JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A CRITICAL INTERPRETATION ON THE CONCEPT OF METABOLIC SYNDROME – A REVIEW STUDY

Diksha Mishra[1], Dr Javin Bishnu Gogoi[2]

1. Research Scholar, Department of Biochemistry, Hemvati Nandan bahuguna medical education university Dehradun, Uttarakhand.
2. Professor and Head, Department of Biochemistry, Soban Singh Jeena Govt Institute of Medical Sciences and Research Pandekhola Almora Uttarakhand.

Corresponding Author- Diksha Mishra, Research Scholar, Department of Biochemistry, Hemvati Nandan bahuguna medical education university Dehradun, Uttarakhand.

ABSTRACT

Metabolic syndrome is a serious health condition that affects about 23 percent of adults and puts them at high risk for fat-related heart disease, diabetes, stroke and arterial wall disease. With the successful conquest of many chronic infectious diseases in the world, non-communicable disease (NCD) has become a major cause of morbidity and mortality not only in the developed countries but also in the less developed countries. Among all these NCDs, metabolic syndrome has been a real epidemic worldwide. Insulin resistance, visceral cholesterol, atherogenic dyslipidemia, endothelial dysfunction, genetic predisposition, hypertension, hyper-coagulable status and chronic stress are among the many factors that contribute to the development of the syndrome. Chronic inflammation is known to be associated with visceral obesity and insulin resistance, which is characterized by the production of abnormal adipocytes such as tumor necrosis factor α, interleukin-1 (IL-1), IL-6, leptin, and adiponectin. The interaction between the components of the clinical phenotype of the syndrome contributes to the development of its biological phenotype (insulin resistance, dyslipidemia, etc.), a pro-inflammatory state, and alters chronic, subclinical vascular inflammation and the formation of atherosclerotic processes. Lifestyle change is the initial intervention of choice for such people. Modern lifestyle modification therapy integrates specific recommendations regarding diet and exercise with behavioral strategies. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with lifestyle changes. This review provides a summary of the

literature regarding the definition of the syndrome, the epidemiology, the underlying pathogen formation, and the treatment approaches for each risk factor, including metabolic syndrome.

KEYWORDS - Metabolic syndrome, Modern lifestyle, modification therapy etc.

INTRODUCTION

Metabolic syndrome is a serious health condition that affects about 23 percent of adults and puts them at high risk for fat-related heart disease, diabetes, stroke and arterial wall disease. With the successful conquest of many chronic infectious diseases in the world, non-communicable disease (NCD) has become a major cause of morbidity and mortality not only in the developed countries but also in the less developed countries. Of all these NCDs, metabolic syndrome is the most common infectious disease worldwide[(1).]

Metabolic syndrome (MS) is a medical condition characterized by the co-occurrence of metabolic risk factors for both type 2 diabetes and heart disease. Although there are many different definitions of MS, they should all have at least 3 of the following 5 symptoms - namely abdominal obesity, high triglycerides, low high density lipoprotein cholesterol (HDL-C), high blood pressure and high blood sugar[(2)]

The incidence of MS varies from 17% to 37% in different countries. MS with increased morbidity and mortality of various diseases. For example, a meta-analysis including 87 studies and 951,083 subjects demonstrated that MS is associated with a 2-fold increase in morbidity and mortality risk, and a 1.5-fold increase in mortality from all causes. The mortality rate for all causes was 5.5% and cardiac mortality was 9.4% MS

Metabolic syndrome (MED) is a complex of metabolic abnormalities that act as a risk factor for type 2 diabetes (D2D) and heart disease (CVD) (3) It is also known in the literature as Syndrome X, Insulin Resistance, etc. It is not actually a disease, but is defined slightly differently by the galaxy and various systems of risk factors for heart disease.

The global prevalence of METs ranges from 7.9% to 43% in men and 7% & 56% in women. According to the ATP III definition of metabolic syndrome, 24% of American adults have metabolic syndrome (no sexual orientation). American women are more likely to meet the criteria (1.6 times and against men). These numbers can be underestimated as they are at least 10 years old. Metabolic syndrome is widely cited in the literature and has its own ICD-9 index (277.7)[(3).]

Sociological and lifestyle factors have been found to be related to Mets. The aging population (GP) is considered to be the most vulnerable population to the growth of the Mets. In India, G.P. Among the Mets, the prevalence was 42.1% in Hyderabad, 35.6% in Kolkata and 29.9% in Karnataka. The strong connection of the geographical region with the Mets is also noted.In 2014, the WHO estimated that 422 million people worldwide were infected with T2DM, which affects 8.5% of people over the age of 18. The incidence is increasing among people under the

age of 30, especially in low- and middle-income countries. People over the age of 60 are generally defined as being at risk for T2DM. In general, D2DM is a disease that progresses slowly from its onset and can be diagnosed many years later. T2DM is a leading cause of other health problems such as blindness, kidney failure, heart attack, stroke and lower extremity disability. The WHO estimates that 1.6 million deaths are directly due to diabetes, and that almost half of all deaths due to high blood glucose occur before the age of 70.

The world's biggest killers, along with diabetes and heart disease (CVD), cancer and chronic respiratory disease, are estimated at 35 million deaths each year, 80% of which are in low- and middle-income countries. There are cost-effective strategies to control this growing burden, but non-communicable disease (NCD) programs are heavily funded nationally and globally, and prevention is not included in the current Millennium Development Goals. The WHD recently developed an action plan to implement a global strategy for the prevention and control of NCDs. One of the objectives of this program is to develop simple strategies to identify those at high risk, with appropriate and cost-effective interventions. It is recommended as a simple medical tool for predicting metabolic syndrome diabetes and CVD, and as a theoretical basis for understanding at least part of the pathophysiological link between metabolic risk, future diabetes and CVD[(4)] .

High blood pressure is a major risk factor for many diseases, including heart attack and stroke. In 2017, the WHO estimated that more than one billion people had 12.8% of HD, with 57 million disability-adjusted lifetimes (DALYs) or 3.7% of DALYs each year.[(5)]

(Table 1) Diagnostic criteria for metabolic syndrome for ATP III, IDF and Harmonization definitions:-

	National Cholesterol Education Program's Adult Treatment Panel III (ATP III)	International Diabetes Federation (IDF)	Harmonization criterion for Asian Indians (Harmonization)
Abdominal obesity	-	-	-
Male	>=102 cm	≥ =90 cm	≥ =90 cm
Female	>=88 cm	≥ =80 cm	≥ =80 cm
Hyperglycemia	≥= 100 mg/dl	≥ =100 mg/dl	≥ =100 mg/dl
Hypertriglyceridemia	≥ 150 mg/dl	≥ 150 mg/dl	≥ 150 mg/dl
Low HDL cholesterol	-	-	-
Male	< 40 mg/dl	< 40 mg/dl	< 40 mg/dl
Female	< 50 mg/dl	< 50 mg/dl	< 50 mg/dl
Elevated blood pressure level	≥130/>= 85mmHg	≥130/>= 85mmHg	≥130/>= 85mmHg

Diagnostic criteria	3/5 risk factors	Must have abdominal obesity + other risk factors	3/5 risk factors

However, there is limited information describing the effect of new criteria on the prevalence of metabolic syndrome. Until recently, T2DM and metabolic syndrome were considered adult diseases. Urbanization, unhealthy diet and increasing sedentary lifestyles contributed to the increase in obesity worldwide, especially in developing countries. For young people with increasing rates of obesity, T2DM and metabolism. It is clear that this metabolic syndrome can develop at a young age and can progress into adulthood. Because the risk factors for this syndrome begin at an early age & it is important to study the prevalence of metabolic syndrome in the younger population.

PATHOPHYSIOLOGY OF METABOLIC SYNDROME

Mets are a chronic low-level inflammatory condition resulting from complex interactions between genetic and environmental factors. Many factors include insulin resistance, intestinal fat, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hyper-coagulable state, and chronic stress syndrome (Figure 1)[6]

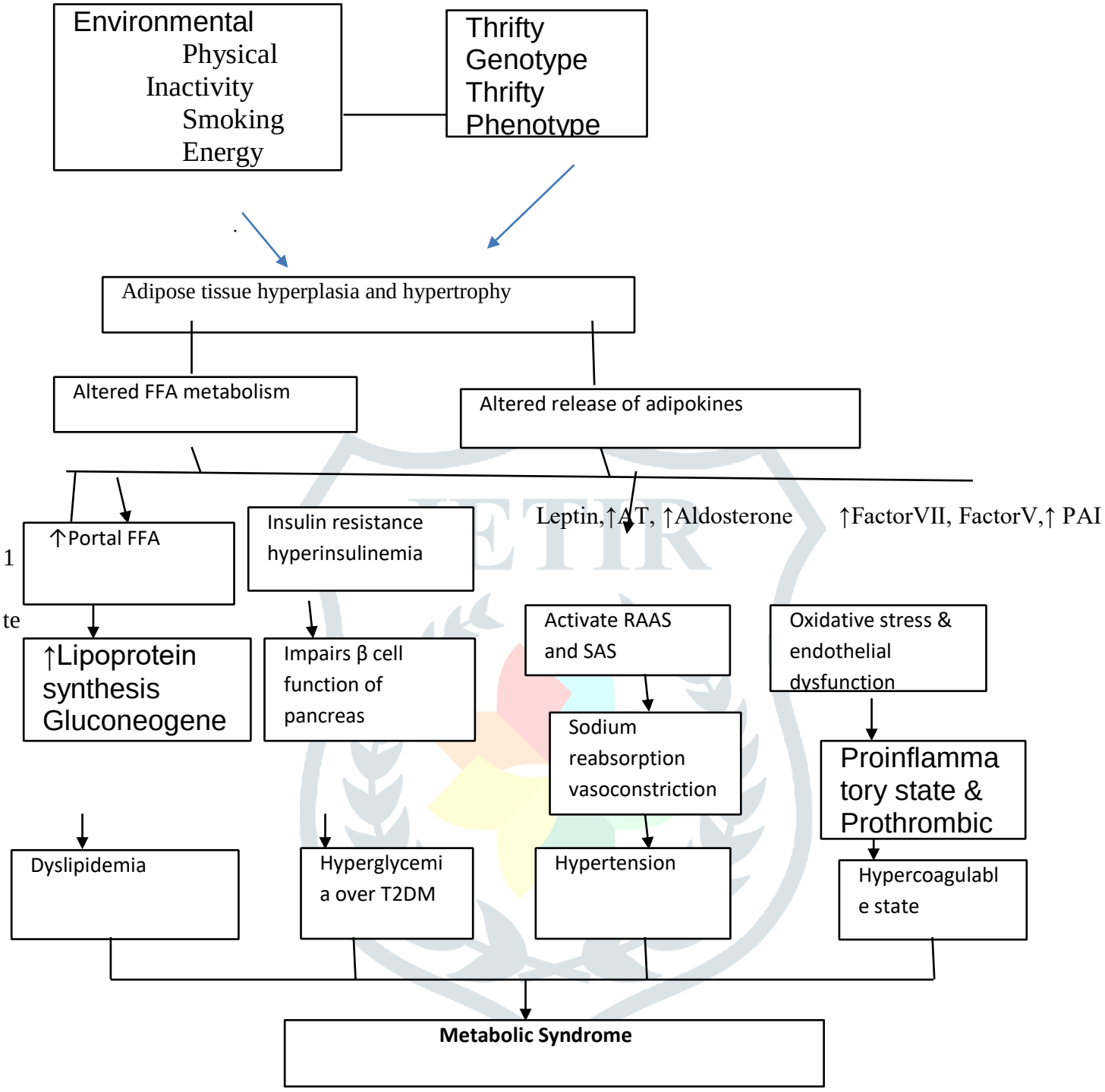


FIGURE 1 SCHEMATIC PRESENTATION OF THE METS

1. ABDOMINAL OBESITY:

Obesity is becoming an epidemic worldwide [7]. Obesity can be defined as excess body fat. Surrogate marker body mass index (BMI) for body fat, which is divided by weight (kg) divided by height squared (square meters). Clinically, a BMI of 25-29 kg / m2 is called overweight; High BMI (30 kg / m^2) is called obesity. A good way to define obesity is in terms of body fat percentage. It can be measured by a number of methods (skin-fold thickness, bioelectrical impedance, underwater weight). In terms of body fat percentage, obesity can be defined as 25% or more in men and 35% or more in women. Percentage of body fat measurement is rarely used in clinical practice, however, due to discomfort and cost. The best way to estimate obesity in clinical practice is to measure waist circumference. This is because high levels of abdominal fat are associated with metabolic risk factors [8].

The prevalence of overweight (body mass index (BMI) 25 to 29.9 and obesity (BMI) 30% is approximately 66% in the United States. Between 1988 and 2000 obesity increased from 23 to 30.5% and this increase occurred in both men and women. For women and those of all ages. Since then, there has been a growing trend, especially for teenagers and men. Obesity is also rising in other industrialized countries. Metabolic syndrome, formerly known as Syndrome X, is a major evolution of obesity which is also growing

When the waist circumference is 102 cm or more in men or 88 cm or more in women, the term abdominal obesity may apply. The advantage of measuring waist circumference is that high abdominal fat is more associated with the presence of metabolic risk factors than body fat. Cut points are arbitrary to define abdominal obesity. It is possible in individuals, the accumulation of abdominal fat can provoke or increase metabolic risk factors. It is unique in some populations; For example, a cut point has been identified around the lower waist circumference to define abdominal obesity in the Asian population.

There is good evidence for many genetic patterns that contribute to obesity. Parental body mass index is a significant factor of childhood obesity and family studies of childhood obesity suggest that the heredity of obsolete symptoms is up to 30-50%. Furthermore, there is evidence that genetic influences play an important role in determining body fat content, energy intake and energy expenditure. Although the remainder of obesity appears to be largely a polygenic determinant, several identical gene mutations (melanocortin 4 receptor genes, fat mass and obesity -associated genes, leptin and leptin receptor genes, or proopiomelanocortin genes) have been found simultaneously. Accounts can be searched for 11% of human obesity cases [9].

Obesity increases insulin resistance, which increases glucose production in the liver and lowers glucose in muscle and adipose tissue. At the same time, developing β-cell dysfunction inhibits the compensatory increase of insulin secretion. Loss of insulin resistance and compensatory insulin response leads to the development of T2D. With some clinics the incidence of T2D has changed in parallel with the changes in the esophagus. Up to 45% of cases of diabetes in children and adolescents due to T2D are now reported. This is evidence of genetic predisposition.

Developing particularly high-risk insulin resistance in the Middle East and Asia (especially Chinese and Indian) populations that develop a lower body mass index and smaller T2D than those found in the Western population. More detailed genetic studies have now shown that variations in at least 13 genes are associated with significant changes in insulin resistance [9]

RELATIONSHIP OF VISCERAL FAT TO METABOLIC SYNDROME

1. The hyper lipolysis state of omental adipose tissue, which reflects resistance to insulin action, contributes to the high concentration of free fatty acids in the liver (via portal circulation), leading to hyperinsulinemia in many hepatic metabolic processes. There is a decreased insulin secretion, glucose intolerance (increased liver glucose production) and hypertriglyceridemia (increased VLDL-apolipoprotein-B secretion; Adipose tissue is an important endocrine organ that is the source of adipocytes and inflammatory cytokines such as interleukin (IL) -6 (IL-6) and tumor necrosis
2. Factor (TNF) - (to name a few) insulin resistant which contributes to the obstructive, pro-inflammatory, -thrombotic and hypertensive state of visceral obesity. In this third scenario, inactive individuals who are unable to store their energy surplus in subcutaneous adipose tissue are characterized by the accumulation of fat in unwanted areas such as the liver, heart, skeletal muscle, and pancreas [10].
3. An increase in intra-abdominal fat accumulation, indicated by a larger waist circumference, may play a direct mediating role in the development of metabolic syndrome. Large amounts of FFI released by the intra-abdominal fat mass active in metabolism are believed to interfere with liver insulin clearance through the portal system in the liver. Intra-abdominal fat, which consists of primary brown adipose tissue (mainly omental and retroperitoneal), exhibits a higher mitochondrial density and lipolysis and glycolysis rate than subcutaneous white adipose tissue. Intrabiom fat is mainly involved in the high turnover distribution of FFA to other abdominal organs. Metabolic problems arise when abdominal fat develops. Intrabiomic adipose tissue is an active endocrine organ that contains many active factors, including leptin, adiponectin, resistin, interleukins (IL-1) and IL-6, and tumor necrosis factor alpha (TNF-A), 1 energy. Control. . Imbalanced release of these factors by expanded intra-abdominal fat mass is associated with increased metabolic disorders [11].

The following is a list of commonly referred factors in the development of metabolic syndrome:

1. Non-Esterified Fatty Acids (NEFAs)
2. Inflammatory cytokines
3. PAI-1
4. Adiponectin
5. Leptin
6. Resistin

It was initially suggested that high fatty acids inhibit glucose oxidation (glucose-fatty acid cycle) (12). Recent research suggests that increased muscle levels of diacylglycerol stimulate serine phosphorylation of insulin receptors and thereby inhibit normal insulin signaling. Other mechanisms have been proposed and play a role (13). Insulin resistance in muscle leads to hyperglycemia;The latter is clinically evident in those individuals with a defect in the ability to secrete insulin. The influx of excess NEFAs into the liver increases the triglyceride content in the liver (fatty liver) (14). Fat accumulation in the liver produces insulin resistance just like in muscle. Decrease in insulin action in the liver enhances gluconeogenesis and hepatic glucose production; It increases hyperglycemia in patients with reduced insulin secretion capacity. Increased fat in the liver also promotes the development of atherogenic dyslipidemia. It stimulates the formation and secretion of most LDL (VLDL) cells. The result is serum levels of triglyceride, apo B and small LDL cells. Excess serum triglycerides lower HDL-cholesterol concentrations by converting VLDL triglycerides with HDL cholesterol esters. HDL-cholesterol lowering occurs in people with esophageal-induced fatty liver by increased synthesis of hepatic lipase; Lipase degrades HDL cells, converting large HDLs into smaller HDLs. Whether high NEFA levels contribute to high blood pressure or the inflammatory condition is an important but unresolved question. Hypotheses have been developed to link high NEFA levels with high blood pressure. It remains to be determined whether the link is causal or not. Furthermore, fat accumulation in the liver has been reported to be associated with increased hepatic synthesis of PAI-1, fibrinogen, and inflammatory cytokines, which are the major mediators of high blood pressure and proinflammatory states

1. TNFα- It is a paracrine mediator in adipocytes and appears to act locally to reduce the insulin sensitivity of adipocytes. Evidence suggests that TNFα induces adipocytes apoptosis and promotes insulin resistance by the inhibition of the insulin receptor substrate 1 signalling pathway. The paracrine action would further tend to exacerbate the FFa release inducing an atherogenic dyslipidemia, plasma TNFα is positively associated with the body weight , WC and TGs while a negative association exists between the plasma TNFα and high density lipoprotein cholesterol (HDL-C)
2. CRP- Elevated levels of CRP are associated with an increased WC, insulin resistance, BMI, and hyperglycemia and are increased with the number of the Mets components. It is more likely to the elevated in obese insulin resistant but not in insulin- sensitive subjects. In addition it has been demonstrated that regardless of the presence or degree of the Mets in an individual, CRP levels independently predicted the occurrence of future CVD events because the Mets has been linked with a greater chance of future CVD events, CRP levels may be an important independent predictor of unfavourable outcomes in the Mets.
3. IL-6 – Adipose tissue and skeletal muscles released IL-6 in humans. It has both an inflammatory and anti-inflammatory action, IL-6 is also expressed in the several regions of the brain such as the hypothalamus in which it controls the appetite and energy intake. It is a systematic adipokine which not only impairs insulin sensitivity but is a major determinant of the hepatic production of the CRP. IL-6 is capable of suppressing lipoprotein lipase

activity and shows positively association with the BMI, fasting insulin and the development of T2DM and negatively associated HDL-C[12]

4. PAI-1-Adipose tissue also synthesizes PAI-1. Reports suggest that abdominal adipose tissue is more active in PAI-1 synthesis than low-body adipose tissue. Fatty liver can be another source of PAI-1. The result is high PAI-1 levels in obese people and high plasma fibrinogen observed in such individuals contributing to prothrombotic status.[13]
5. Adiponectin- Other adipose tissue products. Many other products of adipose tissue affect the development of metabolic syndrome. However, their exact role must be fully determined. adiponectin is an important product. This substance has been reported to have anti-inflammatory and anti-atherogenic properties. Those with obesity usually have low levels of adiponectin and may therefore lose its protective effects against metabolic syndrome[14]
6. Leptin- Leptin also plays a systemic role beyond suppressing adipose tissue-derived appetite. Whether the systemic effects of leptin on the central nervous system are direct or secondary is currently under discussion.regardless, this hormone has been reported to have a beneficial effect on the liver to protect against fatty liver. Its mechanism may be to increase fatty acid oxidation in the liver [15].

Finally, resistin is an adipose tissue-derived hormone that inhibits insulin action. Whether or not there is a physical role in humans has not yet been determined [16]

INSULIN RESISTANCE:-

Insulin resistance (IR) is defined as a defective metabolic response to insulin to suppress glucose uptake and / or blood glucose release and circulating glucose release in skeletal muscle and adipose tissue. The metabolic response to IR and subsequent hyperinsulinemia can be attributed to the development of serious health consequences such as overweight, hypertension, hyperlipidemia, heart disease and type-2 diabetes (T2D) . The chance of disposing of insulin-mediated glucose varies widely in a large population. Type 2 diabetes develops when insulin-resistant individuals do not maintain the level of hyperinsulinemia needed to overcome insulin resistance. Most individuals are able to maintain the level of compensatory hyperinsulinemia needed to maintain normal or near glucose tolerance. Unfortunately, this charitable endeavor of the pancreatic beta cell is a mixed blessing. Although compensatory hyperinsulinemia inhibits the development of frank hyperglycemia, glucose intolerance in insulin resistant / hyperinsulinemic individuals may be associated with increased risk of high plasma triglyceride and low risk of high-density lipoprotein cholesterol (HDL-C) and, to a lesser extent, risk. High blood pressure. In 1988, it was proposed that people who exhibited these abnormalities related to insulin resistance / compensatory hyperinsulinemia significantly increased their risk of heart disease (CVD). Since the importance of insulin resistance and associated abnormalities as CVD risk factors was not widely appreciated at the time, groups of associated abnormalities were subscribed under the rubric of Syndrome X [17].

After insulin binds to the insulin receptor, physiologic insulin signaling occurs, which is ligand-activated tyrosine kinase. Binding of insulin leads to tyrosine phosphorylation of the lower surface and activation of two parallel pathways: the phosphoinositide 3-kinase (PI3K) pathway and the mitogen activated protein (MAP) kinase pathway. The PI3K-Akt pathway is affected, however, the MAP kinase pathway usually acts on insulin resistance. It shifts the balance between these two parallel paths. Inhibition of the PI3K-Akt pathway leads to a decrease in endothelial NO production, resulting in decreased endothelial dysfunction and GLUT4 translocation, which in turn leads to a decrease in skeletal muscle and fat glucose. In contrast, the MAP kinase pathway is not affected, so there is continuous endothelin-1 (ET-1) production, expression of vascular cell synthesis molecules, and mitogenic stimulation of vascular smooth muscle cells. In these ways, insulin resistance can lead to vascular abnormalities in atherosclerosis sufferers. Although insulin-resistant individuals do not need to receive leads to balance medically, they usually have an abnormal fat distribution, which is a prominent feature of body fat. Despite the relative contribution of gut fat and abdominal subcutaneous fat to insulin resistance, the pattern of abdominal (or upper body) obesity is more strongly correlated with insulin resistance and then lower body obesity [(18).]

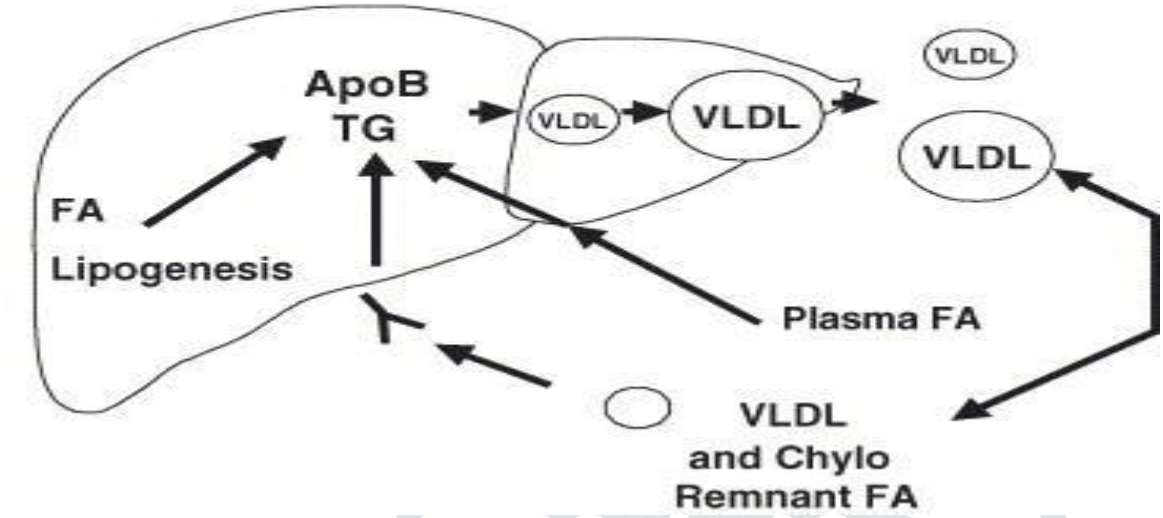
HYPERTENSION:-

Most people with high blood pressure have glucose intolerance and hyperinsulinemia. However, this relationship is not reasonably linked, possibly to controlling blood pressure, or improvement of glucose intolerance or hyperinsulinemia and it is not seen in patients with hypertensive insulinoma. On the other hand, obesity contributes to hypertension and hyperinsulinemia, while weight loss generally improves both of these disorders. Insulin resistance and hyperinsulinemia are caused directly by the action of catecholamine, which is increased independently of the ratio as plasma glucose. Insulin-mediated renal tubular reabsorption raises itself to insulin via sodium, which also raises blood pressure drastically. Studies suggest that both hyperglycemia and hyperinsulinemia activate the renin angiotensin system (RAS) by increasing the expression of angiotensinogen, angiotensin II (AT II) and AT1 receptor in the development of hypertension in patients with insulin in concert. There is also evidence that insulin resistance and hyperinsulinemia lead to SNS activation, and as a result, the kidneys increase sodium reabsorption, increase cardiac cardiac output, and the arteries respond to vasoconstriction as a result of hypertension. Is. It has recently been found that adipocytes also produce aldosterone in response to ATII. In this case, adipocytes can be thought of as a small renin - angiotensin - aldosterone system.[(19)]

DYSLIPIDEMIA:-

High triglyceride and low HDL cholesterol levels are major components of metabolic syndrome. Defects of these components are associated with high levels of plasma small dense low density lipoprotein (LDL) cholesterol, which is the most atherogenic subfraction of LDL, leading to weight gain in individuals. People with high concentrations of these cells are at higher risk for CVD [(20).]

Substrate Driving Forces for the Assembly and Secretion of apoB-Lipoproteins



Increased plasma levels in very low-density lipoproteins (VLDL) are not only common features of insulin resistance and type 2 diabetes mellitus (T2DM) -signed dyslipidemia, but also a central pathophysiological feature of abnormal lipid profiles. The increase in VLDL leads to an increase in the plasma level of TG, which is mediated by the cholesteryl ester transfer protein (CETP) as a result of the conversion process, resulting in low-density lipoprotein (HDL) cholesterol and apolipoprotein A-I and low, dense generation cholesterol ester depleted (LDL) Complex and post-transcriptional regulation of apolipoprotein B (apoB) metabolism by the liver results in increased assembly and secretion of VLDL by the liver. In the presence of low levels of TG and cholesterol, the apo B degenerates through the constitutionally synthesized apo B proteasomal and non-proteasomal pathways. In the presence of excess TGs, and to some extent, cholesterol, and activated microsomal triglycerides transfer proteins, apob is targeted for secretion. The main sources of TG in the liver are: TG releases fast (FA) of adipose tissue lipolysis, surpasses TGFNA in VLDL and Chylomicron residues, and hepatic de novo lipogenesis (FA synthesis from glucose) is all abnormally increased. In insulin resistance. Treatment of dyslipidemia in insulin-resistant individuals and patients with T2DM has been successful in reducing cardiovascular disease; Diet, exercise and weight loss are the appropriate targets for LDL cholesterol, TG and HDL cholesterol treatment when the goals are not achieved.[21]

GENETICS:-

Genetic factors affect every individual part of the syndrome and the syndrome itself. Obesity, family history of type 2 diabetes and / or insulin resistance can greatly increase a person's chances of developing metabolic syndrome. However, there are some genetic predispositions that can lead to metabolic syndrome . This applies to most people of South Asian descent and there are also significant individual and ethnic variations in the clinical

models of metabolic risk factors in obese / insulin resistance. Similarly, the genetic predisposition of defective insulin secretion, when combined with insulin resistance, raises plasma glucose to abnormal levels. According to Neil's genetic hypothesis proposed in 1962, people living in harsh environments with unstable food supplies increase their chances of survival if they can maximize surplus energy storage. Genetic selection is favorable for energy-conserving genotypes in such environments. However, the genetic variants preferred during malnutrition turn negative when nutrition improves. These hypotheses are common genetic variants of the savings genes predicted for the Mets. Another austerity hypothesis was introduced by Hales and Barker in 1992. The saving phenotype hypothesis is that epidemiological associations between poor fetal and infant development and subsequent development of type 2 diabetes occur as a result of poor nutritional effects early in life, producing permanent changes in glucose-insulin metabolism. These changes include reduced ability to insulin secretion and insulin resistance, which, combined with the effects of infertility, aging, and physical inactivity, are important factors in determining type 2 diabetes in many populations. [22]

ENDOTHELIAL FUNCTION

Many metabolic abnormalities found in metabolic syndrome, including hyperglycemia, high fatty acid and insulin resistance, can cause endothelial cell dysfunction by affecting nitric oxide synthesis or degradation. Although the exact mechanism by which metabolic syndrome induces endothelial dysfunction is clearly stated, there is a high risk of increased vascular endothelial damage and heart risk in these patients. The most common metabolic, hormonal, and hemostatic abnormalities in patients with endothelial dysfunction are: hyperinsulinemia, hyperglycemia, elevated fatty acid levels, hypertriglyceridemia, HDL-cholesterol, and low-cholesterol cholesterol. Apolipoprotein B, insulin-1 growth factor levels, increased tissue angiotensin II levels, plasminogen catalyst-1, increased C reactive protein, increased oxidative stress [23]

In addition, a decrease in NO, an important regulator of endothelial homeostasis, and an increase in reactive oxygen species result in endothelial dysfunction and protogenic vascular bed [24].

HYPERCOAGULABLE STATE:-

Metabolic syndrome is characterized by a combination of constipation, chronic inflammation and insulin resistance. The syndrome is characterized by a hypercoagulable state, decreased levels of clotting factor (tissue factor, factor VII and fibrinogen) as well as inhibition of the fibrinolytic pathway (plasminogen activator inhibitor-1 and tissue plasminogen activator activity). At the same time, the presence of endothelial dysfunction and dyslipidemia induces platelet aggregation, thereby increasing the risk of thrombotic events in the arterial and venous systems. In view of the increased incidence of metabolic syndrome at an early age, the occurrence of venous thromboembolism and the impact of interventions on the signs of hypercoagulability of metabolic syndrome for further study [25].

DIET: -

Study by Aljada et al. This shows that high dietary fat intake is associated with oxidative stress and activation of the proinflammatory transcription factor, the molecular factor kappa-beta (NFkB) .High-fiber diets have received much attention in recent years for their supplementation as the incidence of many metabolic disorders such as hypertension, diabetes, obesity as well as heart disease and stomach cancer has decreased[26].

TREATMENT

Mets are chronic low-level inflammatory conditions with severe systemic effects. Clinical identification and management of patients with Mets are important to initiate efforts to adequately implement treatments to reduce the risk of subsequent diseases. Effective preventive measures include lifestyle changes, mainly weight loss, diet and exercise, and the appropriate use of pharmacological agents to reduce specific risk factors in treatment. Medication should be considered for those whose risk factors are insufficient with preventive measures and lifestyle changes. The clinical management of Mets is difficult because there is no known method to prevent or improve the overall syndrome, the background of which must be insulin resistance Therefore, many physicians treat each part of the Mets differently, with a special focus on those parts that are immediately responsible for drug treatment. In fact, it is much easier to prescribe a drug to lower blood pressure, blood sugar or triglycerides than it is to start a long-term strategy to change people's lifestyle, in the hope that they will eventually lose weight and lower blood pressure, blood sugar & triglycerides. For the treatment of risk factors for Mets, the physician is a member of the National Cholesterol Education Program (NCEP) the Seventh Joint National Commission for the Treatment of Blood Pressure (JNC-VII), and American Diabetes Association (ADA), American Heart Association (AHA), and the National Institute of Health Obesity Initiative.[27]

Table 3: Systematic effects of Mets

Renal	Microalbuminuria, hyperfiltration, hyperfiltration, glomerulomegaly, focal segmental glomerulosclerosis, and chronic kidney disease
Hepatic	Increased serum transaminase, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hepatic fibrosis, and cirrhosis
Skin	Acanthosis nigricans, lichen planus, systemic lupus erythematosus, burn-induced insulin resistance, psoriasis, androgenetic alopecia, skin tags, skin cancer, and acne inversa

Ocular	Nondiabetic retinopathy, age related cataract-nuclear, cortical, posterior subcapsular; central retinal artery occlusion, primary open angle glaucoma, oculomotor nerve palsy, and lower lid entropion
Sleep	Obstructive sleep apnea (OSA)
Reproductive system	Hypogonadism, polycystic ovarian syndrome (PCOS), and erectile dysfunction
Cardiovascular system	Coronary heart disease (CHD), myocardial infarction (MI), and stroke
Cancers	Breast, pancreas, and prostate

RISK ASSESSMENT

The goals of treatment are to reduce short-term and lifelong risk. Having Mets per minute indicates a high lifespan risk. A practical approach to estimating complete, short-term CHD / CVD risk in non-diabetic ASCVD or Mets patients is to use the standard Framingham algorithm to estimate the 10-year risk of coronary heart disease (CHD) (10). Cigarette smoking, high blood pressure, total cholesterol, HDL-C and age-related standard Framingham risk equation are associated with an increased risk of CVD in patients with the syndrome. This equation places patients in 3 risk groups based on their 10-year risk of CHD: high-risk (10-year risk mode ≥ 20%), moderately high-risk (10-year risk 10% to 20%) or moderately low risk (10-year risk ≤ 10%), however, patients with ASCVD or diabetes are in the high-risk segment without the need for Framingham risk scoring.

Table 4: Multidisciplinary approach to the Mets.

A: assessment	Calculate Framingham risk score: *high risk* (10-year risk ≥20%), *moderately high risk* (10-year risk 10% to 20%), or *lower to moderate risk* (10-year risk ≤10%). Make a diagnosis of Mets using the diagnostic criteria.
A: aspirin	High risk: aspirin is definitely beneficial. High-intermediate risk (10–20%): aspirin likely to be beneficial. Low-intermediate risk (6–10%): "individual clinical judgment", depending on sex and risk of bleeding. Low risk (<6%): Risk of haemorrhage outweighs the benefits.

B: BP control	Initiate treatment: categorical hypertension (BP ≥ 140/≥90 mm Hg). Patients with established diabetes (≥130/≥80 mm Hg). ACEIs/ARBs first line agents may reduce incident diabetes mellitus. Beta-blockers and thiazides may have an adverse effect on impaired glucose tolerance but outweighed by the benefits of reaching BP goal and lowering the risk of CVD events.
C: cholesterol First target: LDL Second target: non-HDL Third target: HDL Fourth target: CRP	Statin to achieve LDL-C <100 mg/dl in high-risk, <130 mg/dl in intermediate-risk, and <160 mg/dl in low risk patients. Statin intensification, consider niacin and/or fibrates once statin maximized. Consider fibrates, especially for those with combined hypertriglyceridemia/low HDL-C. Consider further reduction in LDL-C with statin therapy to mitigate a risk of low HDL-C, consider niacin.

DYSLIPIDEMIA

The guidelines recommend setting LDL-C targets (Table 5) below 130 mg / dl, with the option to target high-target individuals at least 100 mg / dl. In high-risk patients, LDL-C should be set below 100 mg / dl with a target of less than 70 mg / dl in the "very high-risk" patient (21). The non-HDL-C target is 30 mg / dl higher than LDL-C. In patients with atherogenic dyslipidemia with serum TG levels an200 mg / dl, non-HDL-C becomes the next target of treatment after reaching the LDL-C target. If the TGS level is greater than 500 mg per dl, the importance is reduced by lowering the TGS level to 500 mg or LDL-C to prevent the development of acute pancreatitis. After achieving the LDL-C and HDL-C targets, the tertiary goal is raising HDL-C levels. No targets have been set for raising HDL-C levels, but HDL-C should be increased as much as possible after achieving LDL-C and non-HDL-C targets [(28).]

Risk category	LDL-C goals	Recommendations
Lower risk 0-1 major risk	<160 mg/dl	Lifestyle modifications Consider pharmacotherapy if LDL-C ≥190 mg/dL after lifestyle modifications

factor 10-yr risk <10%		
Moderate risk ≥2 major risk factors 10-yr risk <10%	<130 mg/dl	Lifestyle modifications Consider pharmacotherapy if LDL-C ≥160 mg/dl after lifestyle modifications
Moderately high risk ≥2 major risk factors 10-yr risk 10–20%	<130 mg/dl Optional <100 mg/dl	Lifestyle modifications Consider pharmacotherapy if LDL-C ≥130 mg/dl or optionally ≥100 mg/dl after lifestyle modifications
High risk CHD or CHD risk equivalents	<100 mg/dl Optional <70 mg/dl	Lifestyle modifications Consider pharmacotherapy if LDL-C ≥100 mg/dl or optionally ≥70 mg/dl after lifestyle modifications

Statins/Niacin are considered to be the most effective class of drugs to reduce LDL-C concentrations, at least due to drug-interaction drug interactions and side effects. A reduction of 15 to 60 mg / dl in LDL-C was observed, depending on the dose used and the specific type of statin. Statins increase HDL-C by 5–10%, with higher elevations in low HDL-C and elevated TG, and individuals with lower TGS concentrations, mainly in medium-dose 7-30% [(29)] and a very low density lipoprotein (VLDL) level of 39% . The lipid-lowering or pleiotropic effects of statins have also been implicated in their beneficial effects on inflammation, endocrine function, and CVD events and may therefore be beneficial to individuals with METs [(30)] Statins reduce the incidence of MI or stroke by more than 33% in patients with coronary artery disease. Statins are combined with fibrates, especially fenofibrate and niacin, to achieve the target levels of HDL-C, TG, and HDL-C. All statins had a positive effect on atherogenic dyslipidemia, the greatest effect being on the effect of rosuvastatin.[(31)]

Niacin must have a positive effect on all abnormalities of metabolic dyslipidemia. It is considered to be the most effective agent for increasing HDL-C (15 to 35%) and increasing HDL particle size. Niacin significantly reduces TG (20 to 50%) and LDL-C (5-25%). Niacin also causes beneficial changes in lipoprotein subclasses, as it has been shown to increase the ratio of small to dense LDL-C cells by increasing the number of larger, lighter LDL-C cells and larger HDL-C cells Is gone.[(32)] Combination therapy with niacin and statin may have a greater effect on lipid levels than that given alone.[(33)] The primary limitations to niacin use are flushing (most often associated with instant-release niacin) and hyperglycemia.[(34)] Therefore, if fasting glucose (IFG), weak glucose tolerance (IGT) or nicotinic acid is used in patients with diabetes, its dose should be kept relatively low (e.g., 1 to 2 grams

per day) and should be carefully monitored.[35] Exacerbation of hyperglycemia [36] Niacin has a greater effect on raising HDL-C levels (15% –35%), with a more moderate effect on fibrates (6% –15%) and statins (3% –15%) (123).[37]

Bile acid sequesters (BAs) and cholesterol absorption inhibitors (CAIs) reduce the absorption of intestinal bile acids and cholesterol by lowering LDL-C, respectively. Reduces base LDL-C (101) by 15 to 30%. Azetimbi, the only clinically available CAI, led to a 15–25% reduction in LDL-C. Although both BAS and CAI are effective as monotherapy, they are more beneficial when used in combination with statins, which may be due to their complementary mechanisms.Trial studies have shown that BAS and Azetimbi Mets reduce the risk of major coronary events in patients.[38].

HYPERTENSION

Clear blood pressure (BP / 140 / H 90 mm Hg) should be treated according to the guidelines of USA JNC VII on the prevention, detection, evaluation and treatment of hypertension prevention, diagnosis, evaluation and treatment. Antihypertensive drugs should also be introduced in patients with diabetes at low blood pressure (/ 130 / g80 mm Hg). Blood pressure elevation can often be effectively controlled with lifestyle therapies. 5% of weight loss in obese women reduced systolic blood pressure to 7 mmHg and related to angiotensinogen (27%), renin (% 43%), angiotensin-converting enzyme (−12%), and aldosterone levels. (Ogen31%), and angiotensinogen expression in adipocytes 20%) . A 5 mmHg decrease in systolic blood pressure in the general population is estimated to reduce stroke mortality by 14%, CHD mortality by 9% and all mortality by 7% . However, if blood pressure is not adequately controlled by lifestyle therapies, antihypertensive drugs are usually needed to prevent long-term adverse effects, for example, MI, stroke and CKD. It has been suggested that angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may be first-class agents of the MET, particularly in diabetes or CHD. ARB can be used as an alternative to ACE inhibitors in those who do not tolerate ACE inhibitors or in ventricular dysfunction. Agents of these classes have been shown to be effective in reducing the progression of albuminuria or nephropathy in patients with diabetes. Although several tests have shown that ACE inhibitors and ARBs reduce the risk of diabetes, a recent study conducted directly to investigate the problem found that ACE inhibitor ramipril increased in IFG or individuals did not inhibit the progression of diabetes IGT. In general, treatment with these classes of drugs reduces the rate of new onset diabetes compared with the use of diuretics and / or (-blockers), but the long-term safety and efficacy of β-blockers and diabetics are effective. Is informed. Prevention of heart attack tests (ALLHAT) has been the subject of several clinical trials, including antihypertensive and lipid-lowering treatments in 40,000 patients. Despite a less favorable overall profile for thiazide diuretics, ALLHAT has shown that thiazide-type diuretics provide better CVD results in patients with MET compared with calcium channel blockers, β-blockers, or ACE inhibitors. ALLHAT and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that agents such as thiazide diuretics and β-blockers also reduce

the risk of developing CVD in patients with diabetes. However, agents increase the risk of diabetes. Many patients who require antihypertensive therapy need more than one agent for proper blood pressure control. (39)

INSULIN RESISTANCE AND HYPERGLYCEMIA

At METs, IFG (or IGT, if expected), weight loss, increased physical activity, or both occur in patients who have initiated (or prevented) T2DM In addition, metformin, thiazolidinones and acarbose reduce the risk of T2DM in those with IFG or IGT. Metformin, which has the primary mechanism of action of reducing liver glucose production, has been shown to reduce the progression of diabetes from IGT to 31% in DPP, of which 53% are Mets The metformin-treated DPP group also had a 17% reduction in MET incidence, which was mainly driven by improvement in WC and accelerated glucose uptake, while intensive therapeutic lifestyle changes increased the risk by 58% compared with placebo. However, other cardiovascular risk factors did not improve with metformin as with intensive lifestyle interventions. Studies have shown that metformin actually treats IGT and does not require "prevention" in the long-term follow-up of T2DM. Studies to prevent non-insulin dependent diabetes mellitus (STOP-NIDDM) testing have shown that a drug that affects carbohydrate absorption and is approved for T2DM treatment can improve T2DM with IGT. Has also been shown to reduce. This trial showed that Acarbose treatment was associated with lower CVD and hypertension. The main limitation of the use of this agent is its poor patient tolerance. Pioglitazone has been shown to be associated with hypertension, high blood sugar and many components of the Mets, and decreased urinary albumin / creatinine ratio in TGs. Although the benefit of this approach in Mets or IGT subjects is unclear, it has been concluded that pioglitazone may be useful in the prevention of cardiac events in high-risk patients with T2DM. However, in addition to initial testing with Acarbose, clinical trial evidence is not yet available to suggest that oral hypoglycemic agents in Mets, IGT, or IFGs may reduce the risk of cardiac events.(40)

CONCLUSION

Mets are defined by a group of interacting physiological, biochemical, clinical and metabolic factors that directly increase the risk of atherosclerotic heart disease, type 2 diabetes and all deaths.Many factors include insulin resistance, intestinal fat, atherogenic dyslipidemia, endothelial dysfunction, genetic sensitivity, increased blood pressure, hypercoagulable status and chronic stress metabolic syndrome. Lifestyle change is an early intervention of choice for this population. Modern lifestyle change combines specific recommendations on diet and exercise with medical behavioral strategies Medication should be considered for those whose risk factors are not adequate with lifestyle changes. The real goal for overweight / obesity is to reduce body weight by 7% to 10% over a period of 6 to 12 months. Weight loss should be combined with a minimum of 30 minutes of moderate-intensity physical activity daily. Nutrition therapy calls for reducing saturated and total fat intake; Reduction in the consumption of simple sugars and foods with a high glycemic index; and intake of fruits, vegetables, legumes and whole grains. Statins can be combined with fibrates and niacin to achieve LDL-C, triglycerides and HDL-C target levels. In addition, patients in need of antihypertensive therapy may need one or more agents as first- and second-line agents,

respectively, for proper blood pressure control with ACEI / ARBs and beta blockers / thiazides / CCBs. Metformin, thiazolidinediones and acarbose reduce the risk of type 2 diabetes mellitus in those with IFG or IGT.

REFERENCES

1. Saklayen MG. The Global Epidemic of Metabolic Syndrome. Curr Hypertens Rep. 2018;20 2 :1–8.
2. Xu H, Li X, Adams H, Kubena K, Guo S. Etiology of metabolic syndrome and dietary intervention. Int J Mol Sci. 2019;20 1 :1–19.
3. Cowey S, Hardy RW. The metabolic syndrome: A high-risk state for cancer? Am J Pathol. 2006;169 5 :1505–22.
4. Nolan PB, Carrick-Ranson G, Stinear JW, Reading SA, Dalleck LC. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: A pooled analysis. Prev Med Reports Internet . 2017; 7: 211–5. Available from: http:// dx.doi.org/ 10.1016/ j.pmedr.2017.07.004
5. Apidechkul T. Prevalence and factors associated with type 2 diabetes mellitus and hypertension among the hill tribe elderly populations in northern Thailand. BMC Public Health. 2018;18 1 :1–17.
6. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: Mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol. 2007;2 3 :550–62.
7. Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab. 2004;89 6 :2595–600.
8. Gregory JW. Prevention of Obesity and Metabolic Syndrome in Children. Front Endocrinol Lausanne . 2019;10 October :1–9.
9. Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal Obesity and the Metabolic Syndrome: Contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol. 2008;28 6 :1039–49.
10. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovasc Dis. 2016;5:204800401663337.
11. Cho J, Hong H, Park S, Kim S, Kang H. Insulin resistance and its association with metabolic syndrome in Korean children. Biomed Res Int. 2017;2017.
12. Reaven G. Metabolic syndrome or insulin resistance syndrome? Different names, different concepts, and different goals. Endocrinol Metab Clin North Am. 2004;33 2 :283–303.
13. Nieuwdorp M, Stores ESG, Meijers JCM, Büller H. Hypercoagulability in the metabolic syndrome. Curr Opin Pharmacol. 2005;5 2 SPEC. ISS. :155–9.
14. N. Abate, M. Chandalia, P. G. Snell, and S. M. Grundy, “Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men,” Journal of Clinical Endocrinology and Metabolism, vol. 89, no. 6, pp. 2750–2755, 2004.
15. L. J. Martin, K. E. North, T. Dyer, J. Blangero, A. G. Comuzzie, and J. Williams, “Phenotypic, genetic, and genome-wide structure in the metabolic syndrome,” BMC Genetics, vol. 4, supplement 1, article S95, 2003.

16. P. Poulsen, K. Levin, I. Petersen, K. Christensen, H. BeckNielsen, and A. Vaag, "Heritability of insulin secretion, peripheral and hepatic insulin action, and intracellular glucose partitioning in young and old Danish twins," Diabetes, vol. 54, no. 1, pp. 275–283, 2005.
17. J. V. Neel, "Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"?" The American Journal of Human Genetics, vol. 14, pp. 353–362, 1962.
18. C. N. Hales and D. J. P. Barker, "Type 2 non-insulin-dependent diabetes mellitus: the thrifty phenotype hypothesis," Diabetologia, vol. 35, no. 7, pp. 595–601, 1992.
19. D. G. Harrison, "Cellular and molecular mechanisms of endothelial cell dysfunction," Journal of Clinical Investigation, vol. 100, no. 9, pp. 2153–2157, 1997.
20. A. Aljada, P. Mohanty, H. Ghanim et al., "Increase in intranuclear nuclear factor κB and decrease in inhibitor κB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect," The American Journal of Clinical Nutrition, vol. 79, no. 4, pp. 682–690, 2004.
21. L. F. Lien, A. J. Brown, J. D. Ard et al., "Effects of PREMIER lifestyle modifications on participants with and without the metabolic syndrome," Hypertension, vol. 50, no. 4, pp. 609–616, 2007.
22. Nieuwdorp M, Stores ESG, Meijers JCM, Büller H. Hypercoagulability in the metabolic syndrome. Curr Opin Pharmacol. 2005;5 2 SPEC. ISS. :155–9.
23. Wong ND. Intensified screening and treatment of the metabolic syndrome for cardiovascular risk reduction. Preventive Cardiology. 2005;8 1 :47–54.
24. Deen D. Metabolic syndrome: time for action. The American Family Physician. 2004;69 12 :2875–2887.
25. National Cholesterol Education Program NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III . Third Report of the National Cholesterol Education Program NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult treatment panel III final report. Circulation. 2002;106 25 :3143–3421.
26. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. Journal of the American Medical Association. 2003;289 19 :2560–2572.
27. American Diabetes Association. Clinical practice recommendations 2005. Diabetes Care. 2005;28 supplement 1 :S1–79.
28. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report. National Institutes of Health. Obesity Research. 1998;6 supplement 2 :51S–209S.
29. Bellentani S, Grave RD, Suppini A, et al. Behavior therapy for nonalcoholic fatty liver disease: the need for a multidisciplinary approach. Hepatology. 2008;47 2 :746–754.
30. Donato KA. Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. Archives of Internal Medicine. 1998;158 17 :1855–1867.

31. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and post heparin plasma lipase activity in previously sedentary adults. Diabetes Care. 2003;26 3 :557–562.
32. Van Gaal LF, Wauters MA, De Leeuw IH. The beneficial effects of modest weight loss on cardiovascular risk factors. International Journal of Obesity. 1997;21 supplement 1 :S5–S9.
33. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly TONE . TONE Collaborative Research Group. Journal of the American Medical Association. 1998;279 11 :839–846.
34. Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D. Long-term effects of modest weight loss in type II diabetic patients. Archives of Internal Medicine. 1987;147 10 :1749–1753.
35. Ross R, Janssen I, Dawson J, et al. Exercise-induced reduction in obesity and insulin resistance in women: a randomized controlled trial. Obesity Research. 2004;12 5 :789–798.
36. 48. Hill JO, Wyatt HR. Role of physical activity in preventing and treating obesity. Journal of Applied Physiology. 2005;99 2 :765–770.
37. Haslam DW, James WPT. Obesity. The Lancet. 2005;366 9492 :1197–1209.
38. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus with lifestyle intervention or metformin. The New England Journal of Medicine. 2001;344 18 :1343–1350.
39. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. The New England Journal of Medicine. 2002;346 6 :393–403.
40. Tortosa A, Bes-Rastrollo M, Sanchez-Villegas A, Basterra-Gortari FJ, Nũnez-Córdoba JM, Martinez-Gonzalez MA. Mediterranean diet inversely associated with the incidence of metabolic syndrome: the SUN prospective cohort. Diabetes Care. 2007;30 11 :2957–2959.