A Comprehensive of Metabolic Syndrome

K. Malleswari¹*, D. Rama Brahma Reddy², M. Shahina Begum³

Associate Professor, ¹Principal and Professor, ²Student, ³Department of pharmaceutics
Nalanda Institute of Pharmaceutical Sciences, Kantepudi (V), Sattenapalli (M), Guntur (Dist), 522438, Andhra Pradesh, India,

Abstract: Metabolic syndrome (MetS) represents a cluster of metabolic abnormalities that include hypertension, central obesity, insulin resistance, and atherogenic dyslipidemia, and is strongly associated with an increased risk for developing diabetes and atherosclerotic and non atherosclerotic cardiovascular disease (CVD). The pathogenesis of MetS involves both genetic and acquired factors that contribute to the final pathway of inflammation that leads to CVD. MetS has gained significant importance recently due to the exponential increase in obesity worldwide. Early diagnosis is important in order to employ lifestyle and risk factor modification. Here, we review the epidemiology and pathogenesis of MetS, the role of inflammation in MetS, and summarize existing natural therapies for MetS.

Keywords: Metabolic syndrome, nutraceuticals, cardiovascular disease, hypertension, obesity, insulin resistance, atherogenic dyslipidaemia

I. INTRODUCTION
Metabolic syndrome is a clustering of at least three of the following five medical conditions: abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (HDL). Metabolic syndrome is associated with the risk of developing cardiovascular disease and type 2 diabetes. In the U.S., about 25% of the adult population has metabolic syndrome, a proportion increasing with age, particularly among racial and ethnic minorities.¹² Insulin resistance, metabolic syndrome, and pre diabetes are closely related to one another and have overlapping aspects. The syndrome is thought to be caused by an underlying disorder of energy utilization and storage. The cause of the syndrome is an area of ongoing medical research.

II. PATHOPHYSIOLOGY
It is common for there to be a development of visceral fat, after which the adipocytes (fat cells) of the visceral fat increase plasma levels of TNF-α and alter levels of other substances (e.g., adiponectin, resistin, and PAI-1). TNF-α has been shown to cause the production of inflammatory cytokines and also possibly trigger cell signaling by interaction with a TNF-α receptor that may lead to insulin resistance.³ An experiment with rats fed a diet with 33% sucrose has been proposed as a model for the development of metabolic syndrome. The sucrose first elevated blood levels of triglycerides, which induced visceral fat and ultimately resulted in insulin resistance. The progression from visceral fat to increased TNF-α to insulin resistance has some parallels to human development of metabolic syndrome. The increase in adipose tissue also increases the number of immune cells, which play a role in inflammation. Chronic inflammation contributes to an increased risk of hypertension, atherosclerosis and diabetes.⁴ The involvement of the endocannabinoid system in the development of metabolic syndrome is indisputable.⁵ Endocannabinoid overproduction may induce reward system dysfunction and cause executive dysfunctions (e.g., impaired delay discounting), in turn perpetuating unhealthy behaviors. The brain is crucial in development of metabolic syndrome, modulating peripheral carbohydrate and lipid metabolism.⁴
Metabolic syndrome can be induced by overfeeding with sucrose or fructose, particularly concomitantly with high-fat diet.\(^7\) The resulting oversupply of omega-6 fatty acids, particularly arachidonic acid (AA), is an important factor in the pathogenesis of metabolic syndrome. Arachidonic acid (with its precursor – linoleic acid) serves as a substrate to the production of inflammatory mediators known as eicosanoids, whereas the arachidonic acid-containing compound diacylglycerol (DAG) is a precursor to the endocannabinoid 2-arachidonoylglycerol (2-AG) while fatty acid amide hydrolase (FAAH) mediates the metabolism of anandamide into arachidonic acid.\(^8\) Anandamide can also be produced from N-acylphosphatidylethanolamine via several pathways. Anandamide and 2-AG can also be hydrolyzed into arachidonic acid, potentially leading to increased eicosanoids synthesis.

III. EPIDEMIOLOGY

Worldwide prevalence of MetS ranges from <10% to as much as 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied, and the definition of the syndrome used.\(^8\) In general, the IDF estimates that one-quarter of the world’s adult population has the MetS. Higher socioeconomic status, sedentary lifestyle, and high body mass index (BMI) were significantly associated with MetS. Camerone et al. have concluded that the difference in genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education all influence the prevalence of the MetS.\(^9\) The observed prevalence of the MetS in National Health and Nutrition Examination Survey (NHANES) was 5% among the subjects of normal weight, 22% among the overweight, and 60% among the obese.\(^10\) It further increases with age (10% in individuals aged 20–29, 20% in individuals aged 40–49, and 45% in individuals aged 60–69).\(^11\) The prevalence of MetS (based on NCEP-ATP III criteria, 2001) varied from 8% to 43% in men and from 7% to 56% in women around the world. Park et al. noticed that there is an increase in the prevalence of MetS from 20 years old through the sixth and seventh decade of life for males and females, respectively. Ponholzer et al. reported that there is high prevalence of MetS among postmenopausal women, which varies from 32.6% to 41.5%. A Framingham Heart Study report indicated that a weight increase of ≥2.25 kg over a period of 16 yr was associated with an up to 45% increased risk of developing the MetS, and it has been shown by Palaniappan et al. that each 1 cm increase in waist circumference (WC) is associated with an adjusted 80% increased risk of developing the syndrome within 5 years. The metabolic alterations occur simultaneously more frequently than would be expected by chance and the concurrence of several factors increases cardiovascular risk over and above the risk associated with the individual factors alone. The risk increases with the number of MetS components present.\(^12\)

IV. SIGNS AND SYMPTOMS

The key sign of metabolic syndrome is central obesity, also known as visceral, male-pattern or apple-shaped adiposity. It is characterized by adipose tissue accumulation predominantly the waist and trunk. Other signs of metabolic syndrome include high blood pressure, decreased fasting serum HDL cholesterol, elevated fasting serum triglyceride level, impaired fasting glucose, insulin resistance, or prediabetes. Associated conditions include hyperuricemia; fatty liver (especially in concurrent obesity) progressing to nonalcoholic fatty liver disease; polycystic ovarian syndrome in women and erectile dysfunction in men; and acanthuses Nigerians.

V. COMPLICATION

Metabolic syndrome can lead to several serious and chronic complications, including type-2 diabetes, cardiovascular diseases, stroke, kidney disease and nonalcoholic fatty liver disease.

VI. CAUSES

The mechanisms of the complex pathways of metabolic syndrome are under investigation. The pathophysiology is very complex and has been only partially elucidated. Most people affected by the condition are older, obese, sedentary, and have a degree of insulin resistance. Stress can also be a contributing factor. The most important risk factors are diet (particularly sugar-sweetened beverage consumption),\(^13\) genetics,\(^14\) aging, sedentary behavior or low physical activity, disrupted chronology/sleep, mood...
disorders/psychotropic medication use, and excessive alcohol used. The pathogenic role played in the syndrome by the excessive expansion of adipose tissue occurring under sustained overeating, and its resulting lipotoxicity was reviewed by Vidal-Puig.\textsuperscript{15} There is debate regarding whether obesity or insulin resistance is the cause of the metabolic syndrome or if they are consequences of a more far-reaching metabolic derangement. Markers of systemic inflammation, including C-reactive protein, are often increased, as are fibrinogen, interleukin 6, tumor necrosis factor-alpha (TNF-\(\alpha\)), and others. Some have pointed to a variety of causes, including increased uric acid levels caused by dietary fructose.\textsuperscript{16}[17]

Research shows that Western diet habits are a factor in development of metabolic syndrome, with high consumption of food that is not biochemically suited to humans. Weight gain is associated with metabolic syndrome. Rather than total adiposity, the core clinical component of the syndrome is visceral and/or ectopic fat (i.e., fat in organs not designed for fat storage) whereas the principal metabolic abnormality is insulin resistance. The continuous provision of energy via dietary carbohydrate, lipid, and protein fuels, unmatched by physical activity/energy demand, creates a backlog of the products of mitochondrial oxidation, a process associated with progressive mitochondrial dysfunction and insulin resistance.

VII. STRESS
Recent research indicates prolonged chronic stress can contribute to metabolic syndrome by disrupting the hormonal balance of the hypothalamic-pituitary-adrenal axis (HPA-axis). A dysfunctional HPA-axis causes high cortical levels to circulate, which results in raising glucose and insulin levels, which in turn cause insulin-mediated effects on adipose tissue, ultimately promoting visceral adiposity, insulin resistance, dyslipidemia and hypertension, with direct effects on the bone, causing "low turnover" osteoporosis. HPA-axis dysfunction may explain the reported risk indication of abdominal obesity to cardiovascular disease (CVD), type 2 diabetes and stroke.\textsuperscript{18} Psychosocial stress is also linked to heart disease.

VIII. OBESITY
Central obesity is a key feature of the syndrome, being both a sign and a cause, in that the increasing adiposity often reflected in high waist circumference may both result from and contribute to insulin resistance. However, despite the importance of obesity, affected people who are of normal weight may also be insulin-resistant and have the syndrome.\textsuperscript{19}

IX. SEDENTARY LIFESTYLE
Physical inactivity is a predictor of CVD events and related mortality. Many components of metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central); reduced HDL cholesterol; and a trend toward increased triglycerides, blood pressure, and glucose in the genetically susceptible. Compared with individuals who watched television or videos or used their computers for less than one hour daily, those who carried out these behaviors for greater than four hours daily have a twofold increased risk of metabolic syndrome.

X. AGING
Metabolic syndrome affects 60% of the U.S. population older than age 50. With respect to that demographic, the percentage of women having the syndrome is higher than that of men. The age dependency of the syndrome's prevalence is seen in most populations around the world.

XI. DIABETES MELLITUS TYPE
The metabolic syndrome quintuples the risk of type 2 diabetes mellitus. Type 2 diabetes is considered a complication of metabolic syndrome. In people with impaired glucose tolerance or impaired fasting glucose, presence of metabolic syndrome doubles the risk of developing type 2 diabetes. It is likely that prediabetes and metabolic syndrome denote the same disorder, defining it by the different sets of biological markers.

The presence of metabolic syndrome is associated with a higher prevalence of CVD than found in people with type 2 diabetes or impaired glucose tolerance without the syndrome. Hypo adiponectinemia has been shown to increase insulin resistance and is considered to be a risk factor for developing metabolic syndrome.\textsuperscript{20}

XII. CORONARY HEART DISEASE
The approximate prevalence of the metabolic syndrome in people with coronary artery disease (CAD) is 50%, with a prevalence of 37% in people with premature coronary artery disease (age 45), particularly in women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., nutrition, physical activity, weight reduction, and, in some cases, drugs), the prevalence of the syndrome can be reduced.

XIII. LIPODYSTROPHY
Lip dystrophic disorders in general are associated with metabolic syndrome. Both genetic (e.g., Berardinelli-Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired (e.g., HIV-related lipodystrophy in people treated with highly active antiretroviral therapy) forms of lipodystrophy may give rise to severe insulin resistance and many of metabolic syndrome's components.

XIV. RHEUMATIC DISEASES
There is research that associates co morbidity with rheumatic diseases. Both psoriasis and psoriatic arthritis have been found to be associated with metabolic syndrome.

XV. CHRONIC OBSTRUCTIVE PULMONARY DISEASE
Metabolic syndrome is seen to be a co morbidity in up to 50 percent of those with chronic obstructive pulmonary disease (COPD). It may pre-exist or may be a consequence of the lung pathology of COPD.\textsuperscript{21}

XVI. DIAGNOSIS
A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity published a guideline to harmonize the definition of the metabolic syndrome.
The previous definitions of the metabolic syndrome by the International Diabetes Federation (IDF) and the revised National Cholesterol Education Program (NCEP) are very similar, and they identify individuals with a given set of symptoms as having metabolic syndrome. There are two differences, however: the IDF definition states that if body mass index (BMI) is greater than 30 kg/m², central obesity can be assumed, and waist circumference does not need to be measured. However, this potentially excludes any subject without increased waist circumference if BMI is less than 30. Conversely, the NCEP definition indicates that metabolic syndrome can be diagnosed based on other criteria. Also, the IDF uses geography-specific cut points for waist circumference, while NCEP uses only one set of cut points for waist circumference regardless of geography.

**XVII. IDF**

The International Diabetes Federation consensus worldwide definition of metabolic syndrome (2006) is: Central obesity (defined as waist circumference ≤ with ethnicity-specific values) AND any two of the following:

- Raised triglycerides: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure (BP): systolic BP > 130 or diastolic BP > 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG): > 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

If FPG is > 5.6 mmol/L or 100 mg/dL, an oral glucose tolerance test is strongly recommended, but is not necessary to define presence of the syndrome. If BMI is > 30 kg/m², central obesity can be assumed and waist circumference does not need to be measured.

**XVIII. WHO**

The World Health Organization (1999) requires the presence of any one of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND any two of the following:

- Blood pressure ≥ 140/90 mmHg
- Dyslipidaemia: triglycerides (TG) ≥ 1.695 mmol/L and HDL cholesterol ≤ 0.9 mmol/L (male), ≤ 1.0 mmol/L (female)
- Central obesity: waist: hip ratio > 0.90 (male); > 0.85 (female), or BMI > 30 kg/m²
- Micro albuminuria: urinary albumin excretion ratio ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g

**XIX. EGIR**

The European Group for the Study of Insulin Resistance (1999) requires insulin resistance defined as the top 25% of the fasting insulin values among non diabetic individuals AND two or more of the following:

- Central obesity: waist circumference ≥ 94 cm or 37 inches (male), ≥ 80 cm or 31.5 inches (female)
- Dyslipidaemia: TG ≥ 2.0 mmol/L and/or HDL-C < 1.0 mmol/L or treated for dyslipidaemia
- Blood pressure ≥ 140/90 mmHg or antihypertensive medication
- Fasting plasma glucose ≥ 6.1 mmol/L

**XX. NCEP**

The U.S. National Cholesterol Education Program Adult Treatment Panel III (2001) requires at least three of the following:

- Central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 35 inches (female)
- Dyslipidaemia: TG ≥ 1.7 mmol/L (150 mg/dl)
- Dyslipidaemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female)
- Blood pressure ≥ 130/85 mmHg (or treated for hypertension)
- Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL)

**XXI. CARDIO METABOLIC INDEX**

The Cardio metabolic index (CMI) is a tool used to calculate risk of type 2 diabetes, non-alcoholic fatty liver disease, and metabolic issues. It is based on calculations from waist-to-height ratio and triglycerides-to-HDL cholesterol ratio. CMI can also be used for finding connections between cardiovascular disease and erectile dysfunction. When following an anti-inflammatory diet (low-glycemic carbohydrates, fruits, vegetables, fish, less red meat and processed foods) the markers may drop resulting in a significant reduction in body weight and adipose tissue.

**XXII. PREVENTION**

Various strategies have been proposed to prevent the development of metabolic syndrome. These include increased physical activity (such as walking 30 minutes every day), and a healthy, reduced calorie diet. Many studies support the value of a healthy lifestyle as above. However, one study stated these potentially beneficial measures are effective in only a minority of people, primarily because of a lack of compliance with lifestyle and diet changes. The International Obesity Taskforce states that interventions on a sociopolitical level are required to reduce development of the metabolic syndrome in populations.

The Caerphilly Heart Disease Study followed 2,375 male subjects over 20 years and suggested the daily intake of an Imperial pint (~568 mL) of milk or equivalent dairy products more than halved the risk of metabolic syndrome. Some subsequent studies support the authors’ findings, while others dispute them. A systematic review of four randomized controlled trials said that, in the short term, a paleolithic nutritional pattern improved three of five measurable components of the metabolic syndrome in participants with at least one of the components.

**XXIII. MEDICATIONS**

Generally, the individual disorders that compose the metabolic syndrome are treated separately. Diuretics and ACE inhibitors may be used to treat hypertension. Various cholesterol medications may be useful if LDL cholesterol, triglycerides, and/or HDL cholesterol is abnormal.

**XXIV. DIET**
Dietary carbohydrate restriction reduces blood glucose levels, contributes to weight loss, and reduces the use of several medications that may be prescribed for metabolic syndrome.

**XXV. TREATMENT**

MetS is a state of chronic low grade inflammation with the profound systemic effects. Clinical identification and management of patients with the MetS are important to begin efforts to adequately implement the treatments to reduce their risk of subsequent diseases. Effective preventive approaches include lifestyle changes, primarily weight loss, diet, and exercise, and the treatment comprises the appropriate use of pharmacological agents to reduce the specific risk factors.

1. **Risk Assessment:** The goals of therapy are to reduce both a short-term and lifetime risk. The presence of the MetS per se indicates a higher lifetime risk. A practical approach to estimate absolute, short-term CHD/CVD risk in patients with the MetS without ASCVD or diabetes is to use the standard Framingham algorithm to estimate a 10-year risk of the coronary heart disease.

2. **Lifestyle Modification:** Lifestyle modification treatment should be delivered by a multi-disciplinary approach (Table 4) and a team composed of physicians and non-physician health professionals, such as dieticians or professionals with a master degree in exercise physiology, behavioural psychology, or health education.

3. **Weight Reduction:** Four therapies can be used for weight reduction: calorie restriction (e.g., 500 kcal/deficit), increased physical activity, behavioural modification, and in appropriate patients, FDA-approved weight-reducing drugs.

4. **Diet:** The effective and healthful methods for the long term weight loss are reduced-energy diets, consisting of a modest500to1000calories/day reduction. Sustained dietary changes may require a referral to a registered dietician to help implement the suggestions and ensure an adequate micronutrient intake (e.g., calcium, iron, and folate) while reducing calories.

**XXVI. CONCLUSION**

MetS is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and all cause mortality. Insulin resistance, visceral adiposity, atherogenic dyslipidaemia, endothelial dysfunction, genetic susceptibility, elevated body pressure, hypercoagulable state, and chronic stress are the several factors which constitute the metabolic syndrome. Lifestyle modification remains the initial intervention of choice for this population. Modern lifestyle modification therapy combines specific recommendations on diet and exercise with behavioural strategies. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with lifestyle changes. A realistic goal for overweight/obese persons is to reduce the body weight by >7% to 10% over a period of 6 to 12 months. Weight reduction should be combined with a daily minimum of 30 minutes of moderate-intensity physical activity. Nutritional therapy calls for allow intake of saturated and total fat intake; reduced consumption of simple sugars and high glycemic index foods; and increased intakes of fruits, vegetables, legumes, and whole grains. Statins can be combined with fibrates and niacin to achieve the target levels of LDL-C, triglycerides, and HDL-C. Further, the majority of patients who need an antihypertensive therapy will likely need more than one agent for the proper blood pressure control with ACEI/ARB sand beta blockers/Thiazides/CCBs as the first and second line agents, respectively. Metformin, thiazolidinediones and a carbazole will lower the risk for type 2 diabetes mellitus in people with IFG or IGT.

**REFERENCE**


