CHAPTER-1

INTRODUCTION

The metabolic syndrome (MetS) is the main health related problem worldwide which is affecting approximately 20-25% of total world’s population. The main reasons for its increasing proportions are:\textsuperscript{1,2}

- Increasing urbanization
- Increased food intake
- Sedentary life style
- Increasing obesity

Metabolic syndrome is a result of complex interrelationship between environmental factors and genetic factors which constitute the number of systemic derangements like resistance of insulin, increased insulin levels, central obesity, hyperglycaemia, atherogenic dyslipidaemia, elevated blood pressure, endothelial dysfunction, low grade chronic inflammation, chronic stress and genetic susceptibility.\textsuperscript{1,3}

For the diagnosis of metabolic syndrome, the criteria of ‘The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)’ is widely used throughout the world as compared to other definitions like WHO, IDF etc because it is more practical.

NCEP ATP III has suggested to use five parameters for diagnosis of the metabolic syndrome which include: waist circumference (for males: more than equal to 102 centimeters; for females: more than equal to 88 centimeters), triacylglycerides\textsuperscript{$\geq$}150mg/dl), high density lipoprotein-cholesterol (for males: <50 mg/dl; for females: <40mg/dl), blood pressure (more than equal to 130/85 mmHg) and fasting blood glucose (more than 100 miligrams per deciliter). If subject meets any of the three criteria out of these five criteria then the subject is diagnosed as metabolic syndrome.\textsuperscript{4}
The risk of CVD development is up by 2 times and the risk of type 2 diabetes mellitus (T2DM) onset is increased by 5 times among the patients (among male and female patients) who are diagnosed with metabolic syndrome when compared to healthy individuals. Several researchers have also claimed the association of MetS with various diseases like fatty liver, chronic renal diseases, mental illness and even in cancer.\(^5\)

Obesity plays a major role in the development of metabolic syndrome. Excessive fat deposited in the adipose tissue increases the body weight in obese people compared to the healthy people which is greater than around 20\%.\(^6\) The major factors that leads to obesity are increased food intake, lack of exercise, sedentary life styles, hypothyroidism, leptin signalling pathway disorder, genetics etc.\(^7\)

Body Mass Index (BMI) which is calculated by weight/height\(^2\) (in kg/m\(^2\)) is the popular method used as a measure of obesity. Some other methods for the measure of obesity which are being used are WC (Waist Circumference), skin fold thickness, waist-hip ratio, densitometry (under water weighing), CT (Computed tomography), MRI (Magnetic resonance imaging) and electrical impedance.\(^8\)

Compared to other anthropometric measures of obesity like skin fold thickness, BMI, WHR, the direct measurement of visceral fat content of the body or central obesity is done by WC because a number of publications show higher correlation of WC with metabolic syndrome. Therefore WC was used as the measure of central obesity to define MetS among other anthropometry measurements like skin-fold thickness, BMI and WHR by NCEP ATP III and WHO.\(^9,10\)

Central-obesity has the risk of increase in development of variety of pathological consequences like insulin resistance, hyperglycaemia, NAFLD (Non-alcoholic fatty liver disease), dyslipidemia, raised blood pressure and low grade chronic inflammation which are the key causal risk reasons for the cause of MetS (metabolic syndrome) and followed by development of T2DM and CVD.\(^11\)

Insulin resistance is characterized with increased insulin level in blood due to defect in insulin signalling pathway and decreased response of insulin receptor of the cell
to insulin. IR is the integral part of MetS which ultimately leads to hyperglycaemia and development of T2DM.

It has been well established that obesity is connected to MetS, T2DM and CVD and the key root for this connection is obesity induced inflammation and insulin resistance through various process which leads to MetS and its morbidities. The major molecular links between obesity and insulin resistance include:- Increased FFAs in obesity that is capable of impairing insulin action by phosphorylation of insulin receptors, altered expression of various circulating peptides or proinflammatory markers produced by adipocytes which are capable of modifying insulin action and Obesity activated pathways like IKKβ/NF-κB pathway, JNK Pathway and Inflammasome pathway which induces production of chemokines and cytokines that lead to insulin resistance.

Due to increased visceral adipose tissue in obesity, free fatty acids (FFAs) are elevated in plasma.\textsuperscript{12, 13} The metabolites of fatty acids activates the serine/threonine kinases followed by the phosphorylation of the IRS-1 complex of insulin signalling pathway and results in defected insulin signalling pathway termed as insulin resistance.\textsuperscript{14}

In obesity, adipose tissues increases the synthesis and secretion of varieties of proinflammatory cytokines and chemokines like MCP-1 (monocyte chemotactic protein-1), adiponectin, leptin, resistin, TNF-α (tumour necrosis factor), IL-1 (interleukin-1), IL-6 (interleukin-6) and IL-8 (interleukin-8) etc. and they promote IR which has been reported by number of publications.\textsuperscript{15, 16, 17, 18}

These pro-inflammatory cytokines and chemokines induces insulin resistance through various mechanisms such as by inducing serine phosphorylation of IRS-1 which further inhibits kinase activity of insulin receptor and downstream signalling via PI3K activation; in 3T3-L1 adipocytes the GLUT-4, IRS-1 and PPAR-γ gene expressions are reduced by cytokines and chemokines; the expression of a protein SOCS-3 which binds to inhibit the insulin receptor is increased by cytokines and chemokines.\textsuperscript{19}
Obesity has also been evidenced to activate some pathways like IKKβ/NF-κB pathway, JNK Pathway and Inflammasome pathway which directly induces the insulin resistance and/or upregulates the synthesis of pro-inflammatory markers which plays a vital role in IR.20

Typical obesity induced dyslipidaemia consists of hypertriglyceridemia and increased free fatty acids level, decreased HDL-Cholesterol and increased LDL-Cholesterol with increased small dense LDL level leading to promotion of insulin resistance causing metabolic syndrome. Overproduction of lipoproteins by liver which contain apo-B (apolipoprotein-B) also results in increased apo-B concentration in plasma.21

A reduction in HDL-C levels and elevated triglycerides are jointly referred to as “atherogenic dyslipidemia”. This disorder also includes insulin resistance and high levels of small-dense LDL particles, although LDL-C levels tend to be normal. Inhabitants of South Asia particularly suffer from atherogenic dyslipidemia and strong associations have been established with this disorder and T2DM, MetS and CVD.22 A modern sedentary lifestyle brought about by the increased urbanization and demographic change, change in migration patterns from the countryside to the city, adulterants in diet as well as faulty composition of diet along with genetic susceptibility are all risk issues for the progress of atherogenic dyslipidemia.23

Hypertension (HTN) is also an important constituent of metabolic syndrome which is defined as increased systolic blood pressure (SBP>140 mmHg) and/or increased diastolic blood pressure (DBP>90 mmHg). Uncontrolled HTN is well established risk factor for CVD which is responsible for 7.5 million deaths per year worldwide.

The type of hypertension primary (or essential) hypertension has prevalence of 95% patients and secondary hypertension has prevalence of 5% patients.24 Essential hypertension is found to be associated with the several metabolic abnormalities and the most common are obesity, glucose intolerance, and dyslipidemia.

In patients with IR, Hyperglycaemia and hyperinsulinemia, the increased expression of angiotensinogen, Angiotensin -II (AT II), and the AT1 receptor have been well evidenced. It further activates the Renin angiotensin aldosterone system (RAAS)
which leads to development of hypertension. It has also been suggested by various researchers that hyperinsulinemia activate the sympathetic nervous system and results in increased renal reabsorption of sodium, increased cardiac output by heart, and vasoconstriction of arteries resulting in hypertension.\textsuperscript{1}

Diabetes mellitus has been agreed as a result of MetS by a large number of researchers. It is a constellation of common metabolic disorders with a specific characteristics or phenotype of hyperglycaemia. The hyperglycaemia is either due to insufficient production of insulin by beta cells of pancreas or due to non-responding receptor of cells for the insulin.\textsuperscript{25}

The complex interplay between environmental and genetic factors causes several types of diabetes. In patients with diabetes, the metabolic dysregulation causes secondary pathophysiological complications in multiple organ systems. The dysregulation of metabolismlinkedto diabetes causes secondary pathophysiological changes in multiple organ-systems resulting in extra burden on the individuals’ health and on the health care system as well. The increasing incidence throughout the globe has predicted Diabetes to be a leading cause of upcoming morbidity and mortality.\textsuperscript{26, 27}

Earlier, Diabetes was classified on the basis of age of onset as juvenile onset and maturity onset diabetes and on the basis of insulin dependency, it was classified as insulin dependent and non-insulin dependent Diabetes. Lately on the basis of pathophysiological causes leading hyperglycaemia, DM has been broadly classified as type 1 DM, type 2 DM, gestational diabetes and various specified diabetes. Both type 1 DM and type 2 DM are featured with hyperglycaemia due to abnormal glucose homeostasis during the course of disease where hyperglycaemia in type 1 is due to absolute or almost insulin deficient whereas type 2 is due to inconstant degrees of IR (insulin resistance) and or diminished insulin discharge. In addition, certain types of Diabetes have been offered fanciful names like brittle diabetes, bronze diabetes etc. Majority of diabetics includes T2DM which consists 90% solely and other 10% due to type 1 DM and Gestational Diabetes.

T2DM and MetS shares most of the common associations with cluster of abnormalities such as hyperglycaemia, increased free fatty acids (FFAs), abdominal
obesity, dyslipidemia, elevated insulin levels, low grade chronic inflammation, increased blood pressure; which have also been defined as Insulin Resistance syndrome. This cluster of abnormalities have also been evidenced with increased risk for CAD.\textsuperscript{26, 27} IR is an essential defect that pave the way for progress of full insulin resistance syndrome as well as let-down of beta cell and type 2 diabetes.\textsuperscript{28}

Over the past couple of decades, the prevalence of Diabetes from approximately 30 million in 1985 has been radically increased to 177 million in 2000 worldwidely\textsuperscript{29} which is further predicted to be raised >642 million diabetic cases by 2040.

The prevalence of T2DM is hiking hastily as compared to T1DM in the world behind the reasons with sedentary life style, increased obesity and reduced physical activity due to increased urbanization and more industrialized. Among the top ten countries regarding prevalence of Diabetes, six countries from the South Asia only have the highest rates. Globally in 2015, an estimated 415 million people have T2DM. 90-95\% of all these diagnosed with T2DM were obese. In respect to India, >69.2 million have been affected with T2DM in 2015.\textsuperscript{30}The raised incidence of Diabetes in India is credited to environment and genetic susceptibility, high calorie diet intake, reduced physical activity, aging and increased urbanization.\textsuperscript{31}DM increases with aging. In either sex, the prevalence is alike throughout most age ranges.\textsuperscript{32}

Cardiovascular disease (CVD) is another morbidity of MetS as a large number of epidemiological studies established the increased risk of CVD in subjects diagnosed with MetS. Universally Cardiovascular diseases (CVDs) have been considered as the leading cause of death and in the context of India 80\% of deaths has been reported associated with CVDs and occur almost equally in either sex.\textsuperscript{33}By 2030, CVDs would overcome as the foremost cause of death over other infectious and non-infectious diseases and estimated with death of 23.6 million due to CVDs.\textsuperscript{34}Most of the constituents of MetS definitions are conversing risk for DMT2 & CVD. Particularly, central obesity, high blood triglyceride, raised LDL and diminished HDL concentrations are linked with a cardiovascular risk.\textsuperscript{6}

Inflammation has also been demonstrated to be linked with obesity and MetS. The inflammation is quite unusual in obesity and MetS and termed as “low grade”
chronic inflammation as it is not the result of infection, do not shows sign of immunity and no massive tissue injury is seen. It is also termed as “metaflammation”, which means metabolically triggered inflammation, as well as “parainflammation” which states the intermediate state between basal and inflammatory states. Evidence from the numerous researchers has publicized the association of MetS with inflammatory markers like CRP, interleukin-6, serum amyloid A, and soluble adhesion molecules. An acute phase reactant C-reactive protein (CRP) is a novel inflammatory marker which is synthesized by the hepatocytes in response to IL-6 and elevated in infection, systemic inflammation and tissue damage. The CRP level measured by using high sensitivity assay techniques with a sensitivity range below 10 mg/L is termed as hs-CRP. Significant correlation between hs-CRP level with central adiposity, elevated triglycerides, diminished HDL cholesterol, hyperinsulinemia and insulin resistance; which are the constituents of MetS; has been reported by numerous researchers. Whereas, some of the publications have validated the association of increased hs-CRP with progression of metabolic syndrome. hs-CRP has also been suggested as an additional marker of metabolic syndrome and/or predictor of MetS using cut off values.

Numerous studies have advised to establish hs-CRP as a robust marker for the prediction of future cardiovascular events like myocardial infarction, ischemic stroke, peripheral vascular disease, and sudden cardiac arrest in subjects with asymptomatic CVDs. Some of the traditional tools like Framingham coronary heart disease risk score, SCORE (Systematic Coronary Risk Evaluation) and Reynolds risk score estimates the absolute 10 years’ risk for cardiovascular events on the basis of traditional risk factors like age, gender, DM, dyslipidemia, smoking and HTN. It stratify the patients to “high risk”, “intermediate risk” and “low risk” where “intermediate risk” guidelines is not clear. Since by using traditional tools clinicians can predict only around 50-60% absolute risk of future coronary events in patients, hs-CRP can increase the accuracy in prediction of cardiovascular risk when added to current strategies for global risk assessment like the Framingham Risk Score (FRS). Assessing only the lipid profile cannot predict the primary risk of CVD, therefore combined hs-CRP is improved tool for primary screening and
prevention of global risk of CVD.\textsuperscript{44} The AHA/CDC (American Heart Association/Centres for Disease Control) for prediction and prevention of CVD risk has classified serum hs-CRP levels for global CVD into three different groups as low risk (1.0 mg/L), average risk (1.0–3.0 mg/L), and high risk (3.0 mg/L).\textsuperscript{37}

Previous studies have depicted possible correlation between obesity, inflammation and insulin resistance with MetS.\textsuperscript{38, 39, 43, 44, 45} Given the fact that Indian population suffer from increased risk of insulin resistance (IR), MetS and DM to changing socio-economic lifestyle, the correlation of inflammation and IR with outcomes of MetS becomes very important. Studying inflammation and IR in patients with MetS will help us understand the implication and outcome of MetS in a better way. This information will also help the physician to develop better treatment strategies for managing patients of MetS, thus improving the prognosis. Therefore, this study was designed to evaluate hs-CRP and IR in patients with MetS.