

METABOLIC SYNDROME AND ITS EFFECTS – A REVIEW**S. Arshad¹, D. Sudheer Kumar² and P. Kishore^{1*}**¹*Department of Pharmacy Practice, Care College of Pharmacy.²Department of Pharmaceutics, Care College of Pharmacy.Article Received on
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Pharmacy.**ABSTRACT**

Metabolic Syndrome is defined as a group of various risk factors which includes physiological, biochemical, clinical and metabolic factors that increases the risk of ASCVD, Type II DM and mortality. Clinically there are various diagnostic criteria for defining metabolic syndrome. Most of the features are common for diagnosing in each definition but they vary slightly in few parameters. The prevalence of Metabolic syndrome across the world is based on the area, age, sex, race, ethnicity of the studied population by using different definitional criteria it ranges from less than 10% to nearly 80%. India occupies one

quarter (25%) of population with metabolic syndrome when they have used WHO or ATP III criteria for defining metabolic syndrome. Abdominal Obesity and Insulin resistance are the main factors that are linked up with many other parameters, which can cause metabolic syndrome. The effect of metabolic syndrome on cardiovascular and renal system is observed and there is an increased risk of cardiovascular and renal complications with metabolic syndrome components if it is not prevented and not controlled. Clinical pharmacist plays a vital role in health care systems by educating the patients regarding metabolic syndrome progression and importance of medication adherence and suitable lifestyle modifications (such as dietary intake and regular exercise) for better longevity and good quality of life.

KEYWORDS: Metabolic syndrome, Risk factors, Insulin Resistance, Abdominal Obesity.**INTRODUCTION**

Metabolic Syndrome is defined as a group of various risk factors which includes physiological, biochemical, clinical and metabolic factors that straightaway increases the risk of ASCVD, Type II DM and cause mortality.^[1,2] Central obesity, HTN, Impaired Fasting Glucose (IFG) / Impaired Glucose Tolerance (IGT) Test, Diabetes Mellitus, Dyslipidaemia^[2],

Insulin Resistance, Visceral adiposity, Endothelial Dysfunction, Hyper coagulable state and chronic stress^[1] are the several factors which constitute metabolic syndrome.

Definition

Clinically there are various diagnostic criteria for defining metabolic syndrome. The most frequently used are WHO^[3], European Group for the Study of Insulin Resistance (EGIR)^[4], National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III)^[5], American Association of Endocrinologists (AACE)^[6] and International Diabetic Federation (IDF).^[7]

Most of the features are common for diagnosing in each definition but they vary slightly in few parameters.

1. Insulin Resistance is mostly focused by WHO, AACE and EGIR.^[8]
2. IDF and NCEP-ATP III focus waist Circumference (WC) and Fasting Blood Glucose (FBG). They both slightly differ by cut-off points.^[2]

Epidemiology

The prevalence of Metabolic syndrome across the world is based on the area, age, sex, race, ethnicity of the studied population by using different definitional criteria it ranges from less than 10% to nearly 80% (2). 20% to 30% adult population have metabolic syndrome in most of the countries.^[9] One third of adults and alarming percentage of children in US are having metabolic syndrome indicated by cross-sectional surveys.^[10] Coming to various developing countries, metabolic syndrome varies from 13% in China to 30% in Iran. India occupies one quarter (25%) of population with metabolic syndrome when they have used WHO or ATP III criteria for defining metabolic syndrome.^[11] A study conducted in Brazil reports that prevalence of metabolic syndrome in women and men was found to be 22.7% and 23.3% respectively.^[12]

Causes of Metabolic Syndrome

Abdominal obesity and insulin resistance have been hypothesized to be the primary factors underlying the metabolic syndrome.^[13]

1. **Abdominal obesity:** Increased oxidative stress in accumulated fat is an important pathogenic mechanism of obesity-associated metabolic syndrome. It is shown that the dysregulated production of “offensive” adipocytokines, such as PAI-1, TNF, IL-6, MCP-

1 and angiotensinogen and of “defensive” adipocytokines, such as adiponectin and leptin, is critically involved in the pathogenesis of metabolic syndrome.^[14] The whole mechanism is illustrated in figure 1.

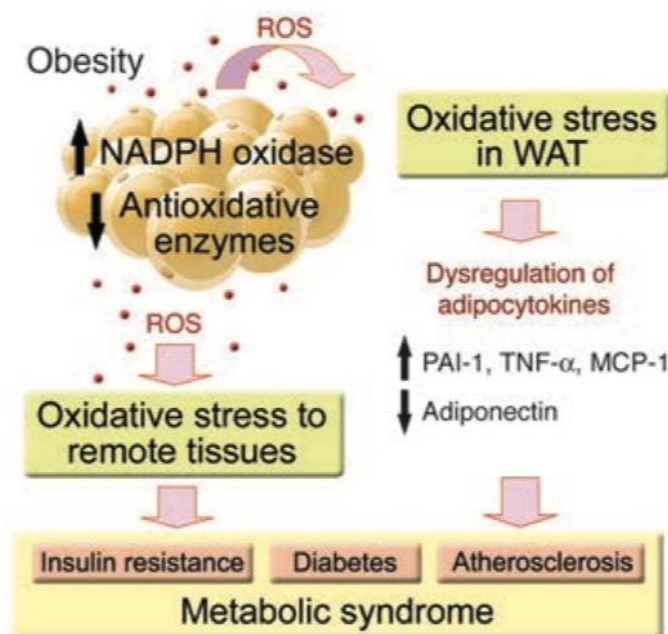


Figure 1: A working model illustrating how increased ROS production in accumulated fat contributes to metabolic syndrome.^[15]

2. Insulin Resistance: Insulin resistance is the main factor, which is linked up with many other parameters to cause metabolic syndrome. Insulin Resistance is associated to various CVD risk factors, such as obesity, hyperglycemia, hypertriglyceridemia, low HDL cholesterol and hypertension.^[16,17] Chronic Stress^[18] is also one of the risk factor. According to a study “the most important environmental cause of insulin resistance is central obesity, it also include sedentary lifestyle and high-fat intake”.^[17] One more important feature of metabolic syndrome that is associated with the degree of insulin resistance is an unduly acidic urine (low urine pH).^[19]

1) Insulin Resistance and Hypertriglyceridemia: Insulin resistance in skeletal muscle is also associated with the *de novo* lipogenesis. The involved mechanism is, whenever muscle glycogen synthesis is decreased, it stimulates to atherogenic dyslipidemia by diverting energy derived from ingested carbohydrate away from muscle glycogen synthesis into increased hepatic *de novo* lipogenesis. This promotes the development of the metabolic syndrome, NAFLD, T2DM, and the associated cardiovascular disease.^[13]

Schematically explained in figure 2.

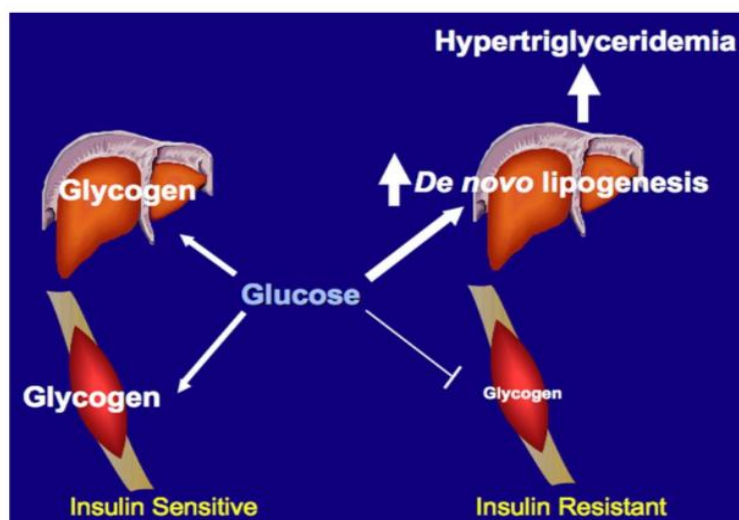


Figure 2: Schematic representation of whole body energy distribution after high carbohydrate mixed meals in insulin-sensitive and insulin-resistant individuals.^[13]

- 2) **Insulin Resistance and Hypertension/Increased Blood pressure:** Insulin resistance for long period of time and hyper insulinaemia is associated with Hypertension. The mechanism involved in this is hypertension was associated with increased levels of plasma catecholamines and suggested enhanced sympathetic nervous system activity, sodium retention, altered membrane ion transport, and proliferation of vascular smooth muscle cells.^[17] According to other study, Both Obesity and Insulin Resistance contribute to the development of hypertension, both independently and collectively. It can be explained as; In Normal individual's introduction of insulin into the bloodstream causes a release of nitric oxide that causes subsequent vasodilation. This is not seen in patients with Insulin resistance and Obesity.^[16]
- 3) **Insulin Resistance and Chronic Stress:** The activation of HPA is the main component of the stress. High catecholamine levels enhance the hypothalamic–pituitary–adrenal (HPA) axis response, and the CRH seems to stimulate sympathetic outflow. Chronic increases in cortisol, catecholamines, and chronic suppression of the growth axis and the reproductive axis. Cortisol interferes at several levels of insulin action. In addition, cortisol inhibits insulin secretion from pancreatic b-cells. In primary cultured adipocytes, synthetic glucocorticoids (dexamethasone) induce progressive insulin resistance by sequentially regulating multiple aspects of the insulin-responsive glucose transport

system.^[18]

Different Body Systems and Metabolic Syndrome

Cardiovascular system and Metabolic Syndrome: As Metabolic syndrome is associated with cardiovascular diseases it has become leading health concern and one fourth of North Americans are affected approximately.^[20]

The AHA/NHLBI 2005^[21] definition is derived from the NCEP—ATP III 2001 definition^[22] and it requires at least 3 or more of the following FIVE cardiovascular risk factors:

1. Central obesity (waist circumference: men >102 cm; women >88 cm).
2. Elevated triglycerides (≥ 150 mg/dl).
3. Diminished high-density lipoprotein (HDL) cholesterol (men < 40 mg/dl; women < 50 mg/dl).
4. Systemic hypertension ($\geq 130/ \geq 85$ mm Hg) or Antihypertensive treatment (BP); and
5. Elevated fasting glucose (≥ 100 mg/dl) or treatment for elevated glucose.

Cardiovascular disease, Insulin resistance and its various group of associated abnormalities (Glucose intolerance, Abnormal uric acid metabolism, Dyslipidaemia, Hemodynamic, Haemostatic, Endothelial Dysfunction) are important risk factors as similar to that of Hypercholesterolemia.^[23] According to the study the appropriate components associated with metabolic syndrome in predicting cardiovascular risks are high blood pressure and cut off point on waist circumference in females and high triglyceride in males, according to criteria defined by IDF (2). A study conducted by Protopsaltis et al. states that the diabetic subjects without known coronary heart disease (CHD), the combination of metabolic syndrome components consisting of diabetes plus hypertension plus low HDL cholesterol was associated with an increased risk of coronary events.^[24] Metabolic syndrome components are known to increase the incidence of atrial fibrillation (hypertension, obesity, and hyperglycemia), other factors, such as an increase in pulse pressure, hypertrophy and alterations in left ventricular diastolic function, atrial dilation and sleep apnoea may also be contributing factors.^[25]

Renal system and Metabolic Syndrome: The prevalence of chronic kidney disease (CKD) is also rising, affecting approximately 8 million adults in the United States.^[26] Metabolic Syndrome has been recognized as a possible risk factor for renal damage, and the increased prevalence of both metabolic syndrome and renal disease justifies the increasing interest

within the nephrology community toward metabolic syndrome as another possible inducing cause of CKD, although the available evidence of a direct causal relationship between metabolic syndrome and development of renal disease is limited.^[27] Few studies states that the relation between metabolic syndrome and early stages of kidney malfunction (*i.e.*, micro albuminuria and low GFR) had first been recognized in the United States, but other reports from Japan, China, and Thailand.^[28] In a study done by sagun et al. they found that the number of CV risk factors and metabolic syndrome parameters increased with variations in GFR. Subjects with one / two risk factors were especially more likely to have lower GFR levels.^[27] It is also observed that in patients with metabolic syndrome, there is an increased risk of micro albuminuria or dipstick-positive proteinuria. As CKD and micro albuminuria are established risk factors for cardiovascular disease, Studies targeting the interrelated individual risk factors included in Metabolic Syndrome with either medications or life style interventions have been shown to slow the progression of CKD.^[29] A study suggests that metabolic syndrome directly contributes to the development of CKD.^[26] One more study reports that metabolic syndrome was significantly and independently associated with a 30% increased risk of CKD during 9 years of follow-up and this risk was greater in persons who developed diabetes during the study.^[30]

Cardiovascular Morbidity and Mortality in Association with Metabolic Syndrome

The clinical and subclinical cardiovascular consequences of metabolic syndrome are many and its impact on cardiovascular morbidity and mortality is observed (12). According to a study it states that metabolic syndrome is associated with 2-fold increase risk for CVD, MI, CVD mortality and stroke, and 1.5-fold increase in risk for all-cause mortality (2). In women, cardiovascular risk present with the metabolic syndrome was highly prevalent than in men (10). All the individual components of metabolic syndrome except abdominal obesity were found to be independent predictors of both cardiovascular events and cardiovascular and diabetes related mortalities.^[31]

Management and Prevention of Metabolic Syndrome

As metabolic syndrome includes group of various factors, which includes cardiovascular and renal risks, so there is no specific or particular treatment to prevent whole syndrome. It is clinically important to manage metabolic syndrome by preventing and controlling the causing risk factors.

The management of risk factors and its complication can be done through pharmacological and non-pharmacological strategies.

Pharmacological Treatment: To treat the risk factors of Metabolic syndrome, physician and other healthcare team in hospital should follow evidence based Medicine (standard treatment guidelines). Most widely used guidelines to treat the metabolic and cardiovascular risk factors are

1. National Cholesterol Education Programme (NCEP).^[32]
2. The American Diabetes Association (ADA).^[33]
3. The seventh Joint National Commission (JNC-VII)^[34] for blood pressure treatment,
4. The American Heart Association (AHA)^[35] and
5. The National Institute of Health Obesity Initiative.^[36]

Non-Pharmacological Treatment: In non-pharmacological management, lifestyle modifications play a key role in preventing or controlling the risk factors of metabolic syndrome. The term lifestyle modification is a very vast which includes numerous factors. In metabolic syndrome, priority must be given to decrease Insulin resistance or Hyper-insulinaemia. The best way to achieve this is lifestyle Intervention-weight reduction, increased physical activity or exercise^[36] and dietary changes. For obese subjects in weight reduction strategy, along with the dietary modifications, minimum 30 minutes of moderate to intensity physical activity preferably walking, prevents cardiovascular and renal complications (1).

Role of Clinical Pharmacist

Clinical Pharmacists plays a vital role in healthcare system in the management and prevention of metabolic syndrome. They educate patients and care takers regarding prevention & controlling of risk factors, complications associated to metabolic syndrome and regarding disease progression. They counsel regarding different life style modification strategies such as increasing physical activity (regular exercise or walking) minimum for 30 minutes (starting with 10-15 minutes initially), dietary restrictions which includes reduced intake of salt, oily food, junk food / fast foods and also to avoid alcohol consumption, smoking, as these are the aggravating factors for hypertension and metabolic syndrome related diseases.

As metabolic syndrome includes cluster of risk factors, patients will be on poly-pharmacy. Hence clinical pharmacists play a key role in treatment and management of metabolic syndrome by monitoring drug related problems such as Medication errors, Drug duplications and check medication adherence.

CONCLUSION

In this review as supporting of all the other studies done previously, the main causing risk factor was found to be Insulin Resistance or Hyper-insulinaemia which leads to various complications such as hyper-triglyceridaemia, glucose intolerance, dyslipidemia, endothelial dysfunction and vascular abnormalities, chronic stress, hypertension and Diabetes Mellitus-II. Another risk factor was found to be Abdominal Obesity (sedentary lifestyle and less physical activity). There is an increased risk of cardiovascular and renal complications with metabolic syndrome components if not controlled. Clinical pharmacist plays a crucial role in health care systems by educating the patients regarding metabolic syndrome progression and importance of medication adherence and suitable lifestyle modifications (such as dietary intake and regular exercise) for better longevity and good quality of life.

Acronyms

ASCVD – Atherosclerosis Cardiovascular Disease

AHA – American Heart Association

AACE – American Association of Endocrinologists

ADA – American Diabetes Association

CVD – Cardiovascular Disease

CHD – Coronary Heart Disease

CKD – Chronic Kidney Disease

EGIR – European Group for the Study of Insulin Resistance

FBG – Fasting Blood Glucose

GFR – Glomerular Filtration Rate

HDL – High Density Lipoprotein

HPA – hypothalamic–pituitary–adrenal

IFG – Impaired Fasting Glucose

IGT – Impaired Glucose Tolerance Test

IDF – International Diabetic Federation

IL – Interlukinin

JNC-VII – Joint National Commission

MI – Myocardial Infarction

NAFLD – Non Alcoholic Fatty Liver Disease

NHLBI – National Heart, Lung, And Blood Institute

NCEP-ATP III – National Cholesterol Education Programme Adult Treatment Panel III

ROS – Reactive Oxygen Species

TNF – Tumour Necrosis Factor

T2DM – Type-II Diabetes Mellitus

WC – Waist Circumference

WHO – World Health organisation

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