OVERVIEW OF THE METABOLIC SYNDROME; AN EMERGING PANDEMIC OF PUBLIC HEALTH SIGNIFICANCE

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ABSTRACT

A cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which occur together have become known as the metabolic syndrome. Over the years various diagnostic criteria have been proposed by different organizations and most recently efforts have been made to unify the diagnostic criteria. This article is aimed at providing an overview of the metabolic syndrome and a rational approach to the management of this very important clinical syndrome.

INTRODUCTION AND HISTORICAL BACKGROUND

The concept of the metabolic syndrome has existed for at least 80 years[1]. It was first described by Kylin, a Swedish Physician, as the clustering of hypertension, hyperglycemia, and gout[2]. Later, in 1947, Vague drew attention to upper abdominal adiposity (android or male-type obesity) as the obesity phenotype that was commonly associated with type 2 diabetes mellitus and cardiovascular disease[3].

The field moved forward significantly following the 1988 Banting lecture given by Gerald Reaven. He described a cluster of risk factors for diabetes and cardiovascular disease comprising hypertension, hyperglycemia, low high-density lipoprotein (HDL) cholesterol, and raised very low-density lipoprotein (VLDL) triglyceride and named it Syndrome X. His main contribution was the introduction of the concept of insulin resistance[4].

The metabolic syndrome is also known as Syndrome X, the insulin resistance syndrome, cardio-metabolic syndrome, dysmetabolic syndrome and the deadly quartet syndrome[5,6]. The constellation include glucose intolerance (type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance), insulin resistance, central obesity, dyslipidemia, and hypertension, all well documented risk factors for cardiovascular diseases. The metabolic syndrome is associated with an increased risk for the development of type 2 diabetes mellitus and cardiovascular disease. People with the syndrome are twice as likely to die from a macrovascular event and three times as likely to have ischemic heart disease and stroke compared with people without the syndrome[7]. The syndrome is affecting the general population in epidemic proportion and is frequently associated with increased risk of cardiovascular morbidity and mortality[8,9].

Epidemiology

Over the past two decades, a striking increase in the number of people with the metabolic syndrome worldwide has taken place. This increase is associated with the global epidemic of obesity and diabetes. With the elevated risk not only of diabetes but also of cardiovascular disease from the metabolic syndrome, there is an urgent need for strategies to prevent the emerging global epidemic[10, 11].

In the United States, the metabolic syndrome is emerging as a major public health problem. Between 1988-1994 and 1999-2000, the age adjusted prevalence of the metabolic syndrome increased dramatically among women (23.5%) and only slightly among men (2.2%). An estimated 55 million adults in the United States had the syndrome in 2000. The age adjusted prevalence was 31.9% among Mexican Americans, 23.8% among non-Hispanic whites, and 21.6% among African Americans[12, 13].

The prevalence of the metabolic syndrome among a multi-ethnic population of 1276 men and women from four communities in Canada was 25.8% [14]. The prevalence in a population based cohort of 1565 individuals with diabetes in Italy was 75.6% [15]. A study done in Oman showed a prevalence of 23.0% in women and 19.5% in men[16]. The prevalence of the metabolic syndrome among healthy elderly South-western Nigerians was 35% [17] while a study done in Benin, Nigeria using three diagnostic tools- World Health Organization (WHO), Adult Treatment Panel (ATPIII) and International Diabetes Federation (IDF) criteria revealed a prevalence of 33.4%, 22.6% and 30.9% respectively[18].

Clinical Diagnosis of Metabolic Syndrome

Many investigations confirm that multiple cardiovascular risk factors of endogenous origin commonly aggregate in one individual. Although the metabolic syndrome is often referred to as a discrete entity, it is important to recognize it as a syndrome and not a defined uniform entity. No single pathogenesis has been elucidated but the syndrome could range from a cluster of unrelated risk factors to a constellation of risk factors linked through a common underlying mechanism.

In the effort to introduce the metabolic syndrome into clinical practice, several organizations have attempted to formulate simple criteria for its diagnosis. The first proposal came in 1998 from a consultation group on the definition of diabetes for the World Health Organization. This group emphasized insulin resistance as the major underlying risk factor and required evidence of insulin resistance for diagnosis[19].

In 1999, the European group for the Study of Insulin Resistance (EGIR) proposed a modification of the WHO definition. This group used the term insulin resistance syndrome rather than metabolic syndrome[20]. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP) introduced alternative clinical criteria for defining the metabolic syndrome. In so doing, the purpose of ATPIII was to identify people at higher long-term risk for arterosclerotic vascular disease (ASCVD) who deserved clinical and lifestyle modification to reduce risk[21].

Clinical measures	WHO (1998)	EGIR	ATPIII (2001)	AACE(2003)	IDF(2005)	IDF/ATPIII 2009
Insulin Resistance	IGT, IFG T2DM or lowered insulin sensitivity plus any two of the following	Plasma insulin > 75th percentile plus any 2 of the following	None but any 3 of the following 5 features	IGT or IFG plus any of the following	None	None Any 3 of the following
Body Weight	Men; waist to hip ratio = 0.90.Women =0.85 and or BMI = 30Kg/m²	WC= 94cm in men and 80cm in women	WC= 102cm in men or= 88cm in women	BMI= 25kg/m²	Increased WC (population specific) plus any 2 of the following	Increased WC (population specific)
Lipid	TG= 150mg/dl and/ or HDL-C= 35mg/dl in men and 39mg/dl in women.	TG=150mg/dl. HDL-C< 39mg/dl in men and women.	TG=150mg/dl. HDL-C < 40mg/dl in men and < 50mg/dl in women.	TG=150mg/dl and HDL-C < 40mg/dl in men or < 50mg/dl in women	TG=150mg/dl or on Rx. HDL-C <40mg/dl in men and <50mg/dl in women or on Rx.	Similar to IDF
Blood pressure	=140/90mmHg	=140/90	=130/85	=130/85	=130 or = 85 or on Rx	Similar to IDF
Glucose	IGT, IFG, T2DM	IGT, IFG (not diabetes)	FBG> 100mg/dl includes diabetes.	IGT or IFG but not diabetes	FBG> 100mg/dl including diabetes.	Similar to IDF
Others	Microalbuminuria			Other features of insulin resistance		

Table 1: Clinical diagnosis of metabolic syndrome

TG-Triglyceride HDL-C –High density lipoprotein IGT –Impaired glucose tolerance IFG- Impaired fasting glucose FBG – Fasting blood glucose T2 DM –Type 2 Diabetes Mellitus BMI- Body mass index Rx- Treatment

In 2003, the American Association of Clinical Endocrinologists (AACE) modified ATPIII criteria to focus on insulin resistance as the primary cause of the metabolic risk factors. Like the EGIR, the term insulin resistance syndrome was used[22]. In 2005, the International Diabetes Federation (IDF) published new criteria that again modified the ATPIII definition. The IDF writing group included several members of the original WHO consultation group. They liked the ATPIII criteria because of its clinical simplicity. They

Population Specific cut off points for waist circumference

	Male	Female
Europeans	≥94cm	≥80cm
South Asians	≥90cm	≥80cm
Japanese	≥85cm	≥90cm
Sub-Sahara Africa	≥94cm	≥80cm

Abnormal Body Fat
General body fat distribution
Central fat distribution
Liver fat content/ myocellular fat
Atherogenic Dyslipidemia
↑ Triglyceride
↓ HDL-C
↑ Small dense LDL particles
Dysglycemia
IFG, IGT
Insulin Resistance
↑ Fasting insulin/pro-insulin
Homeostatic model assessment for insulin resistance
Elevated free fatty acids
Vascular Dysregulation
Hypertension
Measurement of endothelial dysfunction
Microalbuminuria
Chronic renal disease
Pro-inflammatory States
↑ High-sensitivity CRP
↑ inflammatory cytokines (IL-6)
Prothrombotic States
Fibrinolytic factors (Plasminogen activator inhibitor)
Clotting factors (fibrinogen)
Others
Activation of the corticosteroid axis,
polycystic ovarian syndrome
Hyperuricemia, elevated asymmetric dimethylarginine
Non-alcoholic fatty liver/steatohepatitis,
obstructive sleep apnea

Table 2: Components of metabolic syndrome

were of the opinion that abdominal obesity is highly correlated with insulin resistance such that other more laborious measures of insulin resistance were unnecessary[23]. Most recently, efforts have been made to harmonize the criteria proposed by the ATPIII and the IDF consensus was that abdominal obesity should not be a prerequisite for diagnosis rather it should be one of the 5 criteria and the ethnic specific cut-off values as proposed by the IDF should be adopted[24].

Management of the Metabolic Syndrome
The primary goal of clinical management in individuals with the metabolic syndrome is to reduce risk for arterosclerotic vascular disease. Even in people with the metabolic syndrome, first-line therapy is directed toward major risk factors: LDL-Cholesterol above the target goal, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with the metabolic syndrome. For individuals with established diabetes, risk factor management must be intensified to diminish their higher risk for arterosclerotic vascular disease. The prime emphasis in management of the metabolic syndrome is to mitigate the modifiable underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes.

Obesity and Physical Inactivity
Weight reduction deserves first priority in individuals with obesity and the metabolic syndrome. Both weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric diet, increased physical activity and the use of principle of behavioral change. Medications such as phentermine, orlistat, sibrutamine, bupropion and rimonabant may also be of value in some patients when indicated. So also is bariatric surgery which is being used increasingly in the United States for severe obesity.

Increasing physical activity assists in weight reduction and reduces overall ASCVD risk. Current recommendations for the public call for accumulation of greater than 30 minutes of moderate-intensity exercise, such as brisk walking, on most, and preferably all days of the week. Preference is given to 60 minutes of moderate intensity brisk walking to be supplemented by other activities. These activities include use of treadmill, jogging, swimming, biking, golfing, team sports, and resistance training[25-31].

Atherogenic Dyslipidemia
This condition consists of abnormal level of triglycerides and apoB, small LDL particles, and low HDL-Cholesterol. LDL-Cholesterol is the primary target for therapy while the other lipid abnormalities are secondary. LDL-C reduction goals depend on

estimates of absolute risks as recommended by the ATPIII of the National Cholesterol Education Program. A related and potential secondary target is elevated total apoB, this measure denotes the number of atherogenic lipoprotein in the circulation. Statins lower both LDL-C and non-HDL-C by a similar percentage. Moreover statins reduce risk for ASCVD events in patients with the metabolic syndrome. Both fibrates and nicotinic acid reduce non-HDL-C and reportedly decrease the risk for ASCVD[32-34].

Systemic Hypertension
When overt hypertension is present without diabetes or chronic kidney disease, the goal for antihypertensive therapy is a blood pressure of less than 140/90mmHg. In the presence of diabetes or chronic kidney disease, the blood pressure goal is less than 130/80mmHg. Mild elevations of blood pressure often can be effectively controlled with lifestyle therapies such as weight control, increased physical activity, alcohol moderation, sodium reduction, smoking cessation and increased consumption of fresh fruits, vegetables and low-fat dairy products. If hypertension cannot be adequately controlled by lifestyle therapies, antihypertensive drugs usually are necessary to prevent long-term adverse effects[35]. Some investigators support angiotensin-converting enzyme (ACE) inhibitors as first line therapy for hypertension in metabolic syndrome, especially when either type 2 diabetes mellitus or chronic kidney disease is present. Indeed inhibition of the rennin-angiotensin system with ACE inhibitors or Angiotensin receptor blocker (ARBs) may lower risk for diabetes itself[36]. The results of a large clinical trial raised the possibility that use of diuretics in patients with impaired fasting glucose or impaired glucose tolerance may increase the likelihood of progression to type 2 diabetes mellitus, although diuretics do in fact lower the risk for cardiovascular events. Most investigators in the hypertension field believe that the potential benefit of low dose diuretics in combination antihypertensive therapy outweighs their risk especially in blacks[37].

Insulin Resistance and Hyperglycemia
Lifestyle intervention can reduce the risk for conversion of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) to type 2 diabetes. Preliminary reports indicate that metformin, thiazolidinediones or acarbose also reduce risk of type 2 diabetes in people with IFG or IGT[38, 39].

Glycemic control to a hemoglobin AIc of less than 7% will reduce microvascular complications and could reduce the risk for macrovascular disease as well. The use of lipid-altering, anti-hypertensive and anti-diabetic drugs can modify insulin sensitivity and body weight.

Metformin and thiazolidinediones improve insulin sensitivity but have discrepant effects on body weight: metformin reduces weight while thiazolidinediones increase it[40].

Prothrombotic State
This risk factor is characterized by elevations of fibrinogen, plasminogen activator inhibitor 1, and possibly other coagulation factors. The only available clinical approach to reducing an increased risk for arterial thrombosis in patients with diabetes is to give anti-platelet drugs. These drugs are universally recommended unless contraindicated in patients with established cardiovascular disease. In other people with the metabolic syndrome, aspirin prophylaxis is a therapeutic option when the risk for cardiovascular disease events is judged to be relatively high[41, 42].

Pro-inflammatory State
This condition can be identified by elevated cytokines (TNFá and interleukin 6) and acute phase reactants (C-reactive protein and fibrinogen). An elevated C-reactive protein is widely thought to be an indicator of a pro-inflammatory state and to be associated with higher risk for both cardiovascular disease and diabetes. Lifestyle therapies especially weight reduction, will reduce concentrations of this cytokine and thus mitigate an underlying inflammatory state. No specific anti-inflammatory drugs are available to treat this state. However, several drugs used to treat other metabolic risk-factors- statins, fibrates, and thiazolidinediones-have been reported to reduce concentrations of C-reactive proteins[43, 44].

CONCLUSION
Metabolic syndrome represents a constellation of cardiovascular risk factors which increase the risk of arterosclerotic cardiovascular disease and development of type 2 diabetes. Type 2 diabetes poses a major public health problem world-wide with a projected number of over 300 million people by 2025. Risk stratification, early identification and radical intervention will thus help in stemming the tide of this dangerous trend.

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