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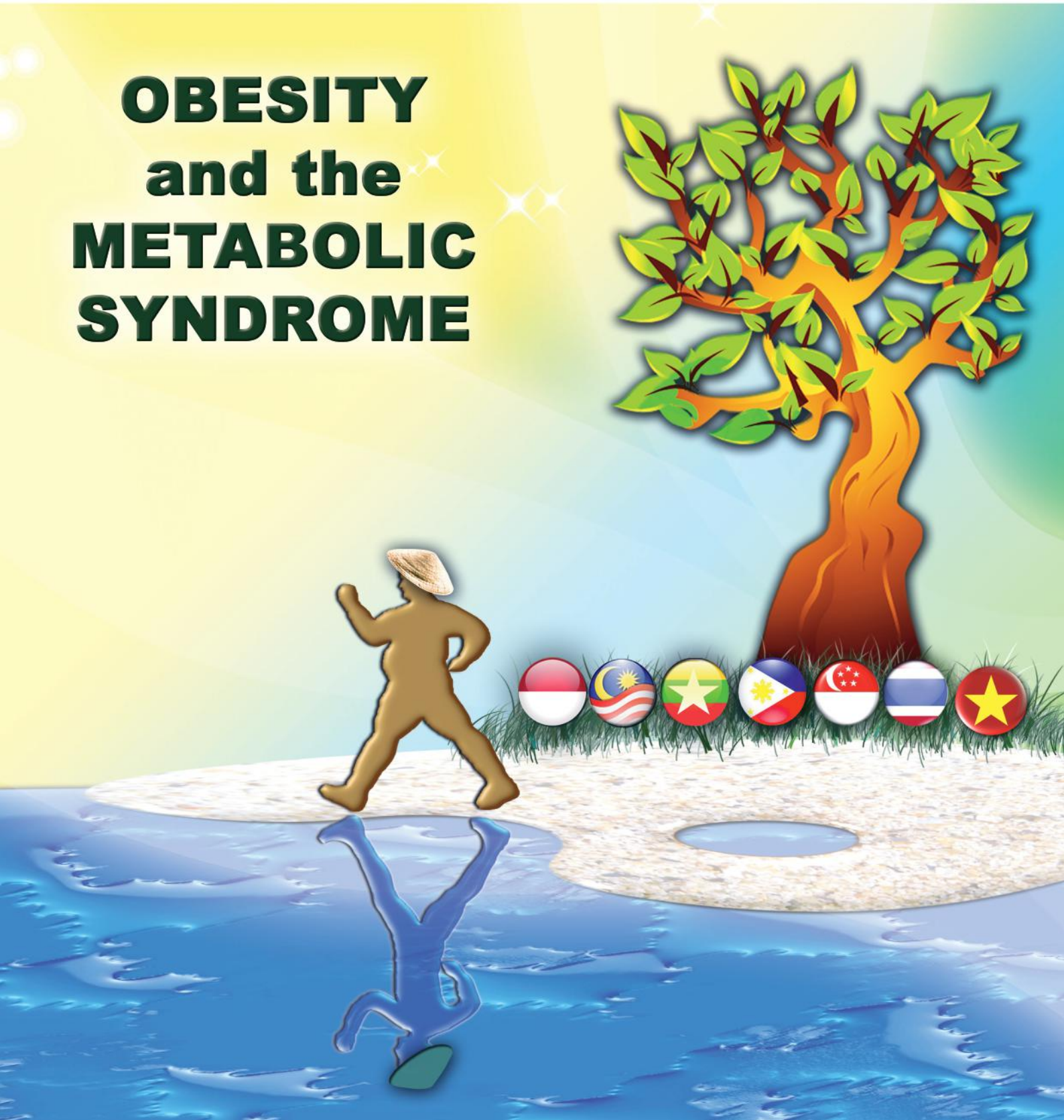
OBESITY and the METABOLIC SYNDROME



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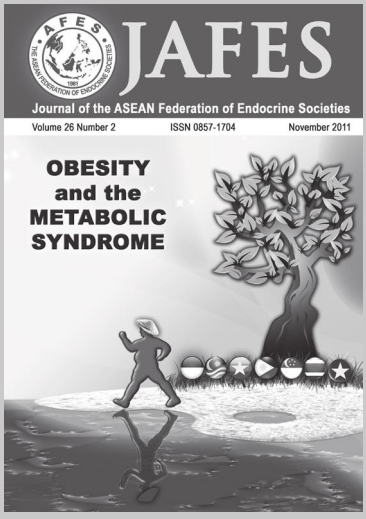

ABOUT THE COVER

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There is a *yin* and *yang* to obesity, a fat belly in the orient has usually been a sign of prosperity, health, wealth and happiness. But now the bad side of being obese has come to the forefront. Adipose tissue, specially in the belly, is now considered a large endocrine organ engulfing the body with good and bad *chi* -- hormones which counterbalance the drive to indulge or the drive to fast, to gain or to suppress appetite. Obesity is a problem of pandemic proportions and its roots in Southeast Asia while sharing commonalities with other Asian and Western cultures, has its unique genetics and more diverse cultural, dietary and culinary heritage. Much is to be done to solve this complex problem of obesity, the approach has to be uniquely ours. There are many miles to go, but we have to take the first steps.

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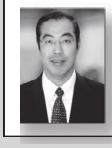

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JAFES: Reducing Obesity and Metabolic Syndrome; Meeting in Ho Chi Minh City, Vietnam for the First Time

The huge success of the 6th Asia-Oceania Conference on Obesity in Manila, Philippines, on August 31 to September 2, 2011, inspired the editorial team to focus on the epidemic of obesity and the metabolic syndrome in the ASEAN Region.

Firstly, the obesity rates in the region are clearly rising, with the epidemic particularly affecting children who comprise a growing segment of the population. Secondly, existing data provide evidence for the strong link between obesity and its cardio-metabolic consequences, which in fact occur even at lower body mass index (BMI) levels, with increasing visceral adiposity. Thirdly, there is a discussion on strategies for prevention and control that are applicable to the region, using population approaches with impact to communities, both urban and rural, and particularly school-based programs. To remind us of this social responsibility and to formalize a commitment within the region, all member countries of the Asia-Oceania Association for the Study of Obesity (AOASO), signed a joint declaration on September 2, 2011, which we publish in this issue.

Impelled by the need to focus on these conditions, the current issue focuses on clinical practice guidelines (CPGs) for obesity in the region. Many of the countries in ASEAN are in the early stages of working on this health issue; few have established country-specific guidelines. Invited reviews provide perspectives on the etiology of the burden of disease, with specific focus on ASEAN initiatives. Dr. Rodolfo Florentino, talks on the double burden of increasing obesity in one segment of the population along with malnutrition in another population segment, a unique but even greater problem occurring in most countries in South East Asia. Pediatrician-geneticist Dr. Eva Cutiongco-dela Paz, reviews the genes related to obesity and its applications in Asia, as we work for effective and specific treatment strategies. Lastly, Dr. Augusto Litonjua, the founding president of the AFES and the Philippine Association for the Study of Overweight and Obesity (PASOO), reviews trends and obesity patterns in the Philippines, elucidating differential phenotype and potential differential genotype of obesity and the metabolic syndrome in this population.

Insightful original work such as a pilot study on the use of neck circumference as a screening measure for abdominal obesity as a surrogate diagnostic test for visceral obesity is presented here. Previous studies in Israeli patients determined a cut-off and this simple screening measure needs to be validated in various ethnic populations. Traditionally, in many Asian countries, we would check whether a pair of pants would fit by trying its waist part, folded flat, around the neck. The study does not provide clear generalizable relationships yet, but is interesting as a pilot: the authors recommend a prospective study with a bigger sample size.

This issue also includes original articles on insulin resistance from Malaysia, prevalence of obesity, metabolic syndrome and diabetes in selected villages in Indonesia as well as risk factors associated with arterial stiffness in Asians with diabetic nephropathy from Singapore. We likewise have a number of interesting case reports and images from endocrinology cases in our region, which often times are no longer seen as clinical presentation in the Western world.

Meanwhile, excitement is building up as AFES countries meet in Ho Chi Minh City, Vietnam for the first time this November. The theme of the 16th AFES congress is "Translating Endocrinology Research into Clinical Care." A JAFES Supplement accompanies this issue with the highlights of the Congress proceedings, including oral and poster research abstracts. Vietnam Association for Diabetes and Endocrinology (VADE) President Nguyen Van Thue provides an introduction to the scientific and social programs for this important biennial meeting.

We encourage our colleagues in ASEAN to spread the word: we have JAFES, the journal that serves as our voice in the region and the world. We are now accessible 24 hours a day, 7 days a week on the internet at this address: http://www.asean-endocrinejournal.org. Authors who wish to submit their manuscripts can now do so not only through e-mail (JAFES@Asia.com) but also through the website. Abstracts and selected articles from the previous issue are currently available for download. For the benefit of our authors and readers, efforts on making JAFES Medline-indexed are now underway.

We are committed to focus on themes that have relevance to our individual and collective countries, and hope to provide an impetus for action. We aim to translate country-specific research to public health programs and policies and clinical practice. Please continue to email me your comments at epaz-pacheco@asean-endocrinejournal.org.

Elizabeth Paz-Pacheco
Editor-in-Chief

JAFES Journal of the ASEAN Federation of Endocrine Societies

ASEAN Federation of Endocrine Societies (AFES)

AFES Vision Statement

Recognized and respected premier regional Endocrine Federation
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Our Patients are our Reason for Existence, We commit to provide quality, cost-effective and preventive endocrine care.

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In order to realize our Vision, the AFES will:

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Greetings from AFES

Dear Colleagues and Friends,

On behalf of the ASEAN Federation of Endocrine Societies and the local Organizing Committee, it is my pleasure to welcome you to the 16th Congress of the ASEAN Federation of Endocrine Societies. Building from successes of the preceding congresses in Kuala Lumpur and Bangkok, this Congress continues to be the leading scientific meeting for colleagues engaged in endocrinology in Southeast Asian countries, and will provide a legacy for those who have come to participate in the meeting.

ASEAN countries collectively represent one of the most dynamic economies and health transitions in the world. With a population of approximately 600 million people (i.e., 9% of the world population), and a combined GDP of $1.8 trillion, the ASEAN economy is ranked as the 9th largest economy in the world and the 3rd largest in Asia. Although the degree of economic development is different among member countries, rapid urbanization and aging of population are common trends in all ASEAN countries. At present, the proportion of population aged 60 years and above in ASEAN countries is around 7%, and it is projected that this proportion will reach ~15% by 2040. With this increase in the aged population, Southeast Asia together with Asia as a whole is emerging as the epicentre of epidemic obesity and diabetes. In 2000, the number of individuals with type 2 diabetes in the Asia Pacific region was estimated to be 30 million, accounting for 20% of the world diabetic cases. In 2010, the number of diabetic individuals in the Asia Pacific region was estimated at 130 million, which is more than 50% of the world prevalence. Moreover, the prevalence of osteoporosis in ASEAN populations is as high as in any other Caucasian populations. Thus, the aging population with its adverse health consequences has many public health implications, and presents a unique opportunity for endocrinologists to engage in research and clinical care.

It is perhaps reasonable to say that by and large, endocrinology research in ASEAN countries is not as advanced as in western countries. Moreover, prevalence of and risk factors for common diseases have not been well documented. However, emerging evidence so far has suggested that characteristics of diseases in ASEAN populations are somewhat different from Caucasian populations. For example, Asian diabetics are younger, have lower body mass index, and are often clustered among those in higher socio-economic groups compared with Caucasian populations. The 130 abstracts presented in this Congress represent a collective effort to document the magnitude, risk factors, treatment and prevention of endocrine disorders not just in ASEAN populations but also in non-ASEAN populations.

Translational research is important for ASEAN countries. Therefore, the theme of the 16th AFES Congress is "*Translating Endocrinology Research into Clinical Care.*" With this theme as a guiding principle, the Congress has several official and satellite sessions on basic and applied research, where the most up-to-date information regarding the science and advances in endocrinology, and particularly, clinical care will be presented by leading ASEAN and international scientists. You will have the opportunity to refresh your knowledge and to meet and interact with leading scientists and physicians of endocrinology.

Ho Chi Minh City or Saigon is considered *The Orient Pearl*, and Saigonese are well-known for being hospitable and friendly people. I hope you will take a little extra time to enjoy the beauty of Saigon and unique cuisine of Vietnam. With that in mind, I wish you the best and have a great scientific exchange, and more importantly, have great fun at this conference, no matter what you accomplish.

I would like to thank everyone who has come to the Congress. Your participation is valuable to the continued success of the Congress.

Nguyen Thy Khue
Chair, AFES 2011 local Organizing Committee
President of the Vietnamese Association of Diabetes and Endocrinology

Images of Asia

Background: *Non (Asian paddy hats) at Hoi An Province, Vietnam (2007)*; Inset (from top to bottom): *Thay Pagoda, North Vietnam (2009); Child of the Mekong Delta (2008); Pagoda Bridge, Hoi An (2007); Mekong Delta (2008). Photographs courtesy of Nguyen Thy Anh, MD.*

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In clinical studies, the most common adverse reactions reported, regardless of investigator assessment of causality, in ≥5% of patients and more commonly than in patients treated with placebo were as follows: diarrhea, upper respiratory tract infection, and headache (for sitagliptin and metformin combination therapy); nasopharyngitis (for sitagliptin monotherapy); and diarrhea, nausea/vomiting, flatulence, abdominal discomfort, indigestion, asthenia, and headache (for metformin therapy).

References: 1. Data on file, MSD Philippines. **2.** Nauck MA, Meininger G, Sheng D, et al; for Sitagliptin Study Group 024. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared to the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab.* 2007;9:194–205.

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JAFES Journal of the ASEAN Federation of Endocrine Societies

A Summary of the Malaysian Clinical Practice Guidelines on Management of Obesity 2004

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Abstract

In 2004, the Malaysian Clinical Practice Guideline for Management of Obesity was published to assist health practitioners in the management of the obese population. This guidelines, based on gathered evidence published up to 2004, defined weight classifications according to BMI suited to the Malaysian population. The guideline also discussed methods of assessing obesity in adults. Recommendations with respect to treatment approach, encompassing lifestyle, dietary, pharmacological and surgical management of obesity in adults, and management approach in children and adolescent were also discussed in detail in the guidelines. The following article summarizes the recommendations that were made in the 2004 guidelines.

Keywords: clinical practice guidelines, obesity management, Malaysia

Introduction

In 1996, the National Health and Morbidity Survey in Malaysia reported a prevalence of 15.1 % overweight and 2.9 % obesity among adult males, whilst in adult females, 17.9 % were overweight and 5.7 % obese[1]. The prevalences did not differ much between rural and urban population, and there were more obese Malays and Indians, compared to Chinese.

These guidelines were developed with the objective of assisting healthcare providers to better diagnose and manage overweight and obese patients. It was a combined initiative of the Malaysian Association for the Study of Obesity (MASO) and the Malaysian Endocrine and Metabolic Society (MEMS). It recommends a multidisciplinary approach in the management of overweight and obese patients in Malaysia.

The evidence from this guideline was collated from several sources, including systematic review of relevant published literature (up to 2004) as identified by electronic search, and reports of relevant expert working groups [2-7].

There are 6 main sections in the guidelines; Section1- Introduction, Section 2- Diagnosis and Assessment of Obesity in Adults, Section 3- Therapy: Overall Approach, Section 4-Therapy: Lifestyle Advice, Section 5- Therapy: Pharmacotherapy and Surgical Therapy and Section 6- Childhood and Adolescent Obesity. Section 7 consists of appendices including behavioural assessment, sample menu plan, food groups and exchange lists, determination of activity status for calculating calorie requirements for weight reduction and maintenance, surgical inventions in obesity and the IOTF cut-off points of BMI for overweight and obesity by sex from 2-18 years, as well as body mass index-for-age percentiles for boys and girls: CDC growth charts: United States.

Definition of Obesity

Obesity is a complex multifactorial condition characterised by excess fat. Generally, men with > 25 % body fat and women with > 35 % body fat are considered obese. The body mass index (BMI), which is defined as Weight (kg) / Height^2 (m^2), is the most widely established and widely used measurement. Evidence from several Asian countries showed that the risk of comorbidities begin to rise at a lower BMI value than that defined by WHO as overweight and obese[8-14h]. At a similar BMI, many Asian populations have a higher body fat content as compared with Caucasian/European population[15-18].

Based on this, the guideline recommends the classification of weight by BMI, according to the risk of comorbidities as stated in Table 1.

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The guidelines also recommended that waist circumference (WC) is used to assess abdominal fat content as it is simple and reliable. WC measurements correlates well with abdominal fat content irrespective of BMI and is a independent risk factor for cardiovascular diseases. It is most useful in patients with normal or overweight BMI but is deemed unnecessary in patients with BMI >35 kg/m^2, as it loses its predictive value.

Current evidence suggests that among Asians, WC of 90 cm in men and 80 cm in women is associated with increased risk of comorbidities[8-11].

Table 1. Classification of weight by BMI

Classification	BMI (kg/m2)	Risk of Comorbidities
Underweight	<18.5	Low (but increase risk of other clinical problems)
Normal range	18.5-22.9	Increasing but acceptable risk
Overweight	≥23	Increased
Pre-obese	23.0-27.5	
Obese I	27.5-34.9	High
Obese II	35.0-39.9	Very High
Obese III	≥40	Extremely High

Excessive weight results in an increase overall mortality and morbidity[19]. The risk of cardiovascular diseases and its risk factors is greatest in patients with abdominal obesity. The relative risk of developing type 2 diabetes, gallstones, fatty liver, dyslipidaemia, metabolic syndrome, breathlessness and sleep apnoea is increased 3-fold. Other increased health risks include coronary artery disease, cerebrovascular disease, cardiac failure, hypertension, hyperuricaemia, cancer (breast, endometrium, colorectal, liver, prostate, gallbladder), polycystic ovarian syndrome, reproductive hormone abnormalities and impaired fertility, low back pain and foetal defects associated with maternal obesity. Weight loss has advantages in reducing these risk factors and the risk of obesity related diseases.

Diagnosis and Assessment of Obesity in Adults

Obesity in adults can be diagnosed by performing a comprehensive medical evaluation which includes patient's family history, physical examination and laboratory tests. An assessment of patient's eating habits including snacking, his/her habitual physical activity (frequency, type, duration) and a psychological status evaluation (body image, eating disorders) should be performed. Additionally, physical examination should include assessment of degree of obesity and body fat distribution with special attention to potential comorbidities. The laboratory tests that should be done are fasting blood glucose, fasting blood lipid profile and biochemistry profile. If indicated, thyroid function should be checked, as well as 24-hour urine free cortisol and investigations to exclude polycystic ovarian syndrome should be carried out.

The current diagnostic criteria of overweight and obesity for adults are set at above 23 kg/m^2 and 27.5 kg/m^2, respectively. In addition to BMI, waist and hip circumferences are also measured for monitoring the abdominal fat distribution and reference value for waist-hip ratio for men and women are 0.90 and 0.85, respectively. Even though BMI is the most established measurement used to monitor the progress of an individual's weight, there are some limitations in estimating the degree of obesity under certain circumstances which include overestimations in very muscular individuals and underestimations in individual who have lost muscle mass.

Obesity-associated diseases which will contribute to added cardiovascular morbidity and mortality for eg, coronary heart disease and cardiovascular risk factors, should be identified. They provide an additional guide to the need and intensity of weight reducing intervention. Identification of other related diseases which are increased amongst obese patients such as osteoarthritis, gallstones and stress incontinence are also crucial in planning for appropriate weight management strategies.

Obesity is primarily caused by the interaction between genetic predisposition and environmental factors. These include social and behaviour factors, sedentary lifestyle, iatrogenic causes, endocrine obesities and genetic obesities. These should be identified and managed appropriately.

Therapy: Overall Approach

The general goals for obesity therapy are to achieve weight loss, maintain lower body weight, prevent further weight gain and to treat the comorbidities/underlying causes. The initial goal of weight loss is to reduce approximately 10% body weight from baseline. A calorie deficit of 500 to1000 kcal/day can result in weight loss at a rate of 0.5 to 1 kg/week. The combined modalities of therapy (diet, physical activity and behavior therapy) must be continued indefinitely to ensure weight maintenance. These are best done in the form of a multidisciplinary team approach, involving physicians interested in management of obesity or endocrinologists, dieticians, physiotherapists, psychologists or psychiatrists, and when indicated, the bariatric surgeon.

The recommended treatment options for the treatment of overweight and obesity in adults depends on different levels of BMI and other risk factors. Lifestyle modifications including dietary intervention, physical activity and behavior therapy is the mainstay of treatment for all levels of BMI. Anti-obesity drugs should be considered at BMI of 27.5 kg/m2 and above, and BMI 25.0-27.4 kg/m2 with presence of more than 2 risk factors. Very low calorie diet as a treatment option can be considered at BMI of 27.5-34.9 kg/m2 with ≥2 risk factors and BMI >35.0 kg/m2 with or without risk factors. Surgery is suggested at BMI of 35.0 to 39.9 kg/m2 with≥2 risk factors and BMI ≥40.0 with or without risk factors. Regular and frequent consultations with the multidisciplinary or obesity team, initially weekly

to biweekly; subsequently monthly for at least a year, is beneficial and a major determinant of successful weight loss and control.

Lifestyle Advice

Lifestyle advice encompasses dietary therapy, physical activity and behavior therapy. Dietary intervention aims to reduce weight through a decrease in calories consumption. Diet strategies include low calorie diet (LCD), lower-fat diet, very low-calorie diet (VLCD), high-protein low carbohydrate diet and dietary education. LCD is where calorie deficit of 500 to 1000 kcal/day from maintenance requirement for weight loss and prevention of weight regain. Reducing fat as part of a low calorie diet is a practical way to reduce calories. Very Low Calorie Diet (VLCD) where calorie restriction between 200 to 800 kcal/day may be indicated for moderately to severely obese patients (BMI > 30 kg/m^2). It can result in quick, short-term weight losses, but medical supervision is required. All weight management strategies should include education in healthy eating habits.

Physical activity should be an integral part of weight loss therapy and weight maintenance because it contributes to weight loss, decreases abdominal fat and increases cardio-respiratory fitness. Individuals require 45 – 60 minutes per day of moderate intensity activity or lesser amounts of vigorous intensity activity. Weight loss is more likely to be achieved and maintained by behavioural modification techniques focusing on lifestyle and attitude. The goal of behaviour therapy is to alter the eating habits of the obese individual.

Pharmacotherapy

Pharmacotherapy is an adjunct to lifestyle changes in some patients with BMI > 27.5 kg/m^2 or BMI > 25 kg/m^2 with comorbidities. Drugs should only be used under careful medical supervision and as part of a long-term treatment strategy. The benefit of pharmacotherapy must be carefully weighed against risks of side effects.

Orlistat: A peripherally acting pancreatic lipase inhibitor. Dose is 120 mg tds with each main meal containing fat (during or up to 1 hour after meal); omit if meal is missed or does not contain fat. Side effects include loose stools and malabsorption of fat soluble vitamins. Contraindications are chronic malabsorption syndrome and cholelithiasis.

Phentermine: An amphetamine derivative that should only be used for < 3months. Dose is 8 mg tds, 30 min before meals or 15-30 mg/day before breakfast or 10-14 hrs before bed. Side effects include increase in blood pressure, insomnia and nervousness. Contraindications are pulmonary hypertension, heart valve abnormalities, moderate to severe hypertension, cerebrovascular disease, severe cardiac disease, hypersensitivity, hyperthyroidism, psychiatric illness, glaucoma and drug/alcohol dependence.

Other drugs that favour weight loss:
Fluoxetine: Anti-depressant and appetite suppressant. Not specifically approved for weight loss. Starting dose is 20mg/day in the morning, may increase by 20mg/day each week to maximum of 60mg/day. Side effects include anxiety, drowsiness, insomnia and nervousness. Contraindications are hypersensitivity and concomitant use of monoamine oxidase inhibitors (MAOIs).

Metformin: Not specifically licensed for obesity but may be useful for managing obesity in patients with dysglycaemia or PCOS. Dose is 500 to 1000 mg bd/tid with meals. Side effects include nausea, flatulence, bloating, diarrhea and rarely lactic acidosis. Contraindications include hypersensitivity, diabetic ketoacidosis, renal dysfunction and acute conditions that may predispose to renal dysfunction (e.g. infection, contrast agents), acute or chronic disease that may cause tissue hypoxia (e.g. cardiac or respiratory failure) and lactation.

Pharmacotherapy is contraindicated in children, pregnant and lactating women and patients who have previously suffered adverse effects from drugs in this category. Combination pharmacotherapy cannot be recommended.

Surgery for Weight Loss

Surgical intervention for obesity can result in substantial and sustained weight loss, but should be reserved for patients above 18 years of age with morbid obesity (BMI > 40 kg/m^2) or BMI of 35-40 kg/m^2 with weight-related comorbidities and have failed other therapies provided by experts in obesity management. In addition, the patient has to be motivated and has no contraindications for anaesthesia and surgery. The common surgical procedures are; gastric banding, gastric bypass (Roux-en-Y) and the biliopancreatic bypass surgery. Complications of surgery include malabsorption, "dumping syndrome," gallstones disease and depression. Lifelong medical and nutrition surveillance after surgical therapy should include monitoring of indices of inadequate nutrition and modification of any preoperative disorders.

Childhood and Adolescent Obesity

Obesity among children and adolescents are commonly due to unhealthy eating patterns and lack of physical activity. Occasionally, it is due to genetic factors or endocrine disorders. It is arbitrarily defined as a BMI greater than the 95th percentile. Childhood obesity is associated with an increase in prevalence of Type 2 diabetes among young. Factors which determine persistence of obesity into adulthood are; onset of obesity after the age of three, degree of obesity and presence of obesity in at least one of the parents.

Management of children and adolescent with obesity is aimed at reducing the amount of body fat. Growing children often do not need to lose weight, however older adolescents who have attained their final height should make efforts to lose excess weight by dietary modification and increase in physical activities. It is recommended to aim for weight loss of 2-4 kg initially, or at a rate of 0.5 to 2 kg per month. This requires continuous good support and commitment from the whole family members.

Conclusion

In the treatment of obesity, the need for multidisciplinary approach cannot be overemphasized. Treatment strategies should be tailored according to the individual needs. The Malaysian Clinical Practice Guideline for Obesity was developed with the hope that it will help strengthen the management of obesity in the country. The full downloaded document (http://www.acadmed.org.my/) is made readily available online for easy reference.

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FEATURE ARTICLE

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A Summary of the Myanmar Clinical Practice Guidelines for the Management of Obesity

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Abstract

There is a significant prevalence of overweight and obesity in Myanmar. It is anticipated that this will impact on the morbidity associated with other lifestyle diseases such as hypertension, Type 2 diabetes and various types of cancer. Recognizing this public health concern, the Myanmar Society of Endocrinology and Metabolism (MSEM) organized a task force for the development of evidence based clinical practice guidelines on obesity.

Key words: obesity, clinical practice guidelines, Myanmar

Introduction

The objective of the Myanmar Clinical Practice Guideline for Obesity is to develop an evidence based guideline for healthcare providers and the public by using data relevant for Myanmar people.

Obesity can be defined simply as a disease in which excess body fat has accumulated to such an extent that health may be adversely affected. However, the amount of excess fat, its distribution within the body, and the associated health consequences vary considerably between obese individuals.

The distribution of fat induced by weight gain affects the risks associated with obesity, and the kinds of disease that develop as a result of obesity. Excess abdominal fat is as great a risk factor for disease as is excess body fat *per se*. "Android obesity" is a result of abdominal fat distribution which is associated with increased risk for obesity related diseases (particularly cardiovascular diseases). In contrast "gynoid" fat distribution, in which fat is more evenly and peripherally distributed around the body, is less serious.

In Myanmar, according to the WHO stepwise approach to NCD surveillance in Yangon in 2003-2004, the prevalence of overweight (Body Mass Index [BMI] 25.0 – 29.9) was 20.6% in males and 29.96% in females, while the prevalence of obesity (BMI≥ 30.0) was 4.77% in males and 10.35% in females. According to the national survey carried out in 2009, the prevalence of overweight was 17.74% in males and 30.27% in females while the prevalence of obesity was 4.27% in males and 8.37% in females. For both sexes, the prevalence of overweight and obesity was 25.38% and 6.8% respectively.

Among children and adolescents aged 10-19 years in Yangon 7.6% were obese at the age of 10-19 years in both sexes. Out of these 8.7% were boys and 6.5% were girls.

The increased risk of overweight and obesity in Myanmar substantially raises the risk of morbidity for hypertension, type 2 diabetes, stroke, gallbladder disease, osteoarthritis, sleep apnoea and respiratory problems, and endometrial, breast, prostate, and colon cancers in the country.

As a contributor to many medical problems and preventable death, overweight and obesity pose a public health challenge in Myanmar today.

The task force for Clinical Practice Guidelines on Obesity was formed by the members of the Myanmar Society of Endocrinology and Metabolism (MSEM). Relevant literature search was done. Recommendations on expected caloric needs and macronutrients proportions for Myanmar were developed by using local data.

Management of Obesity

Management of Adult Obesity

Obesity management encompasses the following four key strategies:

- prevention of weight gain
- promotion of weight maintenance
- management of obesity comorbidities
- promotion of weight loss

Diagnosis and Assessment

Since Myanmar is one of the member countries of the WHO South East Asia Region (SEAR) and previous

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studies on risk factors for noncommunicable diseases have followed the WHO guidelines, the task force decided to adopt the WHO classification for obesity in this guideline.

Body mass index (BMI)

Body mass index (BMI) wt(kg)/ht(m^2) is an internationally accepted measure of general adiposity in adults. BMI takes account of the expected differences in weights of adults of different heights.

Waist Circumference

Waist circumference is at least as good an indicator of total body fat as BMI and is also the best anthropometric predictor of visceral fat.

Table 1. Classification of adult underweight, overweight and obesity according to BMI.

Classification	BMI	Risk of comorbidities
Under weight	<18.50	Low (but risk of other clinical problems increased)
Normal range	18.50 – 24.99	Average
Overweight:	≥ 25.00	
Pre-obese	25.00 – 29.99	Increased
Obese class I	30.00 – 34.99	Moderate
Obese class II	35.00 – 39.99	Severe
Obese class III	≥ 40.00	Very severe

Adapted from the WHO, 2004.

Table 2. Sex-specific waist circumference and risk of metabolic complications associated with obesity

Risk of metabolic complications	Waist circumference (cm)	
	Men	Women
Increased	≥ 94	≥ 80
Substantially increased	≥ 102	≥ 88

Adapted from the NHRMC, 2003.

The World Health Organization (WHO) recommended that an individual's relative risk of type 2 diabetes and cardiovascular disease could be more accurately classified using both BMI and waist circumference

Table 3. Classification of disease risk by WHO BMI categories and waist circumference thresholds.

Classification	BMI (kg/m^2)	Class	Disease Risk * Relative to Normal Weight and Waist Circumference (WC)	
			Men WC 94-102 cm Women WC 80-8 cm	Men WC >102 cm Women WC >88 cm
Normal weight†	18.5 – 24.9		-	-
Overweight	25.0 – 29.9		Increased	High
Obese				
Mild	30.0 – 34.9	Class I	High	Very high
Moderate	35.0 – 39.9	Class II	Very high	Very high
Extreme	40.0 +	Class III	Extremely high	Extremely high

** Disease risk for type 2 diabetes, hypertension, and cardiovascular disease*
† Increased waist circumference can also be a marker for increased risk even in persons of normal weight
Obesity management should be implemented with the following five key steps:

Dietary Measures

Achieving and sustaining appropriate body weight across the lifespan is vital to maintaining good health and quality of life. *Calorie balance over time is the key to weight management.* Calorie balance refers to the relationship between calories consumed from foods and beverages and calories expended in normal body functions (i.e., metabolic processes) and true physical activity.

Table 4. Steps for the management of obesity

Step 1.	History, examination and investigation
Step 2.	Weight loss (1) Lifestyle modification (calorie balance and increase physical activity) (2) Diet • Low-fat, reduced-carbohydrate diet (3) Pharmacotherapy (if required)
Step 3.	Weight maintenance (lifelong) • Lifestyle modification • Pharmacotherapy (if required)
Step 4.	Bariatric surgery (for obese patients who have failed medical therapy)
Step 5.	Management of obesity comorbidities;

Table 5. Long - term goals for obesity therapy

Criteria	Treatment success
Reduction of excess weight	7-10% of initial body weight
Maintenance of BMI	< 25 kg/m^2
Blood pressure	any reduction
Blood glucose	any reduction
Glycaemic control (HbA_1c)	any improvement
Other risk factors	any reduction

Calories consumed must equal calories expended for a person to maintain the same body weight. Consuming fewer calories than expended will result in weight loss, whereas, consuming more calories than expended will result in weight gain.

A calorie deficit of 500 calories or more per day should be an initial goal for weight loss for adults. A greater proportion of the calorie deficit should come from decreased caloric intake with a relatively smaller fraction from increased physical activity. The total number of calories a person needs each day varies depending on a number of factors, including the person's age, gender, height, weight, and level of physical activity. Table 6 provides estimated total caloric needs for weight maintenance based on age, gender and physical activity level for Myanmar.

Table 6. Estimated calorie needs per day by age, gender and physical activity level for Myanmar

Gender	Age (Years)	Physical Activity Level		
		Sedentary	Active	Moderately Active
Male	15-18	1700-2100	2200-2600	2600-3000
	19-30	2000-2400	2400-2600	2800
	31-60	1800-2200	2200-2400	2600-2800
	60+	1600-1800	2000-2200	2200-2600
Female	15-18	1400-1600	1800-2000	2200-2400
	19-30	1600-1800	1800-2000	2000-2200
	31-60	1600	1800	2000
	60+	1400	1600	1800-2000

To manage body weight, people should consume a diet that has an appropriate total number of calories and that is within the Acceptable Macronutrient Distribution Ranges (AMDR). Table 7 mentioned the AMDR which has taken into account both chronic disease risk reduction and intake of essential nutrients for the Myanmar population.

Table 7. Recommended macronutrient proportions by age for Myanmar

	Carbohydrates	Protein	Fat
Young Children (1-3 yrs)	45-65%	5-20%	30-40%
Older Children and Adolescents (4-18 yrs)	45-65%	10-30%	25-35%
Adults (19 yrs and Older)	55-65%	10-15%	15-30%

Carbohydrates, protein and fat should be the main sources of calories in the diet. In the Myanmar diet, most carbohydrates are consumed in the form of starches which are found in foods such as grains, potatoes and other starchy vegetables. A common source of starch in Myanmar diet is refined grains. Most of the Myanmar people tend to eat too much carbohydrates (in the form of rice), which constitutes more than 70% of the total caloric intake per day.

Myanmar cuisine usually contains too much fat in the form of cooking oil, which may constitute more than 35% of the total caloric intake per day. Traditionally, protein intake tends to be lower than 10% of the total calories per day.

It is recommended to consume 5 servings of vegetables and fruits every day. People should be cautious about consuming of sugar-sweetened beverages which provide excess calorie and few essential nutrients to the diet. They should only be consumed when nutrient needs have been met and without exceeding daily calorie limits. It is necessary to take into consideration calories from alcohol intake. Alcohol contributes 7 calories per gram. In the Yangon Division, 25.96% of men and 1.09% of women were current drinkers according to the 2003 – 2004 survey. The national survey on NCD risk factors in 2009 revealed that 31.17% of men and 1.47% of the women were current drinkers.

Physical Activity

Physical activity is the other side of the calorie balance equation and should be considered when addressing weight management. Table 8 shows the guidelines on the recommended physical activity for Myanmar which was adapted from the global guideline for physical activity for health.

Behaviour therapy

Individual or group-based psychological interventions should be included in weight management programmes. Psychological interventions should be tailored to the individual and their circumstances.

The range of appropriate psychological interventions and strategies includes:

- self monitoring of behaviour and progress
- stimulus control (where the patient is taught how to recognise and avoid triggers that prompt unplanned eating)
- cognitive restructuring (modifying unhelpful thoughts/thinking patterns)
- goal setting
- problem solving
- assertiveness training
- slowing the rate of eating
- reinforcement of changes
- relapse prevention
- strategies for dealing with weight regain

Table 8. Recommendation for physical activity

Age Group (5 – 17 Years Old)

1. Children and youth aged 5 – 17 years should accumulate at least 60 minutes of moderate – to vigorous-intensity physical activity daily.
2. Amounts of physical activity greater than 60 minutes provide additional health benefits.
3. Most of the daily physical activity should be aerobic. Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week.

Age Group (18 – 64 Years Old)

1) Adults aged 18 – 64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week **or** do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week **or** an equivalent combination of moderate- and vigorous-intensity activity.
2) Aerobic activity should be performed in bouts of at least 10 minutes duration.
3) For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate-and vigorous-intensity activity.
4) Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.

Age Group (65 Years Old and above)

1) Adults aged 65 years and above should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week **or** do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week **or** an equivalent combination of moderate- and vigorous-intensity activity.
2) Aerobic activity should be performed in bouts of at least 10 minutes duration.
3) For additional health benefits, adults aged 65 years and above should increase their moderate-intensity aerobic physical activity to 300 minutes per week, **or** engage in 150 minutes of vigorous-intensity aerobic physical activity per week, **or** an equivalent combination of moderate-and vigorous-intensity activity.
4) Adults of this age group, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week.
5) Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.
6) When adults of this age group cannot do the recommended amounts of physical activity due to health conditions they should be as physically active as their abilities and conditions allow.

Adapted from the WHO Global Recommendations on Physical Activity for Health. 2010.

Pharmacotherapy

Orlistat should be considered as an adjunct to lifestyle interventions in the management of obesity. Patients with BMI ≥25 kg/m^2(with comorbidities) or BMI ≥30 kg/m^{2}should be considered on an individual case basis following assessment of risk and benefit.

Therapy with orlistat should be continued beyond 12 weeks only if the patient has lost at least 5% of their initial body weight from the start of drug treatment. Therapy should then be continued for as long as there are clinical benefits (e.g., prevention of significant weight regain).This may involve medication use outside current license. Ongoing risks and benefits should be discussed with patients.

Surgery

Bariatric surgery should be considered on an individual case basis following assessment of risk/benefit in patients who fulfill the following criteria:

- Failure to respond to non-surgical treatment including dietary measures and weight-reducing drugs.
- Individuals considering surgery should have received adequate information and understand and accept operative risks.
- Patients with a BMI>40, or BMI >35 with high-risk, life-threatening comorbid conditions.

Surgery should be undertaken only by an experienced surgeon in an appropriate clinical setting under expert medical surveillance, and with access to ventilator facilities and the support of a multidisciplinary team.

Management of Risk Factors and Comorbidity

The following risk factors and comorbidities should be assessed and managed accordingly:

Comorbidities:

- Coronary heart disease
- Other atherosclerotic disease
- Type 2 diabetes
- Sleep apnoea
- Other obesity associated diseases and

Risk factors:

- Smoking
- Hypertension
- High LDL-C
- Low HDL-C
- Impaired fasting glucose
- Family history of premature CHD
- More than 45 years (male) and more than 55 years (female)

Overall Approach to Treatment

Management of Obesity in Children

Obesity is used to refer to children and youth between the ages of 2 and 18 years who have BMI equal to or greater than the 95th percentiles of the age and gender specific BMI charts developed by WHO.

In Pediatrics, the term *"Obese"* is not used to describe the degree of overweight. It is a general descriptive term, but does not necessarily indicate a certain level of overweight.

Classification of Weight by BMI in Myanmar (in Children)

Obesity is used to refer to children and youth between the ages of 2 and 18 years who have body mass indexes equal to or greater than the 95th percentile of the age and gender specific BMI charts developed by WHO.

Overweight – BMI is 85th – 94th percentile.

Obesity – BMI is 95th – 98th percentile.

The overall goals for the family in management of overweight child and adolescence are:

- Strive to maintain current weight as the child grows.
- Consistently adhere to healthier life style patterns to prevent further weight gain.
- Encourage healthy lifestyle patterns for all families.

Short-term goals

- 10% loss of initial body weight in 6 months
- Physical activity of at least 1 hour per day
- Decreased television screen time to < 2 hours per day
- Abstinence from sugar-sweetened beverages
- Intake of proper, balanced meals, including daily breakfast

Long-term goals

- Sustaining an altered lifestyle with behaviors that provide further weight loss or that maintain a declined weight, or that avoid additional weight gain; and maintaining a BMI < 85th percentile, although BMI between 85th - 94th percentile may be healthy in some children
- Refer to a specialist for further assessment in the case of severe obesity where medical risks are present
- Drugs are not recommended for weight loss in children
- Weight loss surgery is not recommended in children

Table 9. Treatment options for different levels of BMI and other risk factors in Myanmar

	Diet	Activity	Drug	VLCD	Surgery
BMI 23 - 25 kg/m^2					
No additional risk	√	√	X		
Increased WC	√	√	X		
DM/CHD/HT/HL	√	√	√		
BMI 25 - 30 kg/m^2					
No additional risk	√	√	√□(Consider)		
Increased WC	√	√	√ (Consider)		
DM/CHD/HT/HL	√	√	√		
BMI > 30 kg/m^2					
No additional risk	√	√	√□(Consider)	√□ (consider in severely obese)	√□ (consider in severely obese)
Increased WC	√	√	√		
DM/CHD/HT/HL	√□(Intensive)	√□(Intensive)	√		

KEY : DM : Type 2 diabetes, CHD : coronary heart disease, HT : hypertension, HL : hyperlipidaemia, √□= yes, X = no, Waist circumference (WC) > 90 cm (men), > 80 cm (women)

Assessment

All patients – should be evaluated using the following tests:

- Blood pressure measurements by using appropriate size cuff obtained on 3 separate occasions and evaluated against Pediatric norms
- Fasting blood sugar level
- Fasting lipid panel
- Liver function panel (ALT and AST) to evaluate for steato-hepatitis

When the child is at the 85th percentile, evaluation begins at 10 years of age, then every 2 years.

Selected patients may need to be referred for specialist care. The following tests may also be requested depending on any suspected or identified comorbid conditions or secondary causes of obesity:

- Free T4 and TSH, if hypothyroidism is suspected
- 24 hours urine free cortisol and creatinine if Cushing's syndrome is suspected
- "Modified" glucose challenge obtaining fasting glucose and insulin level and then 2 hours post prandial glucose level if insulin resistance is suspected.
- For BMI > 95th percentile and 10 years or older, the following tests should be done: non- fasting lipid, HbA1c, ALT should be done
- If there is a positive family history of an early cardiovascular event, obtain lipids beginning at 2 years of age to rule out genetic dyslipidemia.

Prevention of Childhood and Adolescent Obesity

- Counsel about physical activity, sedentary behavior, meal patterns and food choice at every well care visit in all pediatric patients and their patients.
- Both bottle and breast fed children can be overfed, Families should be counseled that babies do not need to finish every bottle. Skim milk can replace whole milk after age two.
- Food should not be offered as a reward by parents and care givers.
- Eat healthy family meals together 3 to 6 times per week with limited food portions.
- Limit sugar – sweetened beverage.
- Recommend at least 5 serving of fruits and vegetables a week. A serving is 1⁄2 cup.
- Recommend a healthy breakfast everyday. Obese children are more likely to skip breakfast or to eat smaller breakfast than leaner children.
- Limit TV time to < 2 hours per day and remove TV from the child's bed room.
- Encourage 60 minutes of physical activity and free play each day.
- Limit eating outside the home, especially fast food.

Treatment failure

If there is no success with basic lifestyle intervention, motivated families should be referred to a family-based program which incorporates nutrition, physical activity and behavioral and involves > 25 hours of contact over a 6 month period.

Referral

Consult/refer if comorbidities persist or if no improvement after 6 months of structured lifestyle.

Conclusion

In conclusion, the following strategies will help reduce obesity in Myanmar:

(1) Changing the lifestyles of the citizens such as avoiding the consumption of Western diets which are high in refined carbohydrates, saturated fats and sugars, and increasing physical activity and avoiding sedentary lifestyles;

(2) Narrowing down the significant gaps in medical services by strengthening the competencie of medical professionals in obesity management; and

(3) Strengthening the community infrastructure and public health systems so as to reduce under-nutrition as well as obesity.

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FEATURE ARTICLE

Recommendations for Obesity Management from Singapore

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Abstract

Obesity, defined as a condition of excessive body fat with adverse effects on health, is an increasing global problem which contributes to chronic disease burden and health care costs. The Singapore Ministry of Health (MOH) released Clinical Practice Guidelines (CPG) in 2004, aimed at providing best evidence-based recommendations for diagnosis, classification, evaluation and multidisciplinary management (diet, physical activity, medication and surgery) of overweight and obesity in adults and the pediatric population. This article summarizes the guidelines, discusses their utility in Singapore and strategies for increasing their use, and briefly outlines updates in management since the CPG's publication. A revised CPG is urgently needed in view of the increasing prevalence of overweight and obesity in Singapore and the numerous advances in the management of overweight and obesity.

Keywords: obesity, weight management, clinical practice guidelines, Asia, Singapore

Introduction

Obesity is defined as a condition of excessive fat accumulation in the body, to the extent that health and well-being are adversely affected.[1] It is a risk factor for numerous diseases including type 2 diabetes, coronary artery disease, infertility and cancer, and is an increasingly important global health problem. In Singapore, the prevalence of obesity [defined as body mass index (BMI) ≥ 30 kg/m^2] has risen from 6.9% in 2004 to 10.8% in 2010, while the prevalence of overweight (BMI 25.0-29.9 kg/m^2) was approximately 25%.[2,3] As expenditure on obesity in developed countries has been estimated to be up to 7% of total health costs due to associated chronic disease complications, treatment of obesity and its primary comorbidities are estimated to cost the Singapore health care system approximately $260 million per year, not including the indirect costs of loss of productivity and absenteeism.[4,5] In view of rising health care expenditure over the last three years, and the approximately 1.5 million adults in the growing Singapore population who are overweight and obese, the reduction in health costs and disability-adjusted life years, and improvement in health and quality of life, are likely to outweigh the costs of implementing government policies and campaigns to reduce overweight and obesity.[2,3,5] The Singapore MOH CPG was released in 2004, with the intent of providing best evidence-based recommendations for diagnosis, classification, evaluation and multidisciplinary management of overweight and obesity, including the growing problem of obesity in children and adolescents.[4] This article aims to provide a brief synopsis of the guidelines, including aspects which are relevant to Singapore; and discuss the utility of the recommendations for management of overweight and obesity, particularly in primary care. We will also outline updates in management published after the release of the guidelines.

Summary of Methodology of CPG Development

The stated aims of the Singapore MOH CPG for Obesity were to provide a framework to assist health care professionals in management of overweight and obesity, review available management options, and aid primary care physicians in referrals to specialists for resistant cases.[4] The CPG was developed by a multidisciplinary workgroup consisting of experts in endocrinology (including a paediatric endocrinologist), psychiatry, sports medicine, bariatric surgery, and primary care; as well as representatives from dietetics, psychology, physiotherapy and the Health Promotion Board (HPB) of Singapore. The workgroup formulated these guidelines by reviewing published international guidelines and current evidence available in the research literature, and considering the characteristics of the Singaporean population. The guidelines were drawn up based on the best available evidence for management of overweight and obesity at the time of development in 2004.[4] The CPG has since been withdrawn pending revision.

Summary of Recommendations

Diagnosis of Obesity

The CPG recommends the use of BMI to define obesity. Current World Health Organization (WHO) and

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international guidelines recommend BMI cut-offs of 25 kg/m^2 and 30 kg/m^2 to define overweight and obesity, respectively (Table 1).[1] However, the relationship between BMI and metabolic risk varies among different ethnic groups and populations.[6-10] Ethnic-specific differences in body size are present in multi-racial Singapore, with overweight and obesity being more prevalent in Malay and Indian adults aged 18-69 years, compared to Chinese.[4] A WHO expert consultation panel review of scientific evidence from various Asian countries including Singapore concluded that Asians, particularly individuals of South Asian (Indian) origin, have a higher percentage of body fat and risk of cardiovascular disease at this BMI cut-off than Caucasian people of the same sex and age. The panel recommended BMI values of 23 kg/m^2 and 27.5 kg/m^2 as cut-off points for public health action in Asians, based on body fat equivalence and co-morbid disease risk (Table 1).[1,8] It is important that BMI cut-offs for Singapore take into account the differences between Chinese, Malays and Indians in body fat percentage and cardiovascular risk for any given BMI.[7,9]

Table 1. Current WHO BMI cut-off points and proposed BMI cut-off points for public health action in Asians.[4]

Cardiovascular disease risk	Asian BMI cut-off points for action (kg/m^2)	Current WHO BMI cut-off points (kg/m^2)
	<18.5	<18.5
Low	18.5 to 22.9	18.5 to 24.9
Moderate	23.0 to 27.4	25.0 to 29.9
High	27.5 to 32.4	30.0 to 34.9
Very High	32.5 to 37.4	35.0 to 39.9
	≥37.5	≥40.0

Waist circumference (WC), measured at the mid-point between the lower costal margin and iliac crest in a standing individual with relaxed abdominal muscles, is the most practical clinical measurement for assessing the severity of abdominal obesity. Abdominal obesity is a major risk factor for development of the metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease. International guidelines recommend cut-offs of 102 cm (male) and 88 cm (female) to define excess cardiovascular and metabolic risk. Based on the WHO expert consultation and data on co-morbid disease risk in the Asia-Pacific Region, the CPG recommended lower WC cut-offs of 90 cm (male) and 80 cm (female) for defining abdominal obesity in Asians.[1,10] Ethnic- and gender-specific cut-offs are also recommended for use in the diagnosis of abdominal obesity in a 2009 consensus statement on definition of the metabolic syndrome from the International Diabetes Federation, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and the International Association for the Study of Obesity.[11]

A variety of methods may be used for body composition analysis, including skinfold thickness, bioelectrical impedance (BIA), isotope dilution techniques (such as deuterium oxide dilution), densitometry (using underwater weighing or air plethysmography), dual energy x-ray absorptiometry and 4-compartment estimation.[4] However, skinfold measurement and BIA are operator- or device-dependent indirect measurements of percentage body fat; while the other methods are too expensive, time-consuming and complicated for routine clinical use.

Weight Management

Overweight and Obese Adults. The CPG recommends targeting modest weight loss in overweight and obese adults, e.g. 10% body weight over 6 months. This results in a reduction in morbidity, and is more realistic than aiming for ideal body weight. Recommendations for management focus on multidisciplinary strategies for lifestyle modification, which combine caloric restriction with increased physical activity. An algorithm for the management of obesity is provided in the CPG, with anti-obesity medication and bariatric surgery as necessary (Figure 1). Patients should be evaluated for secondary causes of obesity, such as medications (including "traditional" medicine which contain corticosteroids, antipsychotics and antidepressants), and genetic or endocrine disorders (Cushing's syndrome, hypothyroidism). Evaluation for comorbidities (e.g. hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, sleep apnea, osteoarthritis) is also recommended. Investigations include thyroid function tests; screening for Cushing's syndrome; and detecting comorbidities, particularly for associated cardiovascular risk factors (e.g. electrocardiogram, fasting lipids and glucose). These should be managed according to best-practice guidelines. The motivation for weight loss and the presence of depression and binge eating disorders must be evaluated, with subsequent behavioral therapy and psychiatric treatment when warranted. The Singapore Chinese Health Study recently found that smoking increases mortality risk in adults with BMI ≥ 27.5 kg/m^2.[12] Smoking cessation efforts should be intensified in obese individuals.

Diet and increased physical activity are the first-line weight-loss strategies for all. Medications serve as adjunctive treatment for the obese individual, or the overweight patient with comorbidities. Very-low calorie diets (VLCD) and low-calorie diets (LCD) may also be used in this group. Bariatric surgery is recommended when lifestyle and pharmacological measures have failed in the severely obese with or without comorbidities (Figure 1). These measures will be discussed in greater detail below.

Diet Modification. Reduction in daily caloric intake by at least approximately 500 kilocalories will produce at least 0.5 kg per week weight loss.[13] This may be achieved by a variety of diets with different macronutrient composition. Balanced nutrition reduction diets moderately restricted in total fat, moderate in carbohydrates (mainly complex

carbohydrates), and moderate in protein result in loss of body weight and body fat, as long as total caloric intake is reduced.[13,14] Weight loss appears to be better associated with reduced caloric intake and prolonged diet duration, rather than the macronutrient content *per se*. This statement is supported by a large two-year study of diets containing different percentages of carbohydrate, fat and protein, but providing the same amount of caloric restriction. The results showed that weight loss and regain was similar in all four diets studied[14]. The guidelines recommend that meals should not be skipped as a weight control method, and should be adequately sized so that snacks are not needed.

Commercially available meal replacements (e.g. Optifast® and Cambridge Weight Plan®) are effective as part of LCD and VLCD for up to 6 months for weight loss; however, sustained modification of food intake is necessary to maintain weight loss.[15] Very low calorie diets may be considered in patients with BMI ≥ 30 kg/m^2 (commensurate Asian cut-point 27.5 kg/m^2) who have failed more conservative weight loss attempts, or those in whom rapid weight loss is a medical necessity (e.g. before bariatric surgery). They should be avoided in children; the elderly; pregnant and breastfeeding women; and patients with psychiatric problems.[4] In addition to lists outlining the caloric content for meat, fish and commercially sold snacks, the CPG also includes data on the serving sizes, calorie content and fat content for food items which are commonly eaten in Singapore (e.g. chicken rice, *satay*, fish head curry and Asian desserts). Compliance with dietary guidelines may be limited by the high calorie and fat content of many readily available Asian foods, the cost of commercial meal replacements, and the difficulty of adhering to low-calorie diets for a prolonged period.[4]

Physical Activity. Moderate-intensity physical activity for 30 minutes, 3 to 5 days per week has been found to reduce cardiovascular disease and overall mortality, but has been unable to induce significant weight loss without caloric restriction.[16,17] The CPG recommends starting low- to moderate-intensity physical activity for 30 to 45 minutes, 3 to 5 days per week (150 min/week); then gradually increasing the intensity, duration and frequency to 45 to 60 minutes on most days or every day (200-300 minutes/week) to prevent weight gain, based on the 2001 American College of Medicine (ACSM) Position Stand on exercise-based weight-loss strategies in adults.[18] The 2009 update of the ACSM statement recommends further increase in physical activity for prevention of weight gain (150 to 250 minutes/week), for weight loss (> 250 minutes/week), and for prevention of weight regain (> 250 minutes/week), based on the findings of the United States National Weight Control Registry.[19] However, the high levels of exercise required to achieve weight loss due to energy deficit similar to that produced by caloric restriction will be difficult for overweight or obese adults to achieve and sustain.[16,17] For adults who are not able or willing to exercise continuously, the Singapore CPG

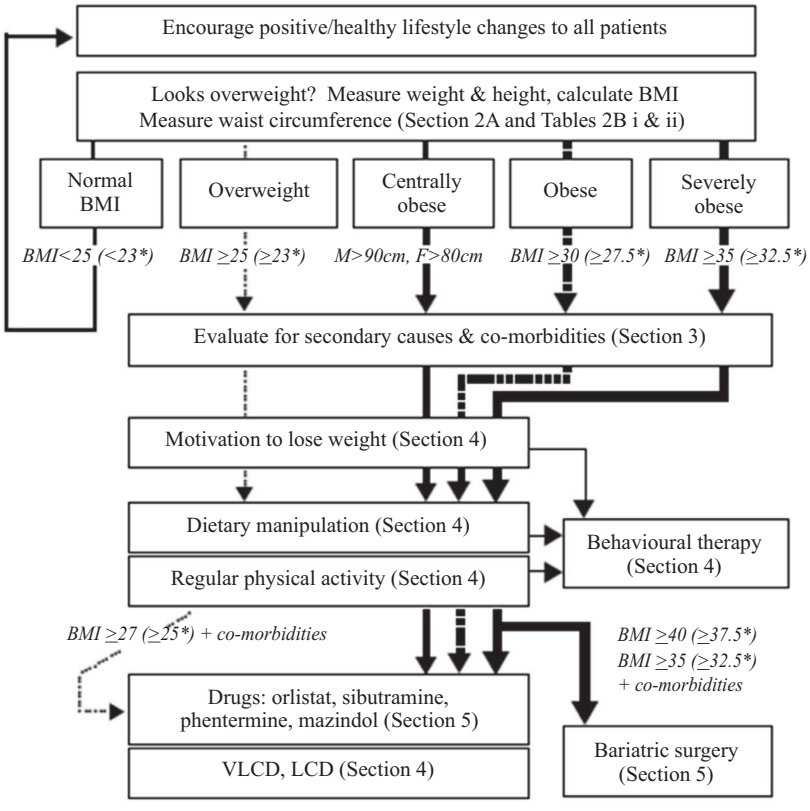

Figure 1. Algorithm for weight management from the Singapore MOH CPG.[4]

recommends accumulation of 30 to 40 minutes of physical activity in the form of intermittent sessions lasting 10 to 15 minutes. Cumulatively, these are not superior to a continuous session of the same duration for weight loss, but do improve cardiorespiratory fitness and reduce coronary risk, and may also improve compliance.[17] The CPG also provides information on caloric expenditure per 30 minutes of gym activities, sports, occupational activities and housework, which are useful for comparison with the food charts.

Behavior Modification. The CPG emphasizes the importance of increasing patient motivation for weight loss. Methods include improving understanding of obesity and associated risks for chronic disease; exploring readiness for sustained lifestyle modification; and developing strategies to address time availability, social support framework and financial status. Weight loss programs incorporating cognitive-behavioral therapy (CBT) are helpful in achieving weight loss and weight maintenance in up to 10% for one to five years of follow-up.[17,20] Recommended CBT techniques include motivational interviewing (recognition of motives for and barriers to weight loss to facilitate behavior change), goal setting and plans of action, self-monitoring of eating habits and activity, cognitive restructuring (identifying and controlling situations which trigger unhealthy eating), stimulus control, relapse prevention and stress management.[4,20] As weight regain is associated with falling-off from behavioral strategies, the CPG recommends that subjects continue with up to 12 months of a program combining behavior therapy, diet and exercise after the initial period of weight loss. However, compliance with CBT may be limited by availability and cost of referral to a psychologist; lack of time for counselling sessions; and reluctance on the part of patients, who perceive obesity to be a purely physical problem.

Anti-obesity Drugs. Pharmacological therapy is indicated for patients with BMI of at least 30 kg/m^2, or with BMI of 27-29.9 kg/m^2 in the presence of comorbidities or complications of obesity (hypertension, type 2 diabetes, hyperlipidemia, coronary artery disease and sleep apnea) who fail to lose weight with therapeutic lifestyle modification.[4,21] Equivalent BMI cut-offs for Asians are 27.5 and 25-27.4 kg/m^2, respectively.[4] At the time of publication of the CPG, sibutramine (appetite suppressant with sympathomimetic activity) and orlistat (inhibitor of digestion and absorption of ingested fat) had been approved for long-term management of obesity. In 2010, sibutramine was withdrawn from the market in North America, Europe, Australia and several Asian countries including Singapore, due to its association with increased risk of cardiovascular events in overweight and obese patients in the Sibutramine Cardiovascular Outcome Trial.[22] Orlistat produces weight loss of 1.3-4.8% at a dose of 120 mg TID at 1, 2 and 4 years, but its use is limited by gastrointestinal effects such as abdominal discomfort, bloatedness, stool leakage and steatorrhoea.[21] In 2010, the U.S. Food and Drug Administration (FDA) approved a revised label for orlistat to include new safety information about cases of severe liver injury reported rarely with its use.[23]

The CPG recommends the sympathomimetic appetite suppressant phentermine for short term (6 to 12 months) weight loss. Metformin is the drug of choice for weight loss in obese diabetic patients, but there is currently limited evidence on its efficacy in people without diabetes.[24] The CPG also notes that the anti-epileptic agents topiramate and zonisamide are effective for inducing 5 to 6 kg of short-term weight loss. At the time of publication, there were limited available data on the safety and effectiveness of combining other anti-obesity drugs. At the time of writing of this article, orlistat is the only anti-obesity agent with long-term safety data approved for use in Singapore. The glucagon-like peptide-1 (GLP-1) analogues exenatide and liraglutide induced up to 7% weight loss when administered to obese type 2 diabetic and non-diabetic adults, with higher doses of liraglutide inducing significantly more weight loss (6 to 7kg) compared to orlistat (4 kg) in non-diabetic obese individuals.[25-28] However, the use of these medications is limited by gastrointestinal side effects, and they are not currently approved for weight loss in people without diabetes.[25-28]

The CPG acknowledges that pharmacological therapy is most effective when combined with diet, physical activity and behavior modification. The paucity of available anti-obesity medications which are safe and effective for long-term use emphasizes the importance of caloric restriction and increased physical activity as the mainstays of weight management.

Bariatric Surgery. Bariatric surgery is defined as gastrointestinal surgery to help severely obese patients lose weight. It is more effective (16 to 35% weight loss in 2 years) than medical management (5 to 8%) for weight loss and maintenance.[29] In accordance with the U.S. National Institutes of Health (NIH) guidelines, the CPG recommended surgery for adults aged 18 to 55 with BMI ≥ 40 kg/m^2 without comorbidities or 35 kg/m^2 with comorbidities (Asian equivalent cut-offs 37.5 and 32.5, respectively), who fail to lose weight by non-surgical methods. In the light of good results for weight loss; improvement of type 2 diabetes, the metabolic syndrome and other obesity-related comorbidities; and cost-effectiveness of surgery in patients with BMI 30 to 35 kg/m^2; the Asian Consensus Meeting on Metabolic Surgery (ACMOMS) recommended that the BMI cut-offs be lowered to 35 and 32 kg/m^2, respectively; and that surgery be considered for Asian adults with BMI≥ 30 kg/m ^{2} with central obesity (WC > 90 cm in males and > 80 cm in females) and at least two features of metabolic syndrome

(raised triglycerides, low HDL cholesterol, hypertension, high fasting plasma glucose).[30] Bariatric surgery has been performed safely and effectively in adolescents and in patients above the age of 65 in centers with high patient volumes and experienced surgeons.[29]

A comparative summary of the efficacy, complications and mortality of surgical procedures, such as gastric banding and gastric bypass, are available in the CPG.[4] Laparoscopic sleeve gastrectomy, which was not discussed in the CPG, has become more popular in clinical practice in Singapore. Laparoscopic procedures are associated with lower morbidity and mortality, near-100% resolution of diabetes, and improvement of other comorbidities using various techniques, such as sleeve gastrectomy, gastric banding and *Roux-en-Y* gastric bypass.[31-33]

The CPG emphasizes the importance of appropriate patient selection, thorough pre-operative evaluation, and the need for multidisciplinary management involving the physician, dietician and psychologist. Surgery entails significant technical issues, complications, and cost; necessitates extensive pre- and peri-operative preparation; and requires lifelong post-operative lifestyle modifications and follow-up for complications. Evidence from longer (more than 10 years duration) post-surgical data illustrating the improvement of mortality and comorbidities in larger populations (such as in the Swedish Obese Subjects Study), and further developments in surgical techniques, appear to support a greater role for bariatric surgery in the management of obesity in the future. [35]

Weight Maintenance

Obesity is a chronic condition requiring lifelong management. Clinical trials have shown that most weight is regained within five years.[13,17] Based on data from U.S. National Weight Control Registry, the CPG recommends that behavioral strategies which may enhance successful long-term weight maintenance include eating a calorie-restricted (approximately 1400 kcal/day), low- to moderate-fat (25% of total caloric intake/day) diet; frequent self-monitoring of body weight; recording food intake and physical activity; maintaining high levels of regular physical activity; and eating breakfast regularly.[17] Epidemiologic, cross-sectional, and prospective correlation studies suggest an essential role for physical activity in weight-loss maintenance, and *post hoc* analysis of prospective trials shows a clear dose-response relationship between physical activity and weight maintenance.[16] Bariatric surgery appears to be associated with greater maintenance of weight loss than medical interventions.[29]

Obesity in Children and Adolescents

The WHO defines childhood overweight as BMI at or above the 85th percentile and lower than the 95th percentile for children of the same age and sex, and obesity as a BMI at or above the 95th percentile, based on growth charts from the US Centers for Disease Control (CDC).[4] However, the CDC charts use data derived from the U.S. population in the 1970's and are not applicable to our local setting. A recent international anthropometric survey defined the BMI percentile curves for Singapore children and teenagers up to 20 years of age, matched to adult cut-offs for overweight and obesity at 25 and 30 kg/m^2, respectively, positioned at age 18 years.[35] The CPG recommends that either the WHO criteria or the adult-matched cut-offs may be used as thresholds for evaluation and weight management. The lack of integration of the WHO definitions with Singapore cut-offs poses difficulties in policy-making and decisions on therapeutic intervention. Moreover, the BMI percentiles corresponding to BMI 23 and 27.5 kg/m^2, as in the adult population, may be more appropriate for defining risk due to overweight and obesity, respectively, in Singaporean children. BMI cut-offs to define underweight in children and adolescents (based on equivalents to BMI < 17 kg/m^2 in adults) have also been obtained for the Singapore population, and are useful for pediatric and adolescent weight management in conjunction with the corresponding definitions of overweight and obesity.[36]

The prevalence of obesity in Singapore children aged 6 to 16 years, based on the WHO definition, was approximately 15%.[37] This is a disturbing statistic, as childhood obesity is an important predictor of adult obesity, and associated chronic diseases will contribute to premature morbidity and mortality. Moreover, obesity has a significant negative impact on the adolescent's health-related quality of life in both the physical and mental domains.[38] The primary goal of childhood and adolescent obesity interventions is to adopt and maintain healthy lifestyle behaviors which still allow growth in height to continue, so that height eventually becomes appropriate for weight, or the BMI percentile becomes reduced.[39] As in adults, the CPG recommends that diet modification and increased physical activity should be the mainstays of weight management in children and adolescents. Important differences for children include the use of less restrictive nutritional plans, rather than diets consisting of drastically altered nutrient composition, VLCD or low-protein diets; and age- and weight-appropriate activities with decreased time spent on sedentary pursuits, with appropriate parental involvement. Multidisciplinary behavior-treatment programs utilizing techniques such as education, target-setting, teaching skills for weight loss, self-monitoring, stimulus control and reinforcement, have shown consistent success in weight loss.[39,40] When the CPG was developed, there was no available data on the long-term efficacy and safety of anti-obesity medications in the pediatric population. A recent meta-analysis of studies on children and adolescents found that sibutramine produced clinically meaningful reductions in BMI and improvements in cardiometabolic risk, while orlistat reduced BMI but had a high prevalence of gastrointestinal

adverse effects.[41] Although the CPG did not recommend bariatric surgery for children below 18 years due to previous paucity of data on safety and concerns about effects on growth, recent guidelines have suggested surgery for adolescents with BMI above 50 kg/m^2, or BMI above 40 kg/m^2 with severe comorbidities in whom lifestyle modifications and/or pharmacotherapy had failed.[40] Centers with experienced surgeons have, with appropriate informed consent protocol for families, performed operations in girls above age 13 years and boys above age 15 years with obesity-related comorbidities.[42]

Quality Indicators

The CPG recommends the use of quality indicators to evaluate the success of weight management programs. Structure indicators include availability of resources and facilities to promote weight loss and maintenance in both the community and health-care settings; and a multidisciplinary weight management team consisting of the primary care doctor, nurse-educator, nutritionist, exercise therapist, behavioural therapist, endocrinologist with specialized training in weight management, respiratory physician, cardiologist and surgeon where necessary. Regular monitoring of performance parameters is recommended: patient education, weight, BMI, WC and blood pressure at least quarterly; and fasting glucose and lipids at least annually. Data on outcome indicators (percentage of weight loss; amount of weight regain; and reduction in BP, LDL cholesterol and blood glucose) should be collected from weight management programs in the community and health-care providers.

Engaging Physicians in the Use of the CPG

The majority (80%) of the CPG's stated target group of primary care practitioners provide care in approximately 2000 private clinics situated throughout Singapore.[43] Referrals to psychologists, dieticians and physical trainers are not readily available in the community as part of a structured weight management program. Physicians and patients may also perceive these additional interventions to be expensive and time-consuming. There are no published data on the rate of implementation of the CPG in the community, or its association with weight loss and improvement in cardiovascular risk factors and obesity-related comorbidities. As such, there is a pressing need to evaluate the effectiveness of the CPG (and subsequent revisions), and to increase engagement of primary care physicians in the adoption of these recommendations. Cost-effective tools, such as postal surveys with incentives for participation, can be developed to monitor CPG usage, obtain feedback on difficulties in compliance, and identify barriers and needs in obesity management in the community.[44] Follow-up targeted clinical tools such as facilitated two-way referral pathways to community-based dieticians, behavioural and sports therapists; and wider access to educational materials and multimedia resources on-line and in print; are useful to bridge the gap in care between general practitioners and specialists in obesity management.[45] Incremental pacing of the introduction of initiatives and guidelines will be helpful in the integration of care and resources in the primary care sector with public health and hospital-based facilities. Involvement of patients will also be facilitated by availability of on-line resources for weight management, such as websites and smartphone applications. Indeed, interactive technology-based interventions have been shown to be superior to self-directed weight control in limiting regain at 24 months after completion of a weight loss program.[46]

Conclusion

The Singapore MOH Clinical Practice Guidelines for Obesity (2004) emphasize the importance of multidisciplinary involvement in weight management, and individualization of management according to patient needs and available diagnostic and treatment options. Its strengths include contributions from relevant allied medical disciplines and community health care experts in addition to medical professionals, the use of the best evidence available at the time of its inception, and inclusion of recommendations and information which are uniquely useful for the local population. Nevertheless, the prevalence of obesity increased after the CPG was released, underscoring the need for measures to improve uptake of the recommendations and acceptability and availability of health care resources. An updated CPG is urgently needed in view of the rapid and numerous advances in knowledge and tools for the management of overweight and obesity.

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FEATURE ARTICLE

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Identification, Evaluation and Treatment of Overweight and Obesity in Adults: Clinical Practice Guidelines of the Obesity Clinic, Wellness Cluster Cipto Mangunkusumo Hospital, Jakarta, Indonesia

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Abstract

Recent surveys have shown that obesity rates are increasing in Indonesia, particularly in urban areas such as the capital city of Jakarta. Cipto Mangunkusumo Hospital, a top referral hospital in Jakarta, established an Obesity Clinic and developed clinical practice guidelines (CPG) for its management. The aim of the CPG was to provide the best evidence-based recommendation for diagnosis, evaluation and multidisciplinary management of overweight and obesity in the adult population. This article summarizes the guidelines.

Keywords: obesity, clinical practice guidelines, Indonesia

Introduction

The prevalence rates of overweight and obesity are increasing rapidly in both developed and developing countries.[1-2] Previously, overweight and obesity were considered primarily problems of developed countries. However, due to lifestyle changes and urbanization, it is now apparent that developing countries are also faced with the same issues.[1-4] Policymakers in developing countries have not paid much attention to the problem of excessive weight gain. Obesity contributes to a variety of serious chronic diseases, and thus to a large health burden. Indonesia is a large and populous country and is one of the economically fast growing nations of Asia, and has undergone rapid urbanization including a move of traditional food systems towards a modern supply chain.[1-4]

Recent surveys have shown that obesity rates are also increasing in Indonesia. Based on the National Basic Health Research in 2007, the prevalence of overweight and obesity, as determined by body mass index (BMI), were 8.8% and 10.3%, respectively. The cumulative prevalence of overweight and obesity was higher in females than in males (23.8% versus 13.9%). Obesity was observed to be more prevalent in urban areas. Furthermore, central obesity, as determined by waist circumference, was present in 18.8%, and was more commonly observed in females (29% versus 7.7% in males) and in urban area dwellers (23.6% versus 15.7% in rural areas).[3]

Similarly, the Indonesian Family and Life Survey (IFLS) of the Rand Institute, conducted in 1993, 1997, 2000 and 2007, showed that the mean BMI values among Indonesian adults has notably increased Indonesian women had higher BMIs than men, and the difference of BMIs between genders increased from 1993 onward. Average BMI levels were higher in urban compared to rural areas. However, the rate of increase in BMI over time among rural dwellers was higher compared to urban area residents. Data from the IFLS represented 83% of Indonesian population; a few remote areas were not included in the survey.[1]

In 2006, we performed an epidemiologic study in Jakarta, the capital city of Indonesia (unpublished data). The survey included 1591 subjects aged 25 to 65 years, of which 41% were male. The prevalence of obesity and central obesity were 52% and 53%, respectively. In addition, the prevalence of obesity increased with age in both genders. There was a decreasing trend noted after the age of 60.

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Table 1. The prevalence of obesity based on age group and sex

	25-<30 y	30-<40 y	40-<50 y	50-<60 y	≥60 y
Male	31.6%	49.2%	67.3%	68.7%	66.7%
Female	18.4%	27.7%	29.8%	35.5%	38.5%

Summary of Methodology of Guideline Development

The guidelines were developed by a multidisciplinary representative group. The Obesity Cluster Team reviewed the Cipto Mangunkusumo guidelines for comprehensiveness and accuracy of interpretation of evidence supporting the recommendations. The guideline development group was able to obtain valuable feedback and suggestions to include additional evidence from the literature and to consider alternative interpretation of data. The participants contributed to and influenced the form of the final guideline, making it a comprehensive report from various geographical origins and medical disciplines.

Summary of Recommendations

Clinical Evaluation of Overweight and Obese Patients

Overweight and obesity are known risk factors for cardiovascular disease. They also contributes to the development of other chronic diseases, including diabetes and gallbladder disease. In this high risk population, early detection and prompt management of obesity and related risk factors are important in reducing the overall likelihood for developing disease and attendant social consequences.[5-12]

Information from the clinical interview. Upon seeing an overweight or obese patient, the physician needs to collect basic information related to risk factors and possible target organ complications. This includes investigating how and why the patient became obese, how the patient copes with it , and any previous efforts for weight reduction. The risk factors for developing overweight and obesity are age, history of weight gain, use of medications affecting weight (contraceptive agents, glucocorticoids, antipsychotic drugs), cessation of cigarette smoking, menopause, pregnancy, patterns of food intake and level of physical activity level. These are also affected by psychosocial issues relating to the patient's readiness for weight reduction.[12]

Clinical evaluation. During the initial consultation, the nurse or physician should document vital signs and anthropometric measurements, which include body weight, height, BMI, waist circumference, heart rate, blood pressure and body temperature.[12]

The BMI is calculated by using the body weight (kg) divided by the square of the height (m). Recognizing the observations that the risk for diabetes and hypertension doubles with a BMI of 25 kg/m^2, a task force from the Asia-Oceania group of the International Association for the Study of Obesity has proposed a different classification for obesity in the Asia-Pacific population. Based on this classification, obesity is defined as a BMI of 25 kg/m^2 or higher; high-risk waist circumference is 90 cm or greater for men, and 80 cm or greater for women.[13-14]

Table 2. Classification of obesity as recommended by the Asia-Pacific Task Force[13]

Classification	BMI (kg/m^2)	Risk of Co-morbidities: Waist Circumference <90cm (men) <80 (women)	Risk of Co-morbidities: Waist Circumference ≥90cm (men) ≥80 (women)
Underweight	< 18.5	Low*	Average
Normal	18.5-22.9	Average	Increased
Overweight	≥ 23		
At Risk	23.0-24.9	Increased	Moderate
Obese I	25.0-29.9	Moderate	Severe
Obese II	≥ 30	Severe	Very Severe

** but increased risk of other clinical problems*

Laboratory tests. Laboratory tests are performed to exclude other endocrine causes, screen for co-morbidities (e.g. dyslipidemia, impaired glucose tolerance) and other target organ complications, if they are indicated. The most important comorbidity is the metabolic syndrome (MetS), a complex of traits that enhance the risk of cardiovascular disease. MetS includes a variety of conditions such as central obesity, hypertension, insulin resistance, dyslipidemia, and diabetes mellitus. Based on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, metabolic syndrome is identified if there are 3 or more of the mentioned conditions present.[15] Other co-morbidities include family history of early cardiovascular disease, cholecystitis/cholelithiasis, obstructive sleep apnea and osteoarthritis.

Clinical plan. Once the workup for etiologic and complicating factors is complete, the risk associated with elevated BMI, fat distribution, weight gain, and level of physical activity can be evaluated.[5-12] An early disease-oriented algorithm was published by Bray et al (Figure 1).[12] The adapted version of National Heart, Lung and Blood Institute (NHLBI) treatment algorithm for overweight and obesity is presented in Figure 2.[10]

In the primary care setting, there are 10 steps to treating overweight and obesity:[12]

1. Measure height and weight.
2. Measure waist circumference.
3. Assess comorbidities.
4. Should your patient be treated?
5. Is the patient ready and motivated to lose weight?
6. Which diet should you recommend?
7. Discuss a physical activity goal. Discuss a physical activity program.
8. Review the Weekly Food and Activity Diary.
9. Give the patient copies of dietary information and exercise prescription.
10. Enter the patient's information and the goals you have agreed on in the weight and goal record.

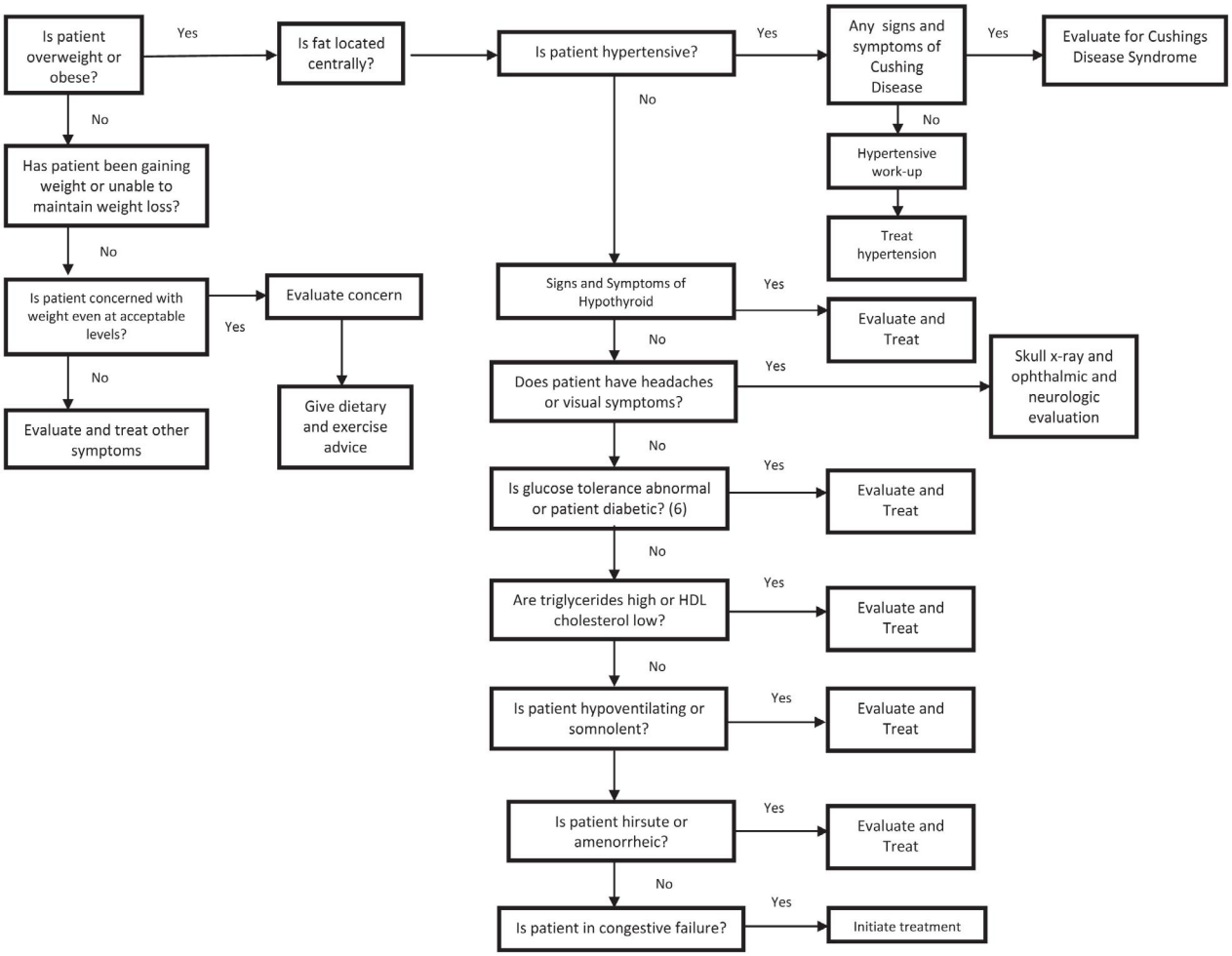

Figure 1. An algorithm for the appropriate indication for laboratory and clinical testing in the evaluation of the overweight or obese patient. Adapted from: Bray GA. Classification and evaluation of the overweight patient. In: Bray GA, Bouchard C, eds. *Handbook of Obesity: Clinical Appications*. 2nd ed. 2002. New York: Marcel Dekker, Inc.; 2002:20.

Weight Management Programs and Support for Weight Loss Maintenance in Adults

In general, among Asians, weight loss therapy is recommended for patients with a BMI of 25 kg/m^2 or greater, and for patients with a BMI between 23 to 24.9 kg/m^2 or a high-risk waist circumference plus two or more risk factors (comorbidities).

The goal of management is to decrease insulin resistance and improve the patient's metabolic profile. The initial goal of weight loss is to reduce baseline weight by 10% within 6 months, at a rate of approximately 0.5 to 1.0 kg (1 to 2 pounds) per week. After the initial goal is achieved, a weight maintenance program should then be included.

Weight management programs should include lifestyle modification and behavioral management.

Lifestyle Modification

Lifestyle modification consists of dietary intervention and increased physical activity. Dietary interventions for weight loss should be calculated to reduce 500 to 1000 kcal from the total daily caloric intake. In general, total daily intake may be prescribed at 1000 to 1200 kcal/day for women and 1200 to 1600 kcal/day for men. Programs should be tailored to suit the dietary preferences of the individual patient.

More weight reduction can be achieved by combining dietary restriction and physical activity. Initially, moderate levels of physical activity for 30 to 45 minutes per day, with a frequency of 3 to 5 times per week, may be applied. Overweight and obese individuals should be prescribed a volume of physical activity to expend approximately 1800 to 2500 kcal/week. This corresponds to approximately 225 to 300 minutes in a week of moderate intensity physical activity. This may be achieved through five sessions lasting 45 to 60 minutes each per week, or lesser amounts of vigorous physical activity.

The physical activity program should be tailored according to the individual's health or physical condition. Moderate-intensity cardiovascular exercise for 20 to 60

minutes (or longer) at least 3 to 5 days per week is recommended initially. Daily exercise, however, is recommended for weight loss. Low-impact activities, such as walking, swimming, water exercise, cycling, and step aerobics are preferred. A strength-training program with 1 to 3 sets of exercises for the major muscle groups, for 10 to 15 repetitions, is recommended at least two days per week. The patient should be advised to start slowly, then gradually increase the frequency, duration and intensity of the exercise. It is important to emphasize adequate fluid intake before, during, and after exercise. The patient should not overdo exercise.[16-18]

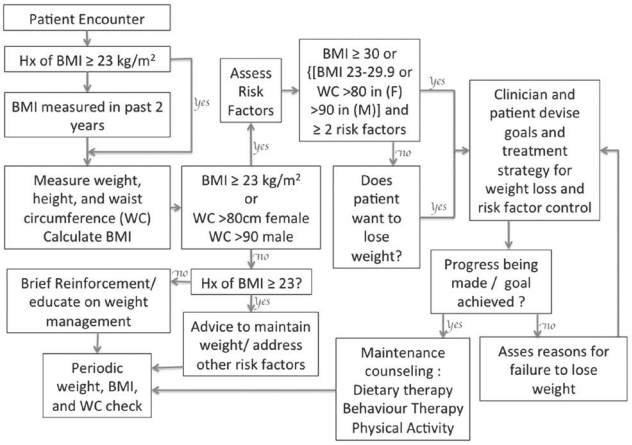

Figure 2. Treatment algorithm of overweight and obesity. The algorithm applies only to the assessment for overweight and obesity and subsequent decisions based on that assessment. It does not reflect the initial general assessment for other cardiovascular risk factors that are indicated. Adapted from: NHLBI Obesity Education Initiative. *The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. National Insitutes of Health, National Heart, Lung, and Blood Institute; October 2000. NIH Publication No. 00-4084.

Behavioral modification

Behavioral modification includes goal setting, self monitoring, stimulus control, cognitive restructuring and prevention of relapse or weight regain.

Pharmacological treatment

Orlistat should be considered as an adjunct to lifestyle modifications in the management of weight loss. Pharmacologic therapy should be considered on an individual case basis in patients with a BMI of 25 kg/m^2 or greater with co-morbidities, or a BMI of 30 kg/m^2 or greater, following careful assessment of risks and benefits. Medications should never be used without concomitant lifestyle modification.

Surgery

Bariatric surgery should be included as part of an overall clinical pathway for adult weight management. Bariatric surgery should be considered on an individual case basis following assessment of risks and benefits in patients who fulfill the following criteria: BMI ≥35 kg/m^2; presence of one or more severe co-morbidities expected to improve significantly with weight reduction (e.g. severe mobility problems, arthritis, type 2 diabetes); and evidence of completion of a structured weight management program involving diet, physical activity, psychological and drug interventions, not resulting in significant and sustained improvement in co-morbidities.

Table 3. Management strategy in obesity treatment. Adapted from: Institute for Clinical Systems Improvement. *Prevention and Management of Obesity (Mature Adolescents and Adults)*. 5th ed. Bloomington, MN; Institute for Clinical Systems Improvement; April 2011.

BMI (kg/m^2)	23.0-24.9	25.0-29.9	≥ 30.0
Risk	Low	Moderate	High
Nutrition	☐	x	x
Physical Activity	☐	☐	☐
Behavioral Management	☐	☐	☐
Medications		☐*	☐
Surgery			x*

**may be considered if with concomitant obesity-related risk factors or diseases are present and with failure of weight loss after lifestyle modification*

Conclusion

Since not all overweight and obese persons show signs and symptoms of co-morbidities, screening and evaluation is important. The goal of management is to decrease insulin resistance and improve metabolic profile among the obese. The combination of reduced caloric intake, physical activity and behavioral therapy, remains the most effective way of reducing and maintaining weight, preventing obesity-related metabolic disorders and improving cardiorespiratory fitness.

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FEATURE ARTICLE

Obesity Treatment Recommendations in the Philippines: Perspective on their Utility and Implementation in Clinical Practice

Gabriel V. Jasul, Jr. and Rosa Allyn G. Sy
for the Philippine Association for the Study of Overweight and Obesity (PASOO)

Abstract

This article briefly reviews the obesity practice recommendations of the Philippine Association for the Study of Overweight and Obesity (PASOO) and the obesity guidelines of the Family Medicine Research Group (FMRG) of the UP-Philippine General Hospital. The two treatment recommendations showed their focus on the primary care setting and several limitations in the development process. The implementation strategies centered on their dissemination among health care professionals although the PASOO included food and activity pyramid guides useful both as patient educational material and as a treatment tool. In spite of their limitations, both sets of recommendations are valuable resources because they effectively promote obesity awareness in the Philippine setting. However, the current sets of obesity recommendations need to be modified and updated to fulfill important requirements for high-quality recommendations backed by a strong Philippine evidence base. Collaboration among important stakeholders in the prevention and control of obesity and other noncommunicable diseases (NCD) is essential to arrive at an integrated approach to obesity.

Keywords: Obesity, obesity treatment, obesity guidelines, Philippines

Introduction

Obesity prevalence is increasing worldwide despite current efforts to curb this modern-day epidemic. The World Health Organization (WHO) noted that as of 2008, 35% of adults aged 20 years and older were overweight (BMI ≥ 25 kg/m$^{2)}$ (34% of men and 35% of women). A near-doubling of the worldwide prevalence of obesity was noted between 1980 and 2008, with 10% of men and 14% of women being obese (BMI ≥ 30 kg/m^2) in 2008, compared with 5% of men and 8% of women in 1980. It was thus estimated that 205 million men and 297 million women over the age of 20 were obese, totalling to more than half a billion obese adults worldwide. Moreover, the WHO projected that by 2015, the worldwide prevalence will be 2.3 billion overweight adults and 700 million obese adults[1].

Epidemiologic data compiled by the International Obesity Task Force (IOTF) showed this same pattern of high and rapidly increasing prevalence of obesity and its comorbidities in many countries in the Western Hemisphere, with reported combined overweight and obesity prevalence rates reaching 30 to 50% of the population in different countries[2]. A shift towards noncommunicable diseases (NCD) has been observed in developing countries largely due to the more than three-fold increase in obesity rates since 1980 in the Middle East, the Pacific Islands, Australasia, India and China[3].

In the Philippines, the National Nutrition and Health Survey (NNHeS) data illustrates the upward trend in overweight and obesity from the first survey in 1987 to the most recent and fifth survey in 2008. Among Filipino adults, the prevalence of overweight (BMI 25 to 29.9, WHO Classification) has jumped from 11.8% in 1987 to 21.4% in 2008 while the prevalence of obesity (BMI>30) tripled from 1.7% in 1987 to 5.2% in 2008 (Table 1)[4].

Table 1. Prevalence of overweight and obesity among Filipino adults 20 years and older

YEAR OF STUDY	BMI 25-29.9	BMI =>30
1987	11.8 %	1.7 %
1993	14.0 %	2.6 %
1998	16.9 %	3.2 %
2003	19.7 %	4.3 %
2008	21.4 %	5.2 %

From the Food and Nutrition Research Institute and the National Nutrition and Health Survey data.

This alarming development happened only within the last two to three decades despite a better understanding of the problem and better tools to manage affected individuals. In fact, several guidelines have been made available since the 1990s specifically formulated for the management of overweight and obesity in different populations. Among these are the US National Heart, Lung and Blood Institute guidelines (US NIH, 1998)[5], the UK National Institute for Health and Clinical Excellence (UK NICE guidelines)[6], the Canadian clinical practice guidelines[7], and the the American College of Physicians guidelines[8], to name a few.

In the Philippines, the clinical practice recommendations on weight management are represented by a limited number of publications. The two readily accessible sets of recommendations are the focus of discussion in this article and these are the Philippine Association for the Study of

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Overweight and Obesity (PASOO) recommendations on the healthy and safe weight management program[9] and the Family Medicine Research Group (FMRG) guidelines for diagnosing and treating obesity in family practice as part of the Guidelines Series of the FMRG the Department of Family and Community Medicine at the University of the Philippines-Philippine General Hospital (UP-PGH)[10].

The objectives of this article are: To briefly review these two sets of recommendations highlighting their distinctive features, to discuss important implications of their usefulness and their implementation in clinical practice vis-a-vis the current challenges in the management of obesity and other lifestyle diseases, and, finally, to present future action plan addressing the issues and limitations seen in these two recommendations.

The PASOO Algorithm/Recommendations for the Healthy and Safe Weight Management Program

Established in March 1994 and fully incorporated as a non-stock, non-profit organization in September 1994, the PASOO formulated its mission of being the pioneer in the prevention and control of obesity and its complications through education, research and advocacy and its vision of an obesity-risk free Philippines. It gained international recognition when it became a full member of the International Association for the Study of Obesity (IASO) on June 21, 1995. Through continuing medical education activities and public awareness campaigns, the PASOO spearheads many initiatives in educating health professionals and lay persons on the nature of obesity, its complications and more important, its prevention and treatment in the country. During its 2nd Annual Convention in 1996, the PASOO put forward its recommendations for a healthy and safe weight management program. Since this initial presentation, this set of recommendations has been highlighted in several scientific fora and has been published several times as part of the Compendium of Philippine Medicine (CPM), an annual publication, now on its 13th edition, containing the latest treatment guidelines, consensus statements and management algorithms from multi-sectoral task force groups, medical societies and training institutions in the Philippines.

Improvement of the initial PASOO recommendations was actively pursued by the PASOO leadership and in 2002, Sy et al[11] formulated the algorithms on the approach to the screening, diagnosis, management, follow-up and prevention of obesity and presented this set of algorithms during the Philippine College of Physicians Annual Convention that year. These algorithms were adapted by the PASOO and were incorporated in the subsequent versions of the PASOO recommendations on a healthy and safe weight management program. The PASOO practice recommendations were last printed as part of the 10th edition of the CPM in 2008.

Important features of the PASOO recommendations include the use of the Asia-Pacific cut-offs in classifying the degree of overweight and obesity, both for the body mass index (BMI) and waist circumference values (Table 2). Risk stratification was applied not only in determining the risk of comorbidities but also in determining the treatment strategy (Table 3). The stepwise approach to a healthy and safe weight management program was incorporated in six (6) algorithms, as follows: classifying patients, work-up for causes of obesity, evaluation of comorbidities and risk factors, preparation of starting the weight management program, treatment according to risk and follow-up (Figures 1 to 6). The algorithms are simplified representations making them a practical guide in the usual clinic setting. These algorithms emphasize basic history taking, clinical examination and minimal essential laboratory work-up. There is an important recommendation for considering referral for specialized evaluation and care when usual care is not successful at several points in the multi-step process. Putting value on monitoring outcomes and preventing weight regain is also apparent in these algorithms. The accompanying two-page discussion summarizes the salient points on dietary therapy, physical activity, behavior modification, and drug therapy. In the latest version of the PASOO recommendations, the Filipino pyramid food and activity guides (Figures 7 and 8) are included as illustrative educational material for health professionals, for patients and for the general public.

Table 2. Classification of risk of co-morbidities based on BMI and waist circumference, adopted and recommended by the PASOO

Classification	BMI	RISK OF CO-MORBIDITIES Waist Circumference	
		<90 cm (men) <80 cm (women)	>90 cm (men) >80 cm (women)
Underweight	<18.5	Low, but increased risk of other clinical problems	Average
Normal weight	18.6 – 22.9	Average	Increased
Overweight	>=23		
At risk	23 – 24.9	Increased	Moderate
Obese I	25 – 29.9	Moderate	Severe
Obese II	>=30	Severe	Very Severe

Apparent limitations of the PASOO recommendations include the limited information regarding its development process, the identification and representation of stakeholders and intended users, the evidence base and grading of these recommendations.

Table 3. Classification of treatment of obesity based on risk, adopted and recommended by the PASOO.

RISK	Calorie intake		Exercise	Drugs	Surgery
	< 800*	> 800			
LOW	3	2	1	NA	NA
MODERATE	2	1 - 2	1	3	NA
HIGH	1	2	1	2	NA
VERY HIGH	1	1	3	1	1-2

Legend:
*NA = Not appropriate, * =Very low calorie diet*
1 = 1st choice, 2 = 2nd choice, 3 = 3rd choice

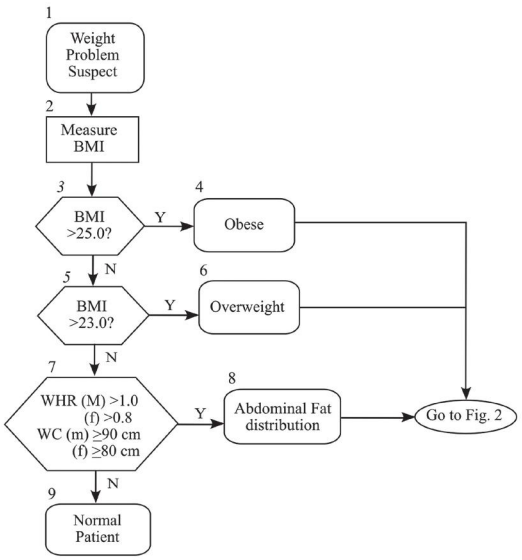

Figure 1. Classifying patients
(from the PASOO Recommendations, reference 9, and the Algorithms on the Approach to the Screening, Diagnosis, Management, Follow-up and Prevention of Obesity, reference 11)

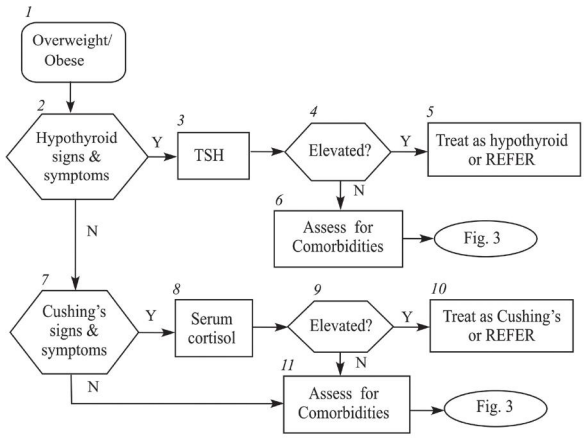

Figure 2. Work-up for causes of obesity
(from the PASOO Recommendations, reference 9, and the Algorithms on the Approach to the Screening, Diagnosis, Management, Follow-up and Prevention of Obesity, reference 11)

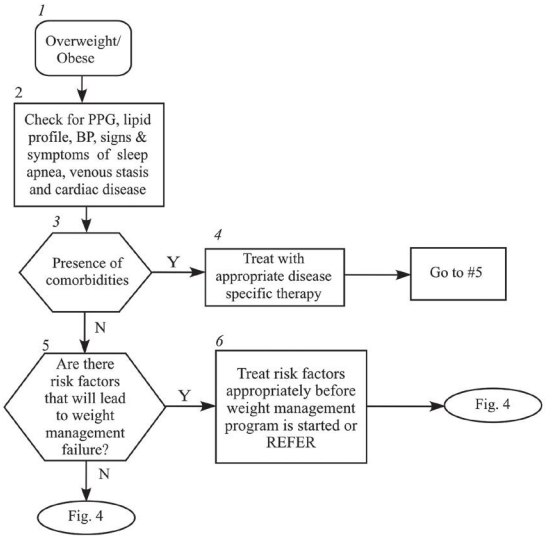

Figure 3. Evaluation of co-morbidities and risk factors
(from the PASOO Recommendations, reference 9, and the Algorithms on the Approach to the Screening, Diagnosis, Management, Follow-up and Prevention of Obesity, reference 11)

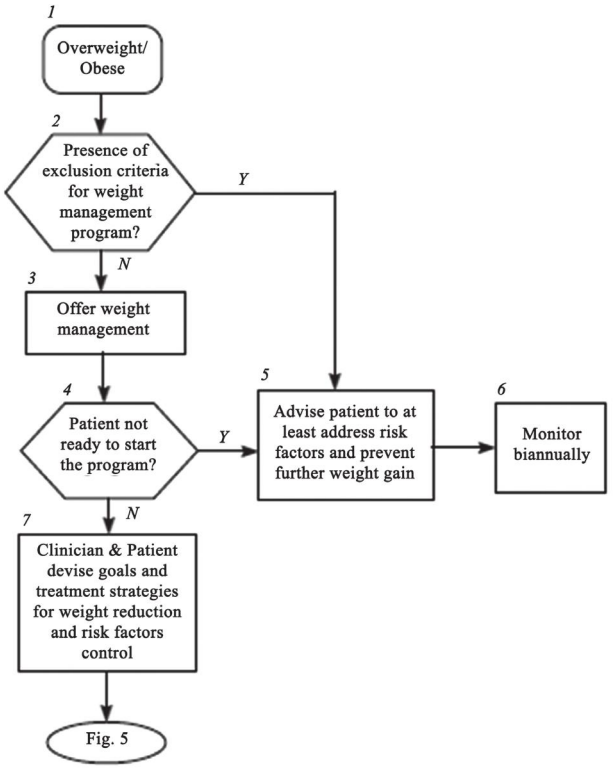

Figure 4. Preparation of starting the weight management program
(from the PASOO Recommendations, reference 9, and the Algorithms on the Approach to the Screening, Diagnosis, Management, Follow-up and Prevention of Obesity, reference 11)

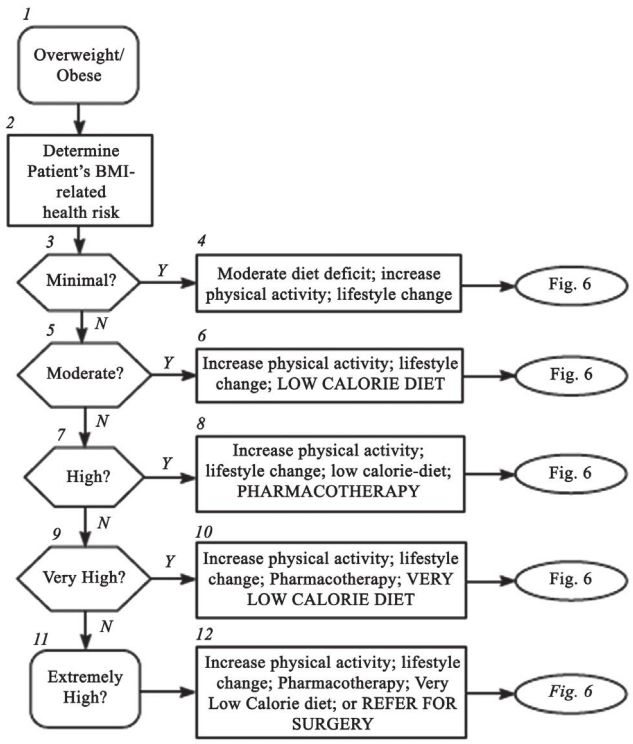

Figure 5. Treatment according to risk.
(from the PASOO Recommendations, reference 9, and the Algorithms on the Approach to the Screening, Diagnosis, Management, Follow-up and Prevention of Obesity, reference 11)

The UP-PGH Family Medicine Research Group (FMRG) Guidelines for Diagnosing and Treating Obesity in Family Practice

Published as part of the Guidelines Series of the FMRG of the Department of Family and Community Medicine and Philippine General Hospital in *The Filipino Family Physician*, the quarterly journal of the Philippine Academy of Family Physicians, the FMRG obesity guidelines were presented as a summary of recommendations in three (3) specific areas: definition of obesity in family practice, diagnostic evaluation of patients with obesity, and therapeutic measures for patients with obesity (Table 4). This five-page article is an attempt at condensing the information gathered from the process that looked at over 60 publications. The grading of the ten (10) recommendations was indicated together with a brief summary of the evidence for each of the recommendations. The significant features of the FMRG guidelines include the concise reporting of the recommendations, with noted grading of the evidence, making them easily perused by intended users in family practice. The WHO cut-offs for both BMI and waist circumference were used in defining obesity.

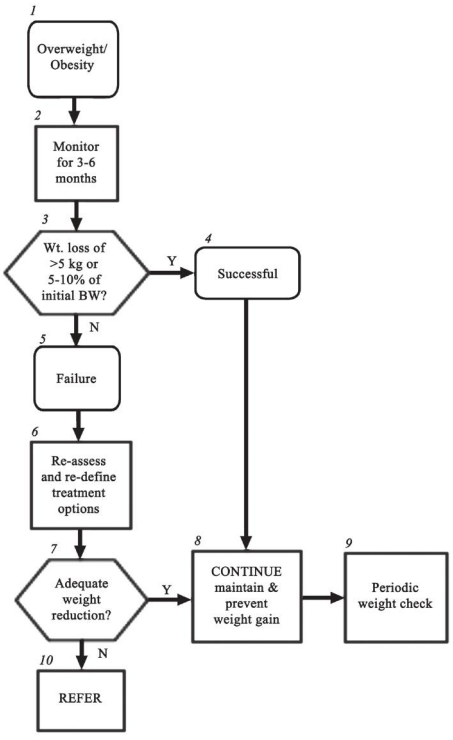

Figure 6. Follow-up
(from the PASOO Recommendations, reference 9, and the Algorithms on the Approach to the Screening, Diagnosis, Management, Follow-up and Prevention of Obesity, reference 11)

Limitations of the FMRG guidelines included an attempt at brevity that might have affected the adequacy of its information. There was no information regarding the review process itself, including the composition of the panel in the publication. Unfortunately, a manuscript of the actual FMRG Guidelines Series was requested but was not available for review as of this writing.

The Utility and Implementation of Obesity Recommendations: Implications in Clinical Practice in the Philippines

The continued rise in the prevalence of overweight and obesity and the failure of current efforts to control and reduce obesity prevalence rates raise several issues, not only in the Philippines but also globally. First, the usefulness of clinical guidelines needs evaluation as to their relevance to realities in clinical practice and their effective implementation in different settings. Second, the ultimate knowledge translation gap appears to contribute to the failure of programs for chronic lifestyle diseases (hypertension, diabetes, obesity). Third, the duplication of programs and disunity of health organization and agencies in addressing the problem of lifestyle diseases lead to a waste of resources. Fourth, the current treatment tools have several limitations and lifestyle modification remains the most important pillar in weight management.

Table 4. Summary of Recommendations from the UP-PGH Family Medicine Research Group Guidelines for Diagnosing and Treating Obesity in Family Practice

Definition of Obesity in Family Practice

Recommendation 1. In family practice, obesity is defined as body mass index (BMI) of 30 kg/m^2 and above. Classification of overweight and obesity is also based on this index. (Grade C)

Recommendation 2. Waist circumference could also be used as an adjunctive measure to define obesity. A waist circumference of >102 cm for males and > 88 cm for females would also warrant a diagnosis of obesity. (Grade C)

Diagnostic Evaluation of Patients with Obesity

Recommendation 3. The following points should be elicited in the history taking of patients with obesity: age, gender, family history of obesity and physical activity. (Grade C)

Recommendation 4. The following information should be included in the physical examination report: height, weight, waist circumference and blood pressure. (Grade B)

Recommendation 5. The following ancillary laboratory procedures should be requested on all patients diagnosed to have obesity: FBS and lipid profile. (Grade B)

Therapeutic Measures for Patients with Obesity

Recommendation 6. The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline to be lost at a rate of 1-2 lbs/week. (Grade A)

Recommendation 7. Low-calories diet is recommended for weight loss in overweight and obese persons (Grade A). reducing dietary fat along with reducing dietary carbohydrates can facilitate caloric reduction (Grade A). Individually planned diet that helps create a deficit of 500-1000 kcal/day should be prescribed as part of therapy (Grade A).

Recommendation 8. Physical activity contributes to weight loss, either alone or in combination with dietary therapy (Grade A).

Recommendation 9. Behavior therapy is a useful adjunct when incorporated into the treatment for weight loss and weight maintenance (Grade B).

Recommendation 10. In instances wherein non-pharmacologic therapy is ineffective after being implemented for 6 months, pharmacological therapy (BFAD approved drug) may be prescribed in combination with non-pharmacological intervention to reduce weight of overweight and obese patients (Grade B).

(From reference 10).

Table 5. Classification of obesity by BMI, adopted and recommended by the UP-PGH Family Medicine Research Group.

	OBESITY CLASS	BMI (kg/m^2)
Underweight		< 18.5
Normal		18.5 -24.9
Overweight		25.0 -29.9
Obesity	I	30.0 -34.9
	II	35.0 -39.9
Extreme Obesity	III	>= 40

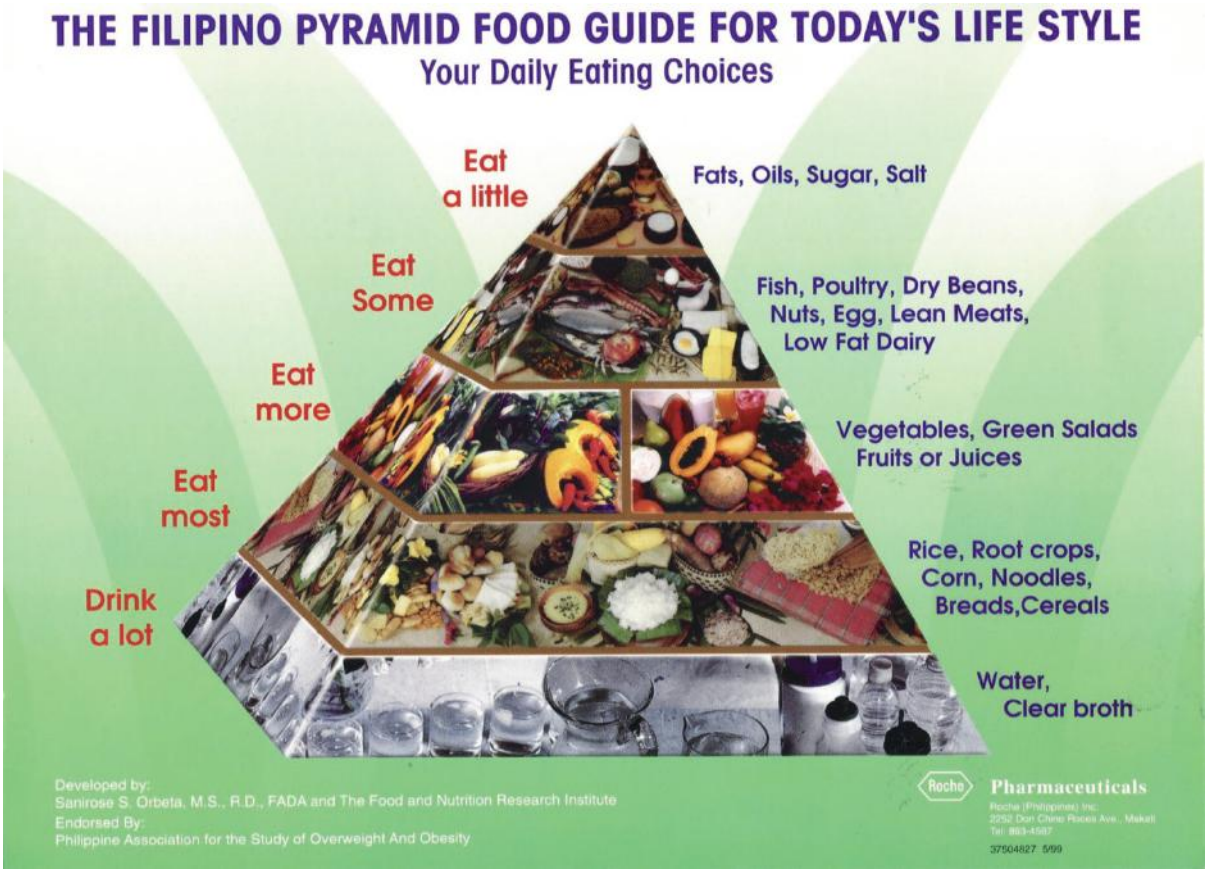

Figure 7. The Filipino Pyramid Food Guide, developed by S. S. Orbeta, and the Food, Nutrition and Research Institute (FNRI) in 1997 and endorsed by the PASOO.

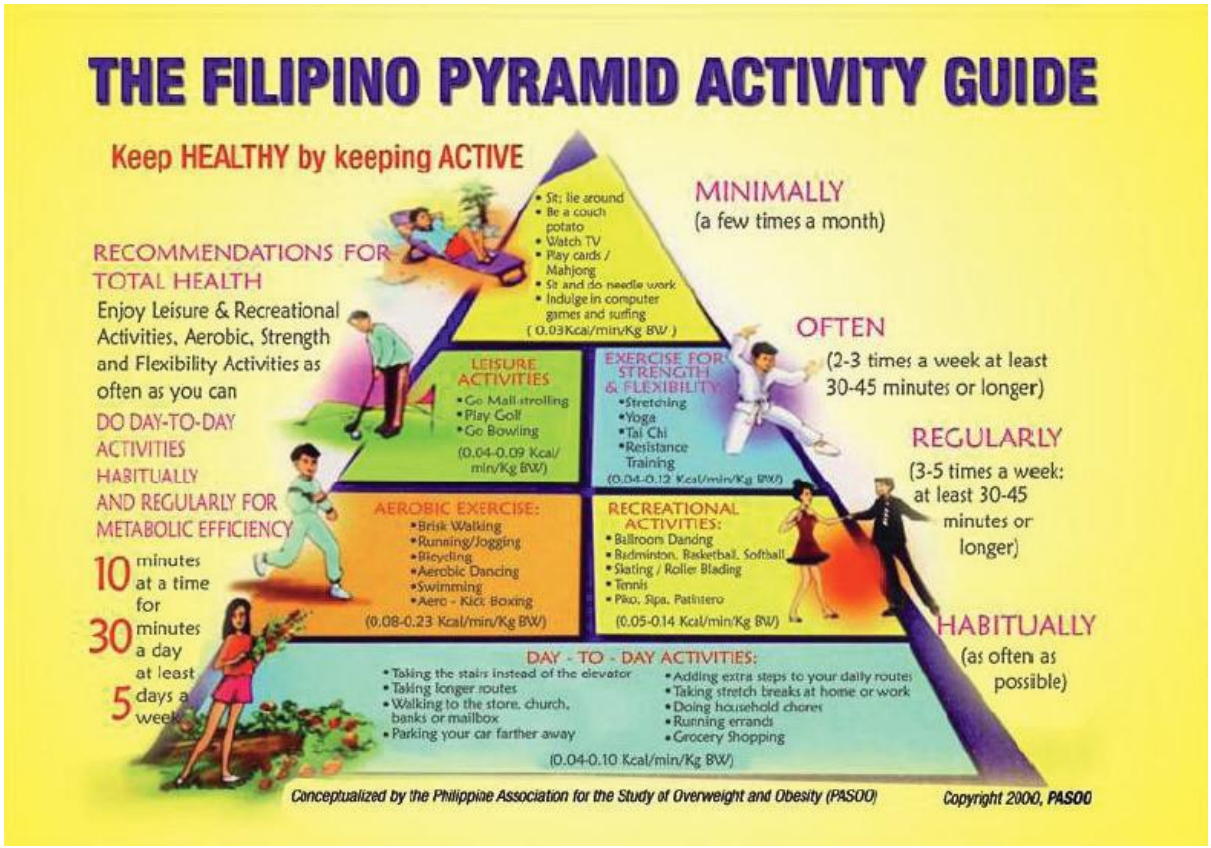

Figure 8. The Filipino Pyramid Activity Guide, conceptualized in 2000 and recommended by the PASOO.

Development of practice guidelines requires a well-planned process that involve careful examination of relevant evidence base and formulation of recommendations addressing important disease-related management issues. Several published guidelines reported the tedious stages of the development process before valuable recommendations were finalized and circulated to end-users and stakeholders[5-8]. Gandjour, et al[12] reported the development process of evidence-based guidelines for the treatment of obesity in Germany and pointed out the fundamental questions that should be addressed in the process. Similarly, Mercer[13] critically appraised the usefulness of guidelines in the management of obesity by illustrating how UK NICE guideline 43, one of the most comprehensive guidelines ever published on obesity, fit in the clinical practice setting. Many of the concepts and challenges in obesity guideline development and implementation discussed in these excellent reviews apply to the current examination of the two sets of Philippine obesity practice recommendations.

Basic questions are related to the goals of the guidelines, the intended target audience (end-users), the choice between adapting foreign guidelines and formulating entirely new set of guidelines with new content and features suited to the local setting and the type of implementation strategy. While, these basic questions were not clearly addressed in the published versions of the two Philippine recommendations, the inherent nature of these guidelines points to a primary care focus adapting published foreign data and modifying them to suit the Philippine situation. Clearly, the strategies employed in implementing these guidelines centered on their dissemination to health care providers in the primary care setting, through scientific fora and publications, i.e, Compendium of Philippine Medicine and the *Filipino Family Physician* journal. Such strategies might have limited extent of information transfer among intended users.

The usefulness of practice recommendations will be enhanced by fulfilling the requirements for a good guideline including validity, reproducibility, reliability, clinical applicability, clinical flexibility, clarity, meticulous documentation, completeness and acceptance by end users. A clear statement of the main purpose/s and the primary target audience sets the direction of the guidelines, encouraging wider use and acceptance. Adaptation to the local conditions, with due consideration to socioeconomic determinants of health care, can likewise increase acceptance and thus the effectiveness of the guidelines in the clinical practice setting. The choice of implementation strategy influences the successful dissemination and utilization of guidelines. The implementation strategy can be categorized as "pull," concentrating on communication to patients, encouraging them to consult physicians, "push," focusing on academic and opinion leaders convincing health professionals to utilize the guidelines, or "mixed pull-push," drawing from both ends and multiple channels[12].

In evaluating these important requirements in the Philippine guidelines, it was apparent that clear statement of goals and target end users and the other requirements were not met satisfactorily. The implementation strategy relied mainly on the push method, concentrating on physicians mainly through conventional channels of dissemination. The use of illustrative pyramid guides both as educational material and as a treatment tool by the PASOO can be seen as representing a mixed pull-push strategy, increasing awareness of obesity and its management through diet and physical activity among health professionals, patients as well as the general public. Indeed, it can be noted that while there were identified insufficiencies in the Philippine guidelines, their contribution in strengthening obesity awareness can be considered an accomplishment of these guidelines. Moreover, those areas of inadequacy are indeed areas for improvement towards the ultimate goal of formulating of high-quality obesity guidelines. The available Philippine guidelines are not ideal and far from perfect but they represent significant steps in that direction.

Issues and Challenges in Obesity Management in the Philippine Setting

Obesity is a complex disorder with multiple interacting contributory factors that include genetic, biologic, behavioural, environmental, as well as socioeconomic elements. Primary preventive care may be the best setting for its management and hence, should be the focus of obesity treatment guidelines. Aggressive lifestyle modification through healthy eating and physical activity has been proven to be an effective and safe intervention both for the prevention and treatment of obesity and its attendant comorbidities. Many of the noncommunicable diseases (NCD), such as diabetes mellitus, hypertension and cardiovascular disease, can be treated or prevented by lifestyle modification. However, there is an apparent knowledge translation gap as lifestyle modification measures are not maximised at different levels of patient care[14].

Severe limitations characterize the current treatment options for obesity. Lifestyle modification is associated with noncompliance, recidivism and behavior-related problems. Behavioral modification is difficult with few trained professionals in this area. Drug therapy is now limited to virtually one drug, orlistat. Phentermine can still be given but only for a very limited period of time (3-6 months). Bariatric surgery for extreme obesity is being performed in several centers in the country and while it has significant weight loss and metabolic benefits, it has limited indications, can be costly and may have associated complications. In this context, lifestyle modification remains the mainstay of obesity management.

Global as well as national health organizations are actively promoting health promotion through unified strategies for the prevention and control of chronic lifestyle diseases. The Philippine Department of Health (DOH) has several projects and publications providing framework for a national program on noncommunicable diseases prevention and control since the 1980s[15]. The need for an integrated approach through collaboration led to the formation of the Philippine Coalition on the Prevention and Control of Noncommunicable Diseases (PCPCNCD) in 2004 convening 43 organizations, including the PASOO. The DOH Manual of Operations for NCD Prevention and Control contains specific information on healthy lifestyle programs and strategies for their implementation[16]. Unfortunately, there appears to be no effective integration of programs and services up to this point. Duplication of programs results in the waste of the already limited resources and ineffective implementation of programs and guidelines issued separately by government and non-governmental agencies. The evidence base for Philippine research on obesity and other NCDs is likewise limited and should be encouraged to provide a strong foundation of a truly Philippine-adapted set of treatment guidelines.

Future Directions and Conclusions

Obesity practice recommendations should be valid, reproducible, reliable, clear, complete, clinically applicable and flexible, and accepted by end users. The availability of such high-quality recommendations in the Philippines is premised on the cooperation of stakeholders in formulating an integrated approach to the problem through strengthening efforts in educating the health care professionals and the public, in pursuing relevant obesity research and in advocating for public policy changes. Multidisciplinary and multi-level collaboration between government and non-goverrmental organizations is essential.

It becomes clear that the problem is not about the availability of obesity guidelines but the more important challenge is unifying and updating current guidelines to be able to come up with high-quality, evidence-based recommendations that are effective and can be implemented in different practice settings, from primary to tertiary levels, across all ages and populations. It is hoped that all stakeholders in the field of obesity and in NCDs, in general, will come together to act against obesity, realizing that obesity is a public health problem requiring public health solutions.

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JAFES Journal of the ASEAN Federation of Endocrine Societies

Obesity Clinical Practice Guidelines (CPGs) for the ASEAN Region: *Facing the Challenge of Malnutrition*

Elizabeth Paz-Pacheco

Overweight and obesity increasingly prevail in the ASEAN region. Using the WHO criteria for overweight (BMI 25-29) and obesity (BMI 30 and greater), countries in the region are reporting rising rates of overweight and obesity. Consider the data from the Western Pacific Region[1]: Malaysia (1996) reports overweight rates of 21.4% in women and 20.1% in men, and obesity rates of 7.6% in women and 4.0% in men. Myanmar (2009) reports 30.2% in women and 17.7% in men being overweight, and 8.4% in women and 4.3% in men being obese. Singapore (1998) reports overweight rates of 20.3% in women and 28.6% in men, and obesity rates of 6.7% in women and 5.3% in men. Indonesia (2001)[2] reports overweight rates 17.4% in women and 10.2% in men, and obesity rates of 4.5 % in women and 1.3 % in men.

The 2008 National Nutrition and Health Survey of the Philippines[3] reports that the prevalence of obesity in 2008 was 5.2% (3.7% and 6.6% for male and female, respectively). Based on WHR, the prevalence of obesity in males in 2008 was 11.1% (12.1% in 2003 and 7.9% in 1998). With a lower, stricter cut-off of≥ 0.85 in females, the prevalence was 65.5% (54.8% in 2003 and 39.5% in 1998).

The Clinical Practice Guideline (CPG) for Malaysia is a comprehensive guideline developed in 2004 and emphasizes the need for a multidisciplinary approach to the prevention and control of obesity. Childhood or adolescent obesity is recognized as an emerging concern, and specific recommendations to address this is included in the practice recommendations.

The CPG for Myanmar highlights the use of the Myanmar diet where most carbohydrates are derived from grains, potatoes, starchy vegetables and refined grains. These constitute 70% of the Myanmar diet. Importantly, it emphasizes age-specific recommendations for physical activity. This CPG includes prevention strategy recommendations particularly for children and adolescents.

The CPG for Singapore was developed by a multidisciplinary work group in collaboration with the Health Promotion Board of Singapore, drawn from best available evidence in 2004. It is a comprehensive set of guidelines, incorporating contributions from para-clinical disciplines, also recognizing the need for specific guidelines for children and adolescents. It emphasizes the importance of quality indicators to evaluate the success of weight management programs. It also includes a user-friendly algorithm, with Asian BMI cut-off points. Meanwhile, the authors indicate a need to review these guidelines, with the influx of new data since 2004.

Indonesia describes the clinical practice guidelines in use at a hospital, Cipto Mangunkusumo, as reviewed by the local Obesity Cluster Team. It includes a comprehensive review of basic clinical evaluation and weight management programs that include pharmacotherapy and bariatric surgery. A treatment algorithm derived from the US NHLBI Obesity Education Initiative completes the recommendations.

The Philippine group reviews the obesity practice recommendations of the Philippine Association for the Study of Overweight and Obesity (PASOO) and the obesity guidelines of the Family Medicine Research Group (FMRG) of the University of the Philippines – Philippine General Hospital. Conclusions derived from this review include: (1) The obesity recommendations need to be modified and updated to fulfill important requirements for high-quality recommendations backed by a strong Philippine evidence base; (2) Collaboration among important stakeholders in the prevention and control of obesity and other noncommunicable diseases (NCD) is essential to arrive at an integrated approach. In addition, the PASOO has embarked on an obesity research agenda prioritization plan, after extensive search of all existing literature carried out among Filipinos within the Philippines and internationally. The research agenda is intended to prioritize research work on urgent questions, without unnecessary duplication in a resource-poor country like the Philippines, with the ultimate objective of translating this research into national health policy and clinical practice.

What outcomes can be expected with the current programs in place in ASEAN? There is a need for country specific efforts, spearheaded by the national government in collaboration with various stakeholders, to provide a long term plan that will allow individuals to eat better and find opportunities to increase physical activity. Research needs to be enhanced in ASEAN to help us better understand the etiology of obesity and to face the challenge of obesity occurring side-by-side with undernutrition in certain sectors of the population. Many of the ASEAN countries continue becoming more Westernized in lifestyle, with fast food outlets rapidly outgrowing the local restaurant facilities. Here high fat, easy to consume, affordable foods become part of the individual country's staple foods and become daily source of nutrition especially for the younger segment of the population. More technology gadgets take children,

adolescents and young adults from outdoor physical activities to indoor sedentary activities. And are these perceived as progress?

The epidemic is upon us. And unless we put our act together to arrest obesity, particularly in children, the burden of the consequences of obesity, diabetes and cardiovascular disease will become inevitable and will take a great toll in our region for many years. The challenge of malnutrition confronts us. We ask AFES to take up this challenge.

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Call to Action Against Overweight and Obesity: Asia-Oceania Perspective

From the 6th Asia-Oceania Conference on Obesity
August 31-September 2, 2011
Manila, Philippines

We, the participants of the 6th Asia-Oceania Conference on Obesity,

Appalled by the rapid rise in the prevalence of overweight and obesity in countries in the region, bringing with it the increasing rate of co-morbidities – cardiovascular disease, diabetes, hypertension, cancer and other chronic diseases;

Reminded of the heavy health and economic burden that obesity imposes on individuals, communities and nations, affecting our country's development;

Convinced that prevention of overweight throughout the lifecycle starting from improvements in maternal and child health in pregnancy is the key to successful public health control;

Realizing most solutions are outside the health system and that population approaches directed to obesogenic environment and practices in communities, schools and work place rather than individual approaches, are necessary to achieve long-term success;

Confident that while standard approaches of self-monitoring, physical exercise, low calorie diets and lifestyle modification remain as the basic strategies in the management of obesity, motivational interviewing and new technological approaches are needed to encourage permanent behaviour change;

Aware of the strong link between obesity and cardio-metabolic risk through complex metabolic pathways and cross-talking of fat cells with distant organs through cytokines and hormones; and

Recognizing the need to re-examine our approach to current therapeutic management with the advent of new drugs and their combinations, and the importance of individualizing therapies and balancing risks;

Hereby declare, as members of our respective associations and societies for the study and control of obesity:

To strengthen networking among members of Asia-Oceania Associations for the Study of Obesity (AOASO), through regional conferences, workshops, training, and collaborative research.

To focus our individual and collective efforts, towards the prevention of obesity throughout the lifecycle starting from conception;

To intensify our efforts to spread public awareness of the dangers of obesity to the health and economic development of individuals, communities and country, and pursue programs of public education on the problem of obesity, its prevention and control;

To advocate a population-based approach towards an anti-obesogenic environment in the home, community and workplace;

To promote positive policies, programs, strategies and therapeutic modalities known to have high potential for success;

To continue the search for improved preventive and therapeutic approaches by keeping abreast with the latest scientific advances; and

To support scientific research to understand better all aspects of obesity – from its pathogenesis to new therapeutic modalities.

In support of this Declaration:

We urge our respective governments to exert their political will to support comprehensive policies, strategies and programs to control the rapidly growing problem of overweight and obesity in our populations, and at the same time examine policy options focusing on food and environments that are responsible for this rising trend;

We entreat all sectors, particularly the media and food industry, to contribute to the efforts of AOASO and its members in pursuing the vision of an obesity risk-free region.

Resolved, as it is hereby resolved,

That copies of this Declaration be furnished to officials of relevant international and government agencies, medical and health associations, non-government organizations, the media and pharmaceutical industries in our respective countries.

Signed:

s 2nd day of September, 2011, at Sofitel Philippine Plaza Hotel, Manila, Philippines.

Signed:

Malaysian Association for the Study of Obesity
(MASO)

Australian and New Zealand Obesity Society
(ANZOS)

Singapore Association for the Study of Obesity
(SASO)

Japan Society for The Study Of Obesity
(JASSO)

Taiwan Medical Association for the Study of Obesity
(TMASO)

Philippine Association for the Study of Overweight and Obesity
(PASOO)

Attested by:

Asia-Oceania Associations for the Study of Obesity
(AOASO)

International Association for the Study of Obesity
(IASO)

FEATURE ARTICLE

JAFES Journal of the ASEAN Federation of Endocrine Societies

The Double Burden of Malnutrition in Asia: A Phenomenon Not to be Dismissed

Rodolfo F. Florentino

Chairman-President
Nutrition Foundation of the Philippines, Inc.

Introduction

Developing countries around the world – including those in Asia – are in a state of rapid economic transition as a result of generally improving incomes, increasing industrialization, urbanization, and globalization. This state has given rise to changing lifestyle and diets, from one with high level of physical activity and diets based mostly on plant foods, to one with a higher level of sedentariness, and a diet of increasing energy density, fat and animal foods and less plant foods – a state of nutrition transition.[1] This in turn has led to an increase in overweight and obesity especially in adults, and a consequent rise in chronic diseases such as cardiovascular disease, hypertension, Type 2 diabetes and other so-called "diseases of affluence." At the same time in these countries, the high rate of undernutrition especially in children remains the major nutrition problem even if it has somewhat improved, resulting in a situation where undernutrition persists at the same time with increasing overnutrition, a phenomenon now known as the dual burden of malnutrition.[2] This situation could be observed within the country, as well as within communities and even in the same household. While undernutrition results in poor growth, stunting and poor resistance to infection in children, and low physical and mental performance in both children and adults, overnutrition results in obesity and its well-established co-morbidities. Moreover, severe nutritional deprivation in fetal and early post-natal period followed by a rapid catch-up growth in early childhood is now known to increase the risk of overweight and obesity, as well as cardiovascular disease, diabetes and other chronic diseases in adolescence and adulthood – following the so-called "Barker hypothesis. "[3] Such a situation calls for over-arching policies, strategies and programs to counter this dual threat to overall health and thus to socio-economic development.

Double burden of malnutrition in Asia

According to the World Health Organization, the global prevalence of obesity in 2008 was as high as 10.0% among males and 14.0% among females, lowest among the low income countries and highest among the high income countries[4] (Figure 1). While the Asian regions, namely, Southeast Asia and Western Pacific, showed the lowest prevalence of obesity among the WHO regions, the prevalence of undernutrition in these two regions was the highest among the regions.

In developing countries in Asia, stunting among children <5yrs ranged from 11.7% to 47.9% and underweight ranged from 4.5% to 43.5% during the decade 2000-2009 (Table 1). However, it could be seen that there were rather large differences among countries in the region, more or less following the state of economic development. In India, the prevalence of underweight children <5 yrs was 43.5% during the 2000-2009 and that of obesity among adult males and females only 1.3% and 2.5%, respectively, in 2008. On the other hand in Malaysia, the prevalence of underweight children <5 yrs was only 16.7% during the 2000-2009, that of obesity among adult males and females was as high as 10.4% and 17.9%, respectively, in 2008. While in Bangladesh, the prevalence of underweight children <5 yrs was 52.0% during the 2000-2009 and that of obesity among adult males and females was only 1.0% and 1.3%, respectively, in 2008, in China, the prevalence of underweight children <5 yrs was only 6.9% during the 2000-2009 and that of obesity among adult males and females was as high as 4.6% and 6.5%, respectively, in 2008. Except for the Pacific island countries like Fiji and Kiribati where the prevalence of obesity is very high, and Japan where the prevalence is very low, the other countries in the region - Cambodia, Laos, Vienam, the Philippines, Indonesia, Thailand, Pakistan and Sri Lanka - more or less followed a similar trend. It also important to note that the rates of undernutrition among children has slowly decreased in these countries from the decade 1990-1999 to 2000-2009, while the rates of obesity, although relatively low, have dramatically increased. As a whole, the double burden of malnutrition is evident among developing countries in Asia.

The latest National Nutrition Survey conducted in the Philippines in 2008[5] (Table 2) gives an even clearer picture of the double burden of malnutrition in an average developing country.

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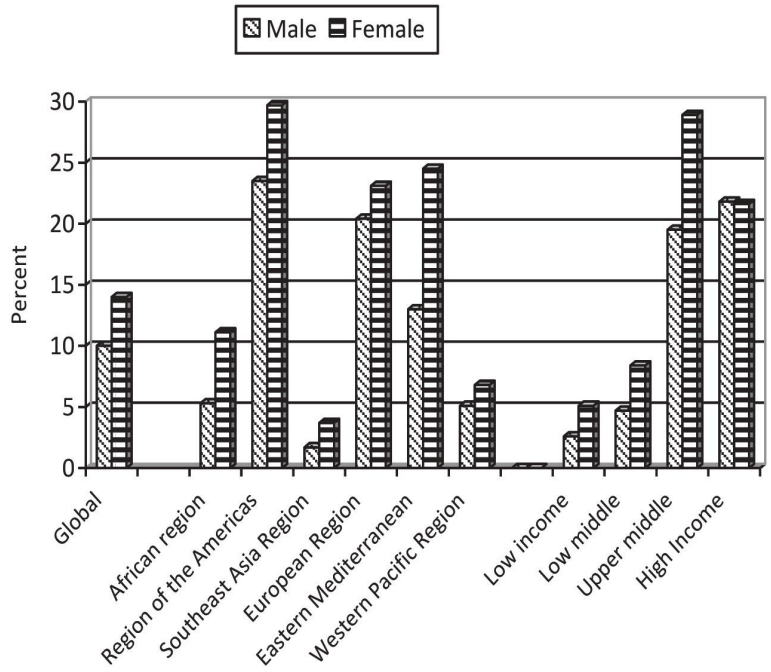

*WHO Health Statistics 2011

Figure 1. Worldwide prevalence of obesity among adults*

Table 1. Prevalence of undernutrtion in children and adults in in some Asian countries*

Country	Children <5 yrs (%)				Adults >20 who are obese	
	Stunted	Underweight		Overweight	Male	Female
	2000-2009	1990-1999	2000-2009	1990-1999	2008	
Bangladesh	43.2	52	41.3	1.1	1	1.3
Cambodia	30.5	42.6	28.8	2	1.6	2.8
China	11.7	6.9	4.5	5.9	4.6	6.5
India	47.9	44.4	43.5	1.9	1.3	2.5
Indonesia	40.1	22.8	19.6	11.2	2.5	6.9
Laos	37.6	35.9	31.6	1.3	1.7	4.1
Malaysia		16.7			10.4	17.9
Myanmar	40.6	25	29.6	2.4	2	6.1
Pakistan	31.5	34.2	31.3	4.8	3.5	8.4
Philippines	33.8	28.3	20.7	2.4	4.5	8.3
Sri Lanka	19.2		21.3	0.9	2.6	7.3
Thailand	15.7	15.4	7	8	4.9	11.8
Vietnam	30.5	31.1	20.2	3	1.2	2

**WHO Health Statistics 2011*

Table 2. Prevalence of malnutrition among children, adolescents and adult Filipinos, 2008*

Year of survey	Children 0-5 yrs			Chilren 6-10 yrs			Adolescents 11-19		Adults	
	Underwt	Stunting	Overwt	Underwt	Stunting	Overwt	Underwt	Overwt	CED	OW/Ob
1990	34.5	39.9	0.6	34.2	44.8	0.1	15.8	2.4	13.9	16.6
1992	34.0	36.8	0.7	32.5	42.8	0.2				
1993	29.9	34.3	0.4	30.5	42.2	0.6				
1996	30.8	34.5	0.5	28.3	39.1	0.4				
1998	32.0	34.0	0.4	30.2	40.8		19.8	2.9	13.2	20.2
2001	30.6	31.4	1.0	32.9	41.1	0.8				
2003	26.9	29.9	1.4	25.3	35.8	1.3	15.5	3.6	12.3	24.0
2005	24.6	26.3	2.0	22.8	32.0	1.6	16.0	4.8		
2008	26.2	27.9	2.0	25.6	33.1	1.6	17.0	4.6	11.6	26.6

**Food and Nutrition Research Institute, 2011*

The 2008 National Nutrition Survey conducted by the Food and Nutrition Research Institute, Department of Science and Technology, covered a random sample of 36,634 households and their members, from all regions of the Philippines. Among the 0-5 yr old children, the prevalence of underweight-for-age was 26.2%, that of stunting, 27.9%, and that of overweight-for-age, 2.0% in 2008. The prevalence of underweight and stunting generally declined from 1990 (34.5% and 39.9%, respectively) to 2008. On the other hand, the prevalence of overweight increased from 0.6% to 2.0% during the same period. Among the 6-10 yr old children, the prevalence of underweight-for-age was 25.6% in 2008, that of stunting was 33.1%, and that of overweight-for-age was 1.6%. (Table 2) The survey also showed a reduction in the prevalence of undernutrition in this age group from that in 1990 (34.2% underweight and 44.8% stunting). On the other hand there was an increase in overweight from 0.1%

in 1990 to 1.6% in 2008. The rate of overnutrition in children may still be low, but the four-fold to sixteen-fold rate of increase in prevalence is significant. Among adolescents, the prevalence of underweight (by BMI-for-age) was 17.0%, while those at risk of overweight was 4.6% in 2008. Among adults, 20 yrs and over, the prevalence of chronic energy deficiency (BMI <18.5) in 2008 was 11.6%, a slight reduction from 13.9% in 1993. On the other hand, the prevalence of overweight (BMI≥25) was 26.6%, a large increase from 16.6% in 1993.

The dual burden of malnutrition has also been clearly noted even in poorer countries in the region like India and Bangladesh.

With the on-going socio-economic transition in India, accompanied by the demographic and health transition and changing food supply and consumption patterns, dual burden of malnutrition has been clearly seen in national nutrition surveys in India.[6] Over the last three decades, there has been a decline in prevalence of both moderate and severe malnutrition including stunting, although the prevalence of underweight and stunting among pre-school children is still unacceptably high. In adults, there has also been a progressive decline in the prevalence of undernutrition and "some increase" in overnutrition in both urban and rural areas. While significant differences in under- and overnutrition could be seen among the states, overnutrition and obesity are emerging as major problems in all states. A study by Subramanian,[7] however, has shown that dual malnutrition is not apparent in very low socio-economic groups.

Studies by Shafique et al in Bangladesh[8] have also shown that double burden of malnutrition exists in both rural and urban poor women. While chronic energy deficiency (CED) continued to be prevalent among Bangladeshi women, 9.1% of urban poor and 4.1% of rural women were overweight (BMI≥25) between 2000 and 2004. During this period, the prevalence of CED decreased (urban poor, from 33.8%n to 29.3%; rural, from 42.6% to 36.6%) but the prevalence of overweight increased (urban poor, from 6.8% to 9.1%; rural, from 2.8% to 5.5%).

Two nationally representative surveys in Vietnam conducted by the National Institute of Nutrition in Hanoi[9], one in 2000 and the other in 2005, also showed a double burden of malnutrition in adults, although there was a shift toward a higher BMI level between the two surveys. The prevalence of overweight increased from 3.5% to 6.6% nationwide, while that of underweight declined although still high, in 2005.

Double Burden of Malnutrition in the Same Household

More recently, it has been shown that double burden of malnutrition occurs not only within the country as a whole, but also within households. This phenomenon has attracted many investigators trying to understand the factors for its occurrence.

Analysis of the 1993 China Health and Nutrition Survey involving 3349 household by Doak, et al[10] revealed 8.1% of all households with underweight and overweight members within the same household. Urban residence and high income were significantly associated with the presence of both forms of malnutrition in the same household. Such households were more likely to own modern appliances such as television, motor vehicle, and washing machine, and more likely to consume a higher percentage of energy from fat and protein than the normal weight households.

The same group of investigators[11] analyzed national surveys conducted between 1988 and 1996 from Brazil, China, Indonesia, the Kyrgyz Republic, Russia, Vietnam and the United States. In six of the countries studied, 22-66% of households had both underweight and overweight persons coexisting in the same household. They also found that the dual burden households was more likely to be urban and of higher income and in countries in the middle range of GNP. In Vietnam and Indonesia, 60% and 40%, respectively of households with an overweight person also had an underweight person.

Garrett and Ruel[12] analyzed 42 Demographic and Health Surveys in Africa, Asia and Latin America conducted between 1992 and 2001. They found that the prevalence of pairs of stunted child and overweight mother was less than 10% among the Asian countries studied. It was, more prevalent in the urban areas in Bangladesh, India and Nepal, and more prevalent in the rural areas in Cambodia, Kazakhstan, Kyrgyz Republic and Uzbekistan, showing that the phenomenon is not necessarily urban. However, the prevalence was found to increase with economic development, and in countries in the midst of nutrition transition.

As part of a multi-center study in Asia on the problem of dual forms of malnutrition in the same household, Agdeppa et al[13] did a study of dual forms of malnutrition in Tondo, Manila. They found that 59% of child-mother pairs were suffering from the two forms of malnutrition, and of this, 8.2% child-mother pairs in the same household had an underweight child and an overweight mother. An in-depth study of these under/overweight child-mother pairs showed that this phenomenon was associated with mother's educational level, mother's occupation, energy intake, the preference of meats sweets and sugars among children, or meats and fried foods among mothers.

In the same series of multi-center studies in Asia, Khor and Shariff[14] reported their case study of this phenomenon among poor Malay rural households. Out of 140 households studied, 52.1% of mothers were overweight, 15.7% of the children 1-6 yrs were underweight, 27.1%

were stunted and 5% wasted. The children from normal weight child-mother pairs had significantly higher intake of total calories, fat and riboflavin than children from underweight children/overweight mother pairs. Mean energy and nutrient intake of mothers from both groups were not significantly different. The study confirmed that inadequate intake of total energy and nutrients as the major factor for underweight children in this community. In another study in Malaysia among indigenous people, Saibul et al[15] found that while food variety may predict a healthier diet in children, it may increase the risk of overweight and obesity in adults.

Conclusion

From national surveys and local studies, it is clear that most countries in Asia suffer from dual burden of malnutrition: on the one hand an unacceptably high rate of undernutrition in the form of underweight and stunting in children and chronic energy deficiency in adults, and on the other hand, a growing rate of overnutrition in the form of overweight and obesity in both children and adults. In fact, in a significant percentage of households, both undernutrition and overnutrition are found at the same time in the same household, for example, an undernourished child and an overweight mother. Both forms of malnutrition constrain the development of the full potential of individuals, communities and nations. Undernutrition affects physical and mental health and performance throughout the lifespan, while overnutrition gives rise to an increasing rate of chronic diseases occurring at earlier and earlier ages. It is becoming clear that this phenomenon arises from a common set of social and economic factors operating in the individual, local and national levels. It is imperative, therefore, to re-examine the current policies, strategies and programs directed to the improvement of nutrition of the population, from one that addresses each form of malnutrition independently, to one where both forms are addressed simultaneously and seen from a holistic perspective. Policies and intervention programs will need to encompass a wide range of sectors, political, economic, agriculture, education, health and industry, involving governments, community and the private sector. Above all, a strong political will based on a full understanding of this dual burden of malnutrition is the key to success.

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REVIEW ARTICLE

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Genetics of Obesity in Asia

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Introduction

The obesity epidemic is recognized globally as a significant public health concern. The World Health Organization estimates that approximately 2-3 billion people will be overweight and over 700 million will be obese by 2015.[1] Earlier identified as a problem confined in developed countries, many developing countries have recently shown a significant rise of obesity cases.[2] It is a major cause of disability and premature deaths in both developed and developing countries from obesity-related diseases such as cardiovascular disease, strokes and complications of diabetes.

Epidemiology of Obesity in Asia

The prevalence rates of obesity are reported to be very high in North America and Europe with much lower rates in Asia.[3] However, it has been recently demonstrated that the number of obese individuals in most Asian countries has increased dramatically.[2] Yoon et al in 2006 reported survey figures from 1993-2001 demonstrating that Thailand had the highest rate of obesity in Asia at 6.8% among adults being obese followed by Singapore at 6%; China, Taiwan and Malaysia had prevalence figures between 4 and 4.4% of obese adults.[4] Hong Kong had 3.8% of obese adults followed by the Philippines at 3.3%, Korea at 3.2% and Japan at 3.0%. India had the lowest percentage of obese adults at 2.2%.[4]

Genetics and Obesity

Although socioeconomic and lifestyle changes are major contributing factors in the development of obesity, it has been proven in many studies that genetics also play a significant role. Obesity is regarded as a multifactorial condition wherein susceptibility is determined by the interplay of genetics and environmental factors.[5] It is generally regarded as a complex genetic disorder. Like many other common chronic conditions such as hypertension, diabetes and cancer, obesity usually has an onset in adulthood, demonstrates familial aggregation and does not show Mendelian patterns of inheritance[6]. Discovering genetic risk factors for complex disorders such as obesity can pave the way for the development of molecular-based susceptibility testing for prediction of disease (presymptomatic testing)[6].

The contribution of genetic factors to obesity has been well established through twin and family studies. Studying sets of twins, who are reared together or apart allows one to determine whether a condition has a strong genetic influence over the environment and vice versa. The heritability of fat mass seen in twin studies was 40-70% while a concordance rate of 0.7-0.9 between monozygotic twins compared to 0.35-0.45 among dizygotic twins has been observed.[8] These studies have proven that heritable factors are responsible for as much as 45 -80 % of variations observed in body mass index among individuals and risk of obesity while heritability of obesity in families have been reported between 20 and 50%.[5,7]

In the three billion base pairs of the human genome, variations exist on the average, every 500 to 1000 base pairs. These stable, heritable variations in the genome are called polymorphisms and are present in greater than 1% of the population. Some of these genetic polymorphisms are functionally significant and can have effects on the gene product. They can be used for disease association studies and can act as markers for disease susceptibility.[9] One of the most widely studied variations are called single nucleotide polymorphisms (SNPs) where a nucleotide base is replaced by another nucleotide base.

Methods of Identifying Genes Associated with Obesity

A number of research tools are now available to study these variations in the genome that may confer an increased susceptibility to obesity among individuals in different populations. These genetic approaches commonly used to identify the genes related to obesity include candidate gene and genome-wide association studies. Candidate gene studies find an association between variants in an individual's genome within or very

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near candidate genes and a disease of interest such as obesity. There is *a priori* knowledge of the biological function of the candidate gene to be tested because of its involvement in regulating the development of the disease being evaluated.[5] Genome-wide association studies on the other hand, involves scanning many markers randomly throughout the genome to find genetic variations associated with a disease. However, there is no *a priori* hypothesis about any particular gene or genes of interest, and its greatest advantage is the discovery of novel genes along biologic pathways with no apparent relation to the pathophysiology of obesity. Genetic studies have repeatedly demonstrated that some genes are associated at a higher frequency among the obese than in the non-obese individuals suggesting that a considerable proportion of weight variation may be due to genetic factors.

It is reported that there are approximately 127 genes associated with obesity from candidate gene association studies.[5] These genes chosen for their role in various metabolic processes have been replicated in many studies worldwide. The genes that have been identified so far are involved in a variety of biological processes that include regulating food intake or how food is efficiently or inefficiently metabolized in the body and subsequently stored as fat. The association of variations found in a number of these genes and risk for obesity will be described in some studies done among different Asian populations.

Studies on Genetics of Obesity amongst Asians

The evaluation of genetic susceptibility loci for obesity has been extensively carried out in the Chinese population. Shi J et al validated five loci from previous genome-wide association studies, obesity-related phenotypes in adult Chinese women. These include *FTO, MC4R, BAT2, SEC16B*, and *SH2B1*. The *FTO* gene is the fat mass and obesity associated gene and is also known as alpha-ketoglutarate-dependent dioxygenase enzyme. It is widely expressed in different tissues with the highest concentration in the hypothalamus and pancreatic cells. The *MC4R*, on the other hand, is the gene that encodes the melanocortin 4 receptor. Both *FTO* and *MC4R* genes have been consistently reported in different populations to be associated with obesity.[10] *MC4R* has been recognized to play a significant role regulation of food intake and energy homeostasis.[5] *BAT 2* is the human leukocyte antigen B (HLAB)-associated transcript 2, a gene highly expressed in the hypothalamus. The other candidate genes were *SEC16* homolog B (Saccharomyces cerevisiae) *(SEC16B)* and *SH2B* adaptor protein 1 *(SH2B1).* It has been suggested through observations that neuronal *SH2B1* protein regulates energy balance and glucose homeostasis, possibly by enhancing hypothalamic leptin signalling.[10] However, the mechanism linking the *BAT2* and *SEC16B* genes to obesity is still unknown. The calculated odds ratios for obesity in these different genes ranged from 1.46 (95% confidence interval (CI): 1.12, 1.92) for *BAT2* to 2.16 (95% CI: 1.39, 3.37) for *MC4R*.[10] Interestingly, the authors further examined a genetic risk score, calculated by summing the number of risk-increasing alleles that each woman carried at these 5 loci, and they found a significant association with the prevalence of obesity. Women carrying 5 or more risk alleles had a 3.13-fold (95% CI: 2.06, 4.77) higher prevalence of obesity than women carrying 1 or no risk.[10]

Another population-based study involving a cohort of 3,210 Chinese Hans conducted by Qi et al, investigated the prohormone convertase (*PCSK1*) gene and predisposition to obesity and type 2 diabetes. This gene encodes an enzyme that converts inactive prohormones such as proinsulin, proglucagon and proopiomelanocortin into biologically active peptide hormones.[11] Mutations in this *PCSK1* lead to impaired glucose tolerance and common variants in this gene have been reported to be associated with obesity among Europeans. The authors sought to replicate these previous studies to determine if the same variants of the *PCSK1* gene might predispose to obesity among the Chinese. They were only able to demonstrate modest evidence for association of the *PCSK1* variant rs6234 with BMI and overweight in men only and not among women and concluded that it may not be an important contributor to obesity in the Chinese population.[11]

Because several independent studies have reported strong associations of variations in the fat mass and obesity-associated (*FTO*) gene with obesity among Europeans, Chang Y-C et al in 2008 did replication studies on the role of these *FTO* gene variants in obesity and type 2 diabetes in the Chinese population. They genotyped 19 single nucleotide polymorphisms of the *FTO* gene and analyzed its association with obesity in 638 cases and 1610 controls. They were able to confirm an association of *FTO* genetic polymorphisms with obesity and BMI in the Chinese population with an effect size on obesity risk and BMI comparable with previously reported risk among the Europeans.[12]

A similar study on *FTO* variants and association with obesity was done among the Chinese and Malay population in Singapore. Tan J et al investigated the association between 9 previously reported *FTO* SNPs with obesity, type 2 diabetes and related traits in participants of the 1998 Singapore National Health Survey which included 2,919 Chinese, 785 Malays, and 594 Asian Indians as well as 2,996 Malays recruited from another study. The investigators found that variants at the *FTO* gene are associated with obesity in ethnic Chinese and Malays living in Singapore.[13]

Likewise, a study on the variations of the *FTO* gene and its association with severe obesity has been conducted among the Japanese by Hotta K et al in 2008. They investigated 15 SNPs on the *FTO* gene using 927 cases of adults with

obesity and 1,527 normal-weight controls. A significant association in intron 1 SNP rs1558902 with severe obesity was found among the Japanese with an odds ratio (OR) adjusted for age and gender of 1.41 [95% confidential interval (CI) = 1.22–1.62; p value of 0.0000041].[14]

Genome-wide association studies have shown that variations in the insulin-induced gene 2 (*INSIG2*) are associated with obesity; such association has been seen in Caucasian populations.[15] *INSIG2* is a ubiquitously expressed gene known to be downregulated by insulin in the liver, involved in fatty acid synthesis and an intermediate in the feedback control of cholesterol synthesis.[15] Hotta K and his colleagues investigated the relationship of the *INSIG2* gene SNP rs7566605 and obesity among the Japanese from a total of 908 severely obese cases and 1,495 controls. The results of this study showed that the rs7566605 SNP of the *INSIG2* gene was significantly associated with obesity with an odds ratio of 1.61 [95% confidential interval (CI) = 1.24–2.09] adjusted for gender and age and may therefore influence the risk of severe obesity in the Japanese population.[16]

Cha S. et al (2009) similarly examined the effect of the rs7566605 polymorphism near the *INSIG2* gene on both obesity- and cholesterol-related traits among 2,364 Koreans. However, they failed to demonstrate any association of the rs7566605 polymorphism with cholesterol- and obesity-related phenotypes, although there was a suggestion of the possible involvement of *INSIG2* with the plasma level of the total cholesterol in women included in this study.[17]

In a study done among Filipinos from Cebu by Marvelle A. et al in 2008, the researchers found a significant association between the FTO gene and susceptibility to obesity.[18] This conclusion was drawn from data gathered from 1,886 adult Filipino women from the Cebu Longitudinal Health and Nutrition Survey (CLHNS) cohort. The researchers investigated the association of obesity related traits and 19 SNPs previously identified in 10 genes namely *ADRB2*, *ADRB3*, *FTO*, *GNB3*, *INSIG2*, *LEPR*, *PPARG*, *TNF*, *UCP2*, and *UCP3* that had been previously reported to be associated with an obesity-related quantitative trait. The other candidate genes included in this study, apart from those previously described in the other studies above, are the *ADRB2* and *ADRB3* genes, which are adrenergic beta 2 and beta 3 receptors with the latter being involved in the regulation of lipolysis and thermogenesis.[5] *GNB3* codes for guanine-nucleotide-binding protein (G protein) and together with *ADRB2* and *ADRB3* are genes which are part of the catecholaminergic pathway. *LEPR* codes for the leptin receptor and is a member of the class 1 cytokine receptor family and thought to be involved in the regulation of body weight. *PPAR-G*, *PPARG*, the peroxisome proliferator-activated receptor gamma, is a nuclear receptor which regulates fatty acid storage as well as glucose metabolism. The uncoupling proteins *UCP2* and *UCP3* function to uncouple ATP production from mitochondrial respiration with an end result of affecting the efficiency of energy metabolism.[19] This candidate gene study done in a cohort of Filipinos was able to show the association of the A allele of *FTO* variant rs9939609 with BMI and waist circumference. They also demonstrated evidence of association with the homozygous T allele of *ADRB3* rs4994 with BMI, waist circumference and percent body fat; however, only the rs4994 SNP reached statistical significance, not observed in previous studies. The authors concluded that a SNP within the first intron of *FTO* was associated with BMI among this cohort of Filipino women from Cebu and as also seen in other population groups, the gene maybe important in susceptibility to obesity.[18]

Conclusions

Knowing the genes related to obesity have far reaching effects individually and globally. Genetic information can be used to predict an individual's predisposition to the development of obesity and its complications. It also allows for the discovery of novel and personalized treatment strategies to be applied to different population groups being cognizant of the fact that inter-ethnic differences exist. The genetic and genomic studies being done among Asian populations will contribute greatly to the wealth of information on genetic predisposition to obesity. These unique and innovative genomic approaches and discoveries may lead to a better understanding of molecular pathways that give rise to obesity and can pave the way to better management and control of obesity, not only in Asia but throughout the world.

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REVIEW ARTICLE

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Population Trends & Obesity Patterns in the Philippines: A Window to the Obesity Epidemic in the Asia-Oceania Region

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Dr. Lee Kaplan, in his lecture at the recently concluded Postgraduate Course in Endocrinology (Harvard Medical School, Boston, MA, USA) described obesity as a very common and growing problem, with a complex physiology and clinically heterogenous picture, resistant to treatment as well as frustrating to manage. It should be a global health problem priority since it is associated with multiple endocrine and metabolic disturbances.

The complications of obesity, as summarized by Kaplan, are metabolic, structural, inflammatory, degenerative, neoplastic, psychological and is associated with 60 medical syndromes and 12 different types of cancer.

What is the problem of obesity in the Philippines, and its determinants?

Adair in 2004,[1] working in Metro Cebu, saw the prevalence of overweight and obesity increase nearly 6 fold from about 6% in 1983 to 1984 to 35% in 1998 to 1999. Weight gain was positively associated with urban residence, improved socioeconomic status, fewer pregnancies and months of lactation, and more "away from home" work hours. The risk of hypertension was independently elevated by high waist-hip ratio and overweight/obesity.

Sy et al,[2] took up the prevalence studies from 1993 to 2008. The rise continued - about 3.4% of their studied population being obese (BMI greater than 30 kg/m^2) in 1993 and climbing to 5.2% in 2008. On the other hand, the overweight subjects in their study population rose from 15.2% to 21.4% in the same period.

In addition to the factors outlined by Adair, some of the dietary characteristics - especially fat - went up from 11.6% in 1984 to 17% in 1999. We also noted the geometric increase of the Philippines' Number 1 fastfood eatery - Jollibee - from 10 stores in 1981 to 600 stores in 2007. These outlets serve calorie dense foods, coming mostly from fats.

The prevalence of the metabolic syndrome - some relationship to the obesity problem?

The literature is rife with reports of the parallel rise of the metabolic syndrome with obesity. This is understandable, since obesity - especially visceral obesity - is part of the syndrome. In the International Diabetes Federation definition, visceral obesity is a *sine qua non* for the diagnosis of metabolic syndrome.

In the NNHeS survey of 2003-2004,[3] the prevalence of the syndrome was 18.6% of the surveyed population (17.5% for males and 19.7% for females). This compares with the prevalences in some Asian countries.

Are the component risks for the metabolic syndrome the same for all populations?

The component of the metabolic syndrome which occurs the highest is low HDL cholesterol, occurring in 60.2% of men and 80.9% of women. This contrasts with abdominal obesity which is present in 17.7% in men and 35.1% in women. Hypertension is present in 33% of the surveyed population, hypertriglyceridemia in 20.6% and FPG greater than 100 mg%, 7.1%.Non-alcoholic fatty liver disease (NAFLD) is increasing in prevalence in the Philippines; associated with obesity (60 %) and diabetes (69%) (Table 1).[4]

If there are no studies as yet, it may be worthwhile to compare the components of the metabolic syndrome of

Table 1. Comparison between studies of the characteristic features of NAFLD* patients[4]

Author of Study	No. of Patients	Age (yrs)	% Female	% Diabetes	% Obesity	% Hepatomegaly
Ludwig (1988)	20	54	65	50	90	67
Diehl (1988)	39	52	81	55	71	20
Lee (1989)	49	53	78	51	69	--
Powell (1990)	42	49	83	36	95	81
Bacon (1994)	33	47	42	21	39	21
Matteoni (1999)	132	53	53	33	70	92
Khurram (2003)	50	47	54	44	66	76
De Lusong(2008)	134	42	71	69	60	56

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Asian countries with those of Western countries. In one study comparing the incidence of dyslipidemia (cholesterol levels above 240 mg%), the US data in 2002 showed 17.1% of their population with hypercholesterolemia present in only 5.4% of the population.

There have been shown in the past studies differential phenotypes for type 2 diabetes mellitus in Asia countries. There is need for more studies involving the differential genotypes for type 2 diabetes mellitus - there have been several in the past, and more are needed to come up with a clearer understanding of the differences of the manifestations of the disease in different populations.

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ORIGINAL ARTICLE

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Insulin Resistance is the Predominant Pathophysiologic Feature of Hyperglycemia in Newly Diagnosed Overweight and Obese Type 2 Diabetes Mellitus in two University Hospitals in Malaysia

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Abstract

Objectives. To examine the profile of insulin resistance and secretory dysfunction and their relationship with clinical/metabolic parameters among patients with newly diagnosed type 2 diabetes mellitus in Malaysia.

Methods. A cross-sectional study of 161 newly diagnosed type 2 diabetic subjects was performed. Fasting blood samples were collected for glucose, insulin and biochemistry. Demographic and anthropometric data were recorded. Homeostatic model assessment (HOMA) was used to estimate insulin resistance (IR) and beta-cell function. Control subjects consist of 45 individuals with normal glucose tolerance.

Results. Our type 2 diabetic subjects had significantly higher HOMA-IR and lower HOMA-%B versus controls (6.4 $\pm$ 5.3 vs. 2.5 $\pm$ 1.5, $p < 0.0001$ and 93.5 $\pm$ 87.8% vs. 201.0 $\pm$ 118.0%, $p < 0.0001$). Elevated body mass index or waist circumference, hypertension and hypertriglyceridaemia were independent predictors for insulin resistance. Low body mass index or waist circumference, hypertriglyceridaemia and increasing age were independent predictors for beta cell dysfunction.

Conclusions. Contrary to a predominantly insulin secretory dysfunction reported by other studies from Asia, our study of largely overweight and obese type 2 diabetic subjects showed a predominance of insulin resistance over secretory dysfunction. Obesity, hypertension and hypertriglyceridaemia were predictive of insulin resistance while being lean with hypertriglyceridaemia and increasing age were predictive of beta cell dysfunction.

Keywords: type 2 diabetes mellitus; insulin resistance; insulin secretory dysfunction; obesity.

Introduction

Both insulin resistance (IR) and insulin secretory dysfunction have been implicated in the pathogenesis of type 2 diabetes mellitus (T2DM). The relative contribution of each varies among individuals of different ethnic or genetic backgrounds. In the Pima Indians and Mexican Americans, insulin resistance is believed to be the primary defect [1]. In comparison, findings from several studies on Asian type 2 diabetic subjects indicate that insulin secretory dysfunction plays a more dominant role [1-3]. This is a pilot study on the relative contribution of insulin secretory dysfunction and insulin resistance among a group of type 2 diabetic individuals in Malaysia. The clinical parameters that have been found to be associated with insulin resistance include regional adiposity, dyslipidemia, hypertension, microalbuminuria and smoking [4-8]. There is very little data on clinical parameters associated with insulin secretory dysfunction.

The objectives of this study are to examine the profile of insulin resistance and insulin secretory dysfunction as well as the clinical/metabolic parameters that predict insulin resistance and secretory dysfunction among newly diagnosed T2DM subjects in Malaysia.

Materials and Methods

This is a dual center, comparative cross-sectional study. All diabetic subjects were recruited from the primary care clinics which provide universal health care at University of Malaya Medical Centre, Kuala Lumpur and the Hospital of University of Science, Kota Bharu. Both were university hospitals which provide tertiary health care service to the western and northern region of Malaysia respectively. All patients with newly diagnosed, drug-naive T2DM from the primary care clinics were recruited consecutively from March to November 2008. Newly diagnosed T2DM was defined as a diagnosis of T2DM made within six months prior to study inclusion. The

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diagnosis of diabetes mellitus was made either by the usual fasting or random venous plasma glucose or after undergoing a 75g oral glucose tolerance test based on the 1998 World Health Organisation's criteria [10]. Diabetic subjects who were below 20 years of age, taking medications that can affect glucose tolerance, diagnosed with type 1 diabetes or pregnant were excluded. Control subjects were recruited from healthy volunteers from the local community. They were required to have a normal oral glucose tolerance test without a positive family history in a first degree relative with T2DM. Attempts were made in order to match the controls to the diabetic subjects in terms of gender distribution, age, ethnicity and body weight. Informed consent was obtained according to the protocols approved by the ethics committees of University of Malaya Medical Centre and the Hospital of University of Science.

A complete medical history, physical examination, collection of anthropometric and demographic data was performed in all diabetic and control subjects. Waist circumference (WC) was measured at the midpoint between the lower costal margin and the iliac crest according to the World Health Organisation's recommendation. For T2DM subjects, venous blood was obtained for fasting plasma glucose (FPG), fasting plasma insulin (FPI), lipid profile, glycated haemoglobin (HbA1c) and anti-glutamic acid decarboxylase (anti-GAD) after an overnight fast of 12 hours while a freshly void midstream spot urine sample was collected for microalbumin and creatinine estimation. Anti-GAD was performed to screen out any type 1 diabetic subjects who may be misclassified as type 2 diabetes. Blood pressure was measured in sitting position after the subjects rested for five minutes for three consecutive readings. The systolic and diastolic blood pressure was derived from an average of the three readings respectively. Mean arterial pressure (MAP) was calculated as the sum of the diastolic blood pressure and one third of the pulse pressure. For control subjects, oral glucose tolerance was performed with 75 g glucose after an overnight fast. We obtained FPI along with FPG before the glucose challenge.

Plasma glucose was measured with the hexokinase method (Siemens Dimension RXL). The intra- and inter-assay coefficients of variation were 0.7 and 1.3 % respectively. Plasma insulin was measured with immunoassay (Cobas) with an intra and inter-assay coefficients of variation of 1.5-2 % and 2.1-2.8 % respectively. This assay does not have significant cross-reactivity with proinsulin. The same assay and laboratory was used for the measurement of plasma insulin for all the diabetic and control subjects at the same time. The plasma triglyceride (TG) and high-density lipoprotein (HDL) cholesterol levels were measured with selective detergent and glycerol kinase method (Siemens Dimension RXL) respectively. HbA1c was performed using the high performance liquid chromatography (Bio-rad) while anti GAD was performed with enzyme-linked immunosorbent assay (Euroimmun). The urine microalbumin and creatinine was performed with immunoturbidmetry method (Roche Lobas Integra 800).

Insulin resistance and pancreatic beta cell function was calculated using the Homeostatic Model Assessment (HOMA) proposed by Matthews et al [10]. The formulas are:

Insulin resistance, HOMA-IR = FPI (μU/ml) x FPG (mmol/L) / 22.5
Beta cell function, HOMA-%B = 20 x FPI (μU/ml) / [FPG (mmol/L) - 3.5]

Statistical Analysis

Numerical values were expressed as means ± standard deviations. Statistical analysis was conducted using the Statistical Package for Social Science (SPSS) version 15. Group means were compared using Student's t-test or Analysis of Variance (ANOVA) where appropriate followed by post-hoc analysis (Tamhane's or Scheffe's). Homogeneity of variances was assessed using the Levene's test. Where the variances were homogenous, Scheffe's post-hoc test was used while Tamhane's test was used when the variances were not homogenous. Pearson's chi-square test was used to test categorical variables between diabetic subjects and controls. Correlation coefficients (r) between HOMA-IR and HOMA-%B with various clinical parameters were calculated using Pearson's correlation. Several stepwise multiple regression analyses that included HOMA-IR, HOMA-%B, age, gender, ethnicity, MAP, body mass index (BMI) or WC, smoking status, urine microalbumin, plasma TG and HDL cholesterol were performed to examine the relative contribution of HOMA-IR and HOMA-%B towards HbA1c, i.e. glycaemic intolerance. Several regression models that included age, gender, ethnicity, BMI, WC, plasma TG and HDL cholesterol, MAP, urine microalbumin and smoking status were also performed to examine the independent relationship between the various clinical or metabolic predictor variables with HOMA-IR and HOMA-%B. To provide a measure of the independent effect of each variable in the model, we report the percent change in R^2 (i.e. the difference between the R^2 from models with and without the variable of interest, divided by the R^2 from the model with the variable). As BMI and WC were highly correlated (r=0.846), they were included in separate models. A p value of < 0.05 was considered statistically significant.

Results

A total of 161 diabetic subjects aged 25-81 years were recruited, 60.9 % being Malay, 19.9 % Chinese, 18.6 % Indian and 0.6% others. Majority (74.5%) of the diabetic subjects were diagnosed via routine screening when they visited the primary care clinics for other conditions

associated with diabetes, e.g. hypertension and dyslipidaemia, and they were diagnosed by two FPG of ≥ 7 mmol/L (41%) or by oral glucose tolerance test (33.5%) when the FPG is impaired as defined by > 5.6 mmol/L. Only 25.5% of the diabetic subjects presented with symptomatic hyperglycaemia with a random plasma glucose of ≥ 11.1 mmol/L upon diagnosis. Of note is that the majority of the diabetic subjects were overweight/obese with a mean BMI of 28.6 ± 5.5 kg/m^2. More than half, 85 (52.8 %) of them were obese (BMI ≥ 27.5) while 59 (36.6 %) were overweight (BMI 23-27.5) as defined by the National Clinical Practice Guidelines on Management of Obesity of Malaysia [11]. Using the Asian cut off point of 90 cm for male and 80 cm for female for central obesity, 121 (75.2 %) of the diabetic subjects were centrally obese [12]. A total of 93 subjects (57.8 %) had positive family history of T2DM in first-degree relatives and 99 (61.5 %) were hypertensive (defined by a blood pressure of ≥ 130 mmHg systolic and or ≥ 85 mmHg diastolic or were on antihypertensive medications). Dyslipidaemia, defined as fasting serum triglyceride (TG) ≥ 1.7 mmol/L or high-density lipoprotein (HDL) cholesterol < 1.04 mmol/L in male and 1.30 mmol/L in female was present in 100 (62.1 %) of the diabetic subjects. A total of 45 control subjects aged 25-72 years old were also recruited concurrently from healthy volunteers. Of these, 24 (53.3%) were overweight while 14 (31.1%) were obese. The baseline characteristics of the diabetic and control subjects are summarized in Table 1.

Table 1. Baseline characteristics of diabetic and control subjects

Parameters	Diabetic Subjects	Control Subjects
N (Male / Female)	161 (*70 / 91)	45 (27 / 18)
Age (years)	*52.2 ± 11.8	44.3 ± 10.2
BMI (kg/m^2)	*28.6 ± 5.5	26.0 ± 3.1
WC (cm): Male / Female	*95.5 ± 10.9 / *93.2 ± 11.8	89.0 ± 8.8 / 83.3 ± 9.3

**p < 0.05 vs. control*
Data is expressed as absolute values or means ± standard deviation.
Statistical Analysis: Student's t-test
BMI, Body Mass Index; WC, Waist Circumference

Table 2 shows the comparison of HOMA-IR, HOMA-%B and other metabolic parameters between the diabetic and control subjects. As expected, the newly diagnosed diabetic subjects had significantly more severe insulin resistance as well as beta cell dysfunction compared to the controls, even after adjustment for difference in age, gender, BMI and WC. HOMA-IR increased 2.6 times while HOMA-%B was reduced by 53.5% among the diabetic subjects compared to the controls. There was a wide variation of insulin resistance as well as beta-cell function among the newly diagnosed diabetic subjects. HOMA-IR ranged from 0.87 to 28.56 while HOMA-%B ranged from 3.2 to 568.0. In the regression model for HbA1c in the newly diagnosed diabetic subjects, there was a predominance of contribution of insulin resistance towards glycaemic intolerance or HbA1c over beta cell dysfunction as indicated by a higher percent change in R^2 values for HOMA-IR (46.3 %) versus HOMA-%B (30.4 %) (Table 3).

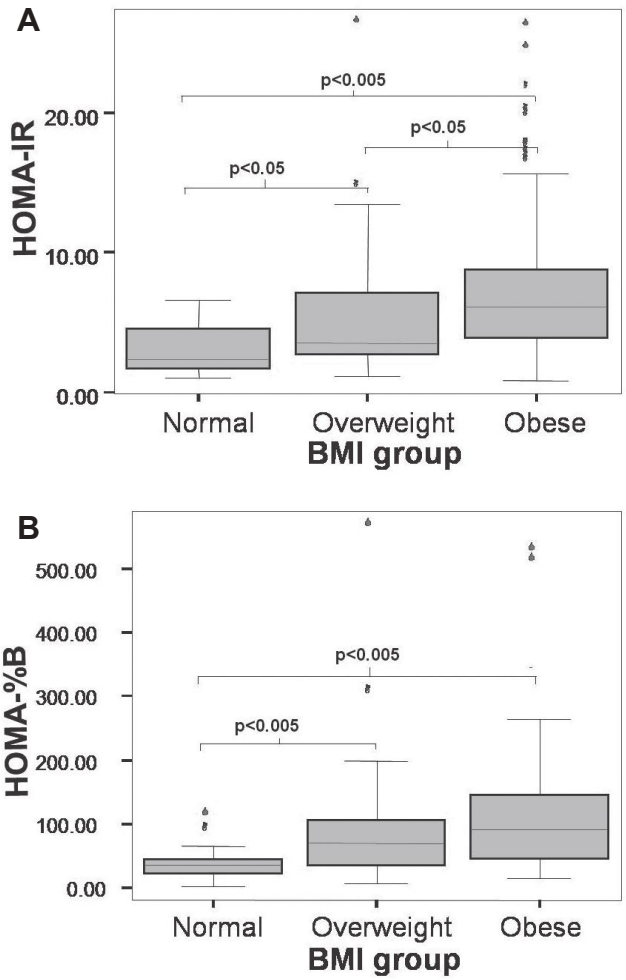

Figure 1 Relationship between a) HOMA-IR and b) HOMA-%B and obesity among newly diagnosed diabetic subjects.

a) HOMA-IR (with the extreme outlier in the normal weight group excluded)

b) HOMA-%B

- Upper and lower borders of the box indicate the 1st and 3rd quartile values while the line in the middle indicates median. The unfilled circles are suspected outliers (≥ 1.5 x IQR above the 3rd quartile) while the * were outliers (≥ 3 x IQR above the 3rd quartile).
- Statistical Analysis: ANOVA
- BMI, Body Mass Index; IQR, Interquartile range

A significant relationship was found between HOMA-IR and HOMA-%B with obesity among the diabetic subjects as shown in Figure 1. The obese diabetic subjects were significantly more insulin resistant than the overweight diabetic subjects. The differences between the obese or overweight versus the normal weight diabetic subjects were statistically significant when an extreme outlier in the normal weight group was excluded (Figure 1a). This particular individual presented with a FPG of 20 mmol/L with HOMA-IR of 28.56 and HOMA-%B of only 37.28%. This individual was probably a case of late diagnosis of advanced T2DM or latent autoimmune diabetes. Beta cell

Table 2. Comparison of indices of glucose homeostasis and metabolic parameters of diabetic subjects versus control subjects.

Parameters	Diabetic Subjects	Control Subjects	*P* value
FPI (μU/ml)	16.6 ± 10.5	11.7 ± 6.5	*0.0034*
HOMA-IR	6.4 ± 5.3	2.5 ± 1.5	**< 0.0001*
HOMA-%B	93.5 ± 87.8	201.0 ± 118.0	**< 0.0001*
FPG (mmol/L)	8.6 ± 3.5	4.8 ± 0.5	**< 0.0001*
HbA1c (%)	8.1 ± 2.2	ND	/
Urine Microalbumin Creatinine Ratio (mg/g) : Male / Female	32.09 ± 45.4 / 35.53 ± 53.2	ND	/

**Adjusted for age, gender, body mass index and waist circumference*
Data is expressed as means ± standard deviation
Statistical Analysis: Student's t-test
FPI, Fasting Plasma Insulin; FPG, Fasting Plasma Glucose; ND, Not done

Table 3. Regression model for HbA1c of the diabetic subjects (model r^2 = 0.482, constant = 8.646 ± 2.376).

Significant predictive variables	% change in R^2	b coefficient ± S.E.	F test *p* value
HOMA-IR	46.9	0.214 ± 0.027	*< 0.0005*
HOMA-%B	30.9	-0.008	*< 0.0005*

Data is expressed as absolute values or means ± standard error.
Statistical Analysis: Step-wise multiple regression; % change in R^2 is the difference between the R^2 from models with and without the variable of interest, divided by the R^2 from the model with the variable.
S.E. standard error
Variables included in the models: HOMA-IR, HOMA-%B, age, gender, ethnicity, mean arterial blood pressure, body mass index or waist circumference, smoking status, urine microalbumin creatinine ratio, plasma triglyceride and high density lipoprotein cholesterol

Table 4. Summary of regression models for HOMA-IR of the diabetic subjects.

Significant predictive variables	% change in R^2	b coefficient ± S.E.	F test *p* value
a) Model 1 (Model R^2 = 0.186, Constant = -13.733 ± 3.665)			
BMI (kg/m^2)	42.5	0.315 ± 0.070	*< 0.0005*
MAP (mmHg)	20.4	0.097 ± 0.034	*0.004*
TG (mmol/L)	15.1	1.044 ± 0.415	*0.013*
b) Model 2 (Model R^2 = 0.179, Constant = -17.631 ± 4.193)			
% WC	40.2	0.112 ± 0.026	*< 0.0005*
MAP (mmHg)	23.5	0.101 ± 0.034	*0.003*
TG (mmol/L)	15.1	1.031 ± 0.417	*0.014*

Data is expressed as absolute values or means ± standard error.
Statistical Analysis: Step-wise multiple regression; % change in R^2 is the difference between the R^2 from models with and without the variable of interest, divided by the R^2 from the model with the variable.
S.E. standard error; BMI, Body Mass Index; MAP, Mean Arterial Blood Pressure; TG, Plasma Triglyceride; % WC, Percentage of waist circumference from normal reference (90 cm for male, 80 cm for female)
Variables included in the models: age, gender, ethnicity, BMI or WC, TG and high density lipoproptein cholesterol, MAP, urine microalbumin creatinine ratio and smoking status

Table 5. Summary of regression models for HOMA-%B of the diabetic subjects.

Significant predictive variables	% change in R^2	b coefficient ± S.E.	F test *p* value
a) Model 1 (Model R^2 = 0.098, Constant = 117.611 ± 86.646)			
BMI (kg/m^2)	34.7	3.687 ± 1.346	*0.01*
TG (mmol/L)	32.7	-12.646	*0.012*
b) Model 2 (Model R^2 = 0.099, Constant = 69.691 ± 97.516)			
% WC	35.4	1.392 ± 0.526	*0.009*
TG (mmol/L)	36.4	-13.5	*0.008*
Age (years)	27.3	-0.792	*0.019*

Data is expressed as absolute values or means ± standard error.
Statistical Analysis: Step-wise multiple regression; % change in R^2 is the difference between the R^2 from models with and without the variable of interest, divided by the R^2 from the model with the variable.
S.E. standard error; BMI, Body Mass Index; TG, Plasma Triglyceride; % WC, Percentage of waist circumference from normal reference (90 cm for male, 80 cm for female)
Variables included in the models: age, gender, ethnicity, BMI or WC, TG and high density lipoproptein cholesterol, MAP, urine microalbumin creatinine ratio and smoking status

dysfunction was significantly more pronounced among the normal weight compared to the overweight or obese diabetic subjects. No significant difference in beta cell function was demonstrated between the overweight and obese group (Figure 1b). These relationships were also demonstrated by the significant correlations between HOMA-IR and HOMA-%B with BMI ($r = 0.351$, $p < 0.005$ for HOMA-IR; $r = 0.266$, $p = 0.001$ for HOMA-%B).

Multivariate analysis conducted to look for independent clinical predictors of HOMA-IR and HOMA-%B among our newly diagnosed T2DM subjects revealed that a raised BMI, WC, MAP and TG were independent risk factors for insulin resistance while a raised TG, a low BMI or WC and increasing age were independent risk factors for beta cell dysfunction (Table 4 and 5). All the non-anthropometric parameters were significant in both models that include BMI and WC respectively (Model 1 and 2) except age which was only significant in the model that included WC for HOMA-%B.

The percent change in R^2 for both BMI and WC were very similar for prediction of both HOMA-IR and HOMA-%B (Table 4 and 5). This implies that neither parameter held a significant advantage over the other in prediction of insulin resistance or beta cell dysfunction. In the subgroup analysis of obese and non-obese diabetic subjects, we found that a raised BMI, WC and TG appeared to play a more important role among the obese diabetic subjects while MAP was only important among the non-obese

diabetic subjects in prediction of insulin resistance. Additionally, we also found that having a low HDL were independent risk factors for insulin resistance among the non-obese diabetic subjects (data not shown).

Discussion

Profile of Insulin Resistance and Secretory Dysfunction

The mean HOMA-IR among our newly diagnosed diabetic subjects in this study was 6.4. This is much higher than those reported in other studies from the Asian region, with values ranging from 2.4-3.5 [1-3, 6, 13]. Our result is more comparable to that of an Italian study with a reported mean HOMA-IR of 5.9 [14]. Similarly, the mean HOMA-%B among our newly diagnosed diabetic subjects was 93.5 %, which is much higher than other studies from the Asian region, with values ranging from 32.4-34.0 % [2, 13]. Our Malaysian data is more comparable to the Insulin Resistance Atherosclerosis Study cohorts in United States of America which reported a mean HOMA-%B of 117.0 %.[15] Despite being part of Asia, the newly diagnosed T2DM subjects in our study appeared to be more insulin resistant than those from other parts of Asia. This is most probably related to the relatively higher BMI in our study subjects compared to that reported from other studies from this region. The mean BMI of the diabetic subjects in our study is 28.6 kg/m^2, which is comparable to the mean BMI of diabetic subjects reported in the Western countries (28.8-29.6 kg/m^2) but is significantly higher than those reported in other studies in the Asian region (21.8-25.5 kg/m^2) [2, 3, 13-17].

All of our diabetic subjects were recruited from urban areas. Urbanisation results in transition from a traditional to a westernised lifestyle characterised by a high fat diet and lack of physical activity. According to the theory of a 'thrifty genotype,' Asians exposed to a Western lifestyle are more predisposed to insulin resistance due to their increased ability to store fat, i.e. they are 'metabolically obese.' [2, 16, 18] Although a wide range of insulin resistance and insulin secretory dysfunction was found among our diabetic subjects, insulin resistance contributes more than beta cell dysfunction towards the severity of glycaemic intolerance. Our study's findings differ from that reported from the other studies in the Asian region that suggest insulin secretory dysfunction is the primary defect of T2DM among Asians [1-3]. This is best explained by the largely overweight or obese population of type 2 diabetes in our study with a mean BMI of 28.6 kg/m^2 as opposed to the much leaner population with a mean BMI of 21.8-25.3 kg/m^2 in the other studies in the Asian region. Numerous studies have shown that obesity is strongly associated with insulin resistance [5, 19-22].

Insulin Resistance: Relationship to Clinical/Metabolic Parameters

Comparing insulin resistance across different degrees of obesity, a direct relationship is observed between insulin resistance across categories of obesity, i.e. obese, overweight and normal when the extreme outlier in the normal weight group was excluded from the analysis. Similar observations have been reported in previous studies [5, 19-21].

We found that both overall and central obesity as measured by BMI and WC were equally predictive of insulin resistance among our newly diagnosed diabetic subjects as indicated by their similar values in percent change in R^2. Similar findings were noted in Molist-Brunet's and Farin's study[23,24]. BMI has been demonstrated to be an important correlate of subcutaneous fat while WC, an important correlate for visceral fat [25, 26]. Taniguchi and Wagenknect et al found that both subcutaneous and visceral fat to be predictive of insulin resistance [5-7, 27]. However, there seems to be ethnic differences in the relationship of regional adiposity with insulin resistance. Abate et al found that subcutaneous fat but not intra or retroperitoneal fat was associated with insulin resistance in non-Hispanic whites with T2DM [19]. Banerji and Gautier et al demonstrated a strong relationship between insulin sensitivity with visceral but not general adiposity in the black and French populations respectively [20, 21]. On the other hand, Kelley et al observed an independent association of insulin resistance with deep subcutaneous abdominal fat over and above that of visceral fat but not superficial subcutaneous abdominal fat among Americans [28].

For our non-obese diabetic subjects, neither BMI nor WC had an independent effect on insulin resistance. Taniguchi et al also found an absence of predictive effect of BMI on insulin resistance among the non-obese diabetic patients in Japan. It was felt that hypertriglyceridemia was more important in that study [5, 6]. However, a raised blood pressure and low HDL seemed to be the more important predictors of insulin resistance among our non-obese diabetic subjects. Our results concur with that of Laakso et al who demonstrated a significant relationship between hypertension and insulin resistance in lean but not obese type 2 diabetic subjects [29].

In the multivariate analysis, WC did not seem to confer any obvious superiority over BMI in prediction of insulin resistance as postulated for Asians with T2DM who are generally centrally obese with relatively lower BMI [16, 22, 30]. This is probably because of the relatively high proportion of obese diabetic subjects in our study. Only 24.8% of our diabetic subjects had BMI below 25 kg/m^2. Hypertriglyceridaemia was found to be a significant predictor for both insulin resistance and beta cell dysfunction among our diabetic subjects. This is consistent with the finding that serum TG as a predictor of progression in glucose intolerance in a longitudinal study done in Malaysia [31]. Hypertriglyceridaemia was also found to be associated with insulin resistance in a few other studies [5-7, 32]. The other clinical parameters that had been

associated with insulin resistance in previous studies include HDL cholesterol, microalbuminuria and smoking. A significant relationship between urine microalbuminuria and insulin resistance was not reproduced in our study. HDL was only significant as a predictor of insulin resistance among the non-obese diabetic subjects. Although blood pressure was one of the independent predictors of insulin resistance, its correlation was weaker than expected. The associations of all these parameters with insulin resistance were probably confounded by the fact that more than half of our diabetic subjects were already on lipid lowering or anti-hypertensive therapy including angiotensin converting enzyme inhibitors or angiotensin receptor blockers at the time of the study.

Insulin Secretory Dysfunction: Relationship to Clinical/Metabolic Parameters

The relationship between beta cell dysfunction and obesity is less straightforward. BMI seemed to play a more prominent role only among the diabetic subjects with normal weight. Once a diabetic subject became overweight or obese, there was no difference in the degree of beta cell dysfunction. As a result, the bivariate analysis between BMI with HOMA-IR and HOMA-%B revealed a weaker correlation for the latter as only 10.4% of our diabetic subjects were of normal weight. In the multivariate analysis, a raised plasma TG, a low BMI or WC and increasing age were independent predictors of beta cell dysfunction. Age was only significant in the model that included WC but not in the model that included BMI. This is probably due to a significant interaction between BMI and age. When the regression model was adjusted for BMI, the effect of age on beta cell function became insignificant. There have been no published studies so far that examines the relationship of various clinical parameters with beta cell dysfunction in diabetic subjects. The mechanisms underlying the relationship between adiposity and insulin secretion are unclear and are further complicated by the effect of co-existing insulin resistance on beta cell function. Increased peripheral insulin levels with development of insulin resistance associated with obesity could be falsely interpreted as increased insulin secretion. BMI did not confer any obvious supremacy over WC in predicting beta cell dysfunction among our diabetic subjects. This can be explained by the relative inaccuracy of anthropometric indices in distinguishing subcutaneous from visceral abdominal fat compared to computed tomography, the modalities used by Wagenknect et al [27]. The direct effect of lipotoxicity associated with hypertryglyceridaemia on beta cell function may explain the direct relationship between TG and beta cell dysfunction.

Study Limitations

There were a few limitations in our study. All the subjects were recruited from two government tertiary health institutions in Kuala Lumpur and Kota Bharu located in urban areas which provide subsidised health care service to the people with limited access to private health care. This limits the generalisability of our findings to the general population in Malaysia. The small sample size also does not allow subgroup analysis especially on the effects on ethnicity. The control subjects selected were slightly younger and less obese than the diabetic counterparts despite attempts made to have these parameters matched during recruitment. Nevertheless, the differences in all parameters compared between the diabetic and control group remained significant after adjustment for age, gender, BMI and WC. We chose the HOMA method proposed by Matthew et al in assessing insulin resistance and beta cell function[12]. Although it is an indirect measurement, it provides an estimation that correlates well with the glucose clamp in subjects with varying degree of glucose tolerance[12]. It measures the basal rather than the stimulated state and has the tendency of overestimation of beta cell function[15,33]. The HOMA-%B values must therefore be interpreted together with the concurrent HOMA-IR. It is technically simple and inexpensive, favouring its use in an epidemiological setting. We did not assess the visceral or subcutaneous abdominal fat directly but used WC and BMI as surrogate measures. BMI and WC are imperfect measures of regional distribution of adiposity, a major determinant of insulin resistance as they do not distinguish visceral from subcutaneous adiposity[34]. A high correlation of 0.85 was found between BMI and WC in our study. This implies that there might be a significant overlap in the type of fat measured by these two surrogates. Previous studies demonstrated that BMI was positively correlated with both subcutaneous and visceral fat[5,27]. BMI also compounds body fat with muscle and skeletal mass making it an imprecise surrogate for overall obesity[34]. A larger sample size with more representation from the rural areas, different ethnic groups as well as a wider range of BMI would also be ideal to generate adequate statistical power to detect differences between subgroups.

Conclusions

The prevalence of diabetes mellitus in Malaysia has increased drastically over the past two decades from 6.3 % in 1986 to 8.2 % in 1996 and 14.9 % in 2006 [35]. Our T2DM subjects recruited from two university hospitals in Malaysia who are largely overweight or obese, behaved more closely to T2DM individuals from the West, with a predominance of insulin resistance over secretory dysfunction rather than a primarily insulin secretory defect contrary to results from other studies from Asia, conducted on subjects with lower BMI. The mean HOMA-IR and HOMA-%B of our type 2 diabetic subjects were more comparable to those of the Caucasians rather than Asian counterparts. It is important in terms of therapeutic strategy for physicians to consider the pathophysiologic processes determining T2DM, i.e. the relative contribution of insulin resistance and impaired insulin secretion. Based

on the results of our study, an obese diabetic subject with hypertension and hypertriglyceridemia is likely to be insulin resistant while a lean diabetic subject with raised plasma TG and increasing age is likely to be insulin deficient. However, co-existing insulin resistance should be suspected if this lean diabetic subject also has hypertension with a low HDL level. Nevertheless, these results need to be verified in a bigger study sample of subjects more representative of the general Malaysian population.

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ORIGINAL ARTICLE

Neck Circumference as a Screening Measure for Abdominal Obesity and its Association with Metabolic Syndrome among High Risk Filipino Patients in Makati Medical Center - a Pilot Study

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Abstract

Objectives. The study aims to determine the cut off level of neck circumference that would correlate with abdominal obesity, using waist circumference as the gold standard; and determine its relationship with metabolic syndrome among high risk filipino patients.

Methods. A total of 425 high risk Filipino patients who sought consult at Makati Medical Center from the period of March to October 2010 were qualified to participate in the study. Pertinent history, including blood pressure measurement and anthropometric measurements such as height, weight, neck circumference and waist circumference were recorded; after an 8 hour overnight fast, blood samples were sent for fasting plasma glucose, HDL cholesterol and triglyceride levels.

Results. Neck circumference cut off levels of ≥ 40cm for males and ≥ 33.8cm for females showed a low sensitivity and moderately high specificity for determining patients with abdominal obesity; 62.07% and 90.09% for males, 67.59% and 85.56% for females, respectively. In terms of determining patients with metabolic syndrome, it has a low sensitivity and specificity. However, obese by neck circumference cut off levels showed significant association (*p value <0.001)* with the component risk factors of metabolic syndrome, except for hypertriglyceridemia. Likewise, neck circumference also showed a strong positive linear relationship with waist circumference.

Conclusion. Neck circumference showed a strong correlation with abdominal obesity, as well as with the component risk factors of metabolic syndrome, and therefore with risk of cardiovascular disease. Above the NC cut off levels, its predictive value for abdominal obesity is high; however, it has a poor ability to detect patients with abdominal obesity in the general population and therefore, cannot be used as a screening test.

Keywords: neck circumference, waist circumference, metabolic syndrome, obesity

Introduction

Obesity is emerging as a health epidemic around the world. According to the Center for Disease Control and Prevention, obesity is rapidly spreading across all regions and demographic groups.[1-2] Obesity is a hallmark of affluence as seen in its high prevalence rate among industrialized countries. This trend is starting to change with recent survey results suggesting obesity is becoming common among children and adults in developing countries like the Philippines. According to the latest survey conducted by the Food and Nutrition Research Institute of the Department of Science and Technology (FNRI-DOST), they found that obese Filipino women outnumber the men. Those most at risk of being obese are 40-59 year-old adults.[3] While obesity and overweight may not be relatively as high in the Philippines compared to US trends, a recent study that assessed the prevalence of the metabolic syndrome (MS) in the Philippines found that abdominal obesity was seen in approximately 17.7% of Filipino men and 35.1% of Filipino women in the study.[4] Various studies have shown that obesity is associated with increased risk of coronary heart disease, diabetes, hypertension and other chronic degenerative diseases.[3, 5-13]

MS is a clustering of several metabolic factors that increases the risk for atherosclerotic cardiovascular disease (ASCVD) and diabetes mellitus (DM). These factors include dysglycemia, high blood pressure, elevated triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels and obesity, in particular central adiposity.[4, 14] Since the first official definition of the MS put forward by a working group of the World Health Organization (WHO) in 1999, a number of different

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definitions have been proposed. Although MS has several definitions, including those by the International Diabetes Federation (IDF) and the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III), for the purpose of this study we will be using the criteria modified by the American Heart Association/National Heart, Lung and Blood Institute (NCEP/ATP III-AHA/NHLBI). Using this criteria, the prevalence of MS in the general population in the Philippines in 2003 to 2004 for adults aged 20 years and above, representing 42.6 million Filipinos, was 18.6%.[4]

In 1999 the WHO definition of MS included a measure of obesity and defined obesity in terms of either body mass index (BMI) or waist-to-hip ratio (WHR). The latest definition is the one of the International Diabetes Federation (IDF), which takes into account evidence that abdominal obesity is the important component of the metabolic syndrome[15] and proposed waist circumference as an indication of abdominal obesity.[5, 14, 16-19]

A simple measurement of waist size is a valuable assessment tool for cardiovascular risk and a strong diagnostic criterion for MS according to a study done by James M. Rippe in collaboration with Weight Watchers International. Stronger relationships between waist size and HDL and total cholesterol to HDL ratio were found compared with BMI. The results confirmed the idea that abdominal fat is linked with higher risk than being generally overweight and also supported the use of BMI to assess overall risk.[6]

BMI and waist circumference (WC) are two commonly accepted anthropometric indices for predicting MS. Also some studies report that WHR identifies patients with abdominal obesity. However, WC has been suggested as being a more practical measure of abdominal fat mass and total body fat and is more closely correlated with abdominal adipose tissue than WHR.[5-6, 17-21] In a study by Wang (2008) in a Chinese population aged 18-85 in China, a comparative validation of three body stature measures, WC, BMI and WHR were done to define which among the 3 measurements is most closely predictive of the non-adipose components of the IDF definition of MS. The study showed that WC is best able to discriminate MS, and is a better predictor than BMI in men. WHR in both sexes is a much weaker predictor.[5]

Jean Vague was the first to show that different body morphologies or types of fat distribution are related to the health risks associated with obesity. He used a neck skin fold in his index of masculine differentiation to assess upper body fat distribution.[22]

Although obesity results in metabolic abnormalities, upper-body obesity is more strongly associated with glucose intolerance, hyperinsulinemia, diabetes, hypertriglyceridemia, gout, and uric calculous disease than is lower-body obesity.[7, 22-25] It is believed that the association of abdominal obesity with cardiovascular disease (CVD) risk factors of the MS was due to accumulation of visceral fat volume. In 2005, the IDF proposed a unified worldwide definition of the MS. In this definition, central obesity was regarded as a prerequisite and incorporated element with different WC cut offs by gender and ethnicity, in which WC of 90cm and 80cm was set for Asians using the IDF worldwide definition of MS.[16]

Waist circumference will be used as the gold standard in this study to determine patients with abdominal obesity, and thus consequently increased their risk for MS. In newly published data by Salomon, et. al., they showed that among males and females, visceral fat thickness showed a strong and significant correlation with WC, and a weak but significant correlation with MS. For males, the minimum visceral fat thickness associated with MS was 17.70 mms, with a mean of 59.39 mms, and the minimum WC associated with MS was 82.50 cms with a mean of 99.74 cms. For females, the minimum visceral fat thickness associated with MS was 10.70 mms, with a mean of 47.77 mms, and the minimum WC was 78.00 cms, with a mean of 92.68 cms.[26] The study involved 311 patients aged 40-65 years old who were admitted in the executive health check-up program at the Makati Medical Center. WC was taken as the circumferential measurement of the area at the midpoint between the lower border of the last rib and the iliac crest. MS was defined according to the 2009 revised criteria proposed by the International Diabetes Federation (IDF), World Heart Federation, International Atherosclerosis Society and National Heart, Lung and Blood Institute (NHLBI).[14] Likewise, in the study by Balkau, et al, WC was used as a measure of abdominal adiposity because of the close correlation between WC and the amount of intra-abdominal fat observed by computed tomography.[9]

Neck circumference (NC), an index of upper-body subcutaneous adipose tissue distribution, was evaluated in relation to cardiovascular (CV) risk factors by Sjo¨stro¨m et al. The neck and thigh circumferences were used as indices of upper- and lower-body subcutaneous tissue distribution, respectively, in a three compartment body composition model. This model of interpretable anthropometry consisted of the visceral and subcutaneous adipose tissue masses as well as the lean body mass. Even after adjusting for these body compartments, NC, an index of upper-body subcutaneous adipose tissue distribution, was positively related to most CV risk factors. At the same time, thigh circumference was negatively related to the risk factors.[25]

All evidence suggests that abdominal fat carries a higher health risk than peripheral fat, and that the visceral fat component correlates the most strongly with increased risk. Whereas computed tomography and magnetic

resonance imaging allow more precise measurement of abdominal fat, they are impractical for routine clinical use.

Several tools that can be used to assess overweight and obesity at primary care facilities include measurements of weight, height, waist and hip circumferences, and calculations of WHR and BMI. However, it is not always practical to use these techniques, especially in busy everyday primary care practice. Such is the case in the local setting, particularly in community health centers and barangays; where physicians and nurses are very limited while patients are one too many. Some techniques would necessitate longer time; even requiring removal of one's clothes in front of strangers, which in a conservative society such as ours, would not be very comfortable and would be frowned upon. And, as previously stated, other procedures such as ultrasound, computed tomography and magnetic resonance imaging are expensive and are primarily used for research purposes.

As a first step to achieve obesity control, it is important to develop a reliable, simple and quick method for the assessment of obesity in primary care clinics in the local setting. NC, an index of upper body obesity, is a simple screening measure that can be used to identify patients who have abdominal obesity.

In a previous study done by Liubov (Louba) and Laor in a family medicine clinic in Israel in 2001, NC as an index of upper-body obesity was found to be a simple and time-saving screening measure that can be used to identify overweight and obese individuals.[23]

Furthermore, in patients who are not ambulatory and cannot tolerate standing position, especially in patients admitted in intensive care units where height and weight measurements cannot be done, NC measurements can take their place. There are also limited epidemiological studies on the clinical significance of NC with regards to its association with obesity and increased risk of CV risk factors that would require a more comprehensive evaluation of their overweight and obesity status.

The purpose of the study is to determine whether measurement of neck circumference (NC) can correlate well with waist circumference measurement. And if so, can it be used as a screening test for identifying patients with abdominal obesity? The study also aims to establish its' association with metabolic syndrome and its' component risk factors and to define the cut off levels of neck circumference that would identify patients with abdominal obesity.

Patient and Methods

Patient Population

An observational, analytical, cross-sectional study was done. Sample population included high risk Filipino patients who were admitted at Makati Medical Center for any reason from the period of March 1 to October 31, 2010. Patients were selected using simple random sampling by lottery method. Using the daily list of hospital admissions, each patient was assigned a unique number. The numbers were placed in a bowl, mixed thoroughly and patients were randomly handpicked by the researcher. Inclusion and exclusion criteria were followed. High risk patients included those patients who were at high risk for obesity or with increased risks for cardiovascular disease. He or she may satisfy any one of the following inclusion criteria: adults > 18 years of age; with strong family history for premature coronary artery disease (CAD) (first degree relative with CAD by age 45 years old or younger) or presence of any one of the components of MS defined as: WC≥90cm in men or ≥ 80 cm in women; triglycerides (TG)≥150 mg/dl or on treatment; HDL < 40mg/dL in men or < 50mg/dL in women or on treatment; blood pressure (BP)≥ 130 mmHg systolic and≥ 85 mmHg diastolic and fasting plasma glucose(FPG) ≥ 100 mg/dL, which includes type 2 DM. Excluded were those patients with known major medical conditions, active inflammatory and neoplastic disease; established CVD (previous myocardial infarction (MI), stroke or CAD) or with known thyroid dysfunction, thyroid mass or nodules or any neck mass. A written informed consent was obtained from all qualified study subjects.

Methods

A total of 425 patients, 224 patients with abdominal obesity and 201 patients without abdominal obesity were qualified to participate in the study. Abdominal obesity was defined as waist circumference (WC)≥90 cm in men or ≥ 80 cm in women.

Anthropometric evaluation was performed only once by the investigator during the patient's hospital stay before the first meal of the day. To minimize inter-observer variability, all measurements were done by the investigator. Body height and body weight were recorded to the nearest 0.5 cm and 0.1 kg, respectively using properly calibrated Detecto® scales. Measurement of the weight was done on an empty bladder, with the patient standing barefoot at the center of the platform, unassisted wearing minimal clothing. Minimal clothing is defined as a single layer of thin clothing, excluding jeans or heavy apparels. Height was measured with shoulders relaxed, shoulder blade, buttocks and heels touching the board, feet flat and heels almost together and on barefoot. Waist and neck circumference measurements were done using a standard non-stretchable plastic tape measure, which was used for the entire duration of the study. WC was measured to within 1 mm at the waist midway between the lowest rib and the iliac crest, with the patient standing at the end of gentle expiration. NC was measured at the level of the cricoid cartilage in women, mid-neck height, between the mid-cervical spine to mid-anterior neck, to within 1 mm. In men with a laryngeal prominence (Adam's apple), NC was measured just below the

prominence.[22-24] All circumferences were taken with the subjects standing upright, shoulders relaxed and facing the author. BMI was derived from body weight in kilograms divided by the square of body height in meters. Data collected include demographic information and a brief medical history.

Blood pressure was measured twice using ALPK2® non-mercurial sphygmomanometer with the arm supported at heart level after sitting quietly for 10 minutes. The systolic BP was defined as the appearance of the first sound (Korotkoff phase 1) and diastolic BP was defined as the disappearance of the sound (Korotkoff phase 5) during deflation of the cuff. There was at least a 30 second interval between the two separate measurements and thereafter the mean of the two measurements was considered as the participant's BP.

Blood samples were drawn from the antecubital vein, after at least 8 hours of overnight fasting. Blood samples were sent to the laboratory of clinical biochemistry at Makati Medical Center for analyses of blood glucose, serum triglycerides and HDL-cholesterol on a Cobas® automated clinical chemistry analyzer by means of standard biochemical procedures.

Definition of Terms

According to the modified criteria by the American Heart Association/National Heart, Lung and Blood Institute (NCEP/ATP III-AHA/NHLBI), MS is defined as the presence of any 3 of the following 5 features: WC ≥ 90cm in men or ≥ 80 cm in women; TG ≥ 150mg/dl or on treatment; HDL < 40mg/dL in men or < 50mg/dL in women or on treatment; BP ≥ 130 mmHg systolic and ≥ 85 mmHg diastolic and FPG ≥ 100 mg/dL, which includes those diagnosed with type 2 DM or on treatment.[4]

Abdominal obesity is defined as WC of more than or equal to 90cm in men or more than or equal to 80 cm in women.

Under the Asia Pacific Guidelines for the classification of obesity [26], a BMI of less than or equal to 18 is classified as underweight; 18-22.9 is normal, 23-24.9 is overweight, 25-29.9 is obese class 1, and a BMI of more than or equal to 30 is under obese class 2.

Statistical Analysis

Continous data were expressed as means and standard deviations, and differences in means were tested using two-sided *t* tests. The differences of categorical data in different groups were compared using Pearson's Chi-square tests. Likelihood estimates (OR) and 95% confidence intervals (CI) were obtained by use of logistic regression analyses in models that adjusted for sex, age and other confounders. Receiver operating characteristic (ROC) curve analysis combined with canonical discriminant functions analysis was employed to determine optimal sex-specific cut-off levels of NC in relation to abdominal obesity. The optimal cut-off points were determined by the point of convergence of sensitivity and specificity, by simultaneously maximizing the two. The Youden's Index (*J*), the maximum potential effectiveness of a biomarker, is a summary measure of the ROC curve used in the study to determine the optimal sex-specific cut-off levels of neck circumference that would correlate with abdominal obesity.

The area under the ROC curve (AURC) was used as a general measure of discrimination of a predictor. A value of $p < 0.05$ on the two-tail test was considered statistically significant.

Results

Characteristics of the Study Population

A total of 425 patients, 227 males and 198 females, participated in the study. Of the 425 patients, 224 patients were obese by abdominal circumference, while 201 patients were not obese by abdominal circumference. Table 1 depicts the demographic profile and clinical characteristics of the study population. The mean age of the study population was 49.35 ± 11.26 years with predominance of males over females. The study population belonging to the obese group were heavier, had a larger WC and a higher BMI. Most of the patients in the obese group fall under the obese class 1 classification (53.6%, 120 out of 224 patients) as compared to the non-obese group, who are mostly classified under normal (39.3%, 79 out of 201 patients).

The difference of the mean levels of fasting TG, although higher and slightly more frequent in the obese arm, was not statistically significant. Reduced HDL-cholesterol was observed to be more frequent in the obese group than in the non-obese group (34.8% vs. 23.4%, p value < 0.05). There were also more patients with elevated fasting plasma glucose or previously diagnosed with type 2 DM in the obese group (42% vs. 23.4%, p value < 0.001). The mean BP of patients in the obese group was also higher at 126.29 ± 12.71/82.28 ± 7.26 mm Hg, p value < 0.001. Consequently, more patients satisfied the criteria of metabolic syndrome in the obese group as compared to the non-obese group, 57.1% and 12.4% respectively. (Table 1 and 2)

Cut off levels of NC for determining abdominal obesity using ROC analysis

In the study population, NC ≥ 40cm for males and ≥ 33.8cm for females were the best cut-off levels for determining patients with abdominal obesity (WC ≥ 90cm in males/80cm in females) using ROC analysis with 62.07% sensitivity, 90.09% specificity and 75.77% accuracy for males and 67.59% sensitivity, 85.56% specificity and 75.76% accuracy for females. The optimal cut-off points

Table1. Clinical characteristics of the study population

		Abdominal Obesity (waist circumference ≥ 90cm in males/80 cm in females)	
	Total, n= 425 Mean +/- SD	**Obese group, n= 224** Mean +/- SD	**Non-obese group, n=201** Mean +/- SD
Age in years	49.35 ± 11.26	50.65 ± 11.28	47.91 ± 11.09
Gender			
Males	227 (53.4%)	116 (51.8%)	111 (55.2%)
Females	198 (46.6%)	108 (48.2%)	90 (44.8%)
Height in cm	162.11 ± 9.07	162.33 ± 9.13	161.86±14.21
Weight in kg	68.14 ± 13.24	73.82 ± 12.98	61.81±10.37
Body Mass Index (BMI)			
Underweight ≤18	5 (1.2%)	0	5 (2.5%)
Normal 18-22.9	92 (21.6%)	13 (5.8%)	79 (39.3%)
Overweight 23-24.9	97 (22.8%)	34 (15.2%)	63 (31.3%)
Obese class 1 25-29.9	173 (40.7%)	120 (53.6%)	53 (26.4%)
Obese class 2 ≥ 30	58 (13.6%)	57 (25.4%)	1 (0.5%)
Average BMI	25.80 ± 3.87	27.89 ± 3.68	23.47 ± 2.52
Waist Circumference in cm	88.14 ± 10.63	95.06 ± 8.73	80.43 ± 6.43
Neck Circumference in cm	36.39 ± 3.81	37.69 ± 3.81	34.95 ± 3.27
Hypertriglyceridemia*	137 (32.2%)	78 (34.8%)	59 (29.4%)
Low HDL cholesterol*	125 (29.4%)	78 (34.8%)	47 (23.4%)
Elevated Fasting Glucose*	141 (33.2%)	94 (42.0%)	47 (23.4%)
Hypertension*	231 (54.4%)	145 (64.7%)	86 (42.8%)
Metabolic Syndrome*	153 (36.0%)	128 (57.1%)	25 (12.4%)
Smoker	122 (28.7%)	73 (32.6%)	49 (24.4%)
Alcoholic Drinker	167 (39.3%)	95 (42.4%)	72 (35.8%)

**Hypertriglyceridemia is defined as triglyceride levels≥ 150mg/dl or on treatment; low high density lipoprotein (HDL) cholesterol level is defined as < 40mg/dL in men or < 50mg/dL in women or on treatment; Elevated fasting glucose defined as fasting plasma glucose of 100 mg/dL, which includes those diagnosed with type 2 DM or on treatment and hypertension is defined as BP ≥ 130 mmHg systolic and ≥ 85 mmHg diastolic*
** Metabolic syndrome is defined as any 3 out of the 5 criteria, using the definition above for hypertriglyceridemia, hypertension, low HDL cholesterol, elevated fasting plasma glucose, including waist circumference levels above or equal to 80cm for women and 90cm for men.*

Table 2. Mean values of the metabolic risk factors of the study population

	Total, n= 425 Mean +/- SD	**Obese group, n= 224** Mean +/- SD	**Non-obese group, n=201** Mean +/- SD	***p* value**
Fasting Triglycerides in mg/dL	137.53 ± 80.08	144.12 ± 73.26	130.19 ± 86.63	0.073
High density lipoprotein (HDL) cholesterol in mg/dL	52.46 ± 15.35	50.85 ± 15.66	54.26 ± 14.83	**< 0.05**
Fasting plasma glucose in mg/dL	102.23 ± 32.53	106.58 ± 37.63	97.38 ± 24.88	**<0.05**
Systolic Blood Pressure in mmHg	123.81 ± 13.78	126.29 ± 12.71	121.04 ± 14.40	**<0.001**
Diastolic Blood Pressure in mmHg	80.99 ± 8.01	82.28 ± 7.26	79.55 ± 8.56	**<0.001**

were determined by the point of convergence of sensitivity and specificity, by simultaneously maximizing the two. The Youden's Index (*J*), the maximum potential effectiveness of a biomarker, is a summary measure of the ROC curve that was used to determine the optimal NC cut off points. (Table 3) The receiver operating characteristic curve analysis was used for each neck circumference value by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) to determine the optimal cut off levels, area under the curve is 0.831 (p value < 0.001 in both males and females). (Figure 1)

Logistic regression analysis showed that neck circumference if positive, has a good probability of determining abdominal obesity in both genders, for every 1 standard deviation increment in NC, the unit odds ratio in males corresponded to 1.87, and 1.94 in females (p value < 0.001). (Figure 2) Neck circumference is a contributing factor to more than half of the variability of waist circumference and has a moderately strong positive linear relationship with waist circumference, $r = 0.74$, p value < 0.001. (Figure 3)

Association of obese by NC and the individual components of MS

Patients who are obese by NC, using cut off levels of more than or equal to 40cm for males and 33.8cm for females respectively, showed a significant correlation with low HDL-cholesterol level, high BP and elevated FPG or the presence of DM. Hypertriglyceridemia did not show significant relationship with NC. The odds of hypertension among patients who are obese, using NC (≥40cm/ 33.8cm) as our parameter, is 1.8 times higher than those who are non-obese; as with low HDL-cholesterol which was found to be 2.05 times higher than non-obese. Likewise, type 2 DM or elevated FPG of more than or equal to 100mg/dL was associated significantly with a 2.28-fold increased likelihood among obese patients. In terms of BMI, patients who are obese using the Asia Pacific Guidelines (BMI of more than or equal to 25) showed a significant correlation with obese by NC, p value of <0.001. On the other hand, excluding the criteria of abdominal obesity, obese by NC showed a significant relationship with 2 out of the 4 components of MS, as well as 3 out of the 4 components of MS, namely: elevated fasting TG, hypertension, low HDL levels, and elevated FPG or the presence of type 2 DM, with p value of <0.001 and 0.001, respectively. (Table 4)

In our study, about 57.1% or 128 out of 224 patients classified with abdominal obesity (WC≥ 90cm in men or≥ 80cm in women) satisfied the criteria of MS. (Table 1) Among males, NC of≥ 40cm emerged as the optimal cut - off level for abdominal obesity, showing a predictive

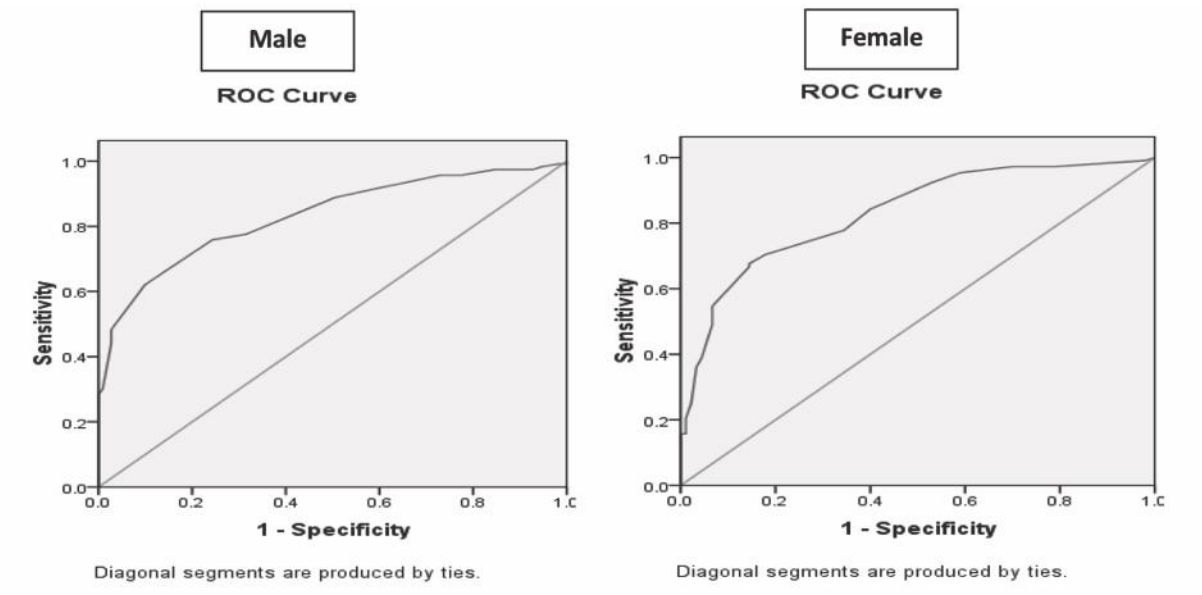

Figure 1. Receiver Operating Characteristics curves (ROC) related to abdominal obesity (waist circumference ≥ 90cm/ 80 cm) and neck circumference in males and females

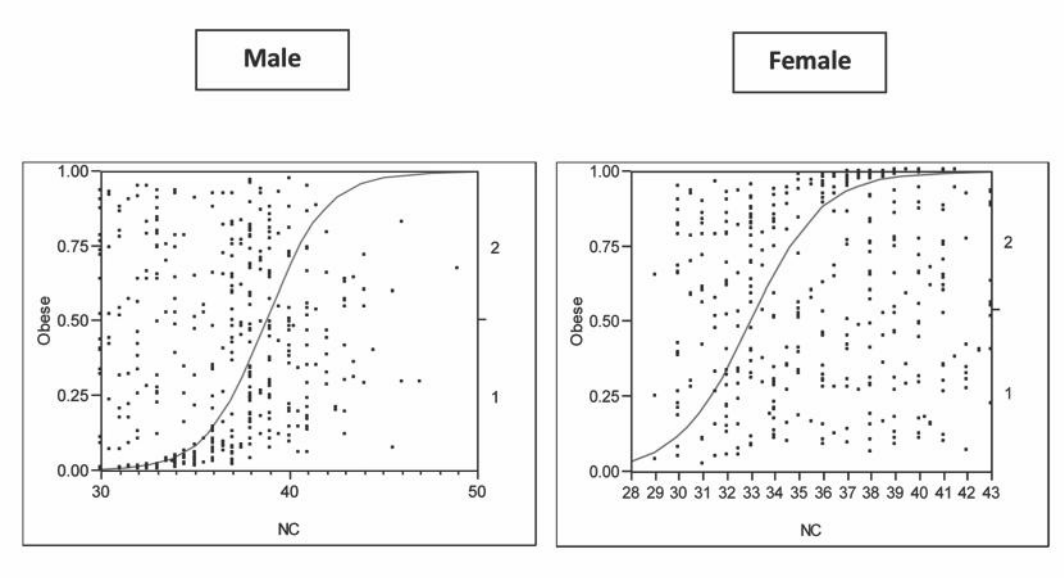

Figure 2. Logistic regression analysis of abdominal obesity by Neck Circumference (NC)

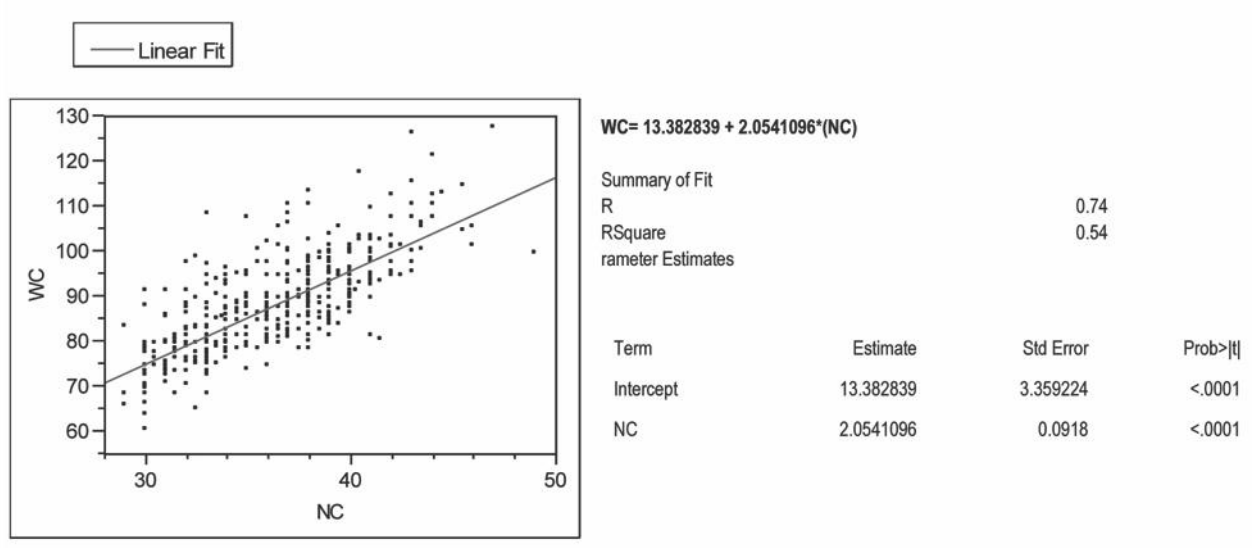

Figure 3. Linear regression analysis of Waist Circumference (WC) by Neck Circumference (NC)

accuracy of 69.16% for MS. The chosen cut off level for females of ≥ 33.8 cm also yielded predictive accuracy of 69.7% and 75.75% for both MS and abdominal obesity, respectively. (Table 5) In comparison, waist circumference or abdominal obesity as a predictor of MS has a relatively better sensitivity of 82.6%, and specificity of 64.7%, respectively.

Discussion

There are various indices that predict specifically intra-abdominal fat, cardiovascular risk factors and disease. These include waist:hip circumference ratio (WHR)[5, 8], waist circumference (WC)[5-6,8-9,11,17-21, 1-34], abdominal sagittal diameter(SAD)[28-29], the ratio of waist:thigh circumference[25]. Recently it was shown that WC and SAD show closer association with visceral abdominal adipose tissue accumulation than WHR does.[28-29] Moreover, the WC and the SAD appeared to be more closely associated with the metabolic variables than the WHR.[28] They also found out that free fatty acid release from upper body subcutaneous fat was larger than that from lower-body subcutaneous fat, a fact that further strengthens the relevance of measuring upper-body subcutaneous adipose tissue depots.[25] WC is therefore widely used as an indirect measure of visceral adipose tissue (VAT); while it is a well-validated anthropometric technique,[5-14,17-21,28-34] there is high measurement variability which rises with increasing BMI.[32] On the other hand, BMI predictably correlated with abdominal subcutaneous adipose tissue ASAT (p = 0.002) but not VAT nor any index of insulin resistance in a study by Yang and colleagues.[32]

Table 3. Neck Circumference (NC) cut off levels for determining subjects with abdominal obesity [Waist Circumference (WC) of ≥ 90cm (males), ≥80cm (females)] using Receiver Operating Characteristic (ROC) Curve analysis

Males					Females				
Cutoff Level (cm)	Sens	Spec	Accuracy	Youden index	Cutoff Level (cm)	Sens	Spec	Accuracy	Youden index
.	0.00%	100.00%	48.90%	0.0000	.	0.00%	100.00%	45.45%	0.0000
49	0.86%	100.00%	49.34%	0.0086	42	0.93%	100.00%	45.96%	0.0093
47	1.72%	100.00%	49.78%	0.0172	41	1.85%	100.00%	46.46%	0.0185
46	3.45%	100.00%	50.66%	0.0345	39.5	2.78%	100.00%	46.97%	0.0278
45.5	5.17%	100.00%	51.54%	0.0517	39	6.48%	100.00%	48.99%	0.0648
44.5	6.03%	100.00%	51.98%	0.0603	38.5	8.33%	100.00%	50.00%	0.0833
44	9.48%	100.00%	53.74%	0.0948	38	15.74%	100.00%	54.04%	0.1574
43.5	12.07%	100.00%	55.07%	0.1207	37.5	15.74%	98.89%	53.54%	0.1463
43	20.69%	100.00%	59.47%	0.2069	37	20.37%	98.89%	56.06%	0.1926
42.5	22.41%	100.00%	60.35%	0.2241	36.5	25.00%	97.78%	58.08%	0.2278
42	28.45%	100.00%	63.44%	0.2845	36	36.11%	96.67%	63.64%	0.3278
41.5	30.17%	99.10%	63.88%	0.2927	35.5	38.89%	95.56%	64.65%	0.3444
41	43.97%	97.30%	70.04%	0.4126	35	49.07%	93.33%	69.19%	0.4241
40.5	47.41%	97.30%	71.81%	0.4471	34.5	54.63%	93.33%	72.22%	0.4796
40.25	48.28%	97.30%	72.25%	0.4557	34	66.67%	85.56%	75.25%	0.5222
40	**62.07%**	**90.09%**	**75.77%**	**0.5216**	**33.8**	**67.59%**	**85.56%**	**75.76%**	**0.5315**
39.5	63.79%	88.29%	75.77%	0.5208	33.5	70.37%	82.22%	75.76%	0.5259
39	75.86%	75.68%	75.77%	0.5154	33	77.78%	65.56%	72.22%	0.4333
38.5	77.59%	68.47%	73.13%	0.4605	32.5	84.26%	60.00%	73.23%	0.4426
38	88.79%	49.55%	69.60%	0.3834	32	92.59%	46.67%	71.72%	0.3926
37.5	90.52%	44.14%	67.84%	0.3466	31.5	95.37%	41.11%	70.71%	0.3648
37	95.69%	27.03%	62.11%	0.2272	31	97.22%	30.00%	66.67%	0.2722
36.5	95.69%	22.52%	59.91%	0.1821	30.5	97.22%	21.11%	62.63%	0.1833
36	97.41%	15.32%	57.27%	0.1273	30	99.07%	2.22%	55.05%	0.0130
35.5	97.41%	14.41%	56.83%	0.1183	29	100.00%	0.00%	54.55%	0.0000
35	97.41%	10.81%	55.07%	0.0822	29	100.00%	0.00%	54.55%	0.0000
34.5	97.41%	7.21%	53.30%	0.0462					0.0000
34	98.28%	5.41%	52.86%	0.0368					0.0093
33	99.14%	1.80%	51.54%	0.0094					0.0185
32.5	99.14%	0.90%	51.10%	0.0004					0.0278
31.5	99.14%	0.00%	50.66%	-0.0086					0.0648
31	100.00%	0.00%	51.10%	0.0000					0.0833
31	100.00%	0.00%	51.10%	0.0000					0.1574

**cut off levels of neck circumference in male and females highlighted in red*

Table 4. Associations of obese by neck circumference with the individual components of Metabolic Syndrome (MS) and Body Mass Index (BMI)

	Obese by neck circumference (males≥40cm/ females ≥33.8cm)		
	Pearson's Chi- square (p value)	95% CI	Odds Ratio Estimate
Fasting Triglyceride ≥ 150mg/Dl	0.165	0.89-2.02	1.34
HDL cholesterol < 40/50mg/dL	**0.001**	**1.35-3.14**	**2.05**
Hypertension ≥ 130/85mmHg	**0.003**	**1.21-2.68**	**1.80**
Presence of type 2 Diabetes or FPG ≥ 100mg/dL	**<0.001**	**1.51-3.45**	**2.28**
****2 out of 4 components of MS**	**<0.001**	**1.76-3.90**	**2.62**
****3 out of 4 components of MS**	**0.001**	**1.43-3.90**	**2.36**
***MS (3 out of 5 components)**	**<0.001**	**3.093-7.227**	**4.728**
Obese by BMI (BMI ≥25)	**<0.001**	**6.40-16.80**	**10.38**

Abbreviations: HDL, high-density lipoprotein, FPG, fasting plasma glucose. Significant values indicated in bold.
**Metabolic syndrome as defined by NCEP/ATP III-AHA/NHLBI, involving 3 out of 5 criteria listed below as follows: elevated triglyceride levels, low HDL cholesterol, hypertension, and presence of type 2 Diabetes or elevated fasting plasma glucose, including waist circumference ≥90cm in males and ≥80cm in females.*
***Metabolic syndrome as defined by NCEP/ATP III-AHA/NHLBI not including waist circumference as a parameter*

Table 5. Sensitivity, specificity and predictive accuracy of optimal cut-offs of neck circumference for abdominal obesity and metabolic syndrome

Neck Circumference cut off for males ≥ 40cm			Neck circumference cut off for females ≥ 33.8 cm		
Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
For Abdominal Obesity ≥ 90cm / 80cm					
62.07%	90.09%	75.77%	67.59%	85.56%	75.75%
For Metabolic Syndrome					
57.1%	77.2%	69.16%	75.80%	66.90%	69.70%

NC used in combination with other measurements in a three compartment model of interpretable anthropometry separates the effects of visceral adipose tissue mass, subcutaneous tissue mass and subcutaneous adipose tissue distribution on metabolic parameters under cross-sectional and longitudinal conditions.[24] These observations indicate that NC as an index of upper body fat distribution can be used to identify overweight and obese patients.[25, 30] Moreover, NC was a better direct predictor of visceral adipose tissue area than WC which is in keeping with the previous observation that as BMI increases waist circumference becomes a weaker marker of visceral adipose tissue in markedly obese patients.[32-33]

As main findings in this cross sectional study among high risk Filipino patients admitted in Makati Medical Center, we found that NC cut off levels of ≥ 40cm for males and ≥ 33.8 cm for females was well correlated with abdominal obesity (WC ≥ 90cm/80cm). NC is a contributing factor to more than half of the variability of waist circumference and has a moderately strong positive linear relationship with waist circumference providing basis for the relationship of neck circumference as a measure for central obesity. NC cut off levels has a high specificity and therefore a high positive predictive value for determining patients with abdominal obesity in both genders, however, with its low sensitivity indices; it has a poor ability to detect patients with abdominal obesity in the general population and therefore will not be a reliable screening measure.

In a similar study by Liubov (Louba) and Laor in a family medicine clinic in Israel in 2001, NC cut off levels of ≥ 37cm for males and≥ 34cm for females correlated with a higher body mass index BMI. Patients above these levels required a more comprehensive evaluation of their overweight and obesity status.[23]

The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults highlights the importance of treating patients with MS to prevent cardiovascular diseases.[34] A major contribution of our present report lies in the indication of the association between NC and the factors of the MS. Using NC cut off levels of ≥ 40cm for males and ≥ 33.8cm for females, a strong association exists between obese by NC and the individual risk factors of Metabolic Syndrome (MS). Despite NC cut off levels being poor predictors of metabolic syndrome, the significant association between NC and the individual components of MS shows the increased probability or likelihood that patients who are obese by neck circumference will also have high blood pressure, diabetes, low HDL levels and increased abdominal girth.

Our study has shown that the odds of developing hypertension and diabetes among high risk patients are almost doubled with the finding of an enlarged neck. Also the risk of having low-HDL cholesterol is doubled as compared with non-obese (by NC) patients. With these results, the likelihood of satisfying the criteria for MS (3 out of 5) based from the NCEP/ATP III-AHA/NHLBI[4] is more than quadrupled (*OR* 4.728, p value <0.001). In a similar subset of the mentioned group by Liubov (Louba) and Laor, higher NC was found to correlate positively with the factors of the MS.[24]

The result of our study is also supported by the study of Yang and colleagues in 2009 which determined that NC correlated highly with VAT area (r 2 = 0.67, p < 0.0001) but not with ASAT area indicating that it is both a powerful and selective marker of visceral adiposity. Also it provides further evidence that the cellular programme for laying down cervical adipose tissue is related to intra-abdominal fat accumulation.[32] Furthermore, our data are in keeping with new data from the Framingham Heart Study presented at the recent American Heart Association's Cardiovascular Disease Epidemiology and Prevention annual conference which showed that increasing NC was correlated with increasing FPG and other parameters of the MS.[36]

Limitations and Recommendations

There are several potential limitations of our study. First, since our study is cross-sectional, we cannot draw conclusions about cause and effect relationships. Second, our research, being a pilot study, has a limited study population. Our study population was limited only to adult high risk urban Filipinos; thus, our results may not be representative of the general population but should apply to this specific sub-set of the Filipino population. Evaluation of neck circumference based on a single measurement might be considered a minor limitation.

From this study, we were able to determine the cut-off values for the neck circumference that correlates with abdominal obesity in adult urban Filipinos at risk for metabolic syndrome and cardiovascular disease. We then recommend that further research, involving large population based studies, be done to validate these findings. Consequently, we hope that the data obtained in this initial investigation be utilized by study groups focusing on obesity and/or metabolic syndrome; and be used in future research re-evaluating recommendations for

Filipinos at risk for Metabolic Syndrome and abdominal obesity.

Conclusion

Neck circumference cut off levels of≥ 40cm for males and ≥ 33.8cm for females showed a strong correlation with abdominal obesity, as well as with the component risk factors of metabolic syndrome, and therefore is correlated with risk of cardiovascular disease. Above the NC cut off levels, its predictive value for abdominal obesity is high; however, it has a poor ability to detect patients with abdominal obesity in the general population. In view of these findings, the authors cannot recommend the use of neck circumference measurement as a screening test for abdominal obesity in the general population.

Acknowledgment
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ORIGINAL ARTICLE

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Prevalence of Obesity, Metabolic Syndrome, Impaired Fasting Glycemia, and Diabetes in Selected Villages of Bali, Indonesia

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Abstract

Aims/Introduction. To know the prevalence of obesity, metabolic syndrome, impaired fasting glycemia and diabetes in the population of Bali.

Materials and Methods. A cross-sectional study enrolling 1840 subjects, aged 13-100 years with male-to-female ratio of 972/868, were studied at seven villages across the island of Bali.

Results: The prevalence of central obesity was 35% (male, 27.5%; female, 43.4%); metabolic syndrome (MS), 18.2% (male, 16.6%; female, 20.0%); impaired fasting glycemia (IFG), 13.1% (male, 14.3%; female, 12.4%); and diabetes mellitus (DM), 5.9% (male, 6.1%; female, 5.7%). The subjects who had 1, 2, 3, 4, and 5 components of MS were 34.6%, 23.8%, 13.0%, 4.3%, and 0.9% respectively. The population in two tourist areas (Legian and Ubud) had the highest prevalence of central obesity (61.2% and 70.1%), but they did not necessarily have a higher prevalence of DM. The two tourist areas (Legian, 24.1%; and Ubud, 21%) as well as Sangsit village (23.3%) have the highest prevalence of MS.

Conclusions. The prevalence of obesity, MS, IFG and DM were comparatively low. Analysis across the villages revealed that higher prevalence of central obesity was not necessarily associated with higher prevalence of DM. There is a need to further study the risk of obesity on MS and DM in tourist areas of Bali.

Key words: obesity, metabolic syndrome, impaired fasting glycemia, diabetes, population of Bali

Introduction

The prevalence of obesity, metabolic syndrome (MS), and diabetes mellitus (DM) are increasing globally. Metabolic syndrome is a cluster of risk factors that predisposes an individual to atherosclerosis which may eventually lead to increased risk of cardiovascular morbidity and mortality. There is now general agreement regarding the criteria (characteristic features) often used for the diagnosis of the syndrome, i.e. glucose intolerance, obesity (Body Mass Index [BMI]), raised blood pressure and dyslipidemia with elevated triglycerides, low levels of high density lipoprotein [HDL] cholesterol; but different definitions use different cut-off points for the parameters used for diagnosis and also different concepts of mandatory inclusion criteria.[1] Although insulin resistance is considered a major pathological influence, only the World Health Organization (WHO) and European Group for the study of Insulin Resistance (EGIR) definitions include it in the diagnostic criteria and only the International Diabetes Federation (IDF) definition uses waist circumference as a mandatory criterion.[1-3] Insulin resistance is closely related to central obesity, i.e. excessive abdominal fat deposition.[2,3] The published prevalence of MS varies because of several factors, e.g. different diagnostic criteria and parameters used, differences in ethnicity, age, and sex. However, the prevalence of MS has the tendency to increase along with the increase in the prevalence of obesity, especially central obesity.[4] The prevalence of impaired glucose tolerance (IGT) and DM are also increasing globally. Around 60% of the obese population also have DM.[5]

The primary objective of the study was to know the prevalence of obesity, MS, glucose intolerance (prediabetes and DM) in the population of Bali. To our knowledge there is a paucity of published baseline data on obesity, MS, and glucose intolerance, i.e., prediabetes and DM, especially for the people of the rural areas of Bali, and will be needed for health intervention and research as the influx of global tourism into the Island would be expected to have a wide ranging impact on the lifestyle and social-economic status of the population.

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Materials and Methods

A cross-sectional survey study was carried out on obesity, MS and its components, and glucose intolerance, i.e., prediabetes and DM in the population of seven villages (6 villages and 1 suburban area) across the island of Bali, Indonesia. The villages were Sangsit (seashore area, 471 subjects), Pedawa (mountainous area, native Balinese, 294 subjects), Ubud (lowland and tourist area, 301 subjects), Tenganan (upland area, native Balinese, 81 subjects), Ceningan (offshore island, 305 subjects), Legian (coastal and tourist area, 288 subjects), and Pengelipuran (upland area, 100 subjects). Purposive sampling was done to represent seashore vs. highland area, native vs. non-native Balinese, and tourist vs. non-tourist area; and to explore differences in prevalence in these settings. Figure 1 is a map of Bali showing the location of the seven villages used in the study. A total number of 1840 subjects were recruited by random sampling (stratified for larger villages by sub-village: Sangsit, Pedawa, Ubud, Legian). The number of samples in each village was primarily based on target sample. The variables measured included age, waist circumference, body mass index, blood pressure, lipid plasma, fasting blood glucose. Fasting blood samples were drawn after at least 10 hours of overnight fasting. Criteria for obesity was based on the 2000 WHO recommendations for the Asia Pacific population.[6] Classification of impaired fasting glycemia (IFG) and DM was based on the American Diabetes Association (2009): i, IFG if fasting blood glucose levels was ≥100 mg/dL and <126 mg/dL; and diabetes if fasting blood glucose level was ≥126 mg/dL.[7] Diagnosis of MS was confirmed based on the criteria of a Joint Statement of IDF, NIH, AHA, WHF, IAS, and IASO (2009). Metabolic syndrome was diagnosed if 3 or more of the following 5 criteria are present: elevated waist circumference (male >90 cm, female >80 cm); elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator; ≥150 mg/dL); reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator; ≤40 mg/dL in males, and ≤50 mg/dL in females); elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator; systolic ≥130 and/or diastolic ≥85 mm Hg); elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator; ≥100 mg/dL).[8]

Statistical methods used for data analysis include descriptive presentation, independent t-test and chi square, with significance value at $p<0.05$.

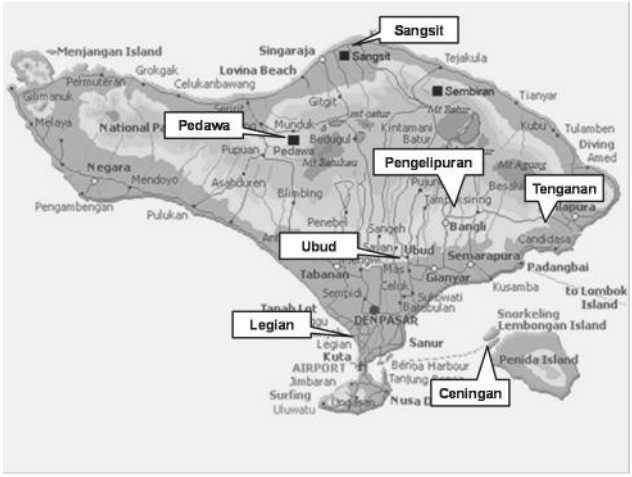

Figure 1. Map of Bali showing the locations of the seven villages used in the study

Results

We found that male subjects had higher stature and body weight, waist circumference, and levels of triglyceride, and lower levels of HDL cholesterol compared to female subjects. In general, the mean values of all the measured variables were within normal ranges (Table 1).

Table 1. Characteristics of the study subjects

	Male (N = 972)	Female (N = 868)	Total (N = 1840)	P (Male *vs.* Female)
Age (years)	44.4±14.4	43.8±14.3	44.1±14.4	0.387
Height (cm)	163.5±7.5	153.0±6.3	158.6±8.7	<0.001
Weight (kg)	61.5±12.9	53.1±11.0	57.6±12.7	<0.001
Body mass index (kg/m2)	22.9±4.2	22.6±4.4	22.8±4.3	0.142
Waist circumference (cm)	82.0±11.7	77.9±12.2	80.1±12.1	<0.001
Systolic blood pressure (mmHg)	120.2±18.2	120.0±19.4	120.1±19.0	0.806
Diastolic blood pressure (mmHg)	77.1±10.7	76.3±10.7	76.8±10.7	0.127
Fasting blood glucose (mg/dl)	94.9±26.0	94.1±34.4	94.6±30.3	0.582
Total-cholesterol (mg/dl)	186.6±38.8	190.0±38.4	188.2±38.6	0.065
LDL-cholesterol (mg/dl)	122.2±31.4	120.9±31.6	121.7±31.5	0.511
HDL-cholesterol (mg/dl)	46.7±11.5	54.2±14.7	50.3±13.6	<0.001
Triglyceride (mg/dl)	133.6±79.2	106.4±63.6	120.7±73.5	<0.001

Table 2. Nutrition states and prevalence of obesity, by sex

	Male (%)	Female (%)	Total (%)	P (Male vs. Female)
Nutrition state				
Underweight (BMI<18.5 kg/m^2)	11.2	14.9	12.9	0.219
Normoweight (BMI, 18.5-22.9 kg/m^2)	45.2	43.1	44.2	
Overweight at (BMI, 23-24.9 kg/m^2)	16.8	16.3	16.6	
Obesity I (BMI≥25-29.9 kg/m^2)	21.1	19.9	20.5	
Obesity II (BMI≥25-29.9 kg/m^2)	5.7	5.8	5.7	
Central obesity (waist circumference, ≥90 cm in male; ≥80 cm in female)	27.5	43.4	35.0	<0.001

Although no differences were found in the prevalence of nutritional state between male and female subjects, central obesity was seen more frequently in female subjects (43.4% *vs*. 27.5%, p <0.001) (Table 2). Analysis across the villages showed that Legian and Ubud, apparently the more prosperous villages as they are popular tourist destinations in Bali, have highest prevalence of central obesity (61.2% and 70.1%, respectively), but comparable prevalence of DM with other villages. Meanwhile, Pedawa village, a mountainous area, and Ceningan village, an offshore remote area, have the lowest prevalence of central obesity (12.8% and 17.7%, respectively).

The prevalence of MS was 18.2%, and analysis by sex and villages showed that 5 out of 7 villages had higher prevalence of MS in the female subjects as compared with that in the male (Figure 2). Figure 3 shows that subjects having 1, 2, and 3 diagnostic criteria of MS were more frequently seen than those having 4 or 5 features, this applies for both the male and female subjects.

Table 3. Prevalence of impaired fasting glycemia and diabetes mellitus, by sex

Classification	Male (%)	Female (%)	Total (%)	P Male vs. Female
Normoglycemia	79.6	80.6	80.7	0.496
Impaired fasting glycemia	14.3	12.4	13.4	
Diabetes mellitus	6.1	5.7	5.9	

Discussion

In our study, although there were no differences in the nutritional state between male and female subjects, central obesity was found more frequently in the female subjects. The total prevalence of central obesity was 35.0%. Analysis across the villages showed that Legian and Ubud, which are the most prosperous villages being popular tourist destinations in Bali, have the highest prevalence of central obesity; and Pedawa village, a mountainous area, and Ceningan village an offshore remote area, have the lowest prevalence of central obesity. The prevalence of overweight and obesity based on the body mass index was 16.6% and 26.2%, respectively.

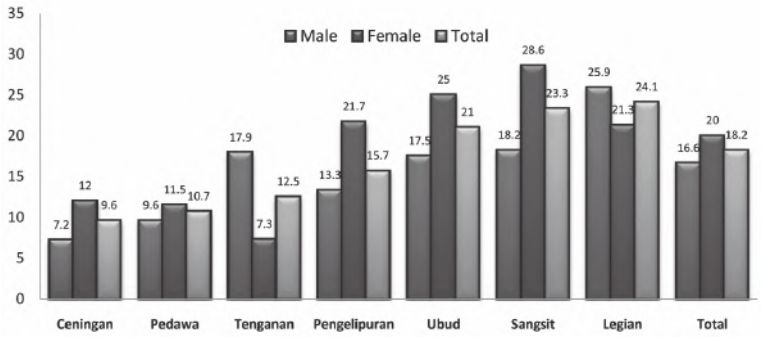

Figure 2. The prevalence of metabolic syndrome by sex and village

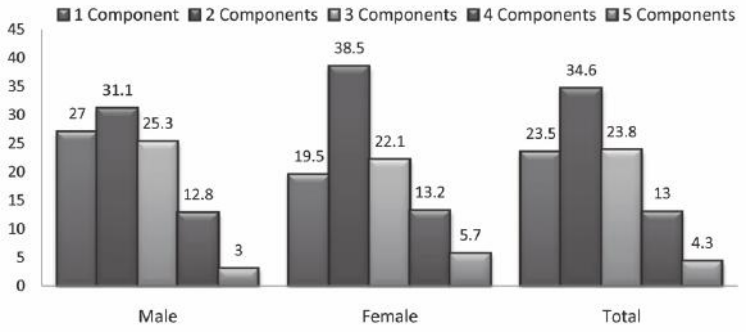

Figure 3. Prevalence of the components of metabolic syndrome by sex

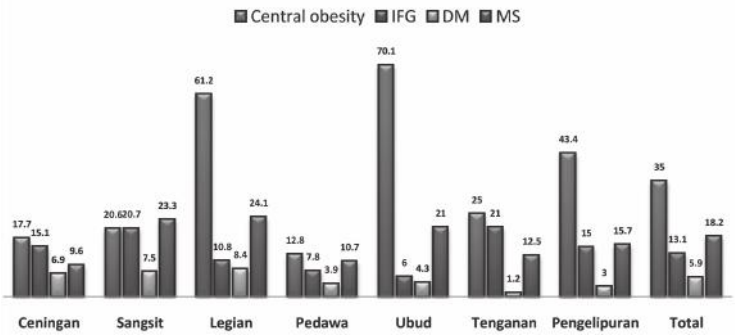

Figure 4. The prevalence of central obesity, impaired fasting glycemia (IFG), diabetes mellitus (DM), and metabolic syndrome (MS,) by village

The prevalence of overweight and obesity in the adult Kuwaiti population were 80.4% and 47.5%. Overweight and obesity rates were higher in women 81.9% and 53% as compared with men 78% and 39.2%, respectively.[9] Age- and gender-adjusted overweight prevalence varied by region of birth and ranged from 24.4% among central Asian migrants to 64.4% among Mexican migrants.[10] Overall, the prevalence of overweight and obesity among Balinese population were lower than other countries.

The prevalence of MS in our study was 18.2%. The prevalence of MS varies according to several factors such as different diagnostic criteria used, differences in ethnicity or race, age, and sex. The Framingham Offspring Study found a prevalence of metabolic syndrome of 29.4% among 1144 males and 23.1% among 1295 females aged 26-82 years.[11] The WHO MONICA study by Marques-Vidal, et al., conducted in France, found a 23% prevalence of metabolic syndrome among males and a prevalence of 12% among females, with the highest prevalence found in the age group of 55-64 years.[12] A study conducted in Makassar, Indonesia, involving 330 males, aged 30-65 years, using the NCEP ATP III criteria found that the prevalence of MS was 33.9%. In the group of males with central obesity, the prevalence increased to 62%.[13] Comparing with other findings, the prevalence of MS among Balinese people was lower than those found in other countries. Low prevalence of MS was especially seen among native Balinese and in people living at some mountainous areas. Food intake and physical activity, beside race or ethnicity, might influence the findings

In our study, the prevalence of IFG and DM were 13.1% and 5.3%, respectively. There was no difference in the prevalence of IFG and DM between male and female subjects. The age-standardized prevalence of DM in 3000 adults (52% women) of Malay ethnicity (40-80 years) in Singapore was 18.4%.[14] The age-adjusted prevalence of IFG and DM diabetes in the Korean population were 23.9% and 7.6%, respectively.[15] A study on US immigrants showed that age- and gender adjusted DM prevalence ranged from 3.1% among European migrants to 10.0% among migrants from the Indian subcontinent. Migrants from the Indian subcontinent had the highest DM prevalence, significantly higher than migrants from any other region, except Mexico and Africa.[10] In this study, the prevalence of IFG and DM was lower than other findings. Similar to MS, the low prevalence of IFG and DM were especially seen among native Balinese and dwellers in some mountainous areas.. Analysis by village showed the prevalence of DM was always lower than that of IFG. The village which has a higher prevalence of IFG actually does not always have a higher prevalence of DM.

Moreover, a summary of the results across the villages indicated that population in highland village (Pedawa) and remote island (Ceningan) have the lowest prevalence of central obesity; conversely the highest prevalence of central obesity were found in tourist areas (Legian and Ubud) population. We have no supporting data but by observation, it may be caused by the difference in income and physical activities of daily living. Similar to obesity, the highest prevalence of MS were also found in two tourist areas, as well as in Sangsit village. The high prevalence of hypertension in Sangsit village (a coastal area) compared with other villages contributed to the higher prevalence of MS in this village. The study showed that a village with a high prevalence of central obesity was not always associated with a high prevalence of MS and DM. Diabetes mellitus, like hypertension, is a common, complex, and multi-factorial disease whose exact underlying mechanism is largely unknown given our current state of research. The result of this study can be a data base for further studies and action plans for health promotion in Bali, especially in tourist areas.

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ORIGINAL ARTICLE

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Risk Factors Associated with Arterial Stiffness in Diabetic Nephropathy in an Asian Population Cohort

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Abstract

Introduction. Individuals with diabetic nephropathy (DN) are at risk for cardiovascular disease. Arterial stiffness summarizes an individual's global cardiovascular risk burden. We investigated the relationship between major modifiable metabolic risk factors (excluding blood pressure) and arterial stiffness DN.

Methods. Cross sectional study of 353 Diabetic Asians with Modified Diet to retard Renal Disease (MDRD) formula estimated glomerular filtration rate (eGFR) <90 mls/min/1.73m^2. Central Aortic Systolic Pressure (CASP), a surrogate measurement of arterial stiffness, was estimated using validated BPro A-Pulse^{TM} tonometry. Visceral fat area (VFA) was estimated by tetrapolar multi-frequency bio-impedence.

Results. Study population: 61% male, 9% current smoker, 84% receiving lipid lowering therapy and 45% taking insulin. Mean age(SD) was 61(9) year, CASP 130.0(21.4) mmHg, HBA1c 8.1(1.7)%, eGFR 50.1(26.8) mls/min/1.73m^2, urinary albumin-creatinine ratio (ACR) 662(1339) mg/g, LDL 2.67(0.92) mM, VFA 130.0(31.9) cm^2. After adjusting for age, gender, ethnicity and smoking status, eGFR (β coefficient=-0.13) and HBA1c (1.66) remained as significant independent predictors of CASP (P<0.05). However, all the tested modifiable risk factors collectively explained only ~10% of variation in CASP.

Conclusion. GFR and HBA1c are modifiable predictive factors for arterial stiffness in DN. However, our results suggested the presence of undiscovered novel risk factors.

Keywords: Diabetic nephropathy, arterial stiffness, central aortic systolic pressure.

Introduction

Asian diabetic individuals are highly susceptible to nephropathy[1]. Diabetic nephropathy (DN) is also associated with increased risk for cardiovascular diseases (CVD)[2]. The mechanism for CVD is likely to be complex and many of the risk factors may be potentially modifiable. These include excessive adiposity (in particular, visceral adiposity), glycemic burden, hypertension, dyslipidemia and deranged bone mineral metabolism[3]. These hemodynamic and metabolic factors lead to impaired endothelial function and vascular injury such as arterial stiffness[4].

Several methods have been described to estimate arterial stiffness with pulse wave velocity (PWV) being considered as "gold standard".[5] Alternatively, central aortic systolic pressure (CASP) is also considered a good surrogate index of arterial stiffness[6]. Recent reports demonstrated that noninvasively measured radial artery pressure waveform can accurately estimate CASP in human[7]. These advances provided safe and reliable method to investigate vascular biology *in vivo*.

Diabetes mellitus is associated with arterial stiffness[8]. However, to the best of our knowledge, little is known about the risk factors (especially those amenable to interventions) associated with arterial stiffness in the subpopulation of DN subjects who are at extremely high risk for CVD[9]. Therefore, we investigated the relationship between potentially modifiable metabolic risk factors and arterial stiffness in a large group of Asian diabetic individuals with a wide range of renal filtration function.

Methods

Patient population

Convenient sampling of 577 consecutive diabetic individuals attending a single hospital-based diabetes

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centre. Diabetes mellitus was diagnosed according to World Health Organization proposed criteria. Subjects with Modified Diet to retard Renal Disease (MDRD) formula estimated glomerular filtration rate (eGFR) <90 mls/min/1.73m^2 (corresponding to stage 2 or more severe) were considered as having chronic kidney disease (CKD) (N=353, 61% of the overall study population). We defined CKD in this manner for the following reasons. Firstly, MDRD formula performs well when eGFR is <90 mls/min/1.73m^2 among diabetic individuals[10]. We did not choose the recently developed CKD-EPI formula because investigators reported that it did not perform better than simpler MDRD formula in diabetic population[11]. Secondly, when eGFR is <90 mls/min/1.73m^2, prevalence of co-morbidities associated with CKD (e.g. hypertension) began to increase markedly suggesting that GFR at this level (or below) is associated with meaningful derangement in renal physiology[12]. Current smoker referred to subjects who have been smoking cigarettes daily for 3 months or more just prior to enrolment into the study.

Central Aortic Systolic Pressure (CASP)

BPro A-Pulse™ (Healthstat, Singapore) noninvasive tonometric device was used to measure CASP based on radial arterial waveform analysis. In this method, the radial waveform is calibrated to brachial blood pressure, measured using standard sphygmomanometry, thereby generating a calibrated radial artery pressure waveform (RAPWF). Using an n-point moving average (NPMA), a mathematical modeling method that acts as a low pass filter to smooth signal data to better determine underlying trends, investigators recently reported that RAPWF analysis could accurately estimate CASP in human[13].

Visceral fat area (VFA)

Inbody S20 (Derwent Healthcare, Newcastle upon Tyne, United Kingdom) tetrapolar multi-frequency bio-impedence method was used to estimate VFA. Validated against VFA derived from computed tomography (CT) at the umbilical level, this convenient method has been reported to accurately estimating VFA[14]. We decided to assess adiposity by measuring VFA in preference over body mass index (BMI) for the following reasons. Firstly, Asians are known to accumulate more body fat at any given BMI. Secondly, epidemiological data suggested visceral adiposity might confer greater burden of cardiovascular dysmetabolism than global obesity. Thirdly, patients with advance CKD may have protein malnutrition and hence sarcopenic. Therefore, their BMI may be low but paradoxically their CVD risk remains elevated. Hence, directly estimating adiposity using VFA may avoid this paradox when studying CKD patients.

Clinical and biochemical parameters

Anthropometric data were measured for all individuals. Two readings of blood pressure were taken from participants after five minutes resting using an automated blood pressure monitor (Dinamap Pro100V2; Criticon, Norderstedt, Germany) by trained observers. A third reading was performed if difference between two readings of systolic blood pressure (SBP) was >10 mmHg or diastolic blood pressure (DBP) was >5 mmHg. The mean values of the closest two readings were calculated. Early morning spot urine sample was collected for albumin and creatinine measurement (albumin over creatinine ratio, ACR) using commercial assay (Immulite, DPC, Gwynedd, United Kingdom) with a lower detection limit of 6 mg/L. Venous blood samples (taken after a 10-hour fast) with EDTA as anticoagulant were kept in icebox immediately after collection and the plasma was separated from erythrocytes by centrifuging at 1500 g for 10 min at 4°C. Plasma creatinine levels were measured by means of Jaffé's kinetic method using a Roche Integra 800 analyzer. Blood lipids [Total cholesterol (TC), triglyceride (TG) and high density lipoprotein (HDL-C)] were measured by enzymatic methods using Kodak Ektachem chemistry slides, which were then read on a Vitros 700 Chemistry Analyser. HDL-C was measured after precipitation with dextran sulphate and magnesium chloride. LDL-C was calculated using Friedewald's formula.

Statistical analysis

Data are expressed as mean±SD. All statistical analysis was calculated using SPSS version 19.0. Chi-square analysis was used to test for difference in categorical variables. Student's t test was employed to compare continuous variables between two groups. Analysis of variance (ANOVA) was used to compare continuous variables between three or more groups. To explore factors potentially predictive of variation in CASP, bi-variate correlational analysis was performed using Pearson Correlation (for normally distributed data) or Spearman's rho method (for non-normally distributed data). Factors significantly correlated with CASP ($P<0.05$) i.e. eGFR and urinary ACR were further tested in multi-variate analysis. General liner model (GLM) was used in multi-variate analysis. Though non-modifiable, the following factors known to influence CASP i.e. age, gender, ethnicity and smoking status were included in the model. Based on biological and clinical considerations, the following factors were also preferentially included i.e. HBA1c, LDL-cholesterol, VFA. Blood pressure was excluded in the final model because BPro A-Pulse™ estimate CASP based on RAPWF was calibrated using brachial blood pressure. Therefore, CASP in our data expectedly showed unacceptably high co-linearity with systolic blood pressure (SBP) ($r=0.87$, $P<0.001$) akin to circular reasoning. In fact, when SBP was included in the model, the overall correlation (R) was inflated to 0.92 suggesting over-fitting (detailed data not shown). Hence, the following modifiable and non-modifiable risk factors were included in our final multi-variate model: Gender, ethnicity, smoking status, age, eGFR, urinary ACR, HBA1c, LDL-

cholesterol and VFA. A two-sided p-value was used and a p-value of < 0.05 was considered statistically significant.

The study was approved by our center's Institution Review Board (IRB) and written informed consent was obtained from all participants.

Results

Among the 353 DN subjects, 94% were type 2 diabetes, 60.6% were male; 62.6% Chinese, 27.8% Malay and 9.6% Indian; 9.4% were current smokers, 84% were receiving lipid lowering therapy, 45% were treated with insulin, 76% were treated with either angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or both. Clinical and laboratory data of the 353 DN subjects are shown in table 1. Most of the study subjects had moderately severe CKD with eGFR averaged at only 50.1(26.8) mls/min/1.73m^2 (range: 2.8 to 89.9) corresponding to stage 3 CKD. There was no difference in CASP between gender, ethnic groups, current smoker vs. non-smoker. Therefore, CASP: male versus female [mean(SD] was 128.9(20.9) mmHg vs. 131.8(22.1) (P=0.22); Chinese versus Malay versus Indians was 128.8(20.6) mmHg vs. 134.6(23.8) vs. 124.5(16.8) (P trend=0.12); Current smoker versus non-smoker was 131.0(21.5) mmHg vs. 124.9(17.6) (P trend=0.11).

Table 1. Clinical and biochemical profile of subjects with diabetic nephropathy (N=353)

	Mean (SD)
Age (years)	61 (10)
Body mass index (kg/m^2)	27.7 (8.9)
Systolic blood pressure (mmHg)	141 (20)
Diastolic blood pressure (mmHg)	79 (11)
HBA1c (%)	8.1 (1.7)
Total cholesterol (mM)	4.58 (1.20)
HDL-cholesterol (mM)	1.19 (0.38)
LDL-cholesterol (mM)	2.67 (0.92)
Triglyceride (mM)	2.04 (1.63)
Glomerular filtration rate (ml/min/1.73m^2)	50.1 (26.8)
Urinary albumin/creatinine ratio (mg/g)	662 (1339)
Visceral fat area (cm^2)	130.0 (31.9)
Percentage body fat (%)	24.7 (9.6)
Central aortic systolic pressure (mmHg)	130.0 (21.4)

When CASP is treated as a continuous variable, bi-variate correlational analysis is shown in table 2a. Only eGFR and urinary ACR were significantly correlated with CASP. Given that BPro A-Pulse™ estimated CASP was derived from RAPWF calibrated with brachial blood pressure, as expected, our data revealed extremely strong correlation between CASP and SBP. Therefore, as explained above, blood pressure was excluded from multi-variate analysis. Normative data of CASP is yet to be established. Therefore, when the normally-distributed CASP is treated as a categorical variable, dichotomized into two groups according to the mean value of 130 mmHg, comparison of risk factors between the two groups is as shown in table 2b. Subjects with high CASP were older (P=0.036), had high systemic blood pressure (P<0.001) and carried greater visceral adiposity (P=0.018).

Table 2a. Bi-variate correlation analysis between central aortic systolic pressure (CASP) and risk factors.

	Coefficient of correlation (r)	P value (2-tailed)
Age	0.096	0.075
Body mass index	-0.13	0.814
Systolic blood pressure	0.87	<0.001
Diastolic blood pressure	0.43	<0..001
HBA1c	0.05	0.39
Total cholesterol	0.07	0.29
HDL-cholesterol	0.06	0.25
LDL-cholesterol	0.06	0.28
Triglyceride	0.02	0.65
Glomerular filtration rate	-0.15	0.005
Urinary albumin/creatinine ratio	0.13	0.023
Visceral fat area	-0.008	0.88
Percentage body fat	0.024	0.66

Table 2b. Clinical and biochemical profile of diabetic nephropathy subjects stratified by study-cohort mean central aortic systolic pressure (CASP) of 130 mmHg

	CASP<130 mmHg	CASP≥130 mmHg	P value
Age (years)	60 (10)	62(9)	0.036
Body mass index (kg/m^2)	27.8 (11.4)	27.7(4.9)	0.91
Systolic blood pressure (mmHg)	127 (13)	157(16)	<0.001
Diastolic blood pressure (mmHg)	76 (10)	85(11)	<0.001
HBA1c (%)	8.3 (1.8)	8.3(1.7)	0.21
Total cholesterol (mM)	4.65 (1.51)	4.6(1.25)	0.92
HDL-cholesterol (mM)	1.23 (0.40)	1.21(0.34)	0.54
LDL-cholesterol (mM)	2.67 (0.80)	2.73(0.99)	0.44
Triglyceride (mM)	2.14 (4.27)	2.14(2.15)	0.98
Glomerular filtration rate (ml/min/1.73m^2)	89.6 (128.9)	83.3(134.8)	0.56
Urinary albumin/creatinine ratio (mg/g)	388 (1152)	564(1150)	0.09
Visceral fat area (cm^2)	124.6 (35.0)	131.4(32.3)	0.018
Percentage body fat (%)	24.4 (10.1)	25.7(9.5)	0.11

Table 3. Multi-variate analysis of predictors of central aortic systolic pressure.

	β	P value	β_1*	P value
Constant	138.5	<0.001	128	<0.001
Age	0.20	0.149	0.185	0.19
Glomerular filtration rate	-0.145	0.021	-0.127	0.045
Albumin/creatinine ratio	0.002	0.167	0.002	0.125
HBA1c	1.79	0.013	1.66	0.024
LDL-cholesterol	0.529	0.693	0.497	0.719
Visceral fat area	0.002	0.954	0.004	0.923

** Adjusted for gender, ethnicity and smoking status*

Results of multi-variate analysis are shown in Table 3. Given that our intention was to focus on major modifiable risk factors for CASP and taking into consideration factors known to affect CASP (e.g. age and smoking status), the following were included in the final model: HBA1c, eGFR, ACR, LDL-cholesterol, VFA, age, gender, ethnicity and smoking status. Our results revealed that HBA1c and eGFR were significant independent predictors of CASP (P<0.05). This relationship was only modestly attenuated when additionally adjusted for gender, ethnicity and smoking status. However, when all the major modifiable risk factors (i.e. HBA1c, eGFR, ACR, LDL, VFA and smoking status) were considered together, they collectively only explained ~10% of CASP variation in this group of DN subjects.

Discussion

In a large, multi-ethnic Asian population with DN, we demonstrated that renal glomerular filtration function and glycemic burden were important independent predictors of arterial stiffness (i.e. CASP). However, the major modifiable risk factors studied collectively accounted for only ~10% of variation in CASP. This suggested the presence of undiscovered novel risk factors which may be amenable to interventions. Future study to uncover these risk factors may reveal novel therapeutic targets.

DN is associated with systemic vascular dysfunction manifesting as arterial stiffness which appears to progress in tandem with severity of CKD[15]. Therefore, it was perhaps not surprising that our data revealed CASP varied inversely with eGFR, i.e. increasing arterial stiffness with worsening renal filtration function. The mechanistic link between renal dysfunction and arterial stiffness is likely to be complex – there are direct and indirect processes. For instance, renal dysfunction is associated with chronic low grade inflammation[16], activation of rennin-angiotensin aldosterone system[17], increased oxidative stress, abnormal tubulo-glomerular feedback[18] and deranged bone mineral metabolism[19]. These factors are known to be associated with vascular dysfunction[20]. Alternatively, arterial stiffness and renal dysfunction may share a "common soil"[21]. There is a growing body of evidence to suggest that components of cardiovascular dysmetabolism not only drive vascular injury but also predispose a person to CKD[22]. Corollary to this, interventions targeted at reducing cardiovascular burden are often reno-protective and vice versa[23]. Therefore, it appears reasonable to consider preservation of renal function as beneficial to prevent arterial stiffness.

Glycemic burden is another purported candidate for reno-vascular injury[24]. The mechanisms have been elegantly summarized by Brownlee et al[25]. Briefly, hyperglycemia is known to drive oxidative stress which leads to diversion of metabolic intermediary towards alternative "shunt pathways" such as polyol pathway, hexo-amine pathway, production of advance glycation end-product and activation of protein kinase C. However, the efficacy of anti-hyperglycemic interventions in ameliorating CVD appeared somewhat difficult to prove in clinical trials[26]. Nevertheless, a few recent meta-analyses lend support to the cardiovascular benefits of reducing glycemic burden[27]. Therefore, optimization of glycemic control remains the cornerstone of diabetes management for the prevention of diabetic vascular complications.

In our cohort of DN patients, we did not observe any association between LDL-cholesterol and CASP. This is consistent with observations from clinical trials in which lipid lowering therapy among individuals on hemodialysis over a period of 3.8 years had no significant effect on fatal or non-fatal CVD[28]. Nevertheless, lipid lowering therapy continued to hold considerable promise as very recent clinical study reported significant reduction in cardiovascular endpoints among individuals with both diabetes and non-diabetes associated CKD[29]. Similarly, we did not observe any association between severity of albuminuria, visceral adiposity and CASP. Although albuminuria has been widely reported as a risk marker for CVD[30], interventional studies successful in achieving significant anti-proteinuria could not uniformly demonstrate a reduction in cardiovascular events[31]. Having said so, in the PREVEND Intervention Trial (PREVEND IT), patients with albuminuria treated with fosinopril did report a trend toward a decrease in cardiovascular events[32]. Therefore, intervention targeted at albuminuria reduction remains a promising therapeutic strategy. As far as we know, there are no high quality clinical trials conducted to specifically test whether interventions targeted at reducing visceral adiposity could ameliorate vascular injury among DN subjects[33]. Taken together, our data supported the notion that conventional major cardiovascular risk factors (e.g. hyperlipidemia, albuminuria and visceral adiposity) might not fully explain the cardiovascular burden in diabetic individuals with CKD[34]. Much needs to be done to better understand the patho-biology behind CKD and CVD. It is thus important to search for novel cardiovascular risk factors (e.g. CKD-metabolic bone disease, adrenomedullin and adiponectin) in this high risk population.

The strength of our study included large, multi-ethnic, high risk (diabetic Asians) population which is largely under-represented in the literature. We used a validated method (BPro A-Pulse™) to measure CASP which is an accepted surrogate measurement of arterial stiffness. In addition, we measured visceral adiposity (i.e. VFA) rather than simpler but non-specific measurement of global obesity (i.e. BMI) in this group of CKD subjects at risk of protein malnutrition. There are however several limitations in our study. Firstly, this is a cross-section ecological study thereby precluding causal inference between risk factors studied and CASP. Therefore, our observations can only be considered as hypothesis-generating. Secondly, we could not include SBP, a major risk factor for vascular injury, in our analysis given that CASP measurement was derived from SBP based on blood pressure calibrated RAPWF. This might have been possible if we had employed PWV ("gold standard") to estimate arterial stiffness. Thirdly, we did not systematically collect high quality information on concomitant medications i.e. type of drugs exposed, dosage and duration exposed etc. As a result, we were not able to account for this when performing statistical adjustment. Fourthly, our study did not include other promising risk markers for arterial stiffness in CKD population e.g. vitamin D. Therefore, our future plan is to study the relationship between traditional and novel risk factors and arterial stiffness (measured by PWV) in a large cohort of Asian diabetic individuals.

In summary, eGFR and HBA1c are important modifiable risk factors for CASP in individuals with DN. However, the role of SBP on arterial stiffness in DN subjects deserves further study. Moreover, our results suggested possible presence of undiscovered novel risk factors which may be amenable to interventions.

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CASE REPORT

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Papillary Carcinoma Arising from Ectopic Thyroid Tissue in the Spinal Cord

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Abstract

Ectopically located thyroid tissue is uncommon and if present, is usually found in the lateral neck. Rarely, this may give rise to a carcinoma. The diagnosis rests on post-surgical histopathologic examination. We present a rare case of papillary carcinoma arising from ectopic thyroid tissue in the spinal cord in a 12-year old girl who developed spinal cord compression T4 level in 2004. She underwent laminectomy with tumor excision and histopathologic diagnosis was ependymoma. The spinal cord mass recurred when she was 17 years old (in 2009) and the tumor was excised. Tissue staining with thyroglobulin, thyroid transcription factor-1 (TTF-1) and epithelial membrane antigen (EMA) were positive. Pathologic diagnosis was papillary carcinoma. Subsequently, she underwent a total thyroidectomy to confirm an occult primary thyroid cancer; however, histopathologic examination of the thyroid was benign. Whole body scan using I-131 did not reveal extrathyroidal uptake. Radioactive iodine ablation was not done. She was maintained on a suppressive dose of levothyroxine. She remained paraplegic, with no evidence of tumor recurrence two years since her last surgery.

Keywords: papillary thyroid carcinoma, spinal cord compression, ectopic thyroid

Introduction

Thyroid tissue in an ectopic location is rare, occurring in 1 out of 100,000 to 300,000 persons; and is usually found in the lateral neck.[1] Ectopic thyroid tissue developing axially is even more rare, with up to 90% of cases being lingual thyroid tissue arising embryologically from a median anlage from the pharyngeal floor.[1,2] Very rarely, ectopic thyroid tissue may give rise to a carcinoma.[3] Carcinogenesis of ectopic thyroid tissue located in midline structures such as lingual thyroid and thyroglossal duct cysts, have a reported incidence of approximately 1%, and usually occurs during the third decade of life. [4] Almost all cases are diagnosed post-surgically on histopathologic examination. Management of these cases is individualized.

Presentation

A 12-year old girl developed progressive bilateral lower extremity weakness and sensory deficit, difficulty in ambulation, and bowel and bladder incontinence in 2004. She had no known exposure to ionizing radiation. Maternal and early pediatric histories were unremarkable. She had no family history of malignancy and thyroid disease. Physical examination revealed a lean build; with vital signs, height and weight appropriate for age. The thyroid gland was not enlarged. Chest and abdominal examination were unremarkable. She had full and equal pulses without peripheral edema. Neuromuscular examination revealed decreased manual muscle strength on the lower extremities, hypoesthesia from T4 dermatomal level and hyperreflexia on both lower extremities. Magnetic resonance imaging (MRI) of the thoracolumbar spine revealed a well-defined enhancing nodule in the spinal cord at the level of T3-T4. The nodule measured 1.16 cm x 1.26 cm x 1.58 cm, with intermediate signal intensity in both T1- and T2-weighted studies, with associated edema above and below the lesion from level T2 down to T8-T9 (Figure 1). She underwent a T3-T4 laminectomy with tumor excision 3 months after initial consult (January 2005). Histopathologic exam revealed a 3.0 cm x 1.5 cm x 0.8 cm mass, microscopically composed of bland cuboidal cells with uniform ovoid nuclei and adequate amphophilic cytoplasm arranged in pseudorosettes, with some cells exhibiting pale-staining to grayish cytoplasm and rare mitotic figures (Figure 2). Immunohistochemical staining for cytokeratin and neuron-specific enolase were positive. Ependymoma was considered in the histopathologic report of the excised mass. Two months postoperatively, the patient had gradual improvement of lower extremity weakness and was able to ambulate by herself. She was then lost to follow up.

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However, in March 2009, the patient developed gradual progressive weakness of both lower extremities, leading to paralysis. A repeat MRI of the thoracic spine showed an avidly enhancing intramedullary nodule at T3-T4 level, appearing bilobed with irregular margins, measuring 1.13 cm x 1.65 cm x 1.63 cm. The nodule was slightly hyperintense in T1-weighted study (Figure 3) and hypointense on T2-weighted imaging, with some extension to the neural canal at the level of T3-T4. A second laminectomy with tumor excision was done in May 2009. Histopathologic examination of the excised 2 cm x 1.5 cm x 0.5 cm mass revealed colloid material within the lumen of follicles or ducts (Figure 4) with papillary architecture and nuclear features consistent with papillary carcinoma. These findings were not seen in the histopathologic examination of the first surgical specimen. Microscopic sections from the second surgical specimen stained positively for thyroglobulin, thyroid transcription factor-1 (TTF-1) and epithelial membrane antigen (EMA) (Figures 5 to 7). The pathologic diagnosis of papillary carcinoma, suggestive of a thyroid primary, supersedes the previous histopathologic diagnosis. Thyroid ultrasound was normal. Thyroid function testing was also normal: thyroid stimulating hormone (TSH) was 1.03 μIU/mL (normal value 0.35 to 4.94), total thyroxine was 9 μg/dL (normal value 4.9 to 11.7), and total triiodothyronine was 1.24 ng/mL (normal value 0.58 to 1.59). Metastatic workup including CT scans of the neck, chest and abdomen did not reveal any metastatic foci.

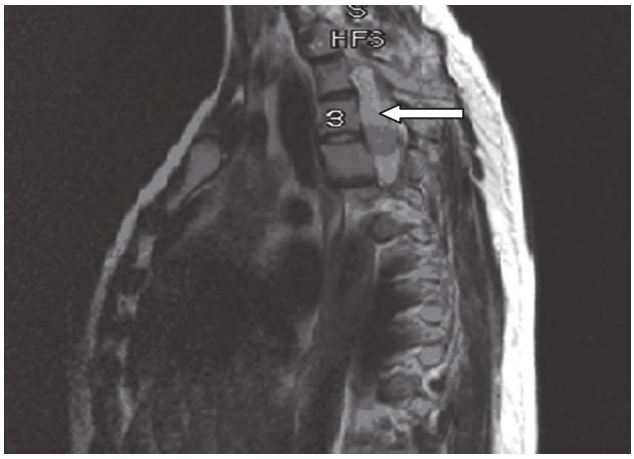

Figure 1. MRI of the thoracolumbar spine, T1 weighted image taken in 2004, showing a well-defined enhancing nodule in the spinal cord at the level of T3-T4 with intermediate signal intensity.

Papillary carcinoma of the thyroid with spinal cord metastasis was the foremost consideration. A total thyroidectomy was performed in July 2009, to confirm occult primary thyroid cancer and to facilitate ablation of residual thyroid tissue for subsequent surveillance for recurrence using radioactive iodine. Histopathologic examination of the thyroid gland revealed nodular hyperplasia after thorough sampling of the entire specimen. Two months after total thyroidectomy, whole body scan using 2 mCi Iodine-131 revealed functioning thyroid remnants in the anterior neck without undue tracer deposition seen elsewhere. Her postoperative stimulated thyroglobulin level was less than 2 ng/mL. She was placed on daily levothyroxine suppressive doses with regular monitoring of thyroid function tests and thyroglobulin level. Radioactive iodine ablation was not indicated since there was no evidence of remaining iodine-avid lesions in the spinal cord. She was placed on physical therapy and rehabilitation program after spinal surgery and thyroidectomy. The patient, now 19 years of age, remains paraplegic, with no evidence of active malignancy both clinically and on imaging studies, two years since her last surgery. Thyrotropin levels are adequately suppressed and serial results of thyroglobulin levels are undetectable.

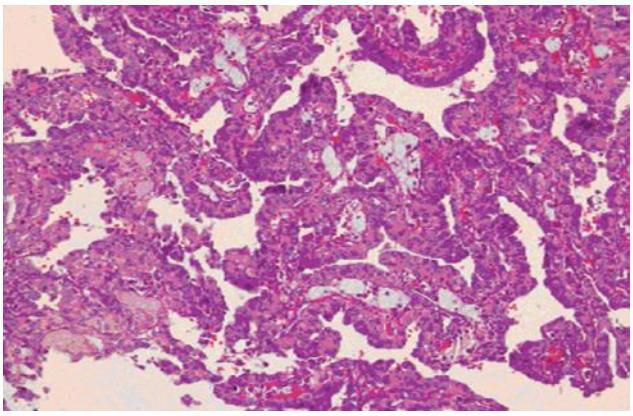

Figure 2. Microscopic examination of the excised spinal cord tumor in 2005 showing bland cuboidal cells with uniform ovoid nuclei and adequate amphophilic cytoplasm, arranged in pseudorosettes; some exhibiting pale-staining to grayish cytoplasm, and rare mitotic figures (*H&E*, x40).

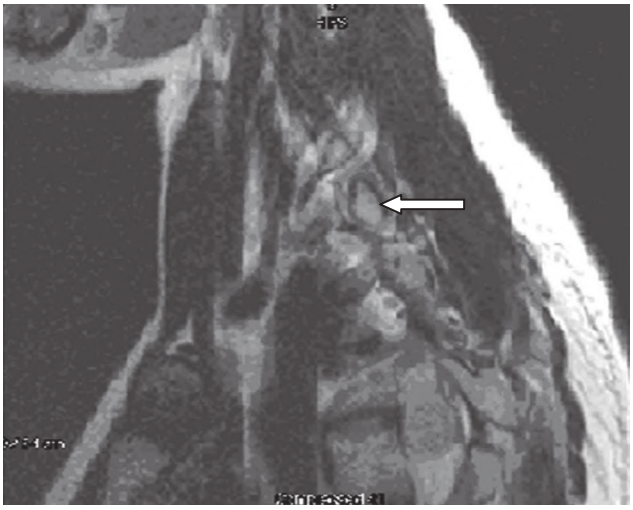

Figure 3. MRI of the thoracic spine T1-weighted image taken in 2009 showing an avidly enhancing intramedullary nodule at T3-T4 level, appearing bilobed with irregular margins, with some extension to the neural canal.

Discussion

Thyroid tissue that is located elsewhere from its expected location anterior to the second to fourth tracheal cartilages is ectopic[5]. Embryologically, the thyroid gland develops from a median anlage and a pair of lateral anlages. The embryologic pharyngeal floor gives rise to the median anlage, whereas the fourth and fifth branchial pouches give rise to the lateral anlage. Its descent follows the heart and great vessels and moves caudally from its origin to its location in the neck in front of the trachea.[6] Aberrant caudal descent of the median anlage during development may give rise to an intrathoracic location of ectopic thyroid tissue. There have been reports of ectopic thyroid tissue occurring in the right ventricle of the heart,[7] aberrant right carotid thyroid tissue,[8] carotid bifurcation,[5] lingual ectopic thyroid,[9] intrathoracic ectopic thyroid,[10] substernal goiter,[11] intralaryngotracheal thyroid[12] and spinal cord[6]. Carcinomas arising from ectopic thyroid tissue are uncommon. They have been reported to arise from thyroid tissue in thyroglossal duct cysts, lateral aberrant thyroid tissue, lingual thyroid and mediastinal and struma ovarii.[2,13] Most tumors in the ectopic locations have been papillary carcinomas, mixed follicular and papillary carcinomas or Hürthle cell tumors.[14,15] However, a carcinoma arising from spinal ectopic thyroid tissue has never been reported in literature.

Differentiating between a metastatic thyroid carcinoma and malignant transformation of an ectopic thyroid tissue is difficult and can only be done after surgery, as in this case. There are no clinical, biochemical, or imaging parameters that may assist in determining the nature of the lesion; and histological examination is always required for definitive diagnosis.[15] True ectopic thyroid tissue has an arterial supply independent of the cervical arteries that supply the thyroid; the cervical thyroid gland is normal or absent with no history of surgery; the cervical thyroid gland does not have a similar pathologic process as the ectopic tumor, and there is no history or evidence of thyroid malignancy.[16]

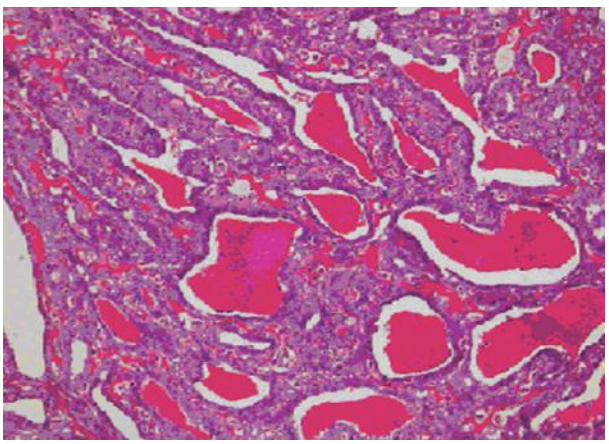

Figure 4. Microscopic exam of excised spinal cord tumor in 2009, showing colloid material within the lumen of follicles, papillary architecture and nuclear features consistent with papillary carcinoma (*H&E*, x40).

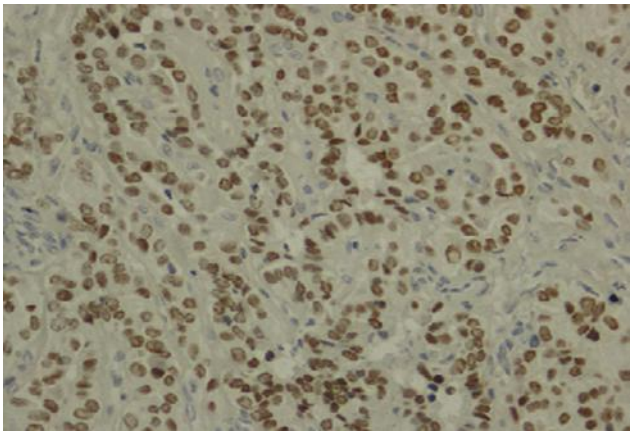

Figure 5. Microscopic exam of excised spinal cord tumor in 2009 (*TTF-1*, x400).

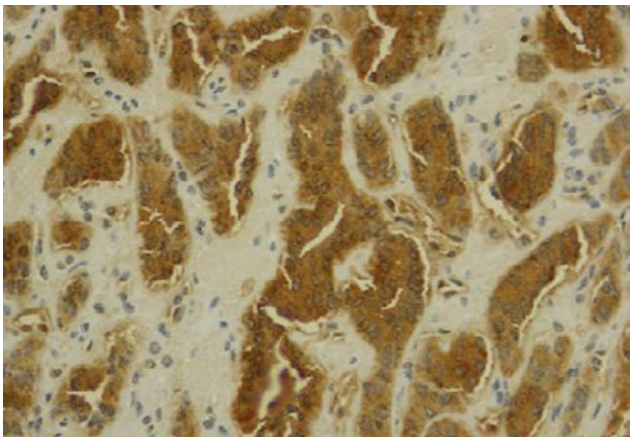

Figure 6. Microscopic exam of excised spinal cord tumor in 2009 (*Thyroglobulin*, x400).

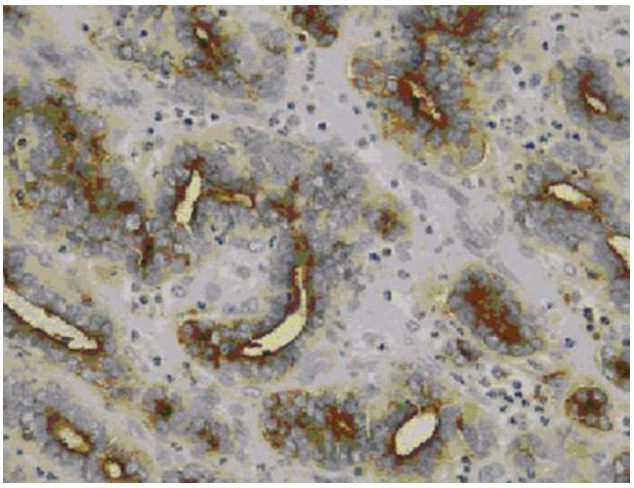

Figure 7. Microscopic exam of excised spinal cord tumor in 2009 (*EMA*, x400).

Although a metastatic papillary thyroid cancer was initially considered, the migration of papillary carcinoma from a primary thyroid to distant sites bypassing cervical lymph nodes is unusual. Also, a review of the post-thyroidectomy histopathology did not reveal malignancy in the thyroid, leading us to conclude that the tumor

excised from the patient's spinal cord was ectopic thyroid tissue that transformed into papillary carcinoma. The postoperative whole body scan that was negative for iodine avid lesions outside the thyroid bed may reflect either complete resection of tumor in the spinal cord or poor iodine avidity. She did not receive high dose radioiodine ablation, and was given a suppressive levothyroxine dose at 100 mcg daily to prevent recurrence.

Conclusion

Metastasis from a primary thyroid carcinoma must first be ruled out before considering malignant transformation of an ectopic thyroid tissue, which is a rare occurrence. There are no clinical, biochemical, or imaging parameters that may assist in determining the nature of these lesions, and histological exam is required for definitive diagnosis. Surgical excision is the treatment of choice. Post-surgical management includes thyrotropin suppression to prevent recurrence. Radioiodine ablation was not thought to be necessary in this case, as there was no evidence of remaining iodine-avid lesions in the spinal cord.

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CASE REPORT

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Meningitis and CSF Rhinorrhea as Initial Presentations of Untreated Macroprolactinoma

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Abstract

Macroprolactinomas often present with hyperprolactinemia or space-occupying symptoms. There are few case reports of macroprolactinomas presenting as meningitis and CSF rhinorrhea. Presented is a case of a 51-year-old Chinese male who presented with meningitis and pneumonia, and thereafter, developed rhinorrhea. Magnetic Resonance Imaging of the brain revealed a macroprolactinoma. He subsequently underwent a trans-sphenoidal hypophysectomy to remove the tumor.

Key words: Macroprolactinoma, Meningitis, Cerebrospinal fluid rhinorhhea

Introduction

Prolactinomas are the most common secretory pituitary tumours, presenting with hyperprolactinemia including secondary amenorrhea, infertility and galactorrhea[1]. Some develop space-occupying symptoms including headache and bitemporal hemianopsia[2]. However, meningitis and cerebrospinal fluid (CSF) rhinorrhea as initial manifestations are extremely rare[3-4].

We present a patient with macroprolactinoma who presented with meningitis and CSF rhinorrhea.

Case Report

A 51-year-old gentleman, married with 3 children, presented with a 4-day history of sore throat and dry cough, associated with fever and headache. He was confused and drowsy prior to admission. Apart from a contact with flu-like symptoms, he had otherwise been well with no preceding symptoms. He had no significant past medical history.

On admission, he was agitated and febrile. Doll's reflex was present. Pupils were reactive. He moved his limbs to painful stimulus. Reflexes were normal. Bilateral crepitations were heard. Chest radiography showed bilateral consolidations. CSF nucleated cell count was 12400 cells/uL, consistent with pyogenic meningitis. Blood and CSF Cultures grew pan-sensitive *Streptococcus pneumoniae*. His random glucose level was 16.5 mmol/L and glycated haemoglobin was 10.5%. Arterial blood gas showed high anion-gap metabolic acidosis, with beta-hydroxybutyrate levels of 4.2 mmol/L.

He was diagnosed with disseminated pneumococcal disease, complicated by diabetic ketoacidosis. He received 2 weeks of ceftriaxone and crystalline penicillin. His blood glucose levels were closely monitored and his insulin infusion was adjusted accordingly. A Magnetic Resonance Imaging (MRI) of his head with contrast was performed to ensure no interval progression on Day 5 of admission. Instead, an incidental pituitary mass was noted (**Figure 1**). Prolactin level was 12867 ng/dL. Apart from low testosterone levels, the other hormone levels were within normal range.

Incidentally, he subsequently complained of left nostril rhinorrhea 6 days after admission, which he previously denied having. CSF rhinorrhea was confirmed as the fluid glucose was 6.2 mmol/L.

Cabergoline was started pre-operatively and he then underwent trans-sphenoidal hypophysectomy. Intra-operatively, the macroprolactinoma was found to have eroded into the sellar floor, resulting in the CSF leak. This erosion was sealed with a fat graft. He was continued on Cabergoline post-operatively as the macroprolactinoma was too vascular to remove completely.

His prolactin levels have since improved within 6 months after discharge with Cabergoline. The macroprolactinoma has remained stable in size and the patient has remained asymptomatic since discharge.

Discussion

CSF rhinorrhea is a well-known complication of dopamine agonist treatment[1], trans-sphenoidal surgery and radiation. However, CSF rhinorrhea as an initial manifestation of untreated macroprolactinoma is rare. Only 21 cases have been reported since 1800s[4-7]. Meningitis is an even rarer initial manifestation. Only 5 cases have

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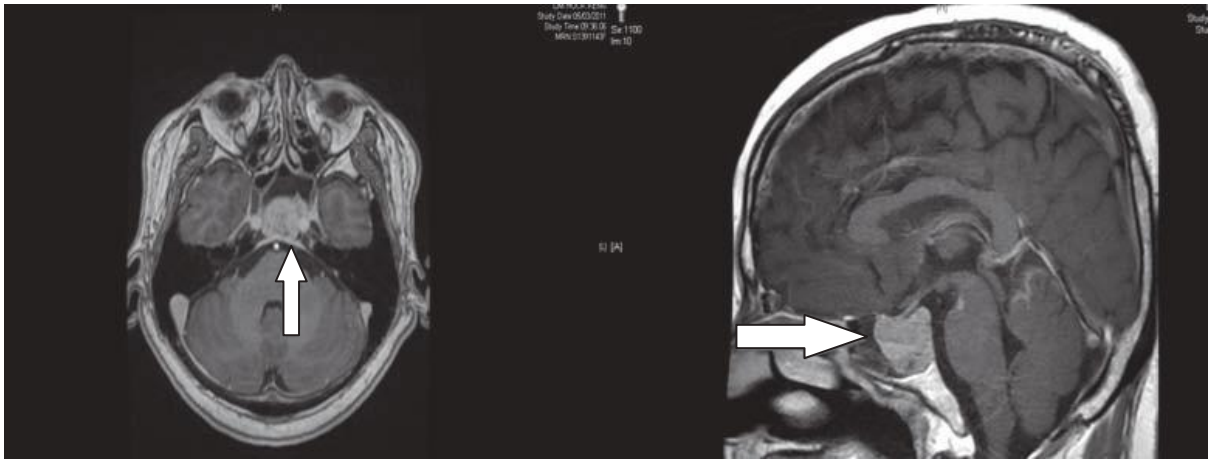

Figure 1. MRI Head with contrast shows the pituitary mass abutting both cavernous internal carotid arteries

been reported. Three cases had prior CSF rhinorrhea. One case developed CSF rhinorrhea 1 year after the meningitis episode[6]. Our case report represents the second case presenting as meningitis, followed by CSF rhinorrhea.

The pathophysiology of CSF rhinorrhea in pre-treatment macroprolactinoma is unclear due to the small case numbers. Current postulations include direct extension and erosion into the sphenoid sinus, allowing fistula communication between the sella and sinuses, thereby allowing CSF leak[7]. Our patient's intra-operative findings were consistent with this hypothesis. Others have postulated that infarction and haemorrhage of the tumour can result in fistula formation through the tumour.

Therefore, recognition of CSF rhinorrhea is important. CSF rhinorrhea is identified by detecting Beta-2-Transferrin or rhinorrhea glucose levels of >0.3 mmol/L (5 mg/dL). However, rhinorrhea glucose is insensitive as external factors like meningitis can confound the result by falsely decreasing the glucose level. Our institution was unable to test for Beta-2-Transferrin, so rhinorrhea glucose was tested.

The sphenoid bone erosion was the likely cause of meningitis in our patient. However, the newly diagnosed diabetes mellitus was a confounding factor as it is known to increase a patient's susceptibility to infection. His initial flu-like symptoms, significant contact history and chest radiography findings led us to assume that he had initially developed pneumonia, which was complicated by meningitis due to his increased susceptibility to infection. We also assumed his rhinorrhea was related to his flu-like symptoms till we discovered the incidental macroprolactinoma. Our patient had not exhibited any signs of a space-occupying lesion or hyperprolactinemia. He fathered 3 children.

Medical therapy in the form of dopamine agonists serves as the first-line therapy for prolactinomas. However, the presence of a fistula mandates surgical intervention. Some advocate removing the macroprolactinoma and repairing the leak[6]. Others promote continued use of dopamine agonist and using muscle flaps to repair the fistula[3]. There is currently no consensus as such cases are too few to conduct comparison studies. We chose the former option and our patient tolerated the procedure well.

Conclusion

CSF rhinorrhea and meningitis as initial presentations of macroprolactinoma are extremely rare. This case serves to illustrate the pitfalls one may encounter and the importance of evaluating the symptoms a patient presents with, no matter how insignificant they may be.

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CASE REPORT

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Seizures and Cardiac Tamponade in Long-Standing Severe Hypothyroidism

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Abstract

We report a patient who presented with a seizure episode and concurrent clinical and echocardiographic evidence of cardiac tamponade caused by severe hypothyroidism. The symptoms improved following immediate tube pericardiostomy and thyroxine hormone replacement. The classic symptoms of severe hypothyroidism are now rarely seen given the wide availability of thyrotropin (TSH) assays and thyroid hormone tablets. The simultaneous occurrence of both symptoms during a single admission has not been previously reported in literature.

Keywords: severe hypothyroidism, myxedema coma, seizure, pericardial tamponade

Introduction

Untreated or unrecognized hypothyroidism may progress to severe decompensation or myxedema coma. This condition is characterized by marked impairment of the central nervous and cardiovascular systems, with a high mortality rate if left untreated. A significant delay in diagnosis may adversely affect the prognosis. Even though sensitive TSH assays are widely available, the recognition and therapy of myxedema coma remains a challenge.

High-dose thyroid hormone replacement is typically recommended for the treatment of myxedema coma. However, the most effective choice whether to use T3, T4 or a combination and amount of thyroid hormone therapy is still controversial.[1] In this article, we report a patient who presented with a rare manifestation of untreated severe hypothyroidism, who subsequently underwent low-dose levothyroxine therapy and pericardiostomy with satisfactory clinical outcome.

Case

A 69-year old Filipino woman presented to us with seizures and pericardial tamponade. Seven months prior to admission, she was noted to have progressive fatigue and lethargy, with inability to perform activities of daily living. She had exertional dyspnea, waxing and waning bipedal edema, decreased bowel movement frequency (2 to 3 times per month) and cold intolerance. She had no apparent paroxysmal nocturnal dyspnea, orthopnea, oliguria, chest pain, syncope or palpitations. On the day of admission, as she was seated waiting for her out-patient clinic consult, she was found to have sudden upward rolling of the eyeballs followed by stiffening of the extremities. There was associated urinary incontinence and loss of consciousness for approximately 5 to 10 seconds. There was no recollection of the event afterward. She was subsequently admitted. On review of her medical history, she had total thyroidectomy in 2007 (Four years PTC) for Hashimoto's thyroiditis, but was poorly compliant with thyroid hormone replacement and stopped taking the medication since October 2010. She had no known history of ischemic heart disease, diabetes mellitus or hypertension.

On examination, the patient was wheelchair borne, conscious, and able to follow commands. She had occasional disorientation, slow and disorganized thought process She had a hoarse voice, and her facial features appeared puffy (Figure 1A). She had dry skin, coarse hair and dystrophic nails (Figure 1B and 1C). She had a visible thyroidectomy scar. Her vital signs revealed a temperature of 35°C/tympanic, a cardiac rate of 55 beats/minute, and a blood pressure of 120/80 mm Hg. She had muffled heart sounds and bibasal rales on auscultation. Her abdomen was soft and flabby, with hypoactive bowel sounds and mild tenderness on all quadrants. She had grade 2 bipedal non-pitting edema. Neurological findings showed a motor strength of 3/5 on all extremities and generalized hyporeflexia, with no sensory deficits and negative Babinski's sign

At the emergency room, a primary neurologic cause was initially considered. Cranial CT scan showed cerebro-

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cerebellar volume loss but no evidence of acute infarction or intracranial hemorrhage. Electroencephalogram (EEG) showed mild diffuse slowing of activities. A standing order of diazepam 10 mg IV was given for frank seizure.

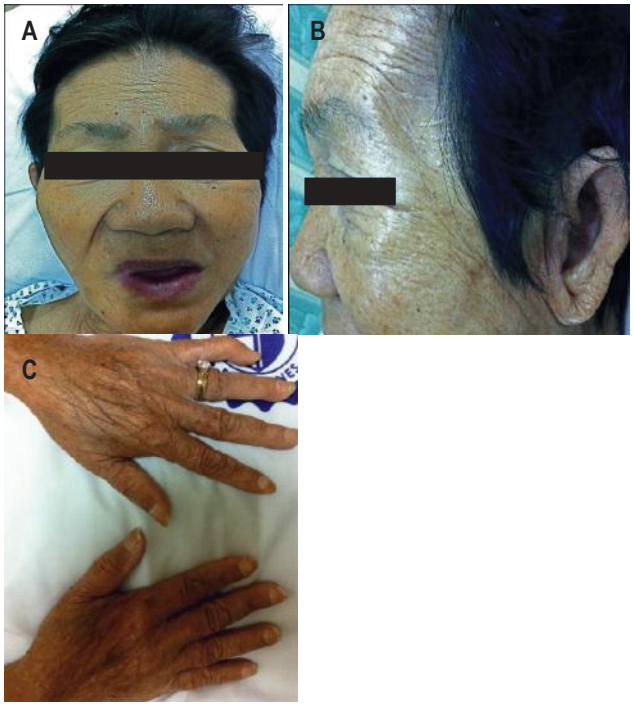

Figure 1. On examination, the patient had coarsened features, sallow complexion and puffy appearance (A). She had non-pitting, waxy, dry edema in the subcutaneous tissues around the eyes and ears, due to the deposition of mucopolysaccharides within the dermis (B). Hypercarotenemia gives the skin a yellow tint (C). The dystrophic fingernails are also notable.

Table 1 lists the relevant laboratory results. Thyroid function testing subsequently confirmed severe hypothyroidism, with elevated TSH (163.10 mU/L) and barely detectable total triiodothyronine (T3) (<0.006 nmol/L) and total thyroxine (T4) (<12.87 nmol/L) levels. Serum electrolytes revealed a low normal serum sodium level (137mmol/L). She had leukopenia with no apparent focus of infection. She also had hypercholesterolemia (LDL-C 6.93 mmol/L) and elevated total creatinine kinase (CK-total 727 U/L). An EMG-NCV revealed focal median neuropathy at the level of both wrists compatible with carpal tunnel syndrome. Plain film of the abdomen showed ileus with fecal retention. Chest X-ray revealed cardiomegaly with no evidence of pulmonary congestion (Figure 2). Electrocardiogram on admission showed sinus arrhythmia with a heart rate of 86 beats/min and diffuse flattened T waves in all leads.

Levothyroxine was initially started at 25 mcg daily, and was then increased to 37.5 mcg daily after the third day. Because of the possibility of concomitant hypocortisolism, the patient was given hydrocortisone 100 mg intravenously every eight hours after a serum cortisol level was obtained.

Table 1. Pertinent Laboratory Examinations

Variable	On Admission	4th week	12th week	Normal Range(SI Unit)
Hemoglobin (g/L)	110	106		116-155
White blood cell (10^9/L)	3440	3650		4800-10800
Sodium (mmol/L)	137	142		136-145
Potassium (mmol/L)	3.6			3.5-5.1
Creatinine (μmol/L)	114.9			0.53-106
Cortisol(baseline) (nmol/L)	278.6			
Cortisol (30mins)	535.2			
Cortisol (60mins)	435.9			
ACTH (pmol/L)	1.89			1.10-10.10.
TSH mU/L	163.10		0.45	0.35-5.50
Total Triidothyronine (nmol/L)	<0.0061	74.24		0.01-0.027
Total Thyroxine (nmol/L)	<12.87			57.9-160.87
Free Thyroxine(pmol/L)			12.61	11.45-22.65
Glucose (mmol/L)	4.4	8.62		4.10-5.88
Cholesterol (mmol/L)	9.04		3.96	<5.18
Triglycerides (mmol/L)	1.68		1.34	0.22-2.26
HDL cholesterol (mmol/L)	0.67		0.59	>0.90
LDL cholesterol (mmol/L)	6.93		2.82	0-4.11
Total Creatinine Kinase (U/L)	727			26-192

A 2D-echocardiogram showed left ventricular hypertrophy, normal right ventricular dimension with evidence of diastolic collapse noted at the right ventricular outflow tract (RVOT), normal right and left atrium, moderate pericardial effusion mostly noted in the lateral portion of the left ventricular free wall with signs of tamponade physiology (Figure 3). A tube pericardiostomy drained 890 mL of straw-colored pericardial fluid. The pericardiostomy tube was removed on the 3rd post-operative day. Cytological examination of the pericardial fluid did not reveal bacterial or viral infection. There were no malignant cells or granulomas seen on examination of the pericardial tissue.

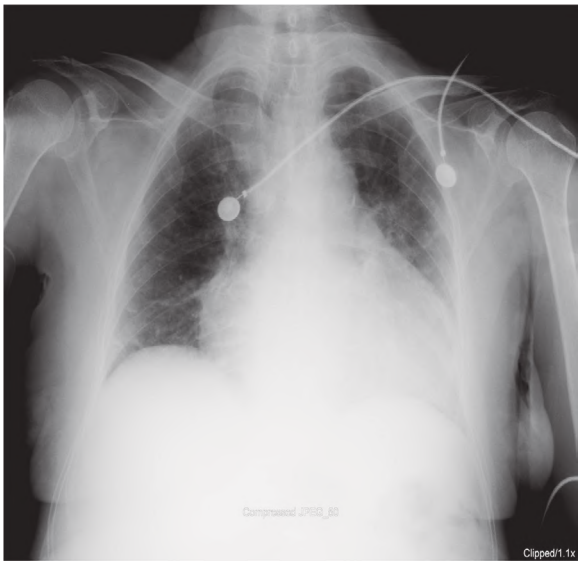

Figure 2. Chest radiograph of the patient showing cardiomegaly.

The patient's subsequent hospital course was uneventful. She remained seizure-free throughout; her breathing improved and her bipedal edema decreased. Hydrocortisone was tapered and discontinued upon note of adequate adrenal reserve from an ACTH stimulation test. The dose of levothyroxine was gradually increased to 100 mcg/day by the fourth week.

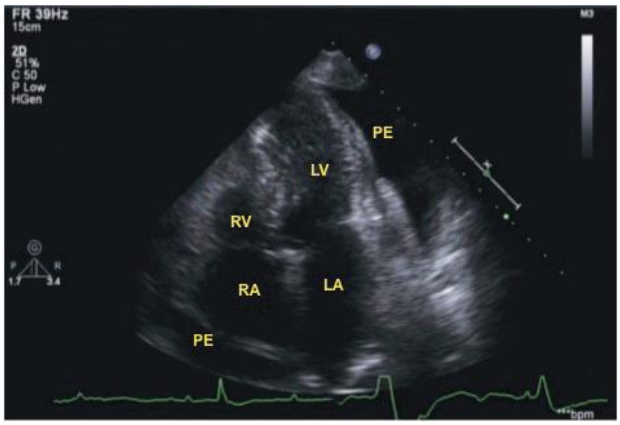

Figure 3. Apical four-chamber echocardiogram showing echo-free space consistent with moderate pericardial effusion: *PE*, pericardial effusion; *RA*, right atrium; *LA*, left atrium; *RV*, right ventricle; *LV*, left ventricle.

Four weeks after hospital discharge, the patient was able to ambulate with minimal assistance (Figure 4). Her bowel movement frequency improved to 2 to 3 times per week. TSH level decreased to 74.24 mU/L, while free T4 was 8.62 pmol/L. Repeat echocardiogram showed no evidence of diastolic collapse and resolution of pericardial effusion. Lipid profile and TSH level normalized after twelve weeks (Table 1).

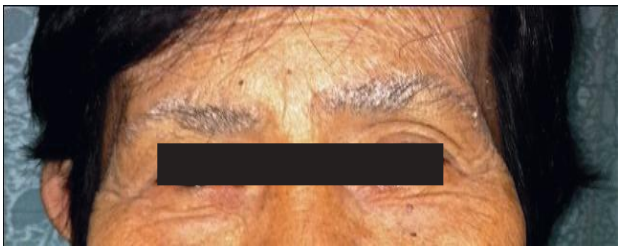

Figure 4. Four weeks after discharge, there was a significant improvement in her facial puffiness. Note the loss of the lateral third of the eyebrows, called Queen Anne's sign.

Discussion

Myxedema coma, a term used interchangeably with severe hypothyroidism, is an endocrine emergency. This is a potentially lethal condition that requires aggressive treatment. The mortality rates may be as high as 25 to 60% even with the best possible treatment.[2-3] The true incidence is unknown, with only over 300 cases reported in literature.[4-5] Environmental factors (such as low ambient temperature), infection, cerebrovascular accidents, drugs (particularly tranquilizers, anesthetics, sedatives, narcotics and lithium), and consumption of raw *bok choy*, may precipitate myxedema crisis.[6] In our patient, the condition resulted from long-standing untreated hypothyroidism.

Essentially, thyroid hormones affect every organ system, including the central and peripheral nervous systems. The absence of coma does not rule out the condition. Some patients manifest with lesser degrees of altered consciousness, like confusion with lethargy. Other neurologic complications include cranial nerve palsies, hoarseness, myopathy, neuropathy, carpal tunnel syndrome, reflex changes, ataxia, and psychotic features, the so-called "myxedema madness."[7] About 25% of patients have focal or generalized seizures.[2] The exact mechanisms are unclear. The possible mechanism of seizure in our patient may be cerebral hypoxia. Brain function is affected by reduction in cerebral blood flow and oxygen delivery, deficiency of T4 and T3, and glucose consumption; as such, it is likely all these factors are probably involved. EEG findings are nonspecific, with slowing and decreased amplitude and rarely with triphasic waves.[8]

Pericardial effusion in hypothyroidism is related to the severity and duration of the disease. Its incidence is reported to be at 3% in early mild stage to 80% when myxedema is present.[9-10] The occurrence of cardiac tamponade in hypothyroidism is uncommon due to the slow accumulation of fluid and the remarkable distensibility of the pericardium.[11] The classic signs of hypotension, muffled heart sounds, jugular vein distention and pulsus paradoxus are not always present.[12] The compensatory tachycardia in a patient with tamponade is usually absent in hypothyroidism, as in our case. Many hypothyroid patients have high serum CK concentrations. The isoenzyme distribution is almost completely MM, with less than 4% constituting MB, indicative of skeletal muscle origin.[13] ECG may reveal low-amplitude QRS complexes, prolonged QT interval, and flattened or inverted T waves. Echocardiography remains the most reliable diagnostic modality with exceptionally high specificity and sensitivity.[14] Echocardiographic features of tamponade include chamber collapse and reciprocal changes in left and right ventricular volumes with respiration.[12] Pericardial fluid exceeding 25-50 ml is seen as an echo-free space through-out the cardiac cycle signifying pericardial effusion.

Thyroid hormone therapy is the cornerstone of treatment of patients with myxedema coma. High dose thyroid hormone replacement has been typically recommended. However, because of the paucity of cases, there are no clinical trials comparing the efficacy of different treatment regimens, and the optimal therapy has yet to be determined. Some experts favor administration of T3 because of its greater biologic activity and more rapid onset of action; others prefer a combination of T4 and T3. Whether patients with myxedema coma should be treated with T4, T3, or both, is still controversial.[1]

Selected cases of myxedema coma can be safely treated with thyroid hormone at doses lower than conventionally recommended.[15] In a hypothyroid patient with cardiac tamponade, the recommended therapeutic regimen is levothyroxine at an initial low dose (25mcg/day), to be

increased gradually. Higher doses may precipitate a cardiac event that may lead to further decompensation towards tamponade.[16] In our case, the treatment given was low dose levothyroxine at 25mcg/day, which was increased gradually to 100 mcg/day by the fourth week. The patient recovered without sequelae.

Our patient presented with the classic manifestations and laboratory abnormalities of severe hypothyroidism. However, the seizure episode with concomitant cardiac tamponade represents an extreme form of complicated hypothyroidism. Early recognition and prompt therapy are essential. In light of the possible adrenal insufficiency due to polyglandular autoimmune syndromes or hypothalamic-pituitary compromise, many experts recommend empiric treatment with stress-dose glucocorticoids (hydrocortisone 100 mg IV every 6-8 hours) until definitive ACTH stimulatory testing is performed and concomitant adrenal insufficiency is ruled out. Pericardial effusion may be easily reversed with thyroid hormone replacement, but tube pericardiostomy is necessary when tamponade or impending tamponade develops.

Lastly, supportive measures, including treatment in an intensive care unit setting; ventilatory support, if indicated; judicious administration of intravenous fluids, electrolytes and glucose; correction of hypothermia by passive rewarming with ordinary blankets and warm ambient temperature; avoidance of hypnotics and sedatives; and treatment of any underlying infection; are also important in the management of the severely hypothyroid patient.

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A Rare Large Cell Neuroendocrine Carcinoma in a 72-year-old Man

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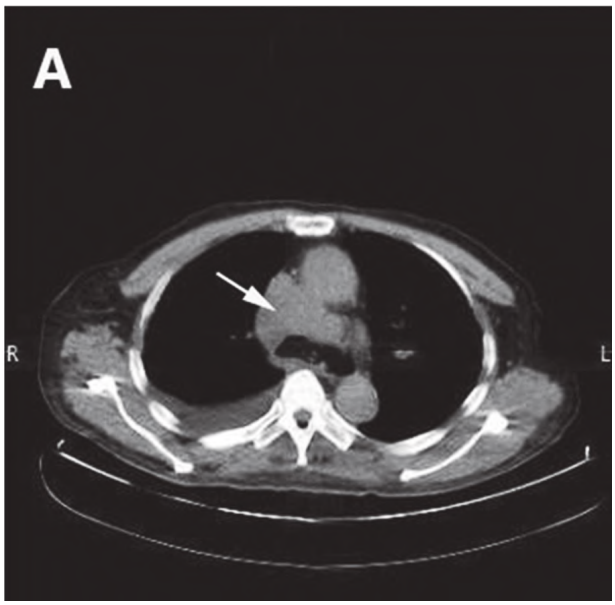
A 72-year-old male, previous smoker presented with cough and shortness of breath of one week duration. His chest x-ray showed linear densities in the right paracardiac and both lung bases. Contrast-enhanced CT scan uncovered multiple, enlarged soft tissue masses in the pretracheal, right paratracheal, subcarinal and right paravertebral regions (Figure 1). There were also reticular ground glass opacities scattered in both lung bases and periphery. No endobronchial mass was seen. The thyroid, adrenal glands, pancreas, liver and the rest of the visceral organs were normal. Mediastinoscopy with excision biopsy was done. Microscopic examination revealed large tumor cells arranged in solid sheets or nests (Figure 2). The differential diagnosis included diffuse large cell lymphoma and poorly-differentiated carcinoma believed to be primary lung versus mediastinal cancer. Positive immunohistochemical staining of tumor cell cytoplasm for Chromogranin, Synaptophysin, and CD 56 (Figure 3), and negative for cytokeratins confirmed the diagnosis of Large Cell Neuroendocrine carcinoma. Whole body [^{18}F]-Fluorodeoxyglucose (FDG) PET-CT scan was done to locate the primary tumor and delineate the extent of disease. There was a mildly enhancing 1.3 x 1.3 cm mass



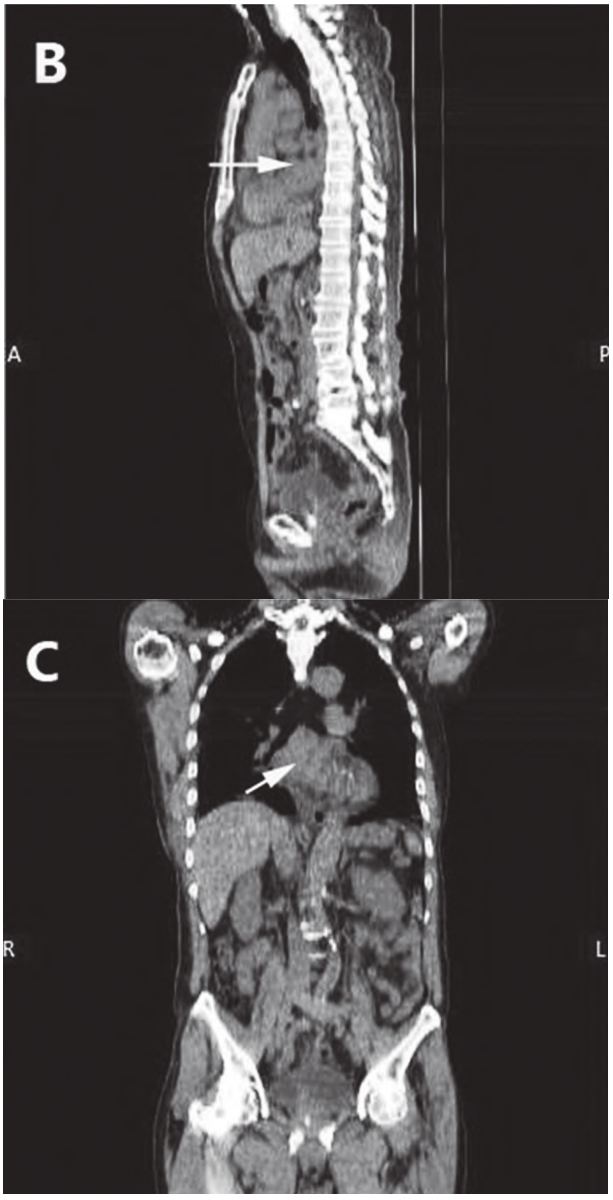


Figure 1. Contrast-enhanced chest CT scan demonstrating multiple, enlarged lymph nodes in the (A) pretracheal (arrow), (B) prevertebral (arrow), and (C) subcarinal (arrow) regions.

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in the right temporal lobe with FDG uptake similar to that of white matter. The previously seen mediastinal and right hilar lymphadenopathies had intense FDG uptake with standardized uptake value (SUV) up to 7.3 g/ml (Figure 4). In contrast, the previously noted reticular ground glass opacities in both lungs had low-grade uptake on PET. There were multiple hypermetabolic lesions in both hepatic lobes with SUV up to 5.4 g/ml (Figure 5) which appeared normal on the initial CT scan. A 24-hour urinary 5-hydroxyindoleacetic acid (5HIAA) was four times elevated, indicative of tumor secretory activity. He underwent chemotherapy with Carboplatin, Etoposide and Topotecan and radiation therapy with complete disappearance of the brain lesion but with further derangement in liver function.

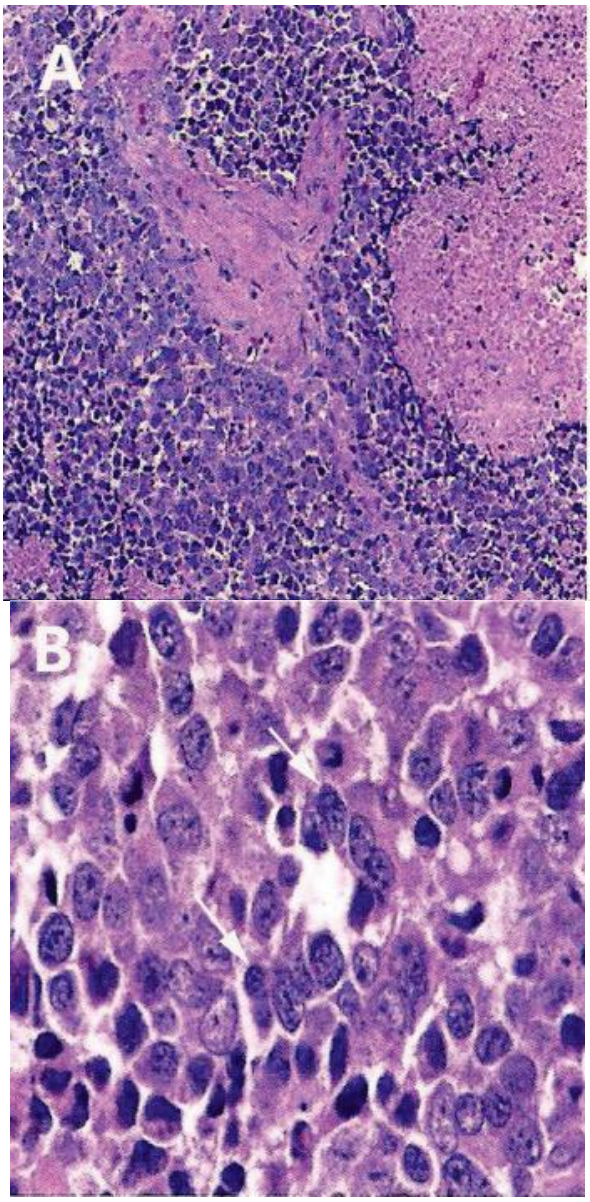

Figure 2. Photomicrographs of a mediastinal lymph node exhibiting (A) proliferation of tumor cells arranged in a diffuse nest pattern (H&E, 40x magnification); and (B) tumor cells with enlarged hyperchromatic and pleomorphic nuclei (arrows) and scanty cytoplasm (H&E, 400x magnification).

Neuroendocrine tumors (NET) are rare, solid malignant tumors that arise from dispersed neuroendocrine cells found throughout the body. According to the 2004 analysis of Surveillance, Epidemiology and End Results (SEER) database, the age-adjusted incidence of NET is of 5.25 cases per 100,000 people.[1] The majority of NETs arise within the gastroenteropancreatic system while the bronchial tract represents the second most frequent primary site.[2] NETs with an undetected primary tumor have been noted in more than 4% of cases in several studies.[2] A primary tumor site could not be found in 4,753 (13%) out of 35,618 NET in the SEER database analysis.[1] NETs may produce a variety of clinical syndromes depending on a multitude of peptides and hormones being secreted. However, most NETs are clinically silent or elicit non-specific symptoms such that diagnosis is often delayed and with metastatic disease at presentation.[1]

The cornerstone of diagnosis of NET is histopathology including immunohistochemistry.[2] Immunohistochemistry is most important for verification of the neuroendocrine nature of the tumor. It is also crucial in characterizing the proliferative potential of the tumor because this has been shown to be of prognostic value. Chromogranin A and/or Synaptophysin positivity are considered sufficient for the diagnosis.[3] A 24 hr urine 5HIAA is a good biomarker of tumor secretory activity and may be predictive of reduced survival.[2]

Several imaging techniques are available for localization of tumor and monitoring disease progression. Somatostatin Receptor Scintigraphy (SRS) has a high sensitivity of 86-95% and should be the initial imaging procedure to localize and establish the stage of disease.[4] However, the difficulty and expense of obtaining an SRS is prohibitive. FDG-PET scanning may be useful in finding a primary tumor and identifying poorly-differentiated anaplastic tumor.[4]

Treatment of metastatic neuroendocrine carcinoma of unknown primary site depends on the pathologic categorization as to whether the tumor is well-to moderately differentiated (large cell tumors) or poorly differentiated (high grade, anaplastic, small cell tumors).[5] SRS is carried out to indicate the presence of somatostatin receptors and imply likelihood to respond to a long-acting somatostatin analogue. If the SRS is negative, other treatment options include hepatic artery chemoembolization (HACE), radioactive microspheres (SIRS) therapy, or conventional chemotherapy considering some of the newer agents, such as tyrosine kinase inhibitors.[3]

Our patient presented with a rare Large Cell Neuroendocrine carcinoma that has metastasized to the mediastinal and hilar lymph nodes, liver and brain but whose primary tumor was undetected. A possible primary lung cancer was highly considered. There was tumor

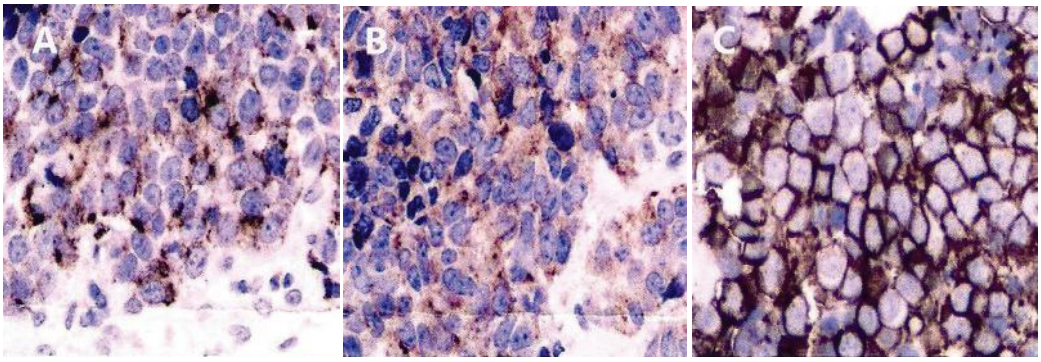

Figure 3. Immunohistochemical examination of a mediastinal lymph node demonstrating positive staining of tumor cell cytoplasm for (A) Chromogranin (B) Synaptophysin and (C) CD56 confirming neuroendocrine carcinoma.

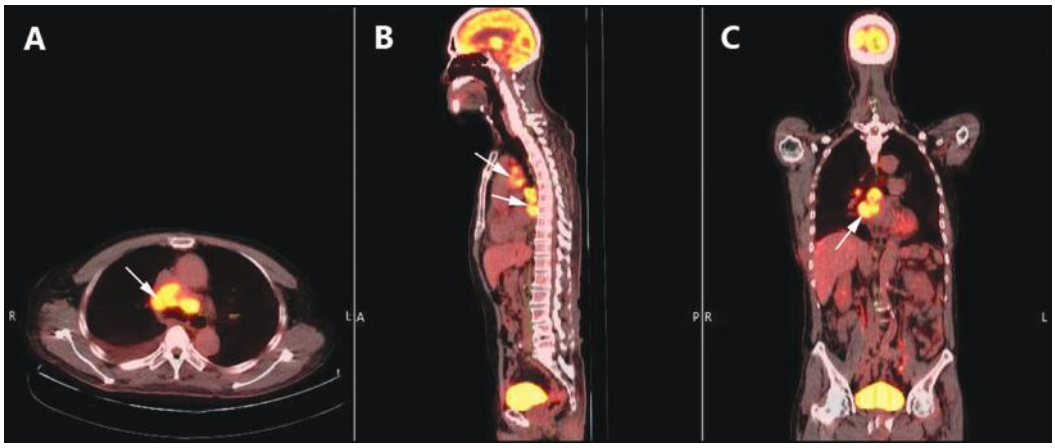

Figure 4. Whole body FDG-PET-CT scan images demonstrating multiple intensely hypermetabolic lymphadenopathies in the (A) paratracheal (arrow), (B) pretracheal and prevertebral (arrows), and (C) subcarinal (arrow) regions.

progression 2 months after chemotherapy and radiation therapy. Our case may benefit from a SRS for further tumor localization and likelihood to respond to somatostatin analogue.

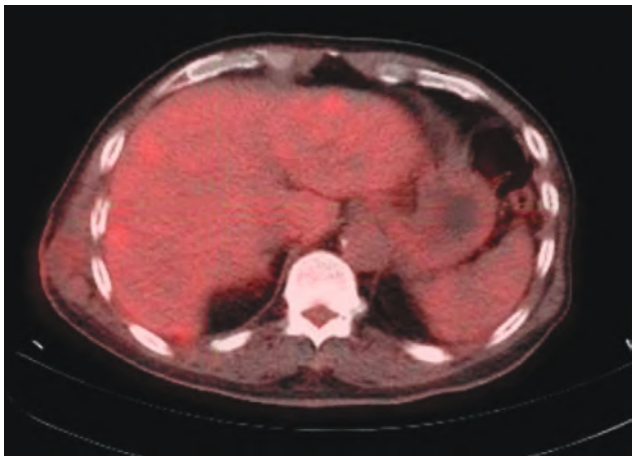

Figure 5. FDG-PET-CT scan image of the liver showing multiple, FDG-avid lesions scattered in both hepatic lobes.

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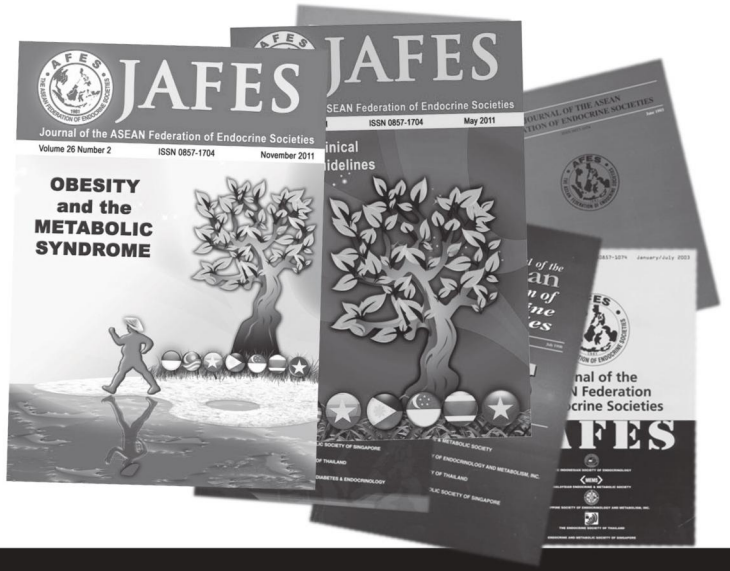

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Victoza® (liraglutide injection)

The Summary of Product Characteristics (SPC) is available at novonordisk.com.

Presentation: Prefilled, disposable pen containing 18 mg of liraglutide in 3 mL of solution. **Indications:** Victoza® is indicated for treatment of adults with type 2 diabetes in combination with metformin or a sulphonylurea, metformin and a sulphonylurea, or metformin and a thiazolidinedione when previous therapy does not achieve adequate glycaemic control. **Dosage and administration:** The starting dose is 0.6 mg once daily. After at least one week, the dose should be increased to 1.2 mg. Based on clinical response and after at least one week, the dose can be increased to 1.8 mg to further improve glycaemic control. Victoza® can currently not be recommended for use in patients with moderate/severe renal impairment or hepatic impairment. Victoza® is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, thigh, or upper arm. Victoza® should not be administered intravenously or intramuscularly. In combination with metformin with or without a thiazolidinedione, no dose adjustment is required. When Victoza® is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions:** Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Due to limited experience, Victoza® is not recommended in patients with inflammatory bowel disease or diabetic gastroparesis. There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and no experience in patients with NYHA class III-IV. Use of other GLP-1 analogues has been associated with the risk of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, discontinuation of medicinal products should be considered. Thyroid adverse events, including increased blood calcitonin, goitre, and thyroid neoplasm, were reported in clinical trials, particularly in patients with preexisting thyroid disease. **Pregnancy and lactation:** Victoza® should not be used in women who are pregnant, who wish to become pregnant, or who are breastfeeding. **Undesirable effects:** The most frequently reported adverse reactions in patients treated with Victoza® are nausea and diarrhea. Less common adverse reactions include headache, vomiting, dyspepsia, upper abdominal pain, constipation, gastritis, flatulence, abdominal distension, gastroesophageal reflux, bronchitis, nasopharyngitis, dizziness, fatigue, pyrexia, decreased appetite, and hypoglycaemia. Patients receiving Victoza® in combination with a sulphonylurea may have an increased risk of hypoglycaemia. The risk can be lowered by a reduction in the dose of sulphonylurea. Few cases (less than 0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza®. A causal relationship between Victoza® and pancreatitis cannot be established nor be excluded.

Victoza® is registered in the Philippines since 14 February 2011.

Full prescribing information available upon request.

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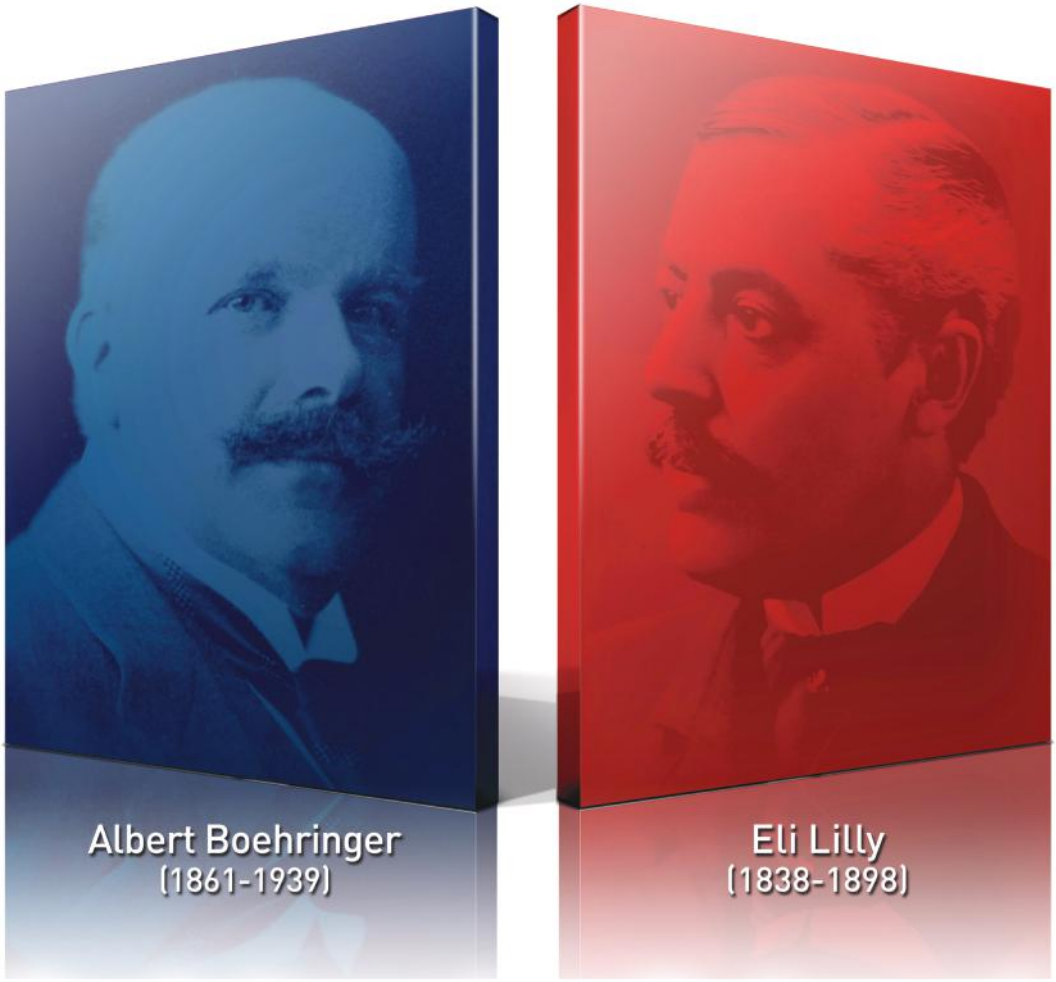

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References:
1 - Campbell IW. Br JDiabetes Vasc Dis 2006;6:207-15.
2 - Donnelly LA *et al.* Diab Obes Metab 2009;11:338-42.
3 - Blonde L *et al.* Curr Med Res Opin 2004;20:565-72.

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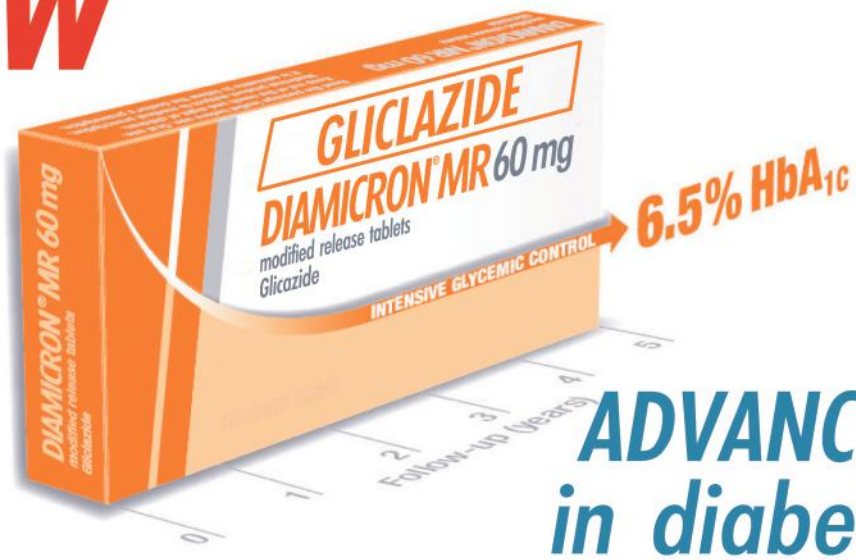

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1.The ADVANCE Collaborative Group. N Engl J Med.2008;358:2560-2572. 2.The GUIDE Study. Eur J Clin Invest.2004;34:535-542. 3. The STENO 2 Group Study. N Engl J Med. 2008;358:580-591. 4. The CONTROL Study.Diabetologia.2009;52:2288-2298. 5. Khalangot M, Tronko M, Kravchenko V et al. Diabetes Res Clin Pract.2009;20:611-615. 6. Diamicron MR 60 mg. Product Monograph.7. Drouin P. and the Diamicron MR Study Group.J Diabetes Complications.2000;14:185-191. 8. Sawada F, Inoguchi T, Tsubouchi H, et al. Metabolism.2008;57:1038–1045. 9. Del Guerra S, D'Aleo V, Lupi R, et al. Diabetes Metab.2009;35:293-298. 10. Katakami N, YamasakiY,Hayashi-Okano R, et al. Diabetologia.2004;47:1906-1913.

1 to 2 tablets* at breakfast

*In most patients

Full prescribing information available upon request.

SERVIER

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