



DIABETES MELLITUS, OBESITY, HYPERTENSION: RISK FACTORS FOR METABOLIC SYNDROME

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ABSTRACT

The Metabolic Syndrome (MS) is a combination of interrelated metabolic abnormalities that significantly increase the risk of cardiovascular disease, Diabetes Mellitus Type 2 (DM2) and Obesity. Based on estimates from the Centers for Disease Control and Prevention, 57 million adults were classified as having metabolic syndrome in 2008, and this number climbed to 79 million in 2012. (Central) Obesity is a hallmark of all Metabolic Syndrome. Obesity as measured by waist circumference or BMI. It is the strongest risk factor for Metabolic Syndrome. Intra-abdominal obesity is direct delivery of pro-inflammatory adipokines and free fatty acids (FFA) to the liver, adversely affecting hepatic metabolism. Excess adipose tissue

associated with obesity promotes the conversion of cortisone to cortisol due to overexpression of 11 β -HSD1. Hypertension is the most significant CVD risk factor involved in MS prognosis. Persistent hypertension is a primary risk factor for stroke, heart attack, heart failure, aneurysm, and end-organ damage leads to imbalance in metabolic disturbance. DM2 is a crucial factor in MS and is highly predictive of Cardiovascular Disease. There is an increase in free fatty acids which promote oxidative stress, endothelial dysfunction, vascular damage, and atheroma formation. These all contributing risk factor promote pathogenesis of MS. Non Pharmacological, Pharmacological treatment and herbal plants available to treat MS. Several Plants showing some good therapeutic activity on MS like *Lonicera japonica*, *Viscum album*, *Litchi chinensis*, *Artocarpus heterophyllus*, *Psidium guajava*, *Polyalthia longifolia*. Among all *Lonicera japonica* may be used to treat metabolic syndrome in future.

Key Words: Metabolic Syndrome, Diabetes Mellitus, Obesity, 11 β -HSD 1.

INTRODUCTION

The metabolic syndrome (MS) is a combination of interrelated metabolic abnormalities that significantly increase the risk of cardiovascular disease, type 2 diabetes mellitus (DM2) and Obesity. Its prevalence is increasing worldwide and is a serious public health problem. Each component of MS is individually associated with an increased risk of cardiovascular disease; however, whether MS leads to greater cardiovascular risk than the sum of its components remains a matter of debate ⁽¹⁾.

The prevalence of the metabolic syndrome has varied markedly between different studies, most likely because of the lack of accepted criteria for the definition of MS. The three most important widely recognized recent attempts to define the metabolic syndrome include the WHO report from 1991 ⁽²⁾, The European Group for the study of Insulin Resistance (EGIR) in 1999, and the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in 2001. More recently, the American College of Endocrinology (ACE) released a position statement on what it refers to as the insulin resistance syndrome, and in 2005 the International Diabetes Federation (IDF) published new criteria for identifying persons with metabolic syndrome. The new IDF definition addresses both clinical and research needs, providing an accessible, diagnostic tool suitable for worldwide use ⁽³⁾.

NEW DEFINITIONS OF METABOLIC SYNDROME

The AHA/NHLBI 2005 ⁽⁴⁾ definition is derived from the NCEP—ATP III 2001 definition ⁽⁵⁾ and requires at least three of the following criteria to be present:

- Waist circumference greater than or equal to 102 cm in men and greater than or equal to 88 cm in women;
- Triglycerides greater than or equal to 1.50 g/L or a specific treatment for elevated triglycerides (TG);
- High density lipoprotein (HDL) cholesterol less than 0.40 g/L in men and less than 0.50 g/L in women or a specific treatment for reduced HDL cholesterol ;
- Systolic BP greater than or equal to 130mmHg or diastolic BP greater than or equal to 85mmHg or antihypertensive treatment (BP);
- Fasting glucose greater than or equal to 1.00 g/L or drug treatment for elevated glucose (G);

The changes that were made in 2005 to the NCEP—ATP III 2001 definition slightly reduced the threshold for waist circumference (it had been strictly greater than 102 cm in men and greater than 88 cm in women) but significantly lowered the threshold for glucose (it had been greater than or equal to 1.10 g/l). Furthermore, individuals treated for dyslipidaemia, hypertension or hyperglycaemia were included. Consequently, based on this new definition, the number of subjects and, therefore, the prevalence of metabolic syndrome increased.

The IDF definition ^[6] requires the presence of abdominal obesity, defined as :

- waist circumference greater than or equal to 94 cm in men and greater than or equal to 80 cm in women (W)
- Triglycerides greater than or equal to 1.50 g/L or a specific treatment for lipid abnormalities (TG);
- HDL cholesterol less than 0.40 g/L in men and less than 0.50 g/L in women or a specific treatment for lipid abnormalities (HDL);
- Systolic BP greater than or equal to 130mmhg or diastolic BP greater than or equal to 85mmhg or antihypertensive treatment (BP);
- Fasting glucose greater than or equal to 1.00 g/L or diabetes (G) ; atleast two of the following criteria:

The IDF definition introduces fundamental changes in the requirements needed for defining metabolic syndrome; it significantly reduces the threshold for waist circumference and glucose and includes treated individuals and those with diabetes.

The definition from the ESC/ESH consensus ⁽⁷⁾ requires at least three of the following five criteria to be present:

- Waist circumference greater than 102 cm in men and greater than 88 cm in women (W);
- Systolic BP greater than or equal to 130mmhg or diastolic BP greater than or equal to 85mmhg (BP);
- HDL cholesterol less than 0.40 g/L in men and less than 0.46 g/L in women (HDL);
- Triglycerides greater than or equal to 1.50 g/L (TG);
- Fasting glucose greater than or equal to 1.0 g/L (G).

The ESC/ESH definition includes a combination of criteria from the NCEP—ATP III 2001 definition (i.e., abdominal obesity, BP and TG) and new thresholds for HDL cholesterol in men and for glycaemia since it does not include treatment for hypoglycaemia or diabetes.

The lack of epidemiological data available for this definition is most likely to be attributed to the fact that it was published only recently. Concerns and criticisms pertaining to the lack of homogeneity among these definitions remain. Lowering the thresholds for several of the components and the inclusion of treated subjects require further studies to determine the impact of these components on morbidity and mortality risk for subjects identified as having metabolic syndrome according to these new definitions.

PREVALENCE

The prevalence of metabolic syndrome is high and increasing among adults parallel with lifestyle risk factors and changes in population demographics. Based on estimates from the Centers for Disease Control and Prevention, 57 million adults were classified as having metabolic syndrome in 2008, and this number climbed to 79 million in 2012⁽⁸⁾. In fact, approximately 1 in 4 adults older than 20 years has this condition⁽⁹⁾. The prevalence of metabolic syndrome varies by age, race/ethnicity, and gender. In the general population, the prevalence of metabolic syndrome is highly age-dependent, ranging from 7% for ages 20 to 29 to more than 40% for those older than 70⁽¹⁰⁾. Among the various ethnicities, Mexican Americans have the highest age adjusted prevalence at 32%⁽¹⁰⁾. Although in the general population the prevalence of metabolic syndrome is similar in men and women, Mexican American and African American women have a higher prevalence than their male counterparts⁽¹⁰⁾. In addition, metabolic syndrome was found to increase markedly in women, independent of other risk factors as hormonal changes occurred during the transition to menopause

HISTORY

The term "metabolic syndrome" dates back to at least the late 1950s, but came into common usage in the late 1970s to describe various associations of risk factors with diabetes that had been noted as early as the 1920⁽¹¹⁾.

The Marseilles physician Dr. Jean Vague, in 1947, observed that upper body obesity appeared to predispose to diabetes, atherosclerosis, gout and calculi⁽¹¹⁾.

Avogadro, Crepaldi and coworkers described six moderately obese patients with diabetes, hypercholesterolemia, and marked hypertriglyceridemia, all of which improved when the patients were put on a hypocaloric, low-carbohydrate diet⁽¹¹⁾.

In 1977, Haller used the term "metabolic syndrome" for associations of obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and hepatic steatosis when describing the

additive effects of risk factors on atherosclerosis. The same year, Singer used the term for associations of obesity, gout, diabetes mellitus, and hypertension with hyperlipoproteinemia⁽¹²⁾.

In 1977 and 1978, Gerald B. Phillips developed the concept that risk factors for myocardial infarction concur to form a "constellation of abnormalities" (i.e., glucose intolerance, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, and hypertension) associated not only with heart disease, but also with aging, obesity and other clinical states. He suggested there must be an underlying linking factor, the identification of which could lead to the prevention of cardiovascular disease; he hypothesized that this factor was sex hormones⁽¹³⁾.

In 1988, in his Banting lecture, Gerald M. Reaven proposed insulin resistance as the underlying factor and named the constellation of abnormalities syndrome X. Reaven did not include abdominal obesity, which has also been hypothesized as the underlying factor, as part of the condition⁽¹⁴⁾.

The terms "metabolic syndrome," "insulin resistance syndrome," and "syndrome X" are now used specifically to define a constellation of abnormalities associated with increased risk for the development of type 2 diabetes and atherosclerotic vascular disease (e.g., heart disease and stroke)⁽¹⁵⁾.

- **Obesity, Diabetes Mellitus, Hypertension, These three disease responsible for pathogenesis of Metabolic Syndrome.**

OBESITY & METABOLIC SYNDROME

(Central) Obesity is a hallmark of all Metabolic Syndrome. Obesity results from chronic positive energy balance and excess energy can be localised in the subcutaneous compartment, intra-abdominally and ectopically (eg . steatosis and intra- and extra-myocellular lipid). This excess stored lipid contributes to metabolic derangements via three mechanisms. Firstly, adipose is a highly active endocrine organ, releasing a vast array of growth factors, lipids and cytokines collectively known as adipokines. These are, in the main, associated with adverse metabolic sequelae and their production is generally increased as fat stores increase. Additionally, many adipokines are differentially released by subcutaneous and intra-abdominal fat, adding mechanistic significance to differences in adipose distribution. Ectopic fat adversely affects tissue metabolism locally, as is seen particularly in the liver, muscle and pancreatic beta cells. Secondly, intrabdominal fat has venous drainage via the portal system

directly to the liver. Thus, a consequence of intra-abdominal obesity is direct delivery of pro-inflammatory adipokines and free fatty acids (FFA) to the liver, adversely affecting hepatic metabolism. Third is the “mechanical” effect of obesity. This includes the relatively obvious effect of diaphragmatic splinting impairing respiratory function, but can be extended to restricting capacity to exercise and the cosmetic aspects which may contribute to psychological components of the Metabolic Syndrome, as part of the response to chronic disease ⁽¹⁶⁾.

Obesity as measured by waist circumference or BMI is the strongest risk factor for Metabolic Syndrome. Obesity reduces the amount of lipoprotein lipase (LpL) action which circulates lipids for clearance and thus interferes with Triacetyl glycerol removal and may cause atherogenesis. Obesity also promotes hyperglycemia by overloading the body with excess fuel. Tissues become insulin resistant leading to abnormal changes in cellular enzyme activities. Hyperglycemia also triggers hyperinsulinemia which causes increased activation of the sympathetic nervous system and hypothalamopituitary adrenal axis. In addition, the excess adipose tissue associated with obesity promotes the conversion of cortisone to cortisol due to overexpression of 11 β -HSD 1. These conditions, if untreated, result in hypertension. Obesity also has an effect on thrombosis and inflammation by increasing the secretion of clotting proteins ⁽¹⁷⁾.

HYPERTENSION & METABOLIC SYNDROME

The role of cardiovascular disease Hypertension (HTN), loosely defined as a blood pressure equal to or greater than 140/90 mm Hg, is the most significant CVD risk factor involved in MS prognosis. HTN is directly caused by increased circulating blood volume, decreased arteriolar elasticity, and endothelial dysfunction which triggers a decrease in production of vasodilators such as nitric oxide (NO) and promotes the circulation of inflammatory cytokines ⁽¹⁸⁾. Persistent hypertension is a primary risk factor for stroke, heart attack, heart failure, aneurysm, and end-organ damage. 11 β -HSD1 enzyme catalyse the interconversion from inactive cortisone to the active cortisone. Upon induction of 11 β -HSD1 enzyme, Excessive glucocorticosteroids generated from Inactive cortisone. glucocorticoids induce the expression of angiotensin- converting enzyme within vascular smooth muscle and significantly decreased the expression level of endothelial nitric oxide synthase (eNOS) in human endothelial cells. It enhance the production of endothelin leads to enhance vasoreactivity of blood vessels as well as inhibition of cofactor tetrahydrobiopterin required

for the synthesis of nitric oxide and impair baroreceptor sensitivity. From above contributing factor leads to endothelium dysfunction arise and introduce various cardiovascular problems. Glucocorticoids play a very important role for the pathogenesis of hypertension by excessive generation of aldosterone with the help of rate limiting enzyme 11β -HSD1⁽¹⁹⁾. So it indicate that 11β -HSD1 play a very important role in regulation of blood pressure by controlling the level of cortisol level.

DIABETES MELLITUS & METABOLIC SYNDROME

Diabetes Mellitus (DM) is a disorder characterized by persistent hyperglycemia due to insulin resistance. Insulin is a pleiotropic hormone which signals a number of cellular processes such as glucoregulation, lipid metabolism, and protein synthesis in multiple tissues. In patients with DM, these actions of insulin are reduced. Consequently, there is an increase in free fatty acids which promote oxidative stress, endothelial dysfunction, vascular damage, and atheroma formation. The clinical results are high BP, HDL suppression, and high triglycerides (TAG) additionally, DM is associated with macrovascular (myocardial infarction, stroke) and microvascular (retinopathy, neuropathy, renal disease) problems which interfere with blood and nutrient delivery to multiple tissues throughout the body. DM is a crucial factor in MS and is highly predictive of Cardiovascular Disease (CVD) risk. In 1999 the San Antonio Heart Study found that insulinresistant patients had a greater incidence of hypertension and dyslipidemia than non-insulin-resistant patients⁽²⁰⁾. Other epidemiological studies have established a similar relationship between hyperglycemia and CVD which implicates the importance of DM as a risk factor for cardiovascular mortality. MS has been documented across all racial groups in the U.S.⁽²¹⁾ and in the rest of the world. However, MS prevalence is greatest amongst Hispanics and blacks, particular in women. The most prevalent combination of risk factors in blacks is obesity/HTN, while in other ethnic groups (White, Hispanics and Asians) it is obesity/DM. The racial disparity is largely attributed to environmental, lifestyle and social factors which influence the incidence of obesity, CVD, and DM⁽²²⁾. glucocorticoids increase hepatic gluconeogenesis which decreases glucose utilization by cells and leads to elevated circulating levels of glucose and insulin resistance. Glucocorticoids (GCs) have been shown to destroy β cells in the islets of diabetic rats, and 11β -HSD1 expression and activity are increased in the islets of diabetic fatty rats with β cell destruction. It may conclude that 11β -HSD1 plays a very important role in development of diabetes and associated vascular complication.

TESTS

A doctor may suspect that a patient has metabolic syndrome if he has central/abdominal obesity and a sedentary lifestyle, but both laboratory and non-laboratory tests are important in establishing the diagnosis. Recommended tests include:

PATHOLOGICAL TESTS

Glucose. Usually a fasting glucose test is performed but, in some cases, a doctor may also order a post prandial glucose (after a meal) or a GTT (glucose tolerance test – several glucose tests that are taken before and at timed intervals after a glucose challenge). The goal of glucose testing is to determine whether a patient has an impaired response to glucose resulting in elevated blood glucose concentrations.

Lipid profile. Measures HDL, LDL, Triglycerides and VLDL. If the triglycerides are significantly elevated, a DLDL (direct measurement of the LDL) may need to be done. There are other laboratory tests that are not recommended for diagnosing metabolic syndrome but that may be ordered by some doctors to provide additional information.

C-peptide. A reliable indicator of endogenous insulin production.

Microalbumin. An early indicator of kidney disease, this test is used to help monitor diabetics and is recommended under the WHO criteria.

Hs-Crp. A measure of low levels of inflammation that may be tested as part of an evaluation of cardiac risk.

Insulin. The fasting insulin test is considered too variable to be clinically useful in diagnosing metabolic syndrome but, if measured, will usually be elevated in those affected. Tests for which the clinical utility in diagnosing metabolic syndrome has not yet been established include plasminogen activator inhibitor-1 (PAI-1) and proinsulin.

NON-PATHOLOGICAL TESTS

Blood pressure: To check for hypertension

Weight and waist circumference. To document abdominal obesity

BMI (Body Mass Index). An alternate measure of obesity that is used by many doctors. ⁽²³⁾

PATHOGENIC RISK FACTORS RESPONSIBLE FOR METABOLIC SYNDROME

(24)

- Overexpression of 11 β - HSD 1
- Abnormal Glucagon like peptide 1 (GLP – 1)
- Induction of Phosphoenol Pyruvate Carboxy Kinase (PEPCK)
- Downregulation of PPAR - γ
- Abnormal Adipokines level
- Abnormal Lipid profile (Cholesterol, TG, LDL, VLDL, HDL)
- Changed in Nitric oxide ,Endothelin, Angiotensin II level. (vascular reactivity)
- Generation of cytokines like TNF - α , IL- 1, IL- 6 , MCP – 1
- Generation of free radicals
- increased in blood pressure
- Disruption of pancreatic β cells.

HOW CAN METABOLIC SYNDROME BE PREVENTED?**NON PHARMACOLOGICAL TREATMENTS**

Making healthy lifestyle choices is the best way to prevent metabolic syndrome. One important lifestyle choice is to maintain a healthy weight. Other than weighing yourself on a scale, there are two ways to know whether you're at a healthy weight: waist measurement and body mass index (BMI). A waist measurement indicates your abdominal fat and is linked to your risk of heart disease and other diseases. To measure your waist, stand and place a tape measure around your middle, just above your hipbones. Measure your waist just after you breathe out. Make sure the tape is snug but doesn't squeeze the flesh. A waist measurement of less than 35 inches for women and less than 40 inches for men is the goal for preventing metabolic syndrome; it's also the goal when treating metabolic syndrome. BMI measures your weight in relation to your height and gives an estimate of your total body fat. A BMI between 25 and 29.9 is considered overweight. A BMI of 30 or more is considered obese. A BMI of less than 25 is the goal for preventing metabolic syndrome; it's also the goal when treating metabolic syndrome⁽²⁵⁾. You can calculate your BMI using the National Heart, Lung, and Blood Institute's online calculator, or your health care provider can calculate your BMI. To maintain a healthy weight, follow a healthy diet and try not to overeat. A healthy diet includes a variety of fruits, vegetables, and whole grains. It also includes lean meats, poultry, fish, beans, and fat-free or low-fat milk or milk products. A healthy diet is low in saturated fat, trans fat, cholesterol, sodium (salt), and added sugar⁽²⁶⁾. Doing physical activity regularly

also can help you maintain a healthy weight. Before starting any kind of exercise program or new physical activity, talk with your doctor about the types and amounts of physical activity that are safe for you. Make sure to schedule regular doctor visits to keep track of your cholesterol, blood pressure, and blood sugar levels. A blood test called a lipoprotein panel will show your levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides⁽²⁷⁾.

PHARMACOLOGICAL TREATMENTS

If lifestyle changes aren't enough, your doctor may prescribe medicines to help you control your risk factors. Medicines may be prescribed to help treat unhealthy cholesterol levels, high blood pressure, and high blood sugar. Unhealthy cholesterol levels are treated with medicines such as statins, fibrates, or nicotinic acid. High blood pressure is treated with medicines such as diuretics or ACE inhibitors. High blood sugar is treated with oral medicines (such as metformin), insulin injections, or both. Low-dose aspirin can help reduce the risk of blood clots, especially for people at high risk of heart disease⁽²⁸⁾.

HERBAL PLANTS

Plant and plant products are being used as a source of medicine since long. The medicinal properties of plants have been investigated in the recent scientific developments activities, no side effects and economic viability. Now no potential allopathic medications are available that can eradicate cause of disease so far but the plant based drugs or their products are the only possible remedies for the treatment, inspite of this, the large plant kingdom has to be explored, as an intention to verify the therapeutic usefulness of plants available at hand. Hence we undertake field surveys and contact with ayurvedic practitioners (vaidyas).

Several Plants showing some good therapeutic activity on Metabolic Syndrome like *Viscum album*⁽²⁹⁾, *Litchi chinensis*⁽³⁰⁾, *Artocarpus heterophyllus*⁽³¹⁾, *Psidium guajava*⁽³²⁾, *Polyalthia longifolia*⁽³³⁾. Nowadays *Lonicera japonica* has also been traditionally indicated for treatment of diabetes, and also having potent anti oxidant property⁽³⁴⁾. *Lonicera japonica* Thunb. (Caprifoliaceae), a widely used traditional Chinese medicine, was known as Jin Yin Hua (Chinese:), Ren Dong and Japanese honeysuckle⁽³⁵⁾. Since 1995, *Lonicera japonica* has been listed in the Pharmacopoeia of the People's Republic of China and more than 500 prescriptions containing *Lonicera japonica* have been used to treat various diseases in China (<http://www.zysj.com.cn>). Chlorogenic acid, rutin, Triterpenoid a major bioactive component in the flower buds of *Lonicera japonica*⁽³⁶⁾, chlorogenic acid has received more and more

attention because of its antioxidant⁽³⁷⁾, 11 β -HSD 1 inhibitory activity⁽³⁸⁾, Considering the importance of plants as a source of medicines, *Lonicera japonica* may be used to treat metabolic syndrome in future.

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