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Review Article

A Review into Biochemistry of Metabolic Syndrome (Met S)

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ABSTRACT

Metabolic Syndrome (Met S) is an emerging health problem and affects approximately 20-25% of the population globally. The syndrome is also described as "Syndrome X", "The Deadly Quartet" and "The Insulin Resistance Syndrome". Physical inactivity, intake of an atherogenic and diabetic diet is risk factors leading to the syndrome (Met S). Clinical symptoms of the disease are obesity, dysglycemia, elevated blood pressure, increased triglycerides levels, decreased levels of high density lipoprotein cholesterol levels, pro-inflammatory and thrombotic states. Insulin resistance and obesity are considered as the main reasons for the development of Metabolic Syndrome (Met S). Biochemical biomarkers which aid as indicators are leptin, adiponectin, leptin: adiponectin ratio, plasminogen activator inhibitor-I, uric acid, interleukin-6, tumor necrosis factor-alpha, interleukin -10, oxidized LDL and paraoxonase- I.

Metabolic Syndrome (Met S) shows specific biochemical effects in the human body and the metabolic abnormalities can be explained genetically by two hypotheses. Various types of diet have their effects on Metabolic Syndrome (Met S). Overall whole, unprocessed plant foods rich in phytochemicals are considered to provide immense benefit. There are also some single nutrients and bioactive compounds which provide direct benefits like ascorbate, hydroxytyrosol, quercetin, resveratrol, tocopherol and anthocyanins.

Changes in lifestyle which includes proper pharmacological treatment, dietary changes promoting weight loss, prevention of obesity, glucose intolerance, insulin resistance, type 2 diabetes, decreased salt and alcohol intake prove beneficial in management of Metabolic Syndrome (Met S). Thus, the syndrome although multifactorial causing immense morbidity and mortality can be treated by effective management of such patients.

Key Words: Metabolic Syndrome (MetS), Syndrome X, Deadly Quartet, The Insulin Resistance Syndrome, Biochemical markers

INTRODUCTION

Globally, Metabolic Syndrome (Met S) is an emerging problem related to health. [1] In the developed and developing nations of the world, the incidence is increasing. In the world, the incidence is increasing. In the world, approximately 20-25% of the population is suffering from Metabolic Syndrome (Met S). [2]

In 1920 Swedish physician, Kylin correlated high blood pressure (hypertension), increased blood glucose (hyperglycemia) and gout; thereby the term Metabolic Syndrome (Met S) originated. Visceral obesity was related to metabolic abnormalities of cardiovascular disease and type 2 diabetes mellitus according to Vague in 1947. Metabolic Syndrome (Met S) is associated with hypertension, hyperglycemia and obesity in the abstract presented by Avogadro and Grenaldi in 1965 at European Association for the Study

of Diabetes. Reavan in 1988 described "a cluster of risk factors for diabetes and cardiovascular disease" known as "Syndrome X" and introduced the symptom of insulin resistance for Metabolic Syndrome (Met S). In addition, visceral obesity or obesity was included as a crucial abnormality. Kaplan in 1989 described the syndrome as "The Deadly Quartet" including visceral obesity, glucose intolerance, hypertriglyceridemia and hypertension. In 1992, the syndrome was renamed as "The Insulin Resistance Syndrome". [3]

Physical inactivity, consumption of an atherogenic and diabetic diet will culminate into Metabolic Syndrome (Met S).Clinical symptoms include obesity, dysglycemia, elevated blood pressure, increased triglyceride (TG) levels, low high density lipoprotein cholesterol (HDL-C) levels, pro-inflammatory and thrombotic states. [4] World Health Organization (WHO) in 1999, National Cholesterol Education Programme (Adult Treatment Panel III) in 2001 and International Diabetes Federation in 2005 defined Metabolic Syndrome (Met S) by various diagnostic criterias. [5]

Insulin resistance and obesity are cited as the main reasons for the manifestation of Metabolic Syndrome (Met S).Due to the pathology which occurs after binding of insulin to its receptor, at the post-receptor level of insulin leads to changes in the intracellular pathways related to insulin. Obesity, sedentary lifestyle, smoking, low birth weight and perinatal malnutrition are contributory to the development of insulin resistance. Some other factors include hormones of adipose tissue, hypothalamus-hypothesis- adrenal axis disorders, lipogenesis, genetic and environmental factors. Insulin resistance leads to dyslipidemia, hyperglycemia, hypertension and obesity which result in Metabolic Syndrome (Met S). [6]

Hyperglycemia and hypertension co-existing in obesity leads to high risk of cardiovascular disease (CVD). Elevated fasting plasma total cholesterol as well as triglycerides (TG) and decreased plasma HDL cholesterol (HDL-C) levels occur in the condition of obesity. Plasma LDL – cholesterol (LDL-C) levels remain elevated or normal but small, dense, atherogenic LDL particles increases especially in patients with insulin resistance associated with visceral obesity. This triggers high risk for the development of atherosclerosis and Metabolic Syndrome (Met S).

Visceral adipose tissue lipolysis leads to increased levels of visceral fats and excessive free fatty acids generated also due to the metabolic complications of obesity free fatty acids (FFA) enter the liver via directly entering the portal vein and are the main cause for development of Metabolic Syndrome (Met S). [7]

Biochemical Biomarkers of Metabolic Syndrome (Met S)

Leptin: Under normal physiological conditions the adipocytes of adipose tissue produce leptin. Functionally leptin reduces appetite, increases energy loss, sympathetic activity, glucose uptake and utilization improving insulin sensitivity. The receptors of leptin are prevalent in hypothalamus, heart, liver, kidneys, pancreas, smooth muscles, endothelium of heart, brain blood vessels. Obesity, insulin resistance, myocardial infarction and congestive cardiac failure are a resultant of elevated leptin. Leptin is the most sensitive biomarker which is indicative of Metabolic Syndrome (Met S) in children, elderly men and women. [8]

Adiponectin: Adiponectin is secreted by the adipocytes, adiponectin is an adipose – derived plasma protein that improves insulin sensitivity and possesses anti-atherogenic effect. Presence of excessive adipose tissue in Metabolic Syndrome (Met S) results in decreased production of adiponectin. Adiponectin activates nitric oxide synthase possesses so protective properties thereby benefits the cardiovascular system. [7] Types of adiponectin are low molecular weight trimer, middle molecular weight hexamer

and high molecular weight (HMW). HMW is the active form causing insulin sensitivity and protection from diabetes development, is anti-atherogenic, increases lipid – oxidations and responsible for vasodilation. HMW adiponectin is a reliable biomarker for Metabolic Syndrome (Met S) and is inversely related.

Leptin: Adiponectin ratio (LAR): This ratio is more beneficial than each factor contributing individually as a biomarker for Metabolic Syndrome (Met S). High LAR is a better biomarker than leptin or adiponectin singly for the diagnosis of Metabolic Syndrome (Met S). LAR is a better biomarker in males than in females due to elevated adiponectin levels in females due to elevated adiponectin levels in females which is protective against Metabolic Syndrome (Met S). Another reason for the ratio differences observed between the sexes being the variations in glucose and lipid metabolisms.

Oxidized LDL (Ox LDL): Ox LDL is a product of lipid oxidation and serves as a biomarker of oxidative stress. Lipid oxidation results in the generation of reactive oxygen species (ROS). Oxidized LDL (Ox LDL) is the products of these components which contribute to dyslipidemia, of cardiovascular disease and Metabolic Syndrome (Met S).Elevated Ox LDL is contributory to obesity and insulin resistance leading to Metabolic Syndrome (Met S).Ox LDL is an important biomarker of Metabolic Syndrome (Met S).Ox LDL is an important biomarker of Metabolic Syndrome during the development of its progress.

Paraoxonase I (PON –I): PON-I is a multipurpose, antitoxic, antioxidant enzyme with antioxidant and anti-inflammatory properties. It reduces lipid peroxidation protects against LDL and tissue from oxidative damage and attenuates Metabolic Syndrome (Met S)

Tumor Necrosis Factor-Alpha (TNF-α): TNF-α is a pro-inflammatory cytokine secreted by visceral adipose tissues during Metabolic Syndrome (Met S). Metabolic syndrome (Met S) is characterized by adipocyte dysregulation which tends to secretes TNF-α which is related with insulin resistance via aberrant activation of mTOR and PKC signaling pathways. TNF-α is significant contributor to development and progression of Metabolic Syndrome (Met S).

Ghrelin: Ghrelin is a hormone secreted by the stomach. Functionally it increases appetite directly via its receptor by increasing peptides such as neuropeptide Y (NPY).Ghrelin possesses vaso protective and lipolytic properties. Metabolic Syndrome (Met S) is associated with lower ghrelin levels although levels are higher in females than in males. Ghrelin acts on the endothelium by preventing proatherogenic changes and improves vasodilation. It reduces effects of endothelium I and improves vasodilation by NO in Metabolic Syndrome (Met S) patients and would be an effective biomarker for Metabolic Syndrome (Met S).

Plasminogen Activator Inhibitor–I (PAI-I): PAI-I is secreted into the blood circulation or extracellular spaces by endothelial cells, adipocytes, vascular smooth muscles, platelets or hepatic cells. Pro-inflammatory and pro-oxidant factors induce secretion of PAI-I under pathological conditions. Inflammatory signaling, insulin resistance and circulation of blood influences and induces the secretion of PAI-I. High PAI-I is linked with severe Metabolic Syndrome (Met S) which is a strong association. The relationship is stronger in males than in females. PAI-I can serve as a biomarker for Metabolic Syndrome (Met S).

Uric Acid: Uric acid is the terminal end product of catabolism of purines, formed in the liver and excreted by kidneys. It functions as an antioxidant, pro - inflammatory and pro-oxidant. Hyperuricemia causes risk of atherosclerosis, myocardial infarction, stroke, cardiovascular risk factors like hypertension and dyslipidemia. Uric acid is increased in Metabolic Syndrome (Met S) as

demonstrated in children, adolescents and adults. However, there is a stronger association between uric acid levels and Metabolic Syndrome (Met S) in females than in males.

Interleukin-6: Interleukin-6 is a pro-inflammatory cytokine with role in natural inflammatory response. As a result of infections and injury it is often secreted by M_1 macrophages. Pro-inflammatory cytokines affect cell-signaling pathways such as mTOR and protein kinase C (PKC) to induce insulin resistance in endothelial cell damage within blood vessels leading to vascular dysfunction and atherosclerosis. IL-6 can cause aberrant insulin receptor activation, abnormal insulin signaling cascades, abnormal insulin action and glucose metabolism. Elevated IL-6 is associated with severe Metabolic Syndrome (Met S) especially during progression and is good biomarker.

Interleukin 10 (IL-10): IL-10 is an anti-inflammatory cytokine and affects systemic inflammation secreted by M_2 macrophages or monocytes which enables tissue remodeling. Inhibits NADPH oxidase and oxidative stress has aberrant insulin receptor substrate (IRS) activation and impaired insulin signaling. IL-10 can restore normal insulin signaling by inhibiting NADPH oxidase –induced oxidative stress or by antagonizing the effects of IL-6 and TNF-α. IL-10 is significantly decreased in Metabolic Syndrome (Met S) in both males and females. When IL-10 and Adiponectin levels are low the risk of Metabolic Syndrome (Met S) is greater. [8]

Biochemical aspects of Metabolic Syndrome (Met S):

Metabolic Syndrome (Met S) increases the triglycerides (TG) in the liver and formation of very low-density lipoprotein (VLDL).Similarly glucose levels increases as well as its conversion to fatty acids. In Metabolic Syndrome (Met S) the levels of TG, VLDL, glucose, fatty acids, leptin increases whereas decreases levels of adiponectin in the blood circulation. Abnormal adipose tissue functioning, hepatic steatosis, cardiac diseases, variations in gastrointestinal functioning, systemic inflammation and chronic diabetic complications occur in Metabolic Syndrome (Met S). [6]

Metabolic Syndrome (Met S) results due to the accumulation of metabolic abnormalities. Two hypotheses have been suggested in this aspect. Neel in 1962 proposed the "thrifty genotype hypotheses" according to which persons in harsh environments and habitats with poor food supply would ensure maximum survival by maximizing the storage of extra energy. Genetics will favor the energy-saving genotypes in such environments. But these genotypes selected during malnutrition would not benefit when dietary sources are available. These thrifty genes may later cause development of Metabolic Syndrome (Met S). Hales and Barker in 1992 suggested "thrifty phenotype hypothesis" accordingly babies facing intrauterine malnutrition adapt to the poor nutrition supply by decreasing energy wastage thereby become "thrifty". This condition enables to resist the poor nutritional conditions in childhood and adult life. However with increase in dietary supply these capacities will not prove of any advantage and there capacities will not prove of any advantage and there capacities will not prove any advantage and there is increased danger of developing Metabolic Syndrome in later life. In support of this hypothesis is the fact that low birth infants may later develop insulin resistance and type 2 diabetes in several populations. According to the "thrifty gene hypothesis" there are several important candidate genes efficiently strong and conserving energy which could later manifest as Metabolic Syndrome (Met S) like genes causing obesity, regulating free fatty acid metabolism, insulin sensitivity, lipid metabolism and inflammation e.g. peroxisomes proliferator-activated receptor (PPAR-γ), adiponectin, CD36, β-adrenergic receptors, insulin receptor substrates (IRS),

tumor necrotic factor (TNF-α), calpain -10 (CAPN 10). [9-13]

Effect of various types of Diet on Metabolic Syndrome (Met S):

Several studies on metabolic Syndrome (Met S) have suggested that whole, unprocessed plant foods rich in phytochemicals are of immense benefit. [14-17] Energy restricted diets are commonly utilized against excess obesity and other aspects of Metabolic Syndrome (Met S).This type of diet provides less calories hence body weight reduction which proves less calories hence body weight reduction which proves to be beneficial in the sequelae of Metabolic Syndrome (Met S). Diets rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential. Omega -3 fatty acids predominant in fishes. Omega -3 fatty acids reduces triglycerides in plasma, plasma C-reactive protein (CRP),cytokines IL-6,tumor necrosis factor –alpha mediated by resolvins, maresins and protectins which and protectins which are metabolic products of EPA and DHA with anti-inflammatory properties. Metabolic Syndrome (Met S) may result due to increased intake of high glycemic index (GI) foods over a period of time, which leads to hyperglycemia, insulin resistance, type 2 diabetes, hypertriglyceridemia, cardiovascular disease, obesity. Dietary total antioxidant capacity (TAC) indicates the diet quality which includes the um of the antioxidant activities amongst the pool of antioxidants inherent in the diet. Antioxidants are functionally important to scavenge the increased free radicals which are known to cause oxidative stress in the condition of Metabolic Syndrome (Met S).Intake of moderate-high protein diets are beneficial to cause diet-induced thermogenesis and feeling of satiety. Thermogenesis is caused due to synthesis of peptide bonds, production of urea and gluconeogenesis which involve higher energy requirements than metabolism of lipids or carbohydrates. Whereas, increase of appetite controlling hormones like insulin, cholecystokinin or glucagon – like peptide I explains the feeling of satiety. Other beneficial effects of moderate –high protein diets are improved glucose homeostasis, lower lipid levels, reduction in blood pressure and lower cardiometabolic disease which are therefore helpful in the management of Metabolic Syndrome (Met S). Mediterranean Diet (Med Diet) is the traditional diet of countries situated around the Mediterranean Sea. This diet includes the increased consumption of extra –virgin olive oil, fruits, vegetables, cereals, whole grains, legumes, seeds and olives; decreased of sweets and red meat and moderate intake of dairy products, fish and red wine. The presence of high amount of dietary fibres inherent in the diet contributes to the weight reduction, feeling of high satiety, high antioxidants and anti-inflammatory properties which reduce morbidity and mortality associated with Metabolic Syndrome (Met S) ascorbate, hydroxytyrosol, quercetin, resveratrol, tocopherol and anthocyanins are worthy of mention. The direct benefits are due to antioxidant, vasodilatory, anti-atherogenic, anti- thrombotic and anti-inflammatory effects of such nutrients and bioactive compounds. [18]

Preventive and Interventional Measures against Metabolic Syndrome (MetS)

As a preventive and interventional approach a change in lifestyle which prevents obesity, glucose intolerance, insulin resistance, diabetes mellitus type 2 by increasing physical activities, healthy diet promoting weight loss moderating the salt intake (Na^+) and alcohol consumption will prove highly beneficial in the management of Metabolic Syndrome (Met S).Pharmacological drug treatments are satisfactory for the hypertension and atherogenic dyslipidemia in Metabolic Syndrome (Met S). The treatment of type 2 diabetes in Metabolic Syndrome (Met S) although difficult in progression with introduction of newer drugs but the obesity

aspect of Metabolic Syndrome (Met S) requires more attention and research . [19,4]

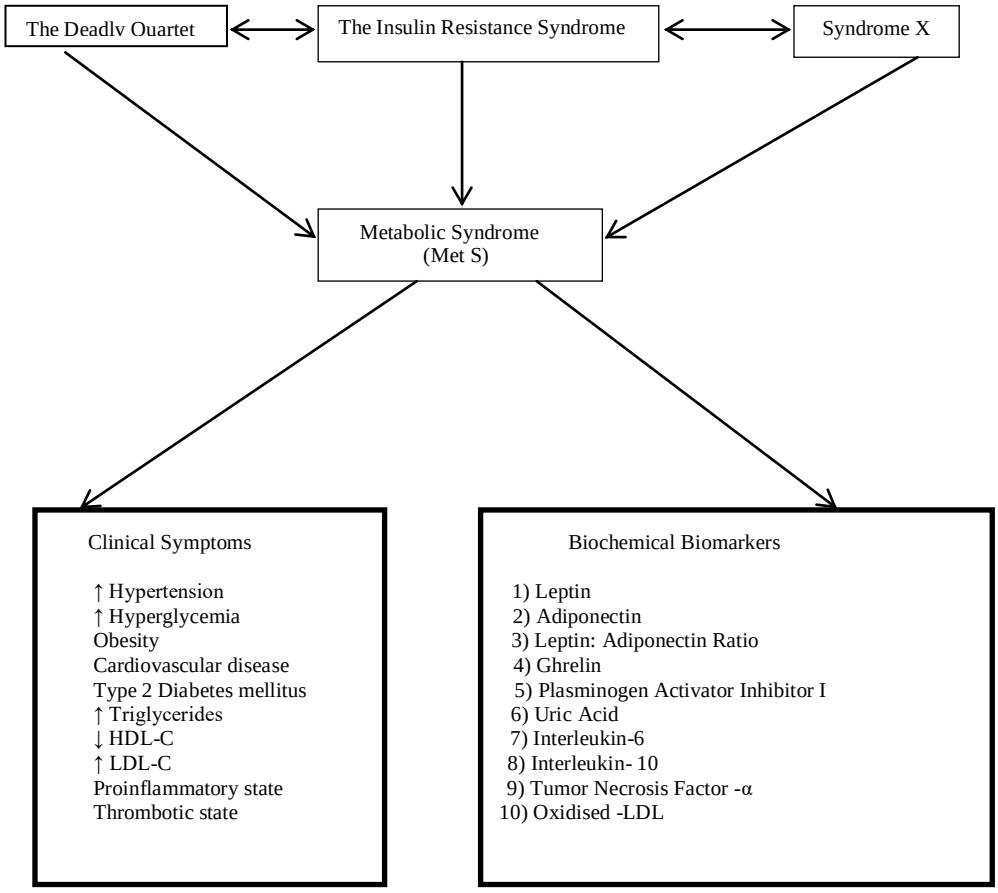

Figure I: Clinical symptoms and Biochemical Biomarkers of Metabolic Syndrome (Met S)

CONCLUSION

Metabolic Syndrome (Met S) is a multifactorial disease with varied clinical symptoms. Biomarkers used effectively will enable in the predicting and monitoring the syndrome. The biochemical sequelae of the Metabolic Syndrome (Met S) is well – explained by the metabolic changes and two hypotheses related to the genes and their expression. Several dietary strategies, changes in lifestyle and necessary pharmacological drugs will directly and positively benefit the management and treatment of Metabolic Syndrome (Met S).

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