Accuracy of Ultrasound Guided-Fine Needle Aspiration Biopsy and Frozen Section Examination Compared with Final Histology Diagnoses.

UTZ GUIDED FINE NEEDLE ASPIRATION DIAGNOSIS / FROZEN SECTION DIAGNOSIS	FINAL HISTOLOGIC DIAGNOSIS	
	BENIGN	MALIGNANT
B / B	29	1
B /M	0	3
M / B	2	1
M / M	0	5
IND / B	20	0
IND / M	0	2
IND / DEF	12	5
INAD/B	9	0
INAD / M	0	1
INAD / DEF	0	0
TOTALS	72	18

B, benign; M, malignant; InD, indeterminate; Def, deferred; InAd, inadequate

Table 4. Accuracy of Combined USG-FNAB and FSE in the Diagnoses of Nodular Thyroid Malignancy. –

Index	Concordant findings (combined FNAB and FSE) N=35	USG-FNAB findings discordant with FSE N=6	FSE findings discordant with USG-FNAB N=6
% Sensitivity	83.3	25	75
% Specificity	100	0	66.7
% PPV	100	33.3	100
% NPV	96.7	0	66.7
Accuracy rate	97.1	16.7	83.3

FNAB, fine-needle aspiration biopsy; FSE, frozen section examination; PPV, positive predictive value; NPV, negative predictive value

The reported sensitivity of FNAB ranges from 54-97% and specificity ranges from 74-98%.[16-25] In this study, the sensitivity for cytologic diagnosis of thyroid malignancy is 70.3%, specificity of 92.8%, positive predictive value of 76.5% and negative predictive value of 90.4%. The sensitivity of our result may be affected by how we chose to define and classify indeterminate FNAB results. Accordingly, the exclusion of indeterminate FNAB diagnoses from the malignant FNAB cases tends to decrease the sensitivity of FNAB for detecting thyroid carcinoma, while increasing its specificity. In our study, indeterminate FNAB diagnoses were separated from the clearly malignant and benign FNAB diagnoses since we intended to calculate the diagnostic accuracy of the USG-FNAB and not to determine its influence on clinical management. Our result translates into a diagnostic accuracy of 87.2% and our data suggest that USG-FNAB is slightly more specific rather than sensitive in detecting thyroid malignancy. Thus, we confirm USG-FNAB a reliable diagnostic test. The reported accuracy rate of FNAB worldwide ranges from 60-98%[14,15,17,18,20-22, 24-25] and our accuracy rate is higher comparing to 67% and 70% accuracy rate reported by Morgan and colleagues of Australia[18] and Leenhardt and colleagues of France,[20] respectively. The false negative rate of our study is 9.6% and this value is in agreement with other studies reporting a false negative rate of 3.6-46%.[16-25] Review of our cases showed that 5 of the 11 false negative cases were papillary microcarcinoma and these lesions may have been missed during the aspiration. Two cases, follicular and Hurthle cell carcinoma diagnosed as nodular and colloid goiter on preoperative cytology, may have resulted from failure to interpret the cytologic specimen. This is due to the fact that FNA is ineffective in recognizing vascular invasion, an obligatory diagnostic criteria for these lesions. Our findings suggest that a negative FNAB should not be used as an assurance of the absence of malignancy. Clinical factors suggestive of malignancy should always be considered in any case. There are several studies delineating the risk factors of malignancy in thyroid nodule and this include history of radiation, local symptoms like recurrent nerve compression or dysphagia, evidence of metastatic disease, tumor size and several sonographic characteristics. These factors may be identified preoperatively, providing an indication for operation. The present study did not specifically analyze these factors.

Indeterminate cytology and inadequate specimen are the two major limitations of FNAB. The indeterminate cytology had been considered the "gray zone" in thyroid FNAB cytology and surgical intervention is generally recommended for these lesions.[26] The rate of malignancy in patients with indeterminate FNAB cytology is reported to be 16-54%.[14,28] Based on the present study, the chance of thyroid malignancy being discovered on histology in indeterminate cytology is 36.5% (27 out of 74 cases) in which 22 (81%) cases were papillary thyroid carcinoma. It is therefore an option to do additional histologic examination like frozen section to confirm the cytology finding and to help the decision making as to the extent of the procedure during thyroidectomy. The accurate diagnosis of malignancy intraoperatively will avoid the need for a completion thyroidectomy in many of these patients.

Frozen section examination has been used by many surgeons to clarify the diagnosis of fine needle aspiration biopsy. The significance of the routine use of this test is still controversial. Some studies suggest the intraoperative FSE of thyroid nodules is not useful and should not be performed routinely.[27,] According to the Johns Hopkins Thyroid Tumor Center[28] and Memorial Sloan-Kettering Cancer Center, [33] the routine use of FS is not warranted because it adds little to the intraoperative decision making. In the contrary, some researchers suggest that FSE is useful to verify FNAB results and that FSE can be expected to influence the choice of surgery in indeterminate FNAB cytology.[26,29,30] This is supported by the Mayo Clinic group which indicated that intraoperative frozen section analysis play an integral role in the management of surgical thyroid patients.[31]

In our series, when frozen section examination was used intraoperatively to determine malignant thyroid nodules, the 83.3% sensitivity, 100% specificity, 100% positive predictive value and 96.4% negative predictive value of our study are comparable with the range reported in other series: sensitivity 19-96%,[13,17,24,30,34-36] specificity 96.5-100%, [13,17,24,30,34-36] positive predictive value 97-100%, [13,17,30,34-36] negative predictive value 81.3-98%. [13,17,30,34-36] This means that intraoperative FSE had a diagnostic accuracy rate of 96.7%, which is higher than FNAB alone. Based on this, we are 100% confident that a benign FSE will have a benign histology. The result also suggests that a malignant FSE finding is useful, despite a benign preoperative cytology, in influencing the intraoperative planning of the extent of surgery. The false negative rate of FSE is 3.6% and this is contributed by occult carcinomas that were missed during the frozen section.

Several series also reported an improved sensitivity and specificity for detection of malignancy when FNAB and FSE are combined and thus recommend both to be used routinely.[17,29-32] When applied to these groups in the present series, the combined test showed an accuracy rate of 97.1% in a concordant FNAB and FSE findings and the result significantly improved the rate of detection of malignancy in nodular thyroid lesions over USG-FNAB alone. Hence, intraoperative FSE complements preoperative FNAB cytology. Although the accuracy rate has improved, the concordant benign cytology and FSE were associated with a 5% false negative rate. The false negative in this series may be contributed by the papillary microcarcinomas which were missed during fine needle aspiration and frozen section.

In the case of discordant USG-FNAB and FSE findings, our result indicate that the frozen section diagnosis is superior than the USG-FNAB, having accuracy rate of 83.3% compared to 16.7%. A similar result reported by Chang et.al.[17] noting that FSE diagnosis is significantly better than FNAB in discordant cases (78.9% vs 21.1%). For that reason, our result suggests that FSE may eliminate FNAB when the findings of both tests are discordant. We identified 3 false negative cases on FNAB that were correctly identified as malignant lesions on FSE. In this case, the reliance on FNAB cytology to determine the extent of surgery would lead to a significant number of completion thyroidectomy. Hence, it is favorable to perform total thyroidectomy when FSE diagnosis is malignant in benign FNA cytology. Another diagnostic dilemma occurs when a malignant FNA cytology meets a benign frozen section diagnosis. In this discordant situation, we identified two false positive cases on cytology that were correctly diagnosed as benign on FSE. In such cases, it is preferable to perform limited surgery following a benign FSE in the face of a malignant cytodiagnosis.

In the case of indeterminate cytology and unsatisfactory FNA result, some studies recommend performing FSE to clarify the preoperative cytology findings. [14, 29] Applying these to the present study, the accuracy (sensitivity, specificity and accuracy rate) of FSE in diagnosing malignant thyroid nodules in cases of indeterminate cytology and FNAB with inadequate specimen is 100%. Our result is better than the 67% sensitivity, 100% specificity and 89% accuracy rate reported by Mandell et.al.[14] Based on our result, we are 100% confident that a malignant FSE will result into a malignant histology in a nodule with indeterminate cytology. This high accuracy rate proved that FSE is a powerful test for intraoperative decision making concerning the extent of thyroidectomy in indeterminate cytologic findings.

The yield of carcinoma for USG-FNAB as diagnostic tool is 28% and that of FSE is 22%. This signifies that both tests increase the yield of malignancy in excised thyroid nodules. The USG-FNAB identified carcinoma in 37.7% (26 out of 34) preoperatively whereas FSE identified 100% of malignancies. This discrepancy is mainly due to the number of indeterminate diagnosis by FNAB cytology which accounted for 29.5% in our series. The diagnosis of follicular carcinoma is defined by vascular or capsular invasion and it is impossible to evaluate these criteria by cytology. These findings suggest that FSE is superior to FNAB in detecting malignant nodular thyroid lesion.

Conclusion

Ultrasound guided FNAB is an accurate preoperative test for the evaluation of nodular thyroid disease. It helps to distinguish malignant from benign lesions for the purpose of selecting patients that need surgical treatment. The intraoperative frozen section is a valuable test for confirming the cytologic diagnosis. It is especially important in identifying malignant thyroid nodule in cases with indeterminate cytology. The combination of USG-FNAB and FSE greatly improves the accuracy rate in thyroid cancer detection.

Our result translates into the following recommendations: (1) USG-FNAB should be the initial diagnostic test to determine malignant nodular thyroid lesions, (2) USG-FNAB should be the triage tool in selecting patients that will undergo thyroidectomy, (3) intraoperative frozen section examination may be use to confirm a malignant or benign FNAB cytology and (3) frozen section examination should be use routinely in cases of indeterminate cytology. The use of FSE in these cases will help the surgeon in decision making during surgery.

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ORIGINAL ARTICLE

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Effect of Insulin Detemir (Levemir®) on Risk of Hypoglycaemia and Glycaemic Parameters: Experience from Real Life Practice in Indonesian Patients with Diabetes Mellitus

Pradana Soewondo[1] and Anand Jain[2]

[1]*Division of Endocrinology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia*
[2]*Novo Nordisk Pharma Operations (BAOS) Sdn Bhd, Kuala Lumpur, Malaysia*

Abstract

Objective. To evaluate the safety and efficacy of insulin detemir in patients with diabetes mellitus in Indonesia.

Methods. This was a multi-centre, prospective, 12-week observational study in patients with diabetes mellitus conducted in Indonesia.

Results. A non-randomized sample of 1290 patients with diabetes mellitus in which most of them were type 2 diabetes (1285 patients, 57.4% males, mean age 54.1 ± 9.0 years, mean BMI 23.5 ± 4.1 kg/m^2, mean duration of diabetes 6.5 ± 4.9 years) were recruited from 121 sites. No serious adverse drug reactions (SADRs) including major hypoglycaemic episodes were reported at 12 weeks. The rate of total and major hypoglycaemic episodes decreased from 0.0248 to 0.0031 episodes/patient years and from 0.0022 to 0 episodes/patient years from baseline to 12 weeks, respectively. Treatment with insulin detemir was associated with a reduction in HbA_{1c} of -2.0%-point (95% CI, -2.13 to -1.93) from baseline to 12 weeks. Insulin detemir also improved FPG. A slight increase of 0.12 kg (95% CI, -0.05 to 0.29) in body weight was observed from baseline to 12 weeks.

Conclusions. 12-week treatment with insulin detemir was safe and well-tolerated in Indonesian patients with type 2 diabetes. It improved glycaemic control, decreased the risk of hypoglycaemia and was relatively weight neutral.

Key Words: Insulin detemir; Indonesia; Safety, Efficacy

Introduction

Diabetes mellitus is a chronic and progressive disease, and is associated with a series of macro- and micro-vascular complications. The Diabetes Control and Complications Trial (DCCT) demonstrated that good metabolic control, resulting from intensive insulin therapy, reduced the risk of development and/or progression of retinopathy, nephropathy and neuropathy in type 1 diabetes[1]. The United Kingdom Prospective Diabetes Study (UKPDS) and other studies showed that intensive glycaemic control in type 2 diabetes could significantly reduce the risk of development and/or deterioration of micro-vascular complications[2,3] and may improve cardiovascular outcomes[3]. An important new insight is the existence of so-called 'glycaemic metabolic memory.' Both DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) and UKPDS follow-up studies[4,5] demonstrated that the level of glucose control in the early years of disease would impact dramatically on the development of later complications. In both studies, in comparison with patients who were not optimally controlled, patients with tighter glycaemic control during the study would develop less micro- and macrovascular complications more than 10 years after discontinuation of the study. These observations emphasize the need to control glycaemia as tight and as early in the disease process as possible.

Insulin treatment is the cornerstone of diabetes management. It is the only means of achieving glycaemic control in insulin deficient patients with type 1 diabetes. It is also the only effective treatment for many patients with type 2 diabetes when deterioration of beta cells has progressed to the point that diet and oral agents have become inadequate to control hyperglycaemia. However, the main limitations to human insulin treatment include weight gain and an increased risk of hypoglycaemia. Furthermore, the desired relatively constant basal insulin level is difficult to obtain with the currently available intermediate-acting insulin preparations.

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Corresponding author: Dr Pradana Soewondo, SpPD-KEMD, Division of Endocrinology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital,Jakarta, Indonesia
Tel. number: +62 21 3907703
Fax number: +62 21 3928659
E-mail: soewondops@yahoo.com

Insulin detemir is a long-acting insulin analogue with improved pharmacological properties providing 24 hour basal insulin coverage. It has been demonstrated that insulin detemir treatment can result in more predictability (lower within-patient variability) of fasting blood glucose values[6,7], reduction of hypoglycaemic episodes[8,9], neutral or less weight gain both in type 1 diabetes and type 2 diabetes[6-9].

Asia is the major site of a rapidly emerging diabetes epidemic[10]. India and China will remain the two countries with the highest numbers of people with diabetes (79.4 million and 42.3 million, respectively) by 2030[10]. In a national study from June 2007 through May 2008 which was designed to estimate the prevalence of diabetes among Chinese adults, 92.4 million adults had diabetes[11]. Additionally, among top ten countries with bigger number of patients with diabetes, four of them are located in Asia: Indonesia, Pakistan, Bangladesh, and the Philippines. The prevalence of diabetes in urban Indonesia was 5.7%, consisting of diagnosed diabetes mellitus 1.5%, estimated undiagnosed diabetes mellitus 4.2% and IGT 10.2%.[12] Due to the high prevalence in Indonesia, diabetes will be a heavy social burden for the country. Until now no clinical data on use of insulin detemir in Indonesian patients was available. Therefore, the study was undertaken to evaluate the safety and effectiveness of treatment of insulin detemir in Indonesian patients with type 1 or type 2 diabetes in clinical setting.

Methods and Materials

Study design

This was a multi-centre, prospective 12-week observational study in patients with type 1 or type 2 diabetes mellitus conducted in Indonesia. Data was collected from the patients' records or self-monitored blood glucose diary or patients' own recollection at baseline and at approximately 12 weeks after starting insulin detemir. Patients were encouraged to comply with the protocol and come for the follow-up visits as per the schedule. All patients were to be prescribed insulin detemir at the discretion of the physician. There was no comparator group and patients served as their own controls (from baseline). Written informed consent was obtained for all patients before any study-related activity. The study was performed in accordance with the Declaration of Helsinki[13] and International Conference on Harmonisation Good Clinical Practice[14].

Patients

Patients with type 1 or type 2 diabetes mellitus including newly diagnosed patients, were included in this study. Patients who were unlikely to comply with protocol, e.g. uncooperative attitude, inability to return for the final visit, patients who had hypersensitivity to insulin detemir or any of the excipients were excluded from the study. Patients were to be withdrawn from the study if they became pregnant or at the discretion of the investigator. At all visits, the number of hypoglycaemic episodes experienced during the past 4 weeks, including the timing (daytime vs. nocturnal) and the number of major episodes, and the 6 most recent fasting plasma glucose values (from patient's self-monitored blood glucose diary) were recorded. Any adjustments to the timing and dose of insulin detemir therapy, including any change to concomitant insulin or oral hypoglycaemic agents were recorded.

Endpoints

The primary endpoint was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic episodes, during 12 weeks of insulin detemir therapy. The secondary endpoints included the number and incidence of hypoglycaemic episodes in the 4 weeks preceding the final visit (12 weeks); incidence of adverse drug reactions (ADRs) and number of serious adverse event (SAE), change in body weight, HbA_{1c}, fasting plasma glucose (FPG) and the variability in FPG.

Major hypoglycaemic episode was defined as an episode with blood glucose <50 mg/dl (2.8 mmol/l), and with severe central nervous system symptoms consistent with hypoglycaemia in which the patient was unable to treat himself/herself, or reversal of symptoms after either food intake or glucagon or intravenous glucose administration.

Statistical analyses

Statistical analyses were performed for all patients, previous treatment with oral anti-diabetic drugs (OAD) and previous treatment with OAD+insulin. The summary of the baseline characteristics and safety data and the analysis of the efficacy outcome variables were based on Full Analysis Set (FAS), which consisted of all patients with a baseline visit, had been treated with insulin detemir at least once and did not use insulin detemir before the start of the study.

All results were interpreted in a descriptive manner. Hypoglycaemic events were expressed as absolute number and the number of episodes/ patient years. All testing used two-sided tests with significance level α= 0.05 and were performed using SAS, Version 9.1 (SAS Institute, Cary, NC).

Results

Baseline demographics and diabetes therapy

Patient demography is summarised in Table 1. Total 1290 patients were recruited in this study – 5 with type 1 diabetes and 1285 with type 2 diabetes. As most of the patient population had type 2 diabetes, this article presents data of type 2 diabetes patients only. In these 1285 patients, 52 patients were on no prior therapy, 832 patients (65.2%) were on only OAD and 232 patients (18.1%) were on OAD+Insulin. However, there were 582 patients (out of 832) who had OAD only at recruitment, shifted to OAD + basal insulin at baseline and continued

Table 1. Baseline Characteristics – type 2 diabetes

	Patients previously on 'OAD + insulin' therapy	Patients previously on 'OAD therapy only'	Total
N	182	582	1285
Age (Mean ±SD), years	56.0 (7.6)	55.4 (8.0)	54.1 (9.0)
Gender, M/F (%)	57.7/42.3	56.2/43.8	57.4/42.6
Weight (Mean ±SD), kg	58.1 (11.1)	63.2 (10.9)	61.9 (11.4)
BMI (Mean ±SD), kg/m^2	22.6 (4.9)	23.9 (3.8)	23.5 (4.1)
HbA_{1c} (Mean ±SD), %	9.2 (1.5)	9.5 (1.7)	9.4 (1.8)
Diabetes duration (Mean ±SD), years	7.3 (5.4)	6.2 (4.7)	6.5 (4.9)
Reason(s) for starting a new therapy, n (%)			
i) Improve glycaemic control	117 (64.3)	551 (94.7)	1078 (83.9)
ii) Try new insulin	144 (79.1)	324 (55.7)	762 (59.3)
iii) Improve weight control	41 (22.5)	259 (44.5)	488 (38.0)
iv) Patient dissatisfaction with current therapy	31 (17.0)	190 (32.6)	373 (29.0)
v) Reduce plasma glucose variability	26 (14.3)	212 (36.4)	348 (27.1)
vi) Unstable diabetes	25 (13.7)	176 (30.2)	306 (23.8)
vii) Reduce risk of hypoglycaemia	62 (34.1)	118 (20.3)	289 (22.5)
viii) Side effects from current therapy	9 (4.9)	56 (9.6)	138 (10.7)
ix) Change due to insulin pen	12 (6.6)	52 (8.9)	130 (10.1)

SD: Standard deviation; Percentages are based on the number of subjects with non-missing values; A subject may have findings in more than one category in 'Reason(s) for starting a new therapy'; BMI: Body Mass Index

on OAD + Basal insulin upto theend of study. Similarly, there were 182 patients (out of 232) on OAD + Basal at recruitment, till the end of study therapy. Only these patients have been included here.

The mean daily dose of insulin detemir at baseline was 13.2U and increased to 14.7U after 12 weeks of treatment. 98.6% patients received insulin detemir once daily at baseline and 97.1% patients were administered insulin detemir once daily after 12 weeks of treatment.

Safety

Adverse events

No SADRs were reported during the study. Two ADRs were reported in this study and both were hypoglycemia. One death was reported. The patient died due to chronic renal failure. The event was assessed as unlikely related to study product.

Body weight

The estimated mean change in body weight from baseline to end of treatment was 0.12 kg (95% CI,-0.05 to 0.29) in all patients. In patients previously treated with OAD only, after transferring to insulin detemir (OAD group), the estimated mean change in body weight from baseline to end of treatment was 0.24 kg (95% CI, 0.01 to 0.46). In patients previously treated with OAD+insulin, after switching to insulin detemir (OAD+insulin group), the estimated mean change in body weight from baseline to end of treatment was -0.91 kg (95% CI, -1.44 to -0.37).

Hypoglycaemic events

The number of hypoglycaemic episodes after 12 weeks of treatment was reduced for overall and major hypoglycaemic episodes by categories of total and time of occurrence (daytime or nocturnal) for all patients, OAD group and OAD+insulin group. (Table 2)

Efficacy

HbA_{1c}

In all patients, the estimated mean change in HbA_{1c} from baseline to end of treatment was -2.0% (95% CI, -2.13 to -1.93). In OAD group, the estimated mean change in HbA_{1c} from baseline to end of treatment was -2.1% (95% CI, -2.23 to -1.97), while in OAD+insulin group, it was -1.6% (95% CI, -2.10 to -1.36). (Table 3)

FPG

In all patients, the estimated mean change in FPG from baseline to end of treatment was -72.9 mg/dL (95% CI, -103 to -60.1) (Table 3). The mean FPG variability was after 12 weeks of treatment reduced by 5.6 mg/dL from baseline. In OAD group, the mean FPG variability was reduced by 4.6 mg/dL from baseline after 12 weeks of treatment. In OAD+insulin group, the mean FPG variability was reduced by 7.6 mg/dL from baseline after 12 weeks of treatment.

Discussion

The results of this cohort of patients from Indonesia with type 2 diabetes suggest that 12-week treatment with insulin detemir improves glycaemic control without increasing the risk of hypoglycaemia and is relatively weight neutral. There were no SADRs, including major hypoglycaemic episodes reported during the study. The rate of SADRs in the Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE) European study cohort was 1%[15]. The lower rate of hypoglycaemic events in the Indonesian patients could be due to the lower dose of insulin detemir administered in this study and the fact the dose remained almost constant during 12-weeks. In general, the safety profile observed in this study was however consistent with the safety profile in PREDICTIVE Europe as well as in clinical trials where, insulin detemir has been shown to have a low risk of

Table 2. Hypoglycaemia Reported during Treatment

	Total hypoglycaemia		Daytime hypoglycaemia		Nocturnal hypoglycaemia	
	All events	Major events	All events	Major events	All events	Major events
Previously on OAD + insulin						
Baseline, N=182						
N (%)	10 (5.5%)	1 (0.5%)	10 (5.5%)	1 (0.5%)	8 (4.4%)	0 (0.0%)
Episodes/patient years	0.0247	0.0014	0.0137	0.0014	0.0110	0.0000
Week 12, N=182						
N (%)	2 (1.1%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Episodes/patient years	0.0055	0.0000	0.0055	0.0000	0.0000	0.0000
Previously on OAD						
Baseline, N=582						
N (%)	23 (4.0%)	2 (0.3%)	21 (3.6%)	2 (0.3%)	19 (3.3%)	0 (0.0%)
Episodes/patient years	0.0202	0.0009	0.0112	0.0009	0.0090	0.0000
Week 12, N=582						
N (%)	5 (0.9%)	0 (0.0%)	5 (0.9%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Episodes/patient years	0.0047	0.0000	0.0039	0.0000	0.0009	0.0000
All patients						
Baseline, N=1285						
N (%)	60 (4.7%)	8 (0.6%)	56 (4.4%)	7 (0.5%)	47 (3.7%)	3 (0.2%)
Episodes/patient years	0.0248	0.0022	0.0153	0.0016	0.0096	0.0006
Week 12, N=1278						
N (%)	8 (0.6%)	0 (0.0%)	8 (0.6%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Episodes/patient years	0.0031	0.0000	0.0027	0.0000	0.0004	0.0000

Table 3. HbA_{1C} and FPG Change during Treatment

Variable (SD)	N	Baseline	Final visit	Absolute change
Previously on OAD + insulin				
HbA_{1c}, %	9	9.0 (1.6)	7.4 (0.8)	-1.6 (0.8)
FPG, mg/dL	59	206.3 (94.8)	140.7 (29.9)	-65.6 (84.9)
Previously on OAD				
HbA_{1c}, %	147	9.5 (1.7)	7.4 (1.0)	-2.1 (1.4)
FPG, mg/dL	342	207.6 (62.6)	134.9 (34.2)	-72.7 (57.1)
All patients				
HbA_{1c}, %	306	9.4 (1.7)	7.4 (0.9)	-2.0 (1.7)
FPG, mg/dL	615	209.3 (64.8)	136.4 (33.0)	-72.9 (61.1)

Data presented as Mean (SD)

hypoglycaemia, in particular, low risk of nocturnal hypoglycaemic episodes.

Furthermore, insulin detemir was weight neutral in the Indonesian study. A small increase in body weight of +0.12 kg was observed after 12 weeks of treatment with insulin detemir in all type 2 diabetes patients treated with insulin detemir. Also this finding is in general, consistent with the finding in the PREDICTIVE European cohort (type 2: -0.4kg)[15-18]. As the Indonesian patient cohort was not as overweight (mean BMI was 23.5 kg/m^2) at baseline compared with the European patients at baseline (mean BMI was 29.5 kg/m^2 for type 2). Furthermore, patients previously treated with OAD showed an increase of 0.24 kg and patients previously treated with OAD+insulin showed a reduction of -0.91 kg in body weight, respectively. These results show the difference between adding insulin detemir to OAD and switching from another insulin to insulin detemir in combination with OAD and suggested that treatment with insulin detemir was weight neutral. Insulin therapy is often associated with weight gain[19]. While the mechanism underlying insulin-associated weight gain is not fully understood, it may result from higher peripheral versus hepatic insulin levels in patients receiving exogenous insulin, more efficient insulin-stimulated lipogenesis, and decreased glycosuria. Body weight is also modulated by the action of insulin at receptors in the brain that, when activated, decrease appetite and food consumption. It may be that the lower weight gains observed in patients treated with insulin detemir versus NPH insulin are related to its avid binding to albumin. Albumin passes freely into the liver via hepatic sinusoids and this may result in increased hepatic and decreased peripheral action for insulin detemir, leading to less weight gain. Binding of insulin detemir to albumin may also enhance its penetration through the blood-brain barrier and action at insulin receptors in the brain[19,20].

The number of total, daytime and nocturnal hypoglycaemic episodes decreased in overall patients after 12 weeks of treatment. This finding is consistent with the observation in other PREDICTIVE cohort studies[16-18] where the frequency of hypoglycaemic episodes decreased after 14 weeks of treatment. Owing to the unique physicochemical structure, insulin detemir shows a relatively flat pharmacokinetic/pharmacodynamic profile and low within-patient variability which may result in reduction in hypoglycaemic events, particularly nocturnal hypoglycaemic events as compared to older basal insulin preparations[21].

Treatment with insulin detemir enabled Indonesian patients with type 2 diabetes to reduce mean HbA_{1c} from 9.4% at baseline to 7.5% after 12 weeks of treatment with a mean reduction of 2.0%-point. In the subgroup analysis, a larger reduction of the mean HbA_{1c} was observed in the subgroup with OAD only as pre-treatment (2.1%)

compared to that in the subgroup with OAD+insulin as pre-treatment (1.6%). However, at the end of treatment HbA_{1c} was comparable in two subgroups (mean HbA1c: 7.4%). The improved glycaemic control observed in the present observational study is strongly supportive of the original physicians' decision to initiate treatment with insulin detemir, which is to improve glycaemic control. Heterogeneity of real-life populations and the absence of a control group in observational studies may limit the conclusions we can draw from them. Furthermore, response rate in terms of HbA_{1c} and FPG measurement (28.6% and 53.1%, respectively) was also low in this study, hence, we should interpret these results carefully. Nevertheless, beneficial information on safety, efficacy and pattern of use of a drug in an extensive patient population can be gained from observational studies.

Conclusion

In conclusion, 12-week treatment with insulin detemir was safe and well-tolerated in Indonesian patients with type 2 diabetes. It improved glycaemic control without increasing the risk of hypoglycaemia and was relatively weight neutral.

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Appendix

The following institutions and persons coordinated the Levemir Study Group: Study Chairman – Pradana Soewondo, Division of Endocrinology, Department of Internal Medicine, Faculty of Medicine, University of Indonesia – Cipto Mangunkusumo Hospital.

The following persons participated in the study (in alphabetical order): Abdul Ghofir, Abdul Kadir, Abiran Nababan, Achmad Rudijanto, Agatha Maharani, Agung Nugroho, Agustina Parmayanti, Aida Mars, Aizil Rifai, Alwi Shahab, Amrizal Amir, An An, Andre Dirjayanto, Anton Cahaya Widjaja, Arles, Arthur L, Asrizal, Boedi Tedjodihardjo, Bowo, Budi Subagijo, Charles Yapiter, Dany Irawan, Davis Ajiariwibowo, Deddy K. Kurniawan, Dede Budiman, Dewanto Tedjopranoto, Djoko Wahono Soeatmadji, Djonie Djunaedi, Eddy Setijoso, Eddy Supriadi, Eduard P. Taliwongso, Etty Aminah, F. Hadi Halim, Faried Sanusi, Febrilla Harmaini, Ferry Usnizar, Franky Kambey, Fuad Hamdun, Gatoet Ismanoe, Gatot Soegiarto, Ginding Seruniwati, Gunawan, H. Edwin Setiabudi, H. Kusdarmadji, H. Lukman L. Tobing, H. Setiawan, H. Ummie Wasitoh, Handi Sutanto, Hans Tandra, Harsinen Sanusi, Hasan Alim, Hasan Halilintar, Hertika Hardja, Ida Ayu Khsanti, IGP Suka Aryana, IN Dwi Sutanegara, Indah Nur Rachmani, Indra Politan, Ishak Dinata, Izwar, JBH Bowo, Jacobus Albertus, Jaowenny L. Lolo, Jimmy Palealu, Johanes Vincentius, Karel Arrahmanda, Kartariadi, Kuntio S. Herlambang, Lalu Ahmadi Jaya, M. Bukhar, M. Jasin Jachja, M. Noer Shoffi, M. Nur Aziz, M. Saugi Abduh, Made Astawa, Mardianto, Mary Elizabeth, Mery Harita, Myrna Martinus, Nandavati Kurnia, Nanny NM Soetedjo, Nono Mattarungan, OK Yulizal, Olly Indrayani, Olly Renaldi, Pandji Mulyono, Paulina, Prasna Pramita, Purnama Nugraha, Ratih Gunadi, Ratni Rahim, Ratna Saraswati, Rayendra, Reynold Malingkas, Ristua Butar Butar, Rizky Perdana, Robby R. Nurtani, Robert Arjuna, Robinson, Salli Rosefi, Sebastianus Jobul, Seson, Sofian, Sugiarto, Sulhani, Sumpena, Susie Setyowati, T. Ivone Wulansari, Tjendrawati Hermawan, Tri Prabowo, Triyanto Sutjahjo, Valentina Mandagi, Veronica Dhian, Waluyo Dwi Cahyono, Wendy Budiawan, Wilif Rizal, Yoseph Chandra, Yuanita Asri Langi, Yulianto Kusnadi, Yunus Tanggo

CASE REPORT

JAFES Journal of the ASEAN Federation of Endocrine Societies

Complete Atrioventricular Block Complicating Hypothyrodism

Ratchaneewan Kwancharoen, Swangjit Suraamornkul, Petch Rawdaree

Endocrinology and Metabolism Unit, Bangkok Metropolitan Medical College and Vajira Hospital, Bangkok, Thailand

Abstract

An 85-year old Thai woman was admitted to the hospital for dyspnea. Her ECG showed complete atrioventricular (AV) block. Her laboratory data upon admission revealed low serum thyroxine level and elevated thyrotropin level. Levothyroxine was started, and the AV conduction block was supported by a temporary pacemaker. At the end of the second week, her free T4 fell within normal range. The temporary pacemaker was subsequently removed. She was discharged without permanent pacing. This case demonstrated that hypothyroidism can cause complete atrioventricular block. Levothyroxine replacement can restore AV conduction in the hypothyroid patient.

Key words: hypothyroidism, atrioventricular block

Hypothyroidism can cause a variety of manifestations, including cardiovascular dysfunction. The more common presenting signs are sinus bradycardia and pericardial effusion.[1] The affected patient usually has severe symptoms. Hypothyroidism rarely causes complete atrioventricular (AV) block.[2] In this paper, we report a case presenting with mild symptoms of hypothyroidism but with the uncommon manifestation of complete AV block. The heart block was subsequently treated with thyroid hormone replacement.

Case Report

A previously well 85-year-old Thai woman consulted for a two-month history of dyspnea. The dyspnea was constant and not apparently aggravated by exertion. She also noted associated leg edema, constipation, cold intolerance and dry skin. She did not experience orthopnea, paroxysmal nocturnal dyspnea, chest pain, syncope, urinary symptoms or unusual weight loss. She had hypertension and dyslipidemia for approximately 2 years, but had no maintenance medication. She did not have any history of thyroid problems; heart disease; and irradiation to, or surgery to the neck area.

On physical examination, she was conscious and cooperative but appeared tired. Her vital signs were as follows: temperature 36.7 °C, blood pressure 120/90, pulse rate 40 beats/minute, and respiratory rate 18 breaths/minute. She had coarse hair, facial puffiness and thinning of the lateral third of the eyebrows. She had no macroglossia. The right lobe of the thyroid gland was not palpable, while the left lobe was firm and mildly enlarged. No superficial lymphadenopathy was detected. Careful examination of the cardiovascular system revealed bradycardia; normal S1 and S2; and no cardiac murmur. Examination of the extremities showed dry, cracked skin with no apparent yellowing of the palms. She had full and slow pulses, and grade 1 bipedal pitting edema. Neuromuscular examination revealed slow relaxation of reflexes.

Laboratory results were as follows: fasting plasma glucose 88 mg/dL, blood urea nitrogen 17 mg/dL, and serum creatinine 1.4 mg/dL. Her lipid profile revealed a total cholesterol level of 180 mg/dL, low-density lipoprotein cholesterol (LDL-C) of 114 mg/dL, high-density lipoprotein (HDL-C) of 31 mg/dL and triglyceride level of 154 mg/dL. Troponin-T level was within normal limits. Her thyroid function tests revealed elevated thyroid stimulating hormone (TSH) (> 75 mIU/L, normal value 0.4 to 4.0 mIU/L), low free T3 (1.0 pg/mL, normal value 2.0 to 4.0 pg/mL), and low free T4 (< 0.30 ng/dL, normal value 1.0 to 2.0 ng/dL). Antithyroglobulin antibody (anti-TG Ab) was > 3,000 IU (normal value 0 to 40 IU), and antithyroperoxidase antibody (anti-TPO Ab) was > 100 IU (normal value 0 to 35 IU).

Her chest x-ray demonstrated normal lung parenchyma and thoracic cage, and mild cardiomegaly. A 12-lead electrocardiogram (ECG) showed complete heart block (Figure 1).

She underwent temporary pacemaker insertion with an output of 40 mA and a set rate 60 beats/minute. The ECG done after the procedure is shown in Figure 2.

On admission, the patient was started on levothyroxine at a dose of 25 mcg/day. This dose was adjusted by increments of 25 mcg every three days until a dose of 100 mcg/day was reached by the tenth hospital day. Her heart rate increased, and some electrical activity was found to be conducted through the atrioventricular node as shown in Figure 3.

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Corresponding author: Ratchaneewan Kwancharoen, MD
Endocrinology and Metabolism unit , Bangkok Metropolitant Medical Collage and Vajira Hospital,Bangkok,Thailand.
E-mail: ratch.kwn@gmail.com

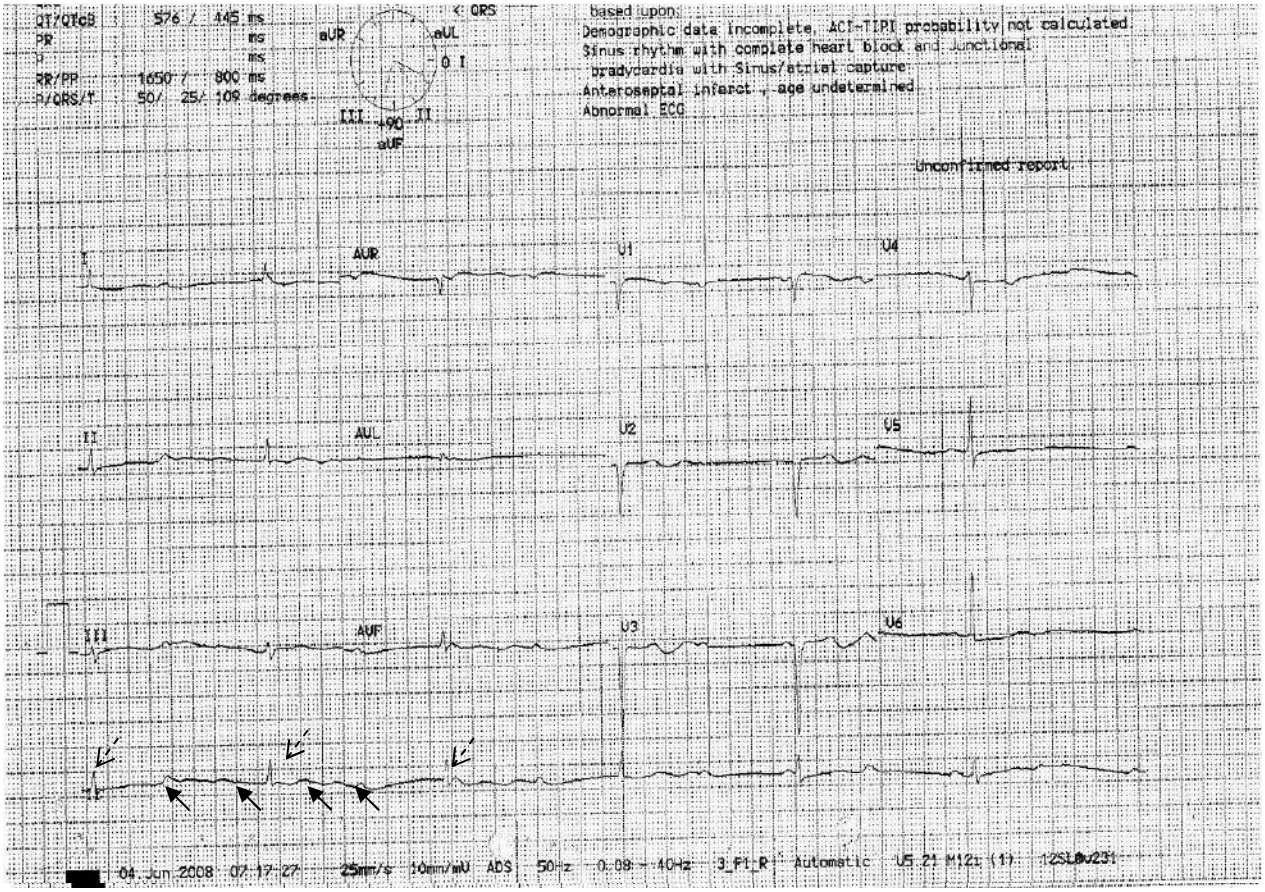

Figure 1. Complete heart block pattern on 12-lead ECG showing unconducted P waves (*bold arrows*) and idioventricular rhythm (*dashed arrows*).

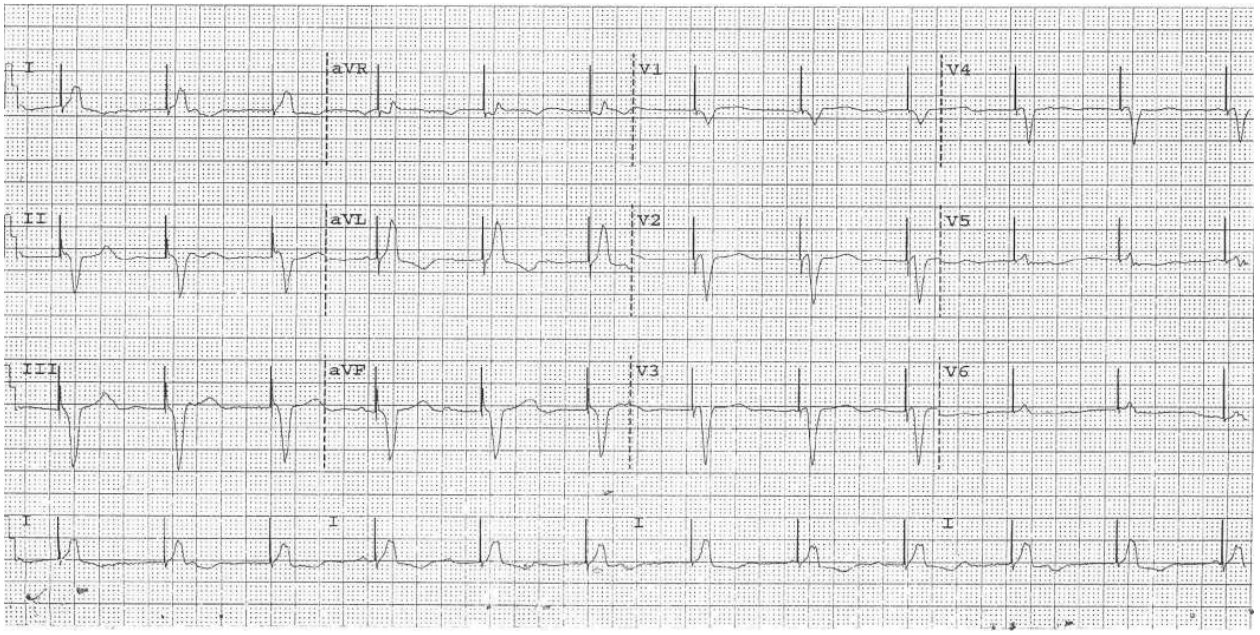

Figure 2. Twelve-lead ECG after temporary pacemaker insertion.

On the second week of levothyroxine replacement, her free T4 level became normal (1.04 pg/mL). Her ECG was compatible with a Mobitz type I atrioventricular block (Figure 4). The temporary pacemaker was subsequently removed. No new conduction blocks were observed on close monitoring during the following week. She was discharged on the third week of her hospital stay.

The patient returned for follow-up 2 weeks after discharge. She did not experience dizziness, dyspnea or syncope. Subsequent ECGs done (Figures 4 and 5) shows

persistence of the same Mobitz type I AV block pattern. Free T4 level was within normal (1.54 pg/mL).

Discussion

Thyroid hormones affect various organs throughout the body, particularly the cardiovascular and autonomic systems. There are three main physiologic mechanisms by which thyroid hormones affect the heart. First, triiodothyronine (T3) binds to the T3 receptor in the nucleus of the cardiac myocyte and causes specific gene expression. The second mechanism is via the effect of T3 on the sensitivity of the sympathetic nervous system. Third, T3 causes changes in the peripheral circulatory system that results in an increase in cardiac filling and changes in cardiac contractility.

Thyroid hormones also play an important role in electrical current generation and conduction in the myocardium. Triiodothyronine increases systolic depolarization and decreases diastolic repolarization. It shortens the duration of the action potential, the refractory period of the atrial myocardium and the atrioventricular nodal period. These changes are caused by increase in sodium pump density and sodium and potassium permeability. For the electrical current generation, T3 causes an increase in the L-type calcium channel at the sinu-atrial node.[2]

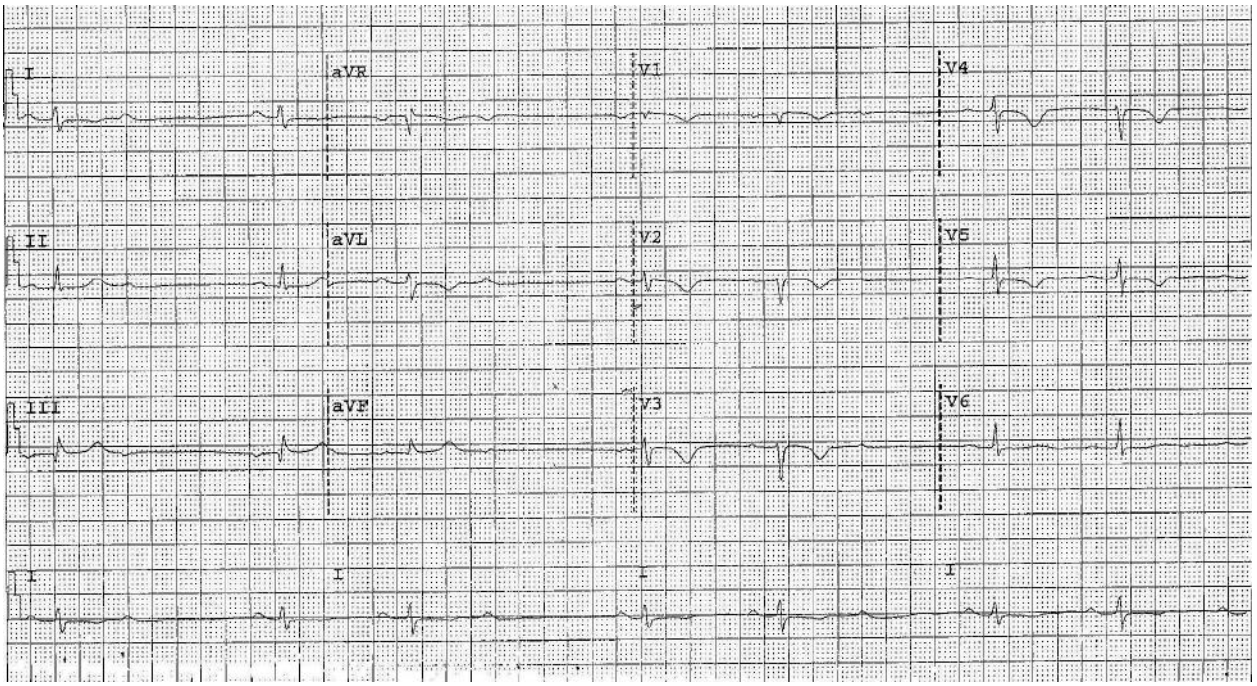

Figure 3. Twelve-lead ECG after 10 days of levothyroxine treatment.

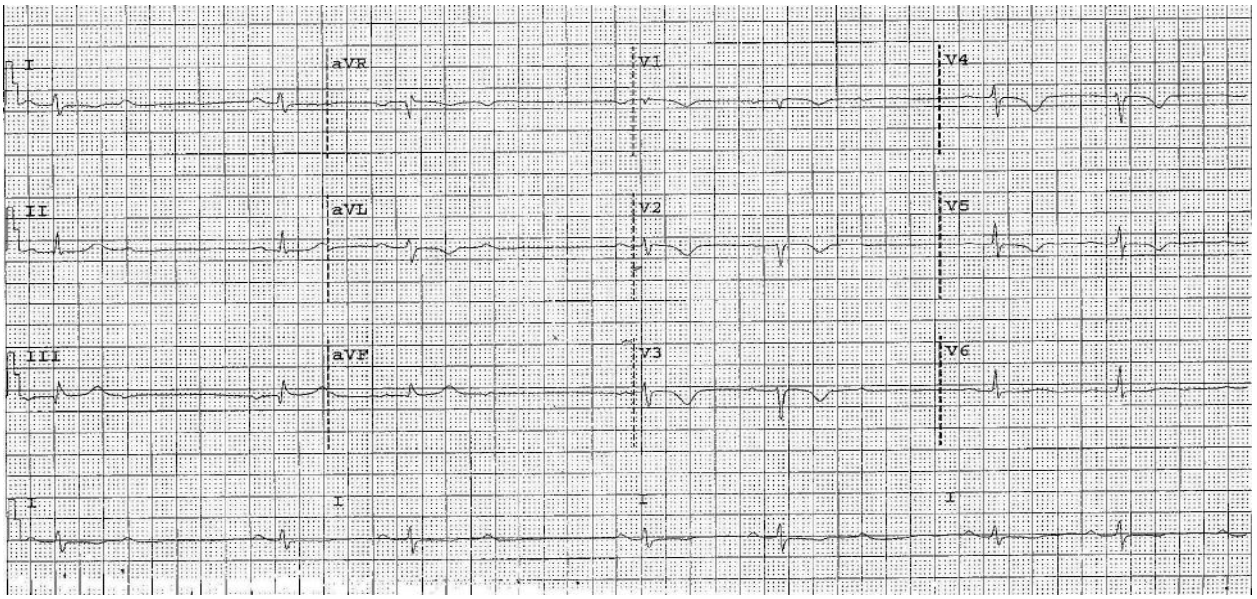

Figure 4. Twelve-lead ECG after 21 days of levothyroxine treatment.

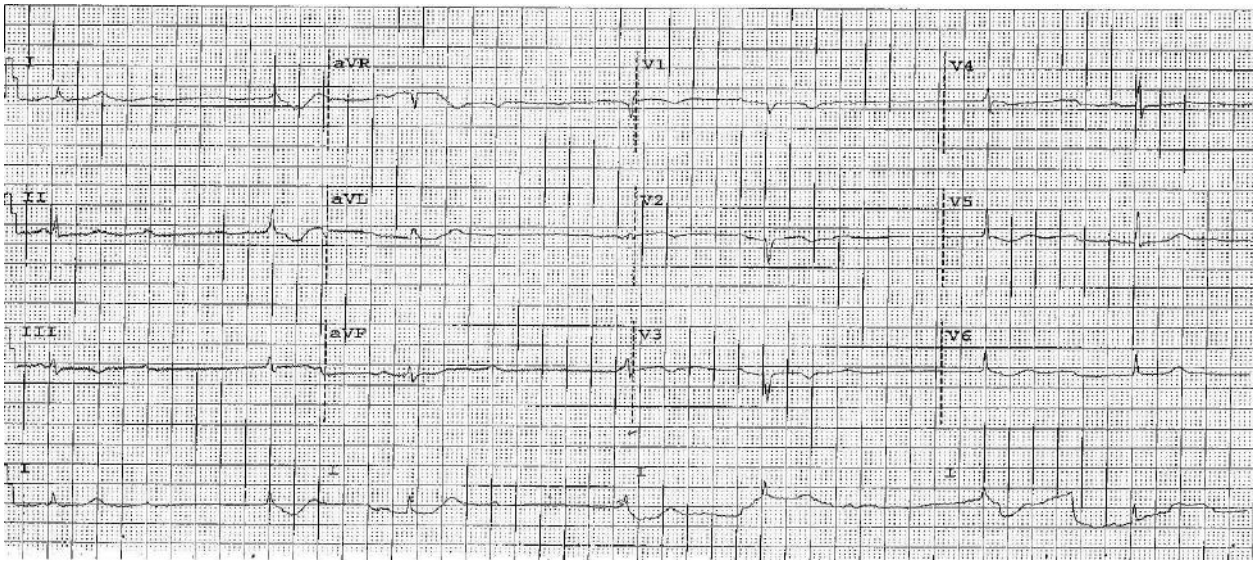

Figure 5. Twelve-lead ECG on the fifth week of levothyroxine treatment.

The cardiac electrical activity changes that can be observed in hypothyroid patients are sinus bradycardia, QT interval prolongation, T wave inversion and AV block. Other cardiovascular effects include increased peripheral vasoconstriction; decreased cardiac contractility; and prolonged diastolic relaxation. Subsequently, cardiac output decreases due to a reduction in stroke volume and heart rate. Changes ensue as a result of the decrease in inotropy and chronotropy, such as narrowing of pulse pressure, prolongation of circulatory time and decrease in peripheral blood flow.[3-5]

The estimated prevalence of hypothyroidism varies, depending on the population studied. In the United States, hypothyroidism affects approximately 0.3% of the general population.[1] Among healthy elderly individuals, prevalence rates range from 0.55 to 1.5%.[6-7] Moreover, asymptomatic hypothyroidism rarely causes cardiovascular morbidity and mortality. Although the AV node is the first part of the AV conduction system to be affected by aging, the prevalence of second and third degree blocks in the general population is only approximately 1%.[8-9]

In this case, the patient had been well until a few weeks before admission, and had never had any prior arrhythmic event. Most case reports of hypothyroid patients with conduction abnormalities describe severe accompanying symptoms, such as myxedema coma. In the absence of these symptoms, conduction abnormality is usually accompanied by other cardiac conditions, such as cardiomegaly or pericardial effusion.[10-12] In contrast, the patient had mild to moderate symptoms of hypothyroidism, but had a severe cardiovascular manifestation of complete AV block.

In previous case reports, conduction blocks were reversed by thyroxine replacement after a few days to a few weeks. Although the patient received an adequate dose of thyroid hormone and became subsequently euthyroid, she did not revert to sinus rhythm. Her ECG tracing revealed a Mobitz type I pattern which was not clinically significant and did not require any treatment. The patient may have had an underlying Mobitz type I abnormality. Finally, she was discharged without the need for a pacemaker.

In conclusion, this case demonstrates an uncommon presentation of hypothyroidism that can cause complete atrioventricular block. The AV block was treated with appropriate diagnosis and management. With prompt recognition and treatment, we were able to avoid invasive procedures and minimize morbidity.

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CASE REPORT

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Temporal Bone and Vertebral Metastases of Papillary Thyroid Carcinoma Manifesting as Cranial Nerve VII Palsy and Spinal Cord Compression

Mark Anthony Sandoval and Laura Rosario T. Acampado

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine,
College of Medicine and Philippine General Hospital
University of the Philippines Manila

Abstract

Cranial nerve VII palsy and spinal cord compression due to bone metastases are unusual manifestations of metastatic papillary thyroid carcinoma. Presented here is the case of a 54-year old man, known to have a goiter, but seeking consult only after he developed right facial weakness. Work up revealed a mass causing lysis of the right temporal bone with resultant facial nerve involvement. The temporal mass was eventually proven to be metastatic papillary carcinoma. The thyroid was subsequently removed, confirming that it was the primary location of papillary carcinoma, follicular variant. Two weeks after total thyroidectomy, he eventually developed symptoms of spinal cord compression due to vertebral metastases. He received external beam radiation therapy to the spine, radioactive iodine and levothyroxine for TSH suppression. The patient is alive 3 years after the diagnosis but the disease has left him with several disabilities.

Keywords: thyroid cancer, papillary thyroid carcinoma, bone metastasis, vertebral, facial nerve (CN VII) palsy, spinal cord compression

The Case

A 54-year-old male consulted for right-sided facial paralysis. Aside from a thyroid mass that was present for the past 6 years, he had no other known illnesses. No previous consults were made for the thyroid mass. He did not have seizures, loss of consciousness, behavioral changes, severe headache, vomiting, gait disturbance, deafness, tinnitus, otalgia nor otorrhea. He denied palpitations, weight loss, tremors, heat intolerance, hoarseness, dysphagia and dyspnea.

Physical examination revealed heart rate of 68 per minute and blood pressure of 120/90 mmHg. Very notable was peripheral or lower motor neuron facial weakness on the right. Extra-ocular muscles were intact. There were no sensory deficits on the face. There was no gross hearing defect. The rest of the cranial nerve examination was normal. Motor and sensory examination of the extremities was likewise normal. There was no dysmetria, dysdiadochokinesia nor ataxia. There was a 4x3 cm hard mass on the right thyroid lobe. No neck nodes were palpated.

Initial assessment was Bell's palsy and a nontoxic solitary thyroid nodule.

Diagnostic Work-up

A CT scan of the head with emphasis on the temporal bone revealed an avidly enhancing, calcified mass measuring 4.0 x 4.0 x 4.8 cm that caused lysis of the right temporal bone. It obliterated much of the mastoid air cells, but spared the cochlea and semicircular canals. It had an intracranial extraaxial extension, occupying the right posterior fossa and compressing the right cerebellar hemisphere. It also extended inferiorly up to the level of the C2 vertebra (Figures 1, 2 and 3). Free thyroxine and thyrotropin levels were normal (Free T4 15.9 pmol/L and TSH 0.93 uIU/mL).

A CT scan of the neck showed a 4.0 x 4.3 x 3.4 cm heterogeneously enhancing, predominantly solid mass with coarse calcifications occupying the right thyroid lobe. This caused displacement of the trachea to the left. There were no enlarged cervical lymph nodes seen (Figure 4).

Fine needle aspiration of the thyroid nodule was unsatisfactory as it was a bloody smear. Chest x-ray did not reveal any lung masses or bone lytic lesions.

Clinical Course

An incision biopsy of the right skull base mass was performed using the post-auricular approach. Microscopic examination revealed metastatic papillary carcinoma (Figure 5).

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Corresponding author: Mark Anthony Sandoval, MD
Section of Endocrinology, Diabetes and Metabolism, Department of Medicine,
College of Medicine and Philippine General Hospital
University of the Philippines Manila
E-mail: markanthony_sandoval@yahoo.com

Figure 1. CT scan (coronal view) showing an enhancing mass with calcification at the right temporal bone with involvement of the mastoid air cells.

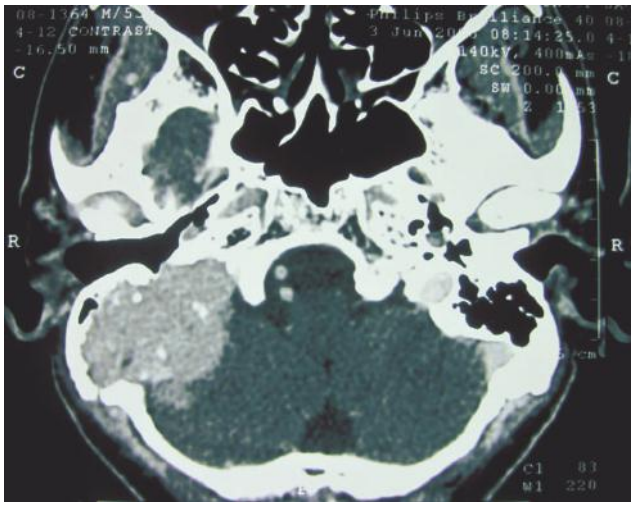

Figure 2. CT scan (axial view) showing a right temporal bone mass with extraaxial extension into the right posterior fossa, compressing the right cerebellar hemisphere.

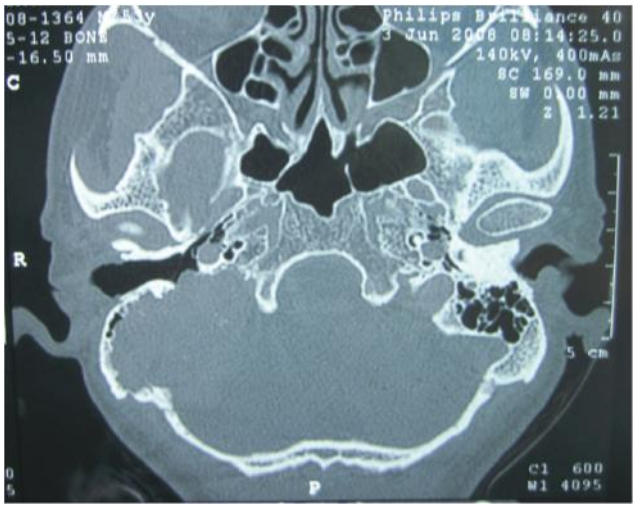

Figure 3. CT scan (axial view) bone window showing lysis of the right temporal bone with disappearance of most of the mastoid air cells.

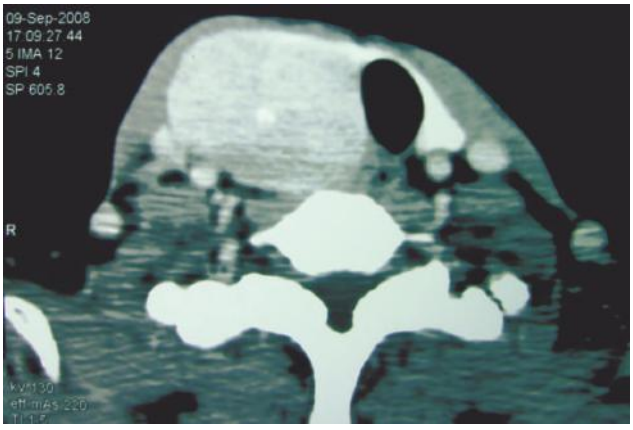

Figure 4. CT scan of the neck (axial view) showing a mass with calcification occupying the right thyroid lobe. Note the displacement of the trachea to the left.

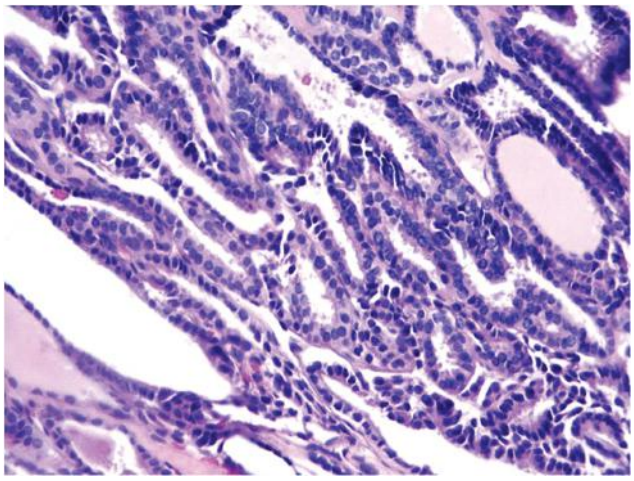

Figure 5. Microscopic examination of the incision biopsy of the right temporal bone mass showing metastatic papillary thyroid carcinoma (400x magnification, H&E stain).

The patient first underwent craniotomy, excision of tumor and partial mastoidectomy on the right. Histopathologic examination revealed metastatic carcinoma, favoring a thyroid origin. Thirteen days after the craniotomy, total thyroidectomy was performed. Histopathologic examination revealed papillary thyroid carcinoma, follicular variant, with involvement of the right recurrent laryngeal nerve. Post-operative staging was T4N0M1 (Stage IV).

Within two weeks after thyroidectomy while waiting for some time to allow TSH to increase in preparation for radioactive iodine therapy, he developed back pain, bilateral leg weakness (motor strength 2/5), decreased sensation on both lower extremities and urinary retention.

Magnetic resonance imaging of the spine revealed multiple masses causing destruction of the T6, L1 and L4 vertebrae, with compression of the spinal cord at the T5-T6

level. Aside from these vertebral masses, abnormal signals were also seen at the T8, T9 and T12 vertebrae.

For the spinal cord compression, he received 30 Gy of external beam radiation directed at the thoracic spine. This resulted in improved sensory function only. Patient remained paraplegic and wheelchair-bound. Urinary retention required the insertion of an indwelling urethral catheter.

Three months after thyroidectomy, he returned for radioactive iodine-131 therapy given at a dose of 200 mCi (7400 MBq). He was pre-treated with oral dexamethasone 5 mg three times daily to prevent worsening of spinal cord compression.

Post-treatment whole body iodine-131 scan revealed functioning thyroid tissue remnants in the neck. There was tracer uptake at the midline thorax, compatible with the known metastases seen on spinal MRI. No tracer uptake was seen at the cranium suggesting that excision of the temporal bone metastasis was complete or that the mass was poor in taking up the radioisotope.

Three months after radioactive iodine, motor strength of the lower extremities improved to 4/5 but patient remained non-ambulatory. Urinary retention was resolved as he no longer required a urethral catheter. Thyroglobulin level remained elevated at 310.4 ng/mL at a TSH level of 0.7 uIU/mL, while on levothyroxine 125 mcg/day, suggestive of persistent disease.

The patient was advised another dose of radioactive iodine therapy and possible spine surgery but declined. He opted for palliative treatment with opioid analgesics and continued levothyroxine treatment for TSH suppression (increased to 150 mcg/day). The patient went back to their home province which is 500 km away from our medical center. The patient is alive three years after the diagnosis but he has not returned for follow-up since.

Final diagnosis was papillary thyroid carcinoma, follicular variant, T4N0M1 (Stage IV) with local invasion to the right recurrent laryngeal nerve (T4) and metastasis (M1) to the following: right temporal bone with involvement of the right facial (CN VII) nerve and with intracranial extraaxial extension to the right posterior fossa, and thoracolumbar vertebrae causing spinal cord compression.

Discussion

Well-differentiated thyroid carcinomas, under which the histologic types papillary and follicular belong, are associated with a good prognosis and impressive cause-specific long-term survival. However, they can also be metastatic, with the lungs and bone being the most common sites of distant spread.[1]

Follicular carcinoma is generally known to be associated more with bone metastases than papillary carcinoma. In a retrospective study involving metastatic differentiated thyroid cancer, follicular carcinoma was found to be the primary tumor for bone metastases in 71% of cases, while papillary carcinoma accounted for only 17%.[2] Also, the bone was the sole site of metastasis in only 12% of papillary carcinoma but in 36% of follicular carcinomas.[3]

In a study of temporal bone metastases, there was only a single case of thyroid cancer out of 47 metastases involving 76 temporal bones. This turned out to be follicular carcinoma. The most common tumor spreading to the temporal bone is breast cancer.[4]

In a case report from India, temporal bone metastasis from differentiated thyroid carcinoma was presented, but again this one proved to be a follicular carcinoma rather than a papillary carcinoma.[5] Medullary thyroid carcinoma has been reported as well to involve the temporal bone.[6] As of this writing, the author's literature search did not reveal any other case of temporal bone metastasis due to papillary thyroid carcinoma.

Thus, the clinical behavior exhibited by this tumor is uncommon for a papillary thyroid carcinoma but would have been expected of a follicular thyroid carcinoma.

For the case being presented here, craniotomy with excision of the temporal bone mass was done first prior to thyroidectomy. The rationale was to avoid the theoretical risk of increased intracranial pressure and herniation that might result from enlargement of the mass once thyroid stimulating hormone (TSH) increases as a consequence of thyroidectomy. Since the mass extended into the posterior cranial fossa, a small increase in tumor size may result in catastrophic tentorial herniation because of the confined space in this region of the cranium.

This phenomenon might actually explain why the patient developed spinal cord compression after he underwent total thyroidectomy. There might have been vertebral metastases to begin with but these were not causing symptoms initially. It is plausible that the increase in TSH that followed thyroidectomy caused the vertebral metastases to enlarge and cause spinal cord compression.

The rise in TSH after thyroidectomy is actually awaited before radioactive iodine therapy is given since this would facilitate uptake of the ablative radioisotope by the tumor cells. The recommended value of 25-30 uIU/mL is usually achieved within a month after total thyroidectomy. One option to avoid having to wait for this period of time to elapse is to administer recombinant human TSH (rhTSH) two days before giving radioactive iodine therapy. Recombinant human TSH, however, is not readily available in our local setting and the cost is prohibitive.

The patient was not able to follow-up anymore after he declined a second dose of radioactive iodine and possible spine surgery. He just opted for palliative treatment. The patient is alive three years after the diagnosis but the disease has left him with significant debilities: facial weakness from the temporal bone metastasis, hoarseness from the recurrent laryngeal nerve involvement, and paraparesis from the vertebral metastases.

Learning points

- Cranial nerve VII palsy and spinal cord compression are unusual manifestations of papillary thyroid cancer.
- Facial weakness was due to facial nerve (CN VII) involvement from temporal bone metastasis.
- Weakness and decreased sensation of the lower extremities, and urinary retention were due to spinal cord compression from thoracolumbar vertebral metastases.
- Though follicular carcinoma is more commonly known to metastasize to bone, this case demonstrates that papillary carcinoma can also widely metastasize to bony structures (temporal bone and vertebrae) with resultant neurologic deficits and debilitating consequences.
- The authors' literature search did not reveal any other case of temporal bone metastases caused by papillary thyroid carcinoma.

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Panhypopituitarism in a patient with Thalassemia Intermedia

Chng Chiaw Ling

Singapore General Hospital

These are the magnetic resonance images (MRI) of the pituitary gland of a 37-year old male with β-thalassemia intermedia diagnosed at age 17, who was referred to the Endocrine clinic by his hematologist for evaluation of hypogonadism. He was on monthly blood transfusion between 2002 and 2007 and was started on iron chelation in 2003, with hemoglobin maintained between 8-9 g/dL. His condition was complicated by pancytopenia secondary to hypersplenism (for which he refused splenectomy) and secondary hemochromatosis affecting the liver and heart. His serum ferritin level was markedly raised at 8325 ng/ml (NR: 13-460) and T2 weighted MRI used to assess the severity of iron loading revealed severe hepatic iron loading and dilated left and right ventricle. The 2D echocardiography showed mild biventricular dilation with normal ejection fraction suggestive of hemosiderotic cardiomyopathy. Physical examination revealed scanty axillary and pubic hair and bilateral small soft testes of 4 ml in volume estimated by Prader Orchidometer (Tanner stage 2). Subsequent endocrine investigations revealed panhypopituitarism (Table. 1)

Table 1. Summary of the results of endocrine investigations and the normal reference ranges

Investigation	Result	Reference range
FSH	0.4 U/L	1.2-8.1
LH	<0.5 U/L	2.0-10.9
Total testosterone	<0.35 U/L	6.1-27.1
ACTH	15.9 ng/L	10.0-60.0
1mcg ACTH	0 min 179 nmol/L	Peak > 550
(Synacthen) test	15 min 355 nmol/L	
	30 min 330 nmol/L	
	45 min 285 nmol/L	
FT4	8.77 mmol/L	9.6-19.1
TSH	0.898 mU/L	0.36-3.24
Prolactin	5.1 ug/L	5.0-27.7
8 am fasting IGF-1	51.3 ug/L	111-210

The suspicion of secondary hemochromatosis affecting the pituitary gland was confirmed with an MRI of the pituitary gland showing a diffuse hypodense pituitary consistent with iron deposition (Fig. 1). He was

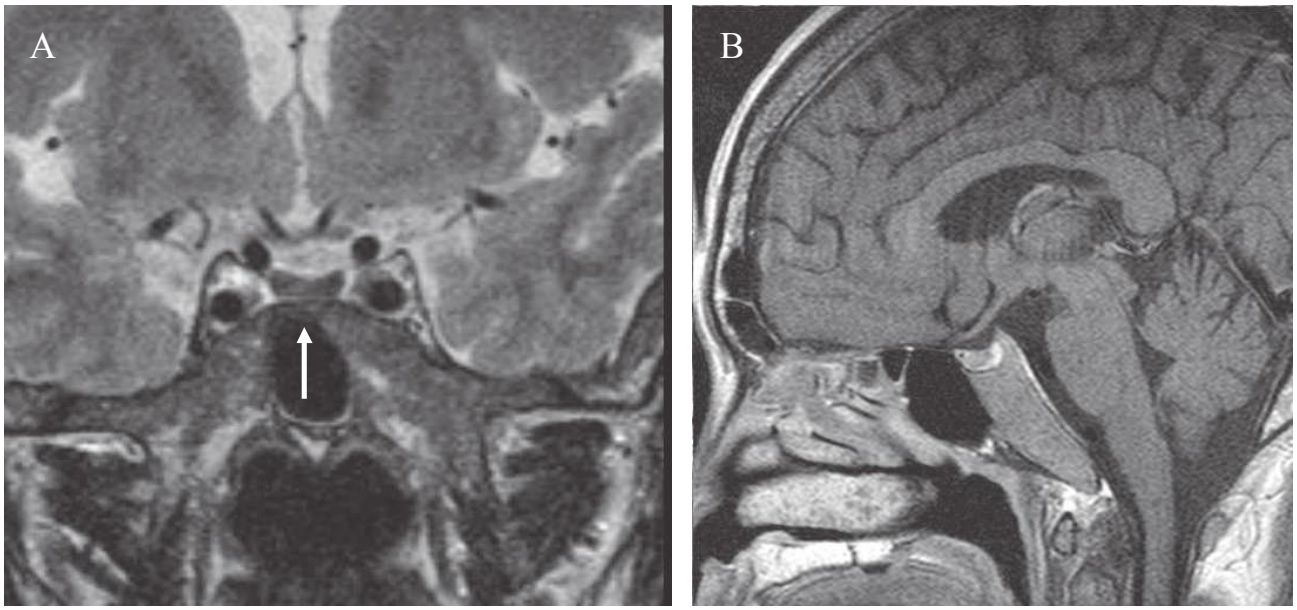

Figure 1. MRI pituitary imaging of the patient (A) Coronal T2 weighted image showing diffuse hypodense pituitary consistent with iron deposition (arrow). The gland is normal size and the stalk is central. No focal lesion was noted in the sellar or suprasellar region (B) Sagittal T1 weighted image showing normal hyperintensity of the neurohypophysis is preserved.

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Corresponding author: Chng Chiaw Ling, MD
Singapore General Hospital
Outram Road, Singapore 169608
Email: chng.chiaw.ling@singhealth.com.sg

commenced on treatment with hydrocortisone, thyroxine and testosterone replacement.

Iron deposition in patients with thalassemia can occur in a number of organs, including the heart, liver and anterior pituitary gland[1]. Factors that predispose to secondary hemochromatosis in thalassemia patients include chronic transfusion therapy (major cause), intestinal iron absorption triggered by chronic anemia, ineffective erythropoiesis, and as recently demonstrated, decreased serum hepcidin[2]. Treatment includes optimal iron chelation and hormone replacement. It is not clear at this point if the pituitary damage from secondary hemochromatosis is reversible although this has been reported in hypopituitarism related to primary hemochromatosis after aggressive iron chelation[3].

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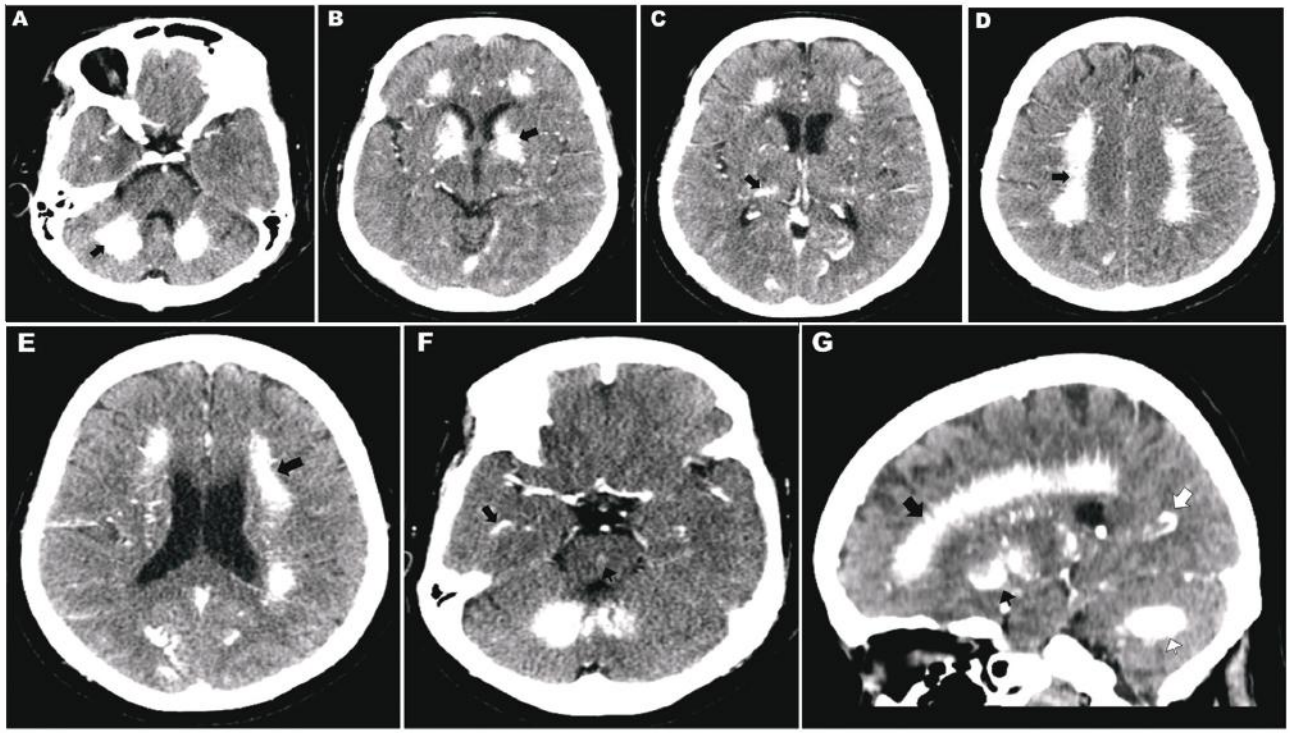
Intracranial Calcification in an Elderly Woman with Carpopedal Spasm

James K. Young and Juan Maria Ibarra Co

Section of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, St. Luke's Medical Center, Philippines

A 66-year old woman presented to us with syncope and carpopedal spasm. The history of her condition started 10 years ago as recurrent loss of consciousness associated with carpopedal spasm occurring at 2-3 times in a year. A medical consult led to a diagnosis of hypocalcemia, and she has since been maintained on oral calcium supplementation. She was admitted to our center after her most recent syncopal attack which lasted for 20 minutes. At the emergency department, she had spontaneous recovery of consciousness without neurologic sequelae. Laboratory investigation showed normal complete blood count, serum sodium, potassium, creatinine and thyrotropin results. The assays for ionized calcium at 0.6 mmol/L (nv -1.0-1.3) and serum magnesium at 1.7 mg/dL (nv 1.8-2.4) were low. Neither the electrocardiogram nor electroencephalogram showed any abnormality. Computed tomography scan of the brain demonstrated diffuse bilateral parenchymal calcification most prominent in both cerebro-cerebellar hemispheres and basal ganglia (Figure 1). She was given calcium gluconate intravenously and maintained on calcium and magnesium supplements and calcitriol per orem.

The patient is hypertensive and has a regular angiotensin receptor blocker. The patient underwent a subtotal thyroidectomy in 1975 for nodular goiter. She denies history of diabetes, cardiac, pulmonary, renal or gastrointestinal diseases. She also denies the same medical condition in the family.



Figures 1A-F Axial view of a Cranial CT scan showing extensive calcification of both cerebellar hemispheres (arrow) in Panel A, bilateral capsuloganglionic regions (arrow) in Panel B, bilateral thalami (arrow) in Panel C, bilateral centrum semiovale (arrow) in Panel D, bilateral corona radiata (arrow) in Panel E and at temporal (arrow) and pons (arrowhead) in Panel F. **Figure 1G** is a sagittal view showing feathery calcification of centrum semiovale (black arrow), basal ganglia (black arrowhead), occipital (white arrow) and cerebellar regions.

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Corresponding author: James K. Young, MD
Diabetes, Thyroid and Endocrine Center, 12th Floor Cathedral Heights Building Complex, St. Luke's Medical Center, QC
Tel: 723-0101 loc 5210
Fax: 723-0101 loc 5210
Email: jameskyoung@doctor.com

The clinical and imaging presentation of our case is compatible with the Fahr's syndrome. Fahr's syndrome refers to a rare neurodegenerative entity characterized as symmetric polytopic calcifications in one or more of the following areas: basal ganglia, cerebral white matter, thalami, internal capsulae, and cerebellum, which can lead to pyramidal, extrapyramidal, cerebellar symptoms, alteration of sensitive perception and psychiatric manifestations. [1-6] There is no cure for Fahr's Syndrome, nor is there a standard course of treatment.[7] Treatment addresses symptoms on an individual basis.[3,8]

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A Case of Multisystemic Langerhans Cell Histiocytosis in an Adult

Chng Chiaw Ling

Singapore General Hospital

A 23-year-old female smoker presented in late 2008 with a large left pneumothorax. She had multiple spontaneous pneumothoraces in 2007 which required pleurectomy. A presumptive diagnosis of lymphangioleiomyomatosis (LAM) was made in 2007 after the high-resolution computed tomography (HRCT) of the thorax revealed bilateral interlobular septal thickening and multiple thin walled cystic air spaces without lobar predilection, and with preservation of lung volumes.

She had new and worsening symptoms of persistent thirst, polydipsia, polyuria, generalized brown papular skin rash and recurrent vulvar ulcerations for one year when she presented in 2008. Endocrinology evaluation revealed central diabetes insipidus (DI) with a normal anterior pituitary axis. MRI of the pituitary gland (Fig. 1) demonstrated classical signs of central DI. A repeat HRCT of the thorax (Fig. 2) revealed extensive cystic lesions of the lungs. The abdominal CT was normal except for multiple focal bony defects at T10 vertebra, both ilia and left trochanter suggesting bone involvement. The diagnosis of Langerhans cell histiocytosis was eventually confirmed on skin and vulvar biopsies demonstrating heavy infiltrates of histiocytes containing abundant foamy to eosinophilic cytoplasm with strong cytoplasmic reaction to CD1a and S100 on immunochemistry staining (Fig.3).

The term Langerhans cell histiocytosis (LCH) encompasses a spectrum of diseases characterized by the proliferation and infiltration of organs by pathological Langerhans cells[1]. Pulmonary LAM, on the other hand, is a rare disease that almost exclusively affects women of childbearing age. It is characterized by proliferation of atypical smooth muscle-like cells with associated cystic changes in the lungs[2], and is sometimes associated with tuberous sclerosis complex[3,4].

In this patient, the initial presentation of recurrent pneumothorax without systemic manifestations of LCH has led to the initial diagnosis of pulmonary LAM. The multiple thin walled cysts on HRCT of the thorax could suggest possible LAM versus late pulmonary LCH, which is unusual for this patient, considering her young age. However, the appearance of additional systemic clinical features associated with LCH eventually prompted re-examination of the initial diagnosis. The involvement of

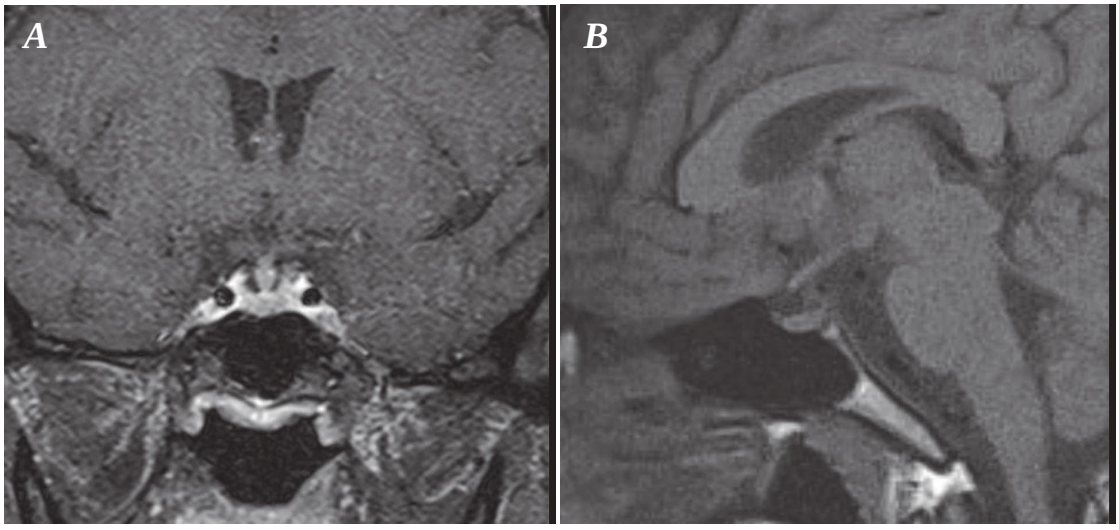

Figure 1. T-1 weighted pituitary MRI of the patient demonstrating (*A*) Thickening of the pituitary stalk (arrow) (*B*) The hyperintense signal in the posterior pituitary was not evident (arrow).

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Corresponding author: Chng Chiaw Ling, MD
Singapore General Hospital
Outram Road, Singapore 169608
Email: chng.chiaw.ling@singhealth.com.sg

the other organ systems (posterior pituitary, skin, mucous membranes and bones) made LCH a more likely diagnosis than LAM, which was later confirmed on histology.

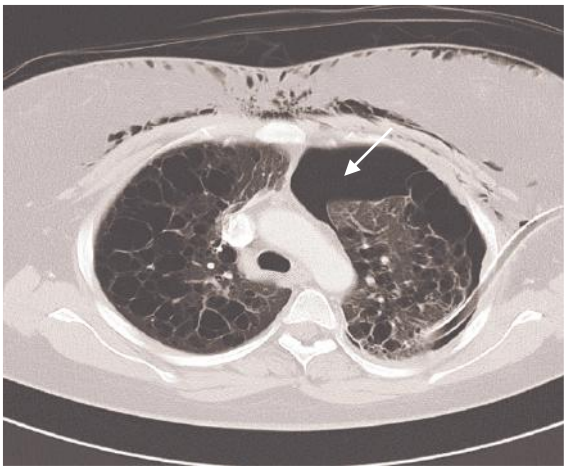

Figure 2. High-resolution CT of the thorax of the patient showing extensive bilateral cystic lesions of the lungs and a left pneumothorax (arrow)

Acknowledgment

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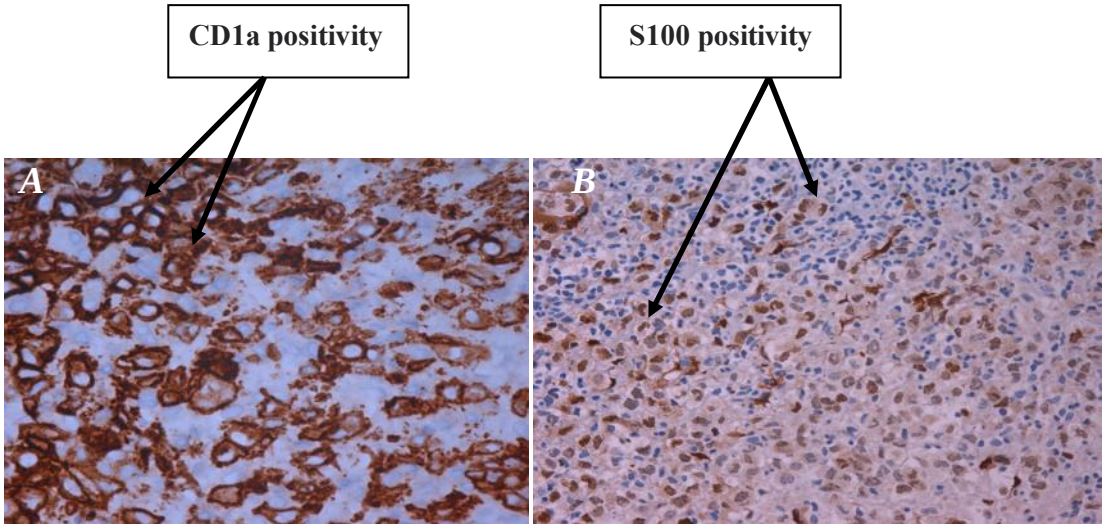

Figure 3. Right axillary biopsy slides (at 40x magnification) demonstrating (A) Diffuse CD1a positive Langerhans cells (B) The Langerhans cells are reactive for S100

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Dermopathy, Acropachy and Orbitopathy in Graves' Disease

James K. Young and Michael L. Villa

Section of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine,
St. Luke's Medical Center, Quezon City, Philippines

A 56-year-old Filipino male presented with bilateral lower limb swelling. The patient was a known smoker with a one-year history of Graves' disease. He was initially treated with methimazole for control of thyrotoxicosis. Five months prior to consultation, he was given oral radioactive iodine (Iodine-131) for the definitive treatment of his thyroid disease. The patient had no clinically detectable extrathyroidal manifestations of Graves' disease at that time. However, within 3 months after definitive treatment, he developed extensive swelling of both lower extremities, notably seen on the pretibial area; mild to moderate ophthalmopathy; and drumstick swelling of the fingers. He also developed symptoms of hypothyroidism. Eye examination revealed bilateral exophthalmos, with Hertel exophthalmometer reading of 22 on the right and 24 on the left eye; edema of the upper eyelids; chemosis; and bilateral conjunctival injection (Figure 1 and 2). The patient also had flesh-colored nodules on his upper arms (Figure 3). The most prominent physical finding was swelling of both lower extremities. Examination of the pretibial area revealed thickened skin, with firm, verrucous, hyperkeratotic nodules surrounded by deep fissures and folds (Figure 4). Thyroid function tests showed a thyrotropin level of 10 μIU/mL (normal value 0.4 to 5.0) and a free thyroxine level of 0.5 ng/dL (normal value 0.8 to 1.9). His TSH receptor antibody (TRAb) was elevated at 28.8 U/L (normal value 0 to 1). Skin biopsy of the lesions located at the arm and at the lower extremity showed myxedematous change in the superficial dermis with abundant dermal mucin, characteristic of pretibial myxedema. Plain radiograph of the fingers was normal. Magnetic resonance imaging (MRI) of the orbit showed proptosis of both globes, with prominence of intraconal and extraconal fat. Levothyroxine was started, which subsequently resulted in a significant improvement of hypothyroidism. The patient was also given steroid injections, topical steroids, and decongestive physiotherapy on his lesions at the lower extremities and upper arm for three months. Oral prednisone was also given which resulted in some improvement of the ophthalmopathy. The patient was followed for 1 year with note of complete resolution of his dermal lesions (Figure 5).

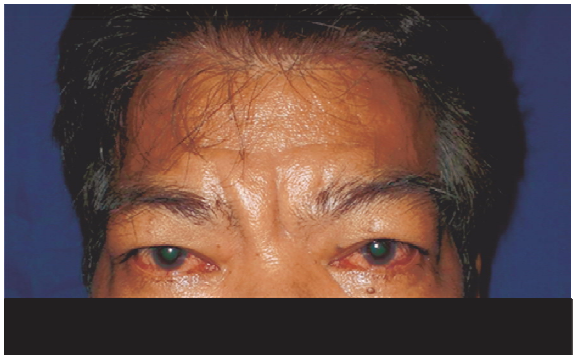

Figure 1. Graves' ophthalmopathy showing bilateral exophthalmos with chemosis and conjunctival injection.

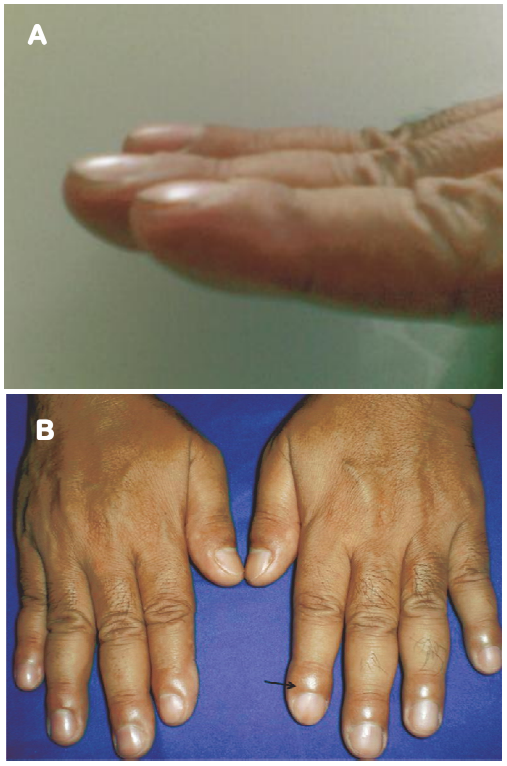

Figure 2. Graves' acropachy showing clubbing of fingers, with a Lovibond angle of greater than 180° (*A*). Accentuated nail curvature and periungual skin thickening (*arrow*) was also noted (*B*).

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Corresponding author: James K. Young, MD
Diabetes, Thyroid and Endocrine Center, 12th Floor Cathedral Heights Building
Complex, St. Luke's Medical Center, QC
Tel: 723-0101 loc 5210
Fax: 723-0101 loc 5210
Email: jameskyoung@doctor.com

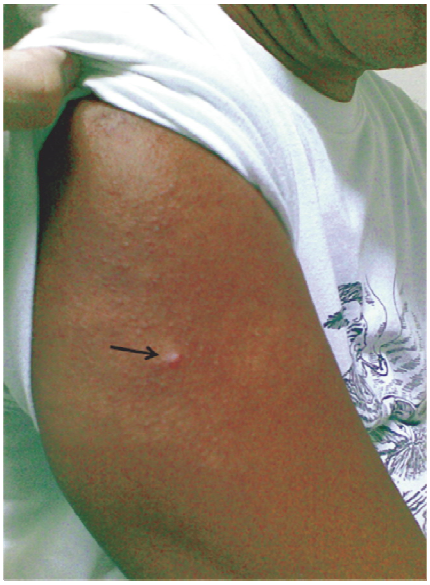

Figure 3. Graves' dermopathy showing flesh colored nodules on the upper arm (*arrow*).

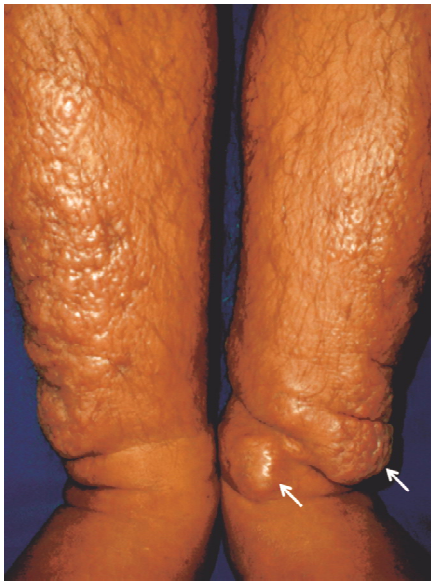

Figure 4. Skin-colored to yellowish, waxy indurated papules; verrucous nodules and plaques (*arrow*) with the characteristic "*peau d'orange* appearance" of both lower extremities demonstrating Graves' dermopathy.

Graves' disease is an autoimmune disorder of the thyroid gland with characteristic peripheral manifestations. The most common extrathyroidal manifestation is ophthalmopathy, present in 50% of patients[1-2]; followed by dermopathy in 4-5%[3-5]; and acropachy in 1%.[6] The triad of dermopathy, acropachy and exophthalmos occurs very rarely, as it is seen in less than 1% of patients with Graves' disease.[7] The treatment of Graves' opthalmopathy is aimed to alleviate symptoms, and prevent disease progression and serious ocular sequelae. Treatment options include systemic glucocorticoid therapy, orbital radiotherapy and orbital surgical decompression.[8-9] The goal of treatment of Graves' dermopathy is to decrease hyaluronic acid production by the fibroblast. This includes intralesional steroid injection; topical steroid with occlusive dressings and compression; systemic steroids; surgical excision; and immunotherapy.[2-3,10] Graves' acropachy generally does not require treatment.[2]

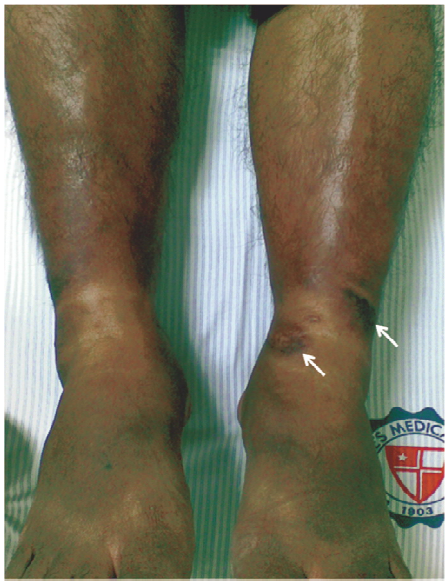

Figure 5. Resolution of dermopathy after intra-lesional steroid treatment and decompression physiotherapy.

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An Unusual Cystic Sellar-Suprasellar Mass in a Young Female

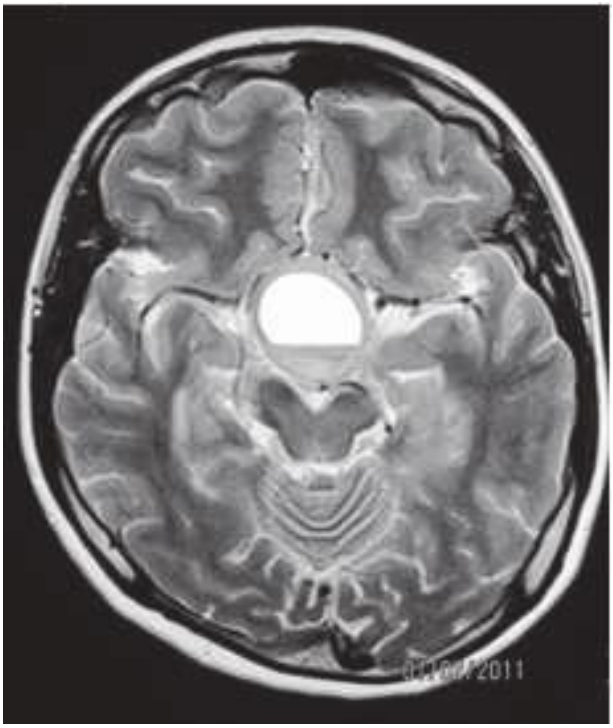
Cristina V. Jaring and Frances Lina C. Lantion-Ang

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine,
College of Medicine and Philippine General Hospital, University of the Philippines Manila

This is the magnetic resonance image (MRI) of the brain of a 23-year-old female with a 20-month history of headache, progressive blurring of vision, somnolence, constipation, cold intolerance and amenorrhea. Physical examination showed bitemporal hemianopsia and decreased muscle stretch reflexes for all extremities. She had normal serum sodium and urine specific gravity, modest elevation of prolactin level, low thyroxine level with inappropriately normal thyrotropin (secondary hypothyroidism), and markedly decreased 8 AM serum cortisol. The MRI of the head with gadolinium showed a moderate-sized peripherally enhancing sellar and suprasellar cystic mass measuring 3.3 x 3.6 x 4.0 centimeters which is partly hemorrhagic or containing proteinaceous material, that causes marked compression of the overlying optic apparatus. Imaging findings are most compatible with a craniopharyngioma.

The clinical impression for this case was a sellar-suprasellar mass, probably craniopharyngioma versus pituitary macroadenoma, with optic chiasm compression and hypopituitarism (Secondary Hypothyroidism, Secondary Adrenal Insufficiency).

Craniopharyngioma is an epithelial neoplasm arising from squamous epithelial rests of the Rathke's pouch and it is the most heterogenous of the lesions involving the sellar region due to their cystic and solid components. It is usually slow-growing and symptoms frequently develop insidiously with most cases becoming obvious only after the tumor has attained a diameter of about 3 cm. The time interval between onset of symptoms and diagnosis ranges from 1-2 years. The most common presenting symptoms are headache due to increased intracranial pressure, endocrine dysfunction resulting from mass compression of



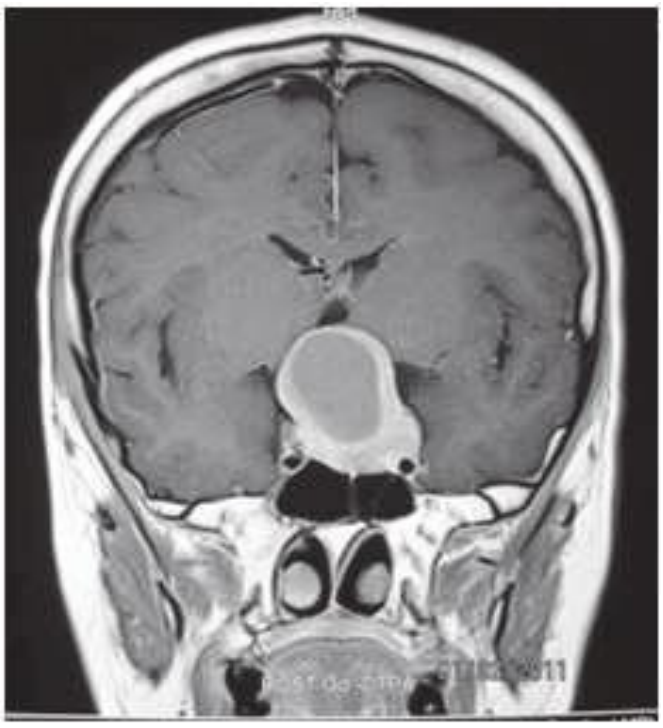


Figure 1. Sellar mass exhibiting pre-existing internal T1 hyperintensity and evidence of sedimentation leveling.
Figure 2. The sellar mass is asymmetric towards the left, extending to the left cavernous sinus region. It causes mild to moderate expansion of the floor of the sella.

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Corresponding author: Cristina V. Jaring, MD
Section of Endocrinology, Diabetes and Metabolism, Department of Medicine,
College of Medicine and Philippine General Hospital
University of the Philippines Manila
Tel: 09178659771, 09228448180
E-mail: cvj521@yahoo.com

the pituitary gland, and visual disturbances from mass compression of the optic chiasm.

The differential diagnosis for tumors in the selar-suprasellar region usually includes pituitary adenoma, craniopharyngioma, and Rathke's cleft cyst. Craniopharyngioma was mainly considered because of its characteristic appearance on MRI that was cystic but with sedimentation leveling signifying that the mass is not purely fluid but has a mixed solid and cystic content. Other MRI features suggestive of craniopharyngioma include its lobulated shape, third ventricle compression by superior tumor extension, and reticular enhancement of the solid portion. In contrast, pituitary adenomas usually have a snowman shape, solid characteristics, and homogenous enhancement of the solid portion. An ovoid shape, small tumor volume, cystic characteristics, and no or thin cyst wall enhancement are noted to be more common in Rathke's cleft cysts.

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1. The manuscript should be encoded using Microsoft Word, double-spaced throughout with 1¼ cm (½ inch) paragraph indentation, with 3-cm margins (1¼ inch) all around on A4 size paper. The preferred font style and size is Times New Roman 12. If the manuscript is sent by postage, one (1) original, one (1) duplicate and one (1) electronic copy (saved in a compact disc) should be submitted.
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3. References should pertain directly to the work being reported.
4. All the sheets of the manuscript should be labelled with the family name of the main author (all in capital letters) and page number (in Arabic Numerals) printed on the upper right corner. All manuscripts not complying with the above shall be promptly returned for correction and resubmission.

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1. The title should be as concise as possible. Only the full names of the authors directly affiliated with the work should be included (First name, Middle initial and Last name). The highest educational attainment or title of the authors should be included as an attachment whenever appropriate; name and location of no more than three institutional affiliations may be included.
2. If the paper has been presented in a scientific forum or convention, a footnote should be provided indicating the name, location and date of its presentation.

Abstract

For original articles, the abstract should contain no more than 200 words with a structured format consisting of the objective, methodology, results and conclusion. For case reports, the abstract should be from 50 to 75 words and need not be structured. At least 3 keywords but no more than 6, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

Text

1. Generally, the text should be organized consecutively as follows: Introduction, Materials and Methods, Results and Discussion, and Conclusion.
2. All references, tables, figures and illustrations should be cited in the text, in numerical order.
3. All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the long names.
4. All measurements and weights should preferably be in System International (SI) units.
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One to Six Authors (Commentary, Online)

Krause RM. The origin of plagues: old and new. *Science*. 1992;257:1073-1078. Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications [Commentary]. J Translational Med. January 20, 2004;2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

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

More than Six Authors

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

Authors Representing a Group

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

Book

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

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Section of Neurology
Department of Medicine
The Medical City
Mandaluyong City, Philippines

Cynthia P. Saloma, PhD
National Institute of Molecular Biology and Biotechnology
University of the Philippines-Diliman
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Wt, % change + insulin - insulin	 -7.6 ± 7 -8.7 ± 6.9	 -0.3 ± 5.1 -0.8 ± 4.7	 NA -5.1 ± 0.5	 NA -5.5 ± 0.5
A1C,%	-0.67 ± 0.02	0.14 ± 0.02	-0.67 ± 1.4	-0.35 ± 0.7
Fasting glucose, mg/dL	-21 ± 0.9	-7.2 ± 0.9	NA	-13 ± 3
TG, mg/dL	-30 ± 2.0	-14.6 ± 1.8	-46 ± 14	-23 ± 6

*ILI, intensive lifestyle intervention

The Look AHEAD Research Group. Diabetes Care 2007. 30:1374-1383.

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		Sun et al.[1+]	Fix et al.[2]	Abbott Study BJ19[3+]	Tatti et al.[4+]	Look Ahead[5+#]	Garvey et al.[6]
Enhance Glycemic Control	Improved FPG	●					
	Improved PPG response		●				
	Improved Insulin response		●				
	Reduced HbA1C	●		●	●		●
Supports Cardiovascular Health	Improved lipid profile			●	●		●
	Improved blood pressure	●			●		●
Supports Weight Management	Decreased waist circumference	●					
	Weight loss	●		●	●	●	●

^ The Glucerna SR formulation used in each study may vary
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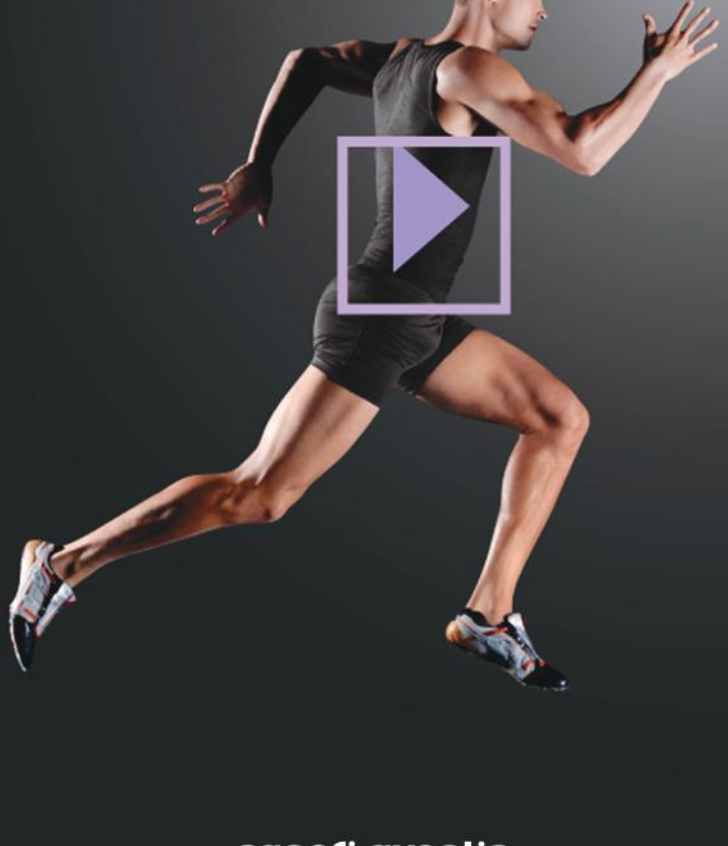

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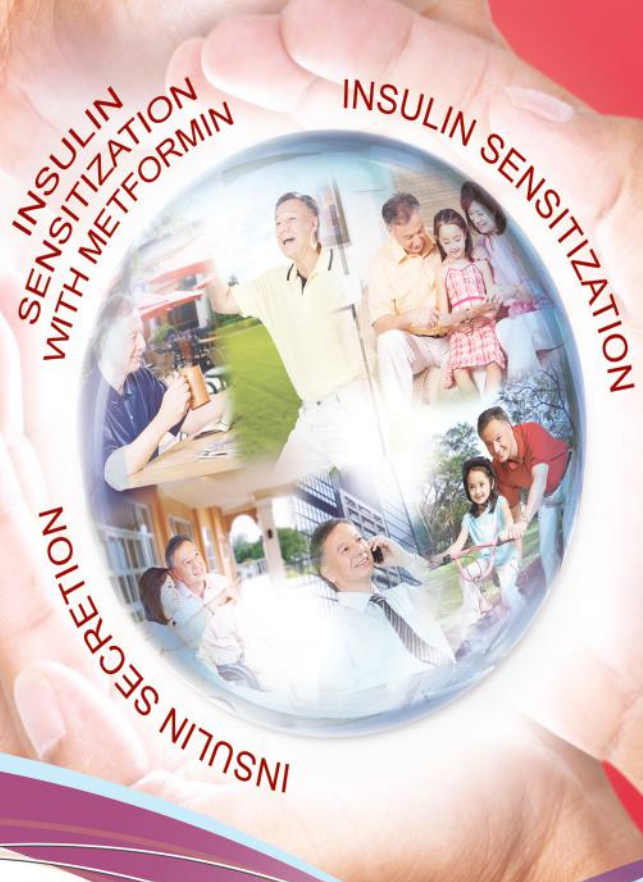

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1 - Campbell IW. Br JDiabetes Vasc Dis 2006;6:207-15.

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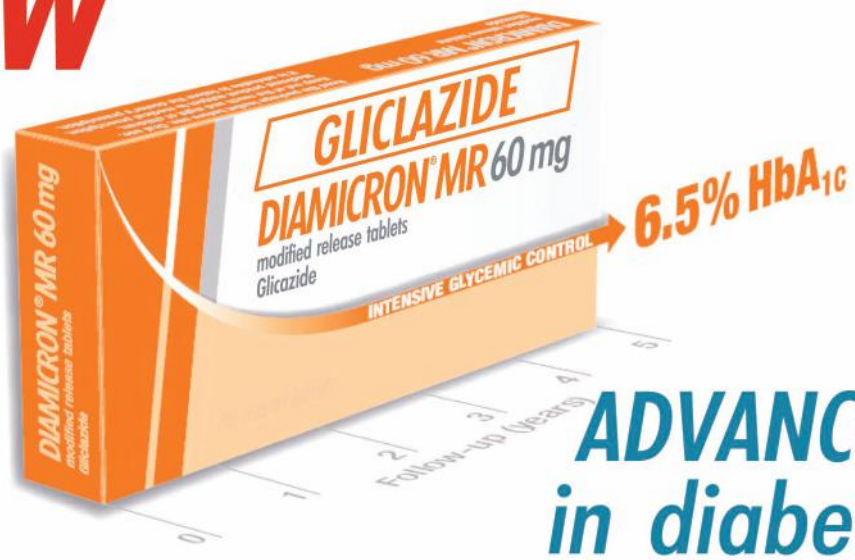

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