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Review Article

Short Review of Metabolic Syndrome

Ritu Devi[1], Sunita Manhas[2], Suvarna Prasad[3], Shubhangi Sharma[1], Neeru Bhaskar[4], Shikhaa Mahajan[2]

[1]Msc. Student, [2]Assistant Professor, [3]Professor & Head, [4]Professor,
Department of Biochemistry, MMIMSR, Maharishi Markandeshwar University, Ambala.

Corresponding Author: Ritu Devi

ABSTRACT

Metabolic syndrome is a groups of disorders, interconnected factors that increase the risk of cardiovascular disease and type 2 diabetes mellitus. It include high blood pressure (hypertension), large line waistline (central obesity), dyslipidemia (increase triglyceride and low level of high density lipoprotein) and increase level of fasting blood glucose. The insulin resistance is play a paramount role in connecting the different components of metabolic syndrome and adding to the syndrome's development. In addition increase free fatty acids, increase oxidative stress and alteration in adipokine profile in patients of metabolic syndrome.

Key words: Metabolic syndrome, obesity, diabetes, hypertension

INTRODUCTION

Metabolic syndrome refers to clustering of risk factors that promote the development of atherosclerotic cardiovascular disease and its clinical role is to identify individuals at risk of this combination. [1] The metabolic syndrome has been called by several other names including Syndrome X, Dysmetabolic syndrome X, Insulin Resistance Syndrome, Reaven Syndrome and the Metabolic Cardiovascular Syndrome, Obesity, Insulin Resistance, Dyslipidemia and Hypertensions are common to all. [2] The combination of central obesity, hyperglycemia, dyslipidemia and arterial hypertension characterize the so-called Metabolic Syndrome (MS). [3] While the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, central obesity and insulin resistance are acknowledged as important causative factors. Central (abdominal) obesity, can be easily assessed using waist circumference and is independently associated with each of the other metabolic syndrome components including insulin resistance, is a prerequisite risk factor for the diagnosis of the syndrome in the new definition. Insulin resistance, which is difficult to measure in day to- day clinical practice, is not an essential requirement. [3]

HISTORY

Interestingly, a description of the Metabolic Syndrome, a condition associating hyperglycemia, hypertension and gout, was published by Kylin, a Swedish physician, in 1923.Insulin insensitivity as a feature of what we now call type 2 diabetes was brought to attention in1936, when the term insulin-resistant was used to describe patients who required very high insulin doses. [4] In 1984, Jarrett suggested that atherosclerosis and type 2 diabetes develop as a result of a shared antecedent and this was developed by Stern in 1995 as the 'common soil' hypothesis.

[5,6] The world health organization(WHO) first defined the syndrome in 1998 and called it the metabolic syndrome, a term that had been that had been used by Zimmet in 1991 to describe this cluster of findings. [7] The WHO criteria for the metabolic syndrome required the presence of diabetes mellitus (DM), impaired fasting glucose, impaired glucose tolerance (assessed by the euglycemia insulin clamp technique) plus two additional factors. [8] In 2001, the national cholesterol education programme adult treatment panel III (NCEP ATP) simplified the definition to make it user-friendly for practitioners (Table 1). The NCEP ATPIII required any 3 of 5 risk factors, abnormal WC, High blood pressure and high fasting plasma glucose concentration. The NCEP ATPIII criteria were updated in 2005 to correspond with the new American Diabetes Association (ADA) standard of a normal fasting glucose level of less than 100 mg/dl. [9]

TABLE 1:-Comparison of WHO, NCEP ATPIII, and IDF Definitions of the metabolic syndrome*[1]

Risk factors	WHO	NCEP ATPIII	IDF
	DM/IFG or IGT or IR plus any ≥2risk factors	Any ≥risk factors	Increased WC(ethnicity specific) plus any ≥2 riskfactors
Obesity	Waist to hip ration> 0.90 in men and >0.85 in women and BMI>30KG/m2	WC≥102cm(40 in) in men or ≥88cm (35 in) in women	WC criteria dependent on ethnicity
Triglycerides	≥150mg/dl	≥150mg/dl	≥150mg/dl or drugs treatment for elevated level
HDL cholesterol	<35mg/dl in men and <39mg/dl in women	<40mg/dl in men and <50mg/dl in women	<40mg/dl in men and <50 mg/dl in women or drugs treatment for reduced level
Blood Pressure	≥140/90mm Hg	≥130 mm Hg systolic or ≥85mmHg diastolic	≥ 130mm Hg systolic or ≥85 mm Hg diastolic or drug treatment for hypertension
Fasting plasma glucose	IGT,IFG or type2 DM	≥110mg/dl	≥110 mg/dl or drug treatment for DM
Microalbuminuria	>30mg albumin/g creatinine		

The co-occurrence of any three of the abnormalities mentioned above metabolic syndrome.

Table 2: Additional metabolic criteria for research pro-inflammatory state 2006.
*Elevated high sensitivity C-reactive protein
*Elevated inflammatory cytokines (eg TNF-alpha, IL-6)
*Decrease in adiponectin plasma levels
Prothrombotic state
*Fibrinolytic factors (PAI-1 etc.)
*Clotting factors (fibrinogen etc.)
Hormonal factors *Pituitary-adrenal axis

In 2009 Alberti et al presented a consensus criterion for the diagnosis of MS –the Joint Interim Statement (JIS) – that was endorsed by several societies, which chose the non-mandatory presence of any of the components, but the presence of at least three altered components in five and the WC measurement according to different ethnicities. Considering that the MS represents a higher risk for cardiovascular disease, DM, mobility alterations, cognitive deficits and depression in the elderly, together with the scarcity of data in Brazil, this study aims at determining the prevalence of MS by four different diagnostic criteria and the agreement between them in a population older than 60 years old. [3]

PATHOPHYSIOLOGY

The current understanding of the pathogenesis of the metabolic syndrome suggest that multiple factors predispose to metabolic susceptibility for instance genetic defects in insulin signaling pathway, various disorders of adipose tissue, physical inactivity, mitochondrial dysfunction, polygenic variability in individual and certain ethnic groups, advancing age and certain drugs.

The underlying pathophysiology of metabolic syndrome is a subject of debate. Initial studies in this area suggest that insulin resistance has a primary role. [10-12]

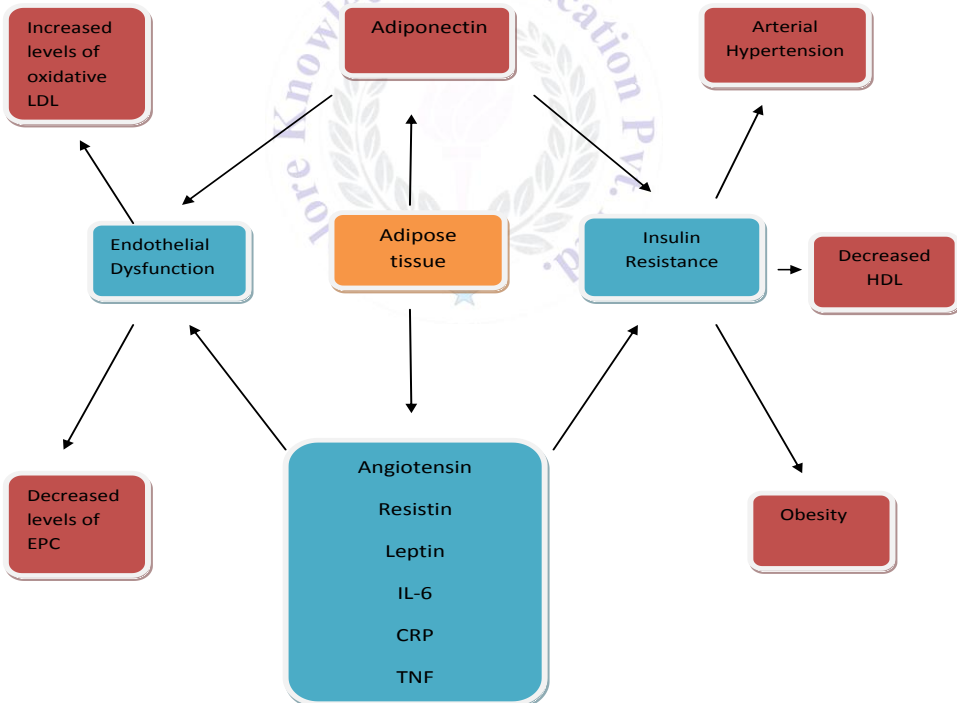
Pathophysiological features of metabolic syndrome

Insulin

Insulin is a hormone produced by the beta cells of the islets of langerhans in the pancreas. [13] Once insulin is secreted into the portal venous system, 50% is degraded by the liver. Unexcreted insulin enter the systemic circulation and binds with receptors in target site. Its receptors stimulate intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling. These initiate a complex cascade of phosphorylation and dephosphorylation reaction, resulting in the widespread metabolic and mutogenic effects of insulin. [14] As an example, activation of the phosphatidylinositol-3-kinase(pi-3-kinase) pathway stimulates translocation of glucose transporters(e.g., GLUT 4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathway induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells. [15]

Insulin resistance

Insulin resistance is defined as a decreased biological response to normal concentration of circulating insulin and is found in both obese, non-diabetic individuals and patients with type 2 diabetes. [14] It is a key feature of the metabolic syndrome and often progresses to type 2 diabetes.Both insulin resistance and type 2 diabetes are characterized by dyslipidemia, which is an important and common risk factor for cardiovascular disease. [16]



FIGER 1:-Pathophysiology of Insulin Resistance, Obesity and Hypertension

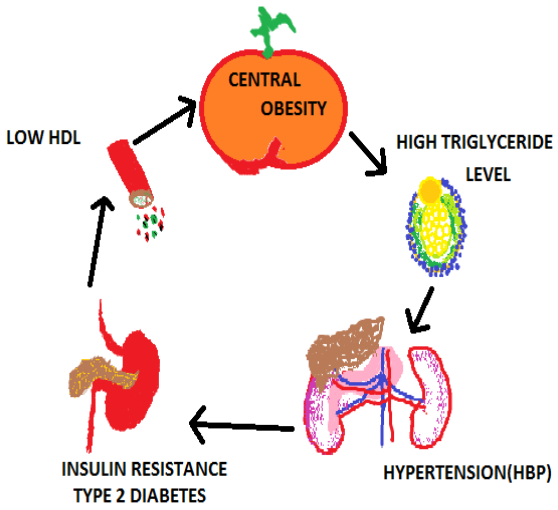
Hyperlipidemia

These lipid abnormalities primarly include hypertriglyceridemia and low High Density Lipoprotein cholesterol (HDL-C) and increased small dense low density lipoprotein(LDL). [15] Hyperlipidemia is a strong risk factor for cardiovascular disease. Hyperlipidemia is referred to as elevated TG or cholesterol.. [17] The problem can be due solely to hereditary factors, but more commonly it is an acquired condition. Increased risk for cardiovascular disease (CVD) is defined by risk factor. These include men with diabetes, having a family history of heart disease in a close male relative younger than age 50 or a close

female younger than age 60, a family history of high cholesterol, or personal history of multiple coronary disease risk factors. [17] Insulin plays an important role in the metabolism of free fatty acid by suppressing their release from adipose tissue, resulting in an increased concentration of plasma free fatty acids [18,19] Excess plasma free fatty acids lead to an increase flux of free fatty acid to liver resultingin an increase in hepatic triglyceride VLDL and cholesterol ester synthesis and secretion. [20,21] Also the lipoprotein excess plasma activity that is already impaired by insulin resistance leads to decreased catabolism of chylomicrons and VLDL. This reduced catabolic activity leads to decreased release of lipoprotein particles that are necessary components in the formation of HDL-cholesterol (HDL-C) [22,23] leading to low HDL-C levels. Other mechanisms for low HDL-C in patients with metabolic syndrome includes the altered or reduced activity of lecithin cholesterol acyl-transferase(induced by the altered lipid fractions such as raised VLDL-C and increased triglycerides). [24,25] Therefore, hyperinsulinemia increases the production and decreases the metabolism of VLDL-C. Although it is not completely clear if isolated triglyceride elevations bear an independent risk for atherosclerosis. [26]

Obesity

Abdominal and central obesity is a major component of metabolic syndrome.Weight gain usually precedes development of the metabolic syndrome. [27] Central obesity and hyperinsulinemia may contribute to an increased risk of cardiovascular disease and stroke. [28] Central obesity is reflection of increased visceral fat, which is expected to have higher rate of flux of adipose tissue derived free fatty acid into the liver through the splanchnic circulation leading to increased very low-density lipoprotein production, hyperglyceridemia, increased glucose release from the liver into systemic circulation and subsequent hyperinsulinemia, and insulin resistance.



FIGER 2:- Central Obesity in Metabolic Syndrome (low HDL)

Coagulation markers

These coagulation markers abnormalities include elevated:- [29]

Plasminogen activator inhibitor-1(PAI): PAI-1 has also been associated with CVD in experimental, clinical and epidemiological studies. Elevated plasma PAI-1 events such as angina pectoris, MI and restenosis after coronary angioplasty. [30]

Tissue plasminogen activator (t-PA): The t-PA antigen level increased in a stepwise fashion depending on the number of clinical characteristics associated with insulin resistance.

Factor8, Von Willebrand factor(vWf):vWf and factor VIII level are positively associated with diabetes, BMI, waist to hip ratio, serum insulin and plasma triglycerides- all components of metabolic syndrome.

Factor 7, 9,10 and Fibrinogen: These factor also elevated in patient with metabolic syndrome and also physiologically linked to microalbuminuria, an important of metabolic syndrome. [31]

Blood pressure (BP)

Additionally, insulin resistance may lead to vasoconstriction, as insulin is a potent vasodilator. Three possible mechanisms by which increased Blood pressure is associated with insulin resistance are:

1. High BP itself could cause insulin resistance

2. Insulin resistance could cause elevated BP
3. Both(elevated BP and insulin resistance)could be consequence of a common genetic trait. [31] it is still unclear by which mechanism insulin causes hypertension. [32]

However, it is well established that insulin itself has direct effects on the vasculature [33] and is a well-known dilator in various tissue in vivo, including vein [34] and brachial artery. [35] It has been suggested that the vasodilatory effect of insulin might contribute to increases in blood pressure. In addition, it has been experimentally shown that overall dyslipidemia could contribute to a chronic increase in vascular tone and consequently to hypertension. [36] Increasing evidence suggests a specific pathophysiology role of the renin angiotensin system(RAS) especially in patients with hypertension in accompaniment with the metabolic syndrome. [36] Plasma reninactivity (PRA) is a powerful cardiovascular risk factor independently of other known risk factors [37] and clear associations between the RAS and metabolic cardiovascular risk factors has been shown. [38-40] Lind was able to confirm in untreated patients with essential hypertension that insulin resistance is related to elevated level of PRA when evaluated by the euglycaemic hyperinsulinaemic clamp. [41] However, the mechanisms connecting high PRA and insulin resistance are as yet unknown. In contrast, a causal association of insulin resistance and compensatory hyperinsulinemia with blood pressure elevation is established. Mechanisms involved in this relationship include insulin-mediated sodium retention, stimulation of the sympathetic nervous system, and promotion of vascular cell's growth or impairment of endothelial nitric oxide(NO) production in insulin-resistant states. [42] There are also accumulating evidence for an involvement of the endothelin system in the development of hyperinsulinemia induced hypertension. [43]

Endothelin-1,which is considered to be the most powerful natural constrictor is the main effector of the endothelin system and mediates its effects via ET-A and ET-B receptor in the vasculature. [44] Although, vasoconstriction is its predominant action, ET-1 can also act on ET-B receptor present in endothelial cells in an autocrine fashion and promote production of ON and vasodilating prostaglandins. [45] Secondary hypertension, in contrast to essential hypertension, is not associated with insulin resistance which makes it less likely that high BP alone is a major cause of insulin resistance. It is plausible that insulin resistance could cause an elevation of BP given that hyperinsulinemia increases renal sodium and water reabsorption leading to extracellular volume expansion and an enhanced sympathetic activity. [46,47] Insulin resistance at a cellular level may lead to intracellular hypernatremia in view of the decreased potassium ion exchange. [48] Additionally, insulin resistance may lead to vasoconstriction, as insulin is a potent vasodilator. [49]

CONCLUSIONS

Life style modification remains the initial intervention of choice for this population. Modern lifestyle modification therapy combines specific recommendation on diet and exercise with behavioral strategies.

A realistic goal for overweight/obese persons is to reduce the body weightby less than 7% to 10% over a period of 6 to12 months. Weight reduction should be combined with a daily minimum of 30 minutes of moderate-intensity physical activity.

Nutritional therapy calls for a low intake of saturated and total fat intake, reduced consumption of simple sugar and high glycemic index food and increase intakes of fruits, vegetables, legumes and whole grains.

Pharmacological treatment should be considered for those whose risk factors are

not adequately reduced with lifestyle changes.

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