**1.INTRODUCTION**

Individuals with cardiovascular disease (CVD) (coronary heart disease (CHD) or cerebrovascular accident) often have a constellation of aetiologically linked cardiometabolic risk factors including dyslipidaemia, high blood pressure and high fasting plasma glucose, which may or may not co-exist with a number of inflammatory markers (e.g. C-reactive protein, uric acid and cytokines) and prothrombotic state (e.g. plasminogen activator inhibitor-1(PAI-1)) 1.

Metabolic syndrome is this multiplex risk factor that arises from insulin resistance along with abnormal adipose deposition and function. Adult Treatment Panel lll (ATP III) identified that, cardio vascular disease (CVD) is the primary clinical outcome of the metabolic syndrome and most people with this syndrome have insulin resistance, thereby confers increased risk for type 2 diabetes. When diabetes becomes clinically apparent, CVD risk rises sharply. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension.

The rise in the prevalence of obesity in India is threatening to increase the burden of atherosclerotic cardiovascular disease(ASCVD). The prevalence of metabolic syndrome worldwide is 20-25% (IDF) 2, 3. Beyond CVD and type 2 diabetes, individuals with metabolic syndrome seemingly are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and also to some forms of cancer.4

Reaven was the first to draw attention to this clustering of metabolic abnormalities, particularly in individuals who are overweight. He coined the name ‘syndrome X’ 5. Other terms have been used previously in the literature such as insulin resistance syndrome and plurimetabolic syndrome, but ‘metabolic syndrome’ has gained international acceptance and International Classification of Diseases coding (E88.81) in the past two decades. While there has been semantic debate as to whether it should be considered a ‘syndrome’, metabolic syndrome has shown extensively to promote the development of diabetes and CVD6,7, and CVD related mortality8-10.

The criteria for the metabolic syndrome have evolved since the original definition by the

World Health Organization in 1998, reflecting the growing clinical evidence and analysis by many consensus conferences and professional organizations.

The appearance of the metabolic syndrome phenotype is indicated by weight gain, particularly an increase in intra abdominal fat accumulation which is evident by a large waist circumference. It is estimated that about a quarter of the world’s adult population have metabolic Syndrome 11.

Those with this syndrome are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome8. In addition to this, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes12 and, the risk increases over time as the number of metabolic syndrome characteristics accumulates. But since its components are all reversible, the diagnosis of insulin resistance and metabolic syndrome early offers an effective treatment approach. Thus, it is imperative for physicians to recognize the presence of features of insulin resistance and metabolic syndrome in their patients and to familiarize themselves with the recommended treatment strategies 13.

South Asia is home to one of the largest population of people with metabolic syndrome. The prevalence of metabolic syndrome in South Asians varies according to region, extent of urbanization, lifestyle patterns, and socioeconomic factors. Recent datas are showing that around one-third of the urban population in large cities of India has metabolic syndrome. All classical risk factors comprising the metabolic syndrome are prevalent in Asian Indians who are residing in India. The increased risk in this population necessitated a lowering of the cut-off values of the risk factors to identify and intervene for the metabolic syndrome to prevent cardiovascular disease. Some interventions in pharmacological and nonpharmacological aspects are underway in metabolic syndrome to assess the efficacy in preventing diabetes and cardiovascular disease in this ethnic population14.

There has been a consistent efforts to evaluate biochemical markers to predict an early onset of metabolic syndrome, severity of insulin resistance and subsequently intervene appropriately by means of lifestyle changes and drug therapy and thereby reducing cardiovascular morbidity and mortality. Studies are lacking in adult Indian population

Tests like Homeostatic Model assessment had been proven to be useful in assessing severity of insulin resistance, but the high cost, need of expertise and the need of multiple parameters for calculation have made it impractical to use as a screening and prognosticative test for widespread use. Thus, a prompt, cost effective and easily available biochemical marker is required to predict an early onset, progression and severity of this syndrome.

Gamma Glutamyl Transferase(GGT) is one such marker which is cost effective, easily available and performed as part of liver function tests and is independent of prandial status too. High levels of GGT have been shown to be associated with high levels of insulin resistance in various studies. High levels of GGT have also been associated in populations with increased risk of atherosclerotic cardiovascular disease15. Several prospective studies reported that baseline serum GGT concentration is an independent risk factor for the development of coronary artery disease, diabetes mellitus, stroke and hypertension.

The purpose of this study is to evaluate the utility of GGT as a measure of insulin resistance in patients with metabolic syndrome.

**2. AIM AND OBJECTIVE OF THE STUDY**

To study the correlation between gamma glutamyl transferase level and insulin resistance in patients with metabolic syndrome.

**3.REVIEW OF LITERATURE**

**HISTORICAL ASPECT**

Gerald B. Phillips, in 1977 developed the concept that risk factors for myocardial

infarction combine to form a constellation of abnormalities (i.e., glucose intolerance,

hyperinsulinemia, hyperlipidemia and hypertriglyceridemia, and hypertension) that is

associated not only with heart disease but also with conditions like aging, obesity and other clinical states. He suggested that, there must be an underlying linking factor, and the identification of which could lead to the prevention of cardiovascular disease. He hypothesized that this factor was sex hormones16,17.

Reaven, in 1988, noted that several risk factors (eg- dyslipidemia, hypertension, hyperglycemia) commonly cluster together. He called this clustering as Syndrome X, and he recognized it as a multiplex risk factor for CVD. Reaven and subsequently others postulated that insulin resistance underlies Syndrome X. Hence the term insulin resistance syndrome is used commonly 18.

Haller used the term "metabolic syndrome" for associations of obesity, diabetes,

hyperuricemia, hyperlipoproteinemia, and hepatic steatosis while describing the additive

effects of risk factors on atherosclerosi19. Singer also used this term for associations of obesity, gout, diabetes mellitus, and hypertension with hyperlipoprotenemia20.

Shea S et al, in their study, showed that obesity is associated with high levels of fasting insulin levels and more future risk of metabolic syndrome in children21.

Study conducted by Cubeddu LX et al showed that impaired β-cell function and increased insulin resistance precedes development of metabolic syndrome and IGT 22.

In a prospective cohort study, Haffner SM et al reported that hyperinsulinaemia precedes metabolic impairment in the insulin-resistance syndrome, suggesting that insulin resistance could be the cause of various risk factors of the metabolic syndrome 23.

Study done by Budak N et al showed low HDL and insulin resistance were the most common criteria for diagnosing metabolic syndrome in 12-19 year adolescents and advocated on the importance of early detection as it helps to prevent diabetes and cardiovascular diseases 24.

Rask-Madsen C et al, in their study, showed that impaired insulin signalling is central to development of the metabolic syndrome and can promote cardiovascular disease indirectly through development of abnormal glucose and lipid metabolism, hypertension, and a proinflammatory state 25.

**METABOLIC SYNDROME DEFINITION**

Various groups have laid out criteria based on certain clinical, anthropometric and biochemical parameters to define the metabolic syndrome. The major and commonly used definitions for metabolic syndrome are provided by the International Diabetes Federation and the revised National Cholesterol Education Program26. The main differences between the two definitions are that, IDF state if BMI>30 kg/m2 central obesity can be assumed and waist circumference does not need to be measured. However, this potentially excludes any subject without increased waist circumference if BMI<30, whereas, in the NCEP definition, metabolic syndrome can be diagnosed based on other criteria and the IDF uses geography-specific cut points for waist circumference, while NCEP uses only one set of cut points for waist circumference regardless of geography. These two definitions are much closer to each other than the original NCEP and WHO definitions.

In this study definition as per IDF has been considered.

IDF CRITERIA27:

The essential presence of central adiposity defined as waist circumference of >/=90cm in

males and >/=80 in females in the Indian population.

Along with central adiposity two of the following four factors should be present to define the

metabolic syndrome:

1. Fasting triglycerides >150 mg/dl or specific medication

2. HDL cholesterol <40 mg/dl for men and <50 mg/dl for women, or specific

medication

3. Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific

medication

4. Fasting plasma glucose 100 mg/dl or previously diagnosed Type 2 diabetes

NCEP CRITERIA:

The US National Cholesterol Education Program Adult Treatment Panel III (2001) requires at least three of the following:

Central obesity: waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches(female)

Dyslipidaemia: TG ≥ 1.695 mmol/L (150 mg/dl)

Dyslipidaemia: HDL < 40 mg/dL (male), < 50 mg/dL (female)

Blood pressure ≥ 130/85 mmHg

Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl)

**EPIDEMIOLOGY OF METABOLIC SYNDROME**

The metabolic syndrome prevalence varies around the world, the variation reflects the age

and ethnicity of the populations studied and the diagnostic criteria applied. In general, the

metabolic syndrome prevalence increases with age. Greater industrialization worldwide is associated with increasing rates of obesity, which is anticipated to increase the prevalence of metabolic syndrome markedly, especially as the population ages. Moreover, the increasing prevalence and severity of obesity in children is initiating features of metabolic syndrome in a younger population28.

Highest prevalence of metabolic syndrome is among the Native Americans, with about 60% of women aged 45–49 and 45% of men aged 45–49 meet the criteria of metabolic syndrome as per the National Cholesterol Education Program and Adult Treatment Panel III (NCEP:ATPIII). In the United States, metabolic syndrome is less common in African-American men and more common in Mexican-American women. On the basis of data from National Health and Nutrition Examination Survey (NHANES) 1999–2000, in United States adults who did not have diabetes, the age-adjusted prevalence of the metabolic syndrome is 28% for men and 30% for women. In France, on evaluation of a cohort of age 30 to 60 years, the prevalence of metabolic syndrome for each sex was <10%, although 17.5% are affected in the age range of 60–64 years29.

The prevalence of metabolic syndrome in the Indian setting has been on the rise, with a

prevalence of 45% in females and 22% in males and the prevalence increasing with increasing age and also in the population belonging to the upper socio-economic strata30.

**PATHOPHYSIOLOGY OF METABOLIC SYNDROME**

The increasing burden of obesity is the driving force behind the rising prevalence of the metabolic syndrome as per many experts 31.This view needs to be harmonized with the insulin resistance hypothesis. The adipose tissue in obese people is found to be insulin resistant, which raises nonesterified fatty acid levels, thereby worsening insulin resistance in muscle32 and altering hepatic metabolism; in addition, the adipose tissue of obesity also exhibits abnormalities in the production of several adipokines that separately affect insulin resistance and modify the risk for atherosclerotic cardiovascular disease33. These abnormalities include increased production of inflammatory cytokines, plasminogen activator inhibitor- 1, and other bioactive products. At the same time the protective adipokines like adiponectin,is reduced 34. Adiponectin, actually reduced with obesity can protect against insulin resistance, metabolic risk factors, and atherogenesis 35-38. Another feature of upper-body obesity is an unusually high release of nonesterified fatty acids from adipose tissue; this contributes to accumulation of lipid in sites other than adipose tissue. Ectopic lipid accumulation in muscle and liver seemingly predisposes to insulin resistance and dyslipidemia 39.

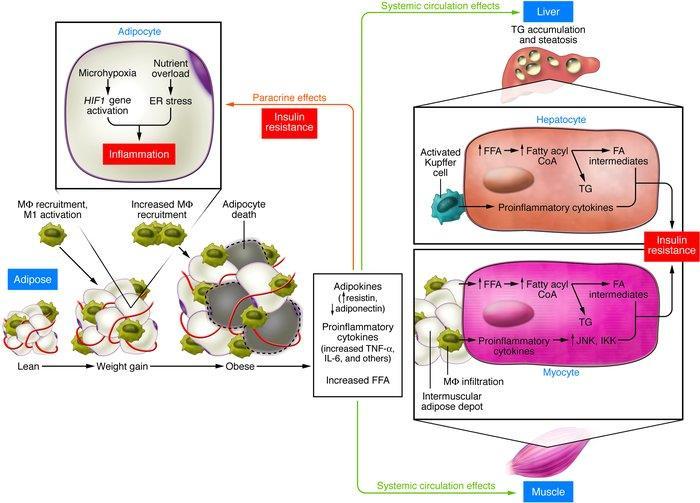


Figure 1.Pathophysiology of Metabolic syndrome. FFA – Free Fatty Acid; TG – Triglyceride.

Free fatty acids (FFA) are from an expanded adipose tissue mass. In the liver, FFAs result in an increased production of glucose, triglycerides and secretion of very low density lipoproteins (VLDL). FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated lipid abnormalities include reductions in high-density lipoprotein (HDL) cholesterol, increased density of low-density lipoproteins (LDL) and increased lipid accumulation in triglyceride (TG). The increase in circulating glucose and FFA, increase pancreatic insulin secretion, thereby causing hyperinsulinemia. Hyperinsulinemia result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and also contribute to the hypertension.



Figure 2. Interaction between exogenous and endogenous factors in Metabolic syndrome. FFA – Free Fatty Acid; CO2 – Carbon Dioxide

A simple way to visualize the pathogenesis of metabolic syndrome is illustrated in the above figure which explains the interaction between exogenous and endogenous factors. Major exogenous factor is obesity, but physical inactivity and excess dietary factors can play a role. The endogenous factors are inherent insulin resistance, dysfunctional adipose tissue, endocrine disorders, and various genetic aberrations.

**METABOLIC SYNDROME AND CARDIOVASCULAR RISK**

LONG-TERM (LIFETIME) RISK :

According to many prospective epidemiologic studies, the metabolic syndrome is accompanied by an increase in relative risk for ASCVD in populations at risk and, the relative risk for ASCVD events is essentially doubled40-42. It is likely that the twofold increase in risk seen in short-term, prospective studies underestimates the long-term impact of the syndrome as the metabolic risk factors tend to worsen with time. Consequently, the earlier metabolic syndrome can be detected and managed, the slower will be the progression.

SHORT-TERM (10-YEAR) RISK :

At present, more intense clinical intervention is driven by short-term risk for ASCVD43. This risk usually is identified as 10- year risk for coronary heart disease (CHD).

According to ATP III guidelines, risk can be stratified into four categories :

1. High risk - 10-year risk for CHD >20 percent and includes patients with clinically

evident ASCVD, diabetes, or enough other major risk factors to raise the risk to this level.

2. Moderately high risk - Two or more major risk factors and a 10-year risk of 10 - 20 percent.

3. Moderate risk - Two or more risk factors, but a 10-year risk <10 percent.

4. Lower-risk - 0 to 1 risk factor and a 10-year risk <10 percent.

Framingham risk scoring should be used to estimate 10-year risk in metabolic syndrome

patients without established ASCVD or type II diabetes mellitus (T2DM)43. Metabolic syndrome is only one part of overall risk assessment for ASCVD, thus it is not an adequate tool to estimate 10-year risk for CHD. These patients must be considered to be at higher lifetime risk for ASCVD, but metabolic syndrome alone is inadequate to guide clinical management for short-term risk reduction.

Besides the simple clinical measures proposed by ATP III, other emerging risk factors are commonly present in patients with metabolic syndrome. Identification of abnormalities in these factors can help to confirm the presence of the syndrome. These emerging risk factors are not necessary for diagnosis, but the presence of several of them will give strong confirmation of the presence of a systemic metabolic disorder and confirmation of a higher risk status can be obtained by the finding of significant subclinical atherosclerosis.

**ETIOLOGY AND COMPONENTS OF METABOLIC SYNDROME**

OBESITY

It is well established that the high prevalence of metabolic syndrome worldwide is secondary to a rising prevalence of obesity and the metabolic syndrome prevalence rises in parallel with increasing obesity44-49. Physical inactivity also is associated with a higher prevalence of metabolic syndrome50. The mechanisms whereby obesity results in metabolic syndrome are being increasingly understood51. Adipose tissue releases several products that appear to worsen metabolic syndrome52. During the fasting state, adipose tissue triglyceride undergoes lipolysis and releases nonesterified fatty acids (NEFA). But if NEFA supply exceeds needs for energy utilization, they accumulate in muscle and liver. This accumulation is called ectopic fat. When fat accumulates in muscle and the liver, insulin resistance is increased. This change plus other metabolic alterations predisposes to the metabolic syndrome52.

Only a portion of patients with obesity develop metabolic syndrome. It appears that an

individual must be metabolically susceptible to developing the syndrome, and when obesity

is acquired, the syndrome becomes manifest.

Insulin is a major regulator of adipose tissue metabolism. Dysfunctional forms of adipose tissue can result from genetic forms of insulin resistance. When genetic defects occur in insulin-signaling in adipocytes, suppression of lipolysis and other products is impaired. In addition, adiponectin release is reduced53. All of these will accentuate ectopic fat distribution and metabolic syndrome. Moreover, defective insulin signaling in other tissues such as muscle and liver most likely will accentuate metabolic syndrome54,55.

DYSLIPIDEMIA

In general, FFA flux to the liver is associated with increased production of apoB-containing,

triglyceride-rich very low density lipoproteins (VLDLs). The atherogenic dyslipidemia consists of an aggregation of lipoprotein abnormalities including elevated serum triglyceride and apoB, increased small LDL particles, and a reduced level of HDL-C. Among triglyceride-rich lipoproteins, remnant lipoproteins almost certainly are the most atherogenic. Many studies further suggest that the smallest particles in the LDL fraction carry the greatest atherogenicity. The atherogenic potential of lipoprotein remnants and small LDL could be confounded in part by their common association with an increased total number of apoB-containing lipoproteins in circulation; this increased number is reflected by an elevation of serum total apoB56. Finally, the lipoprotein field widely holds that low levels of HDL are independently atherogenic ; multiple mechanisms are implicated to explain this relationship57. The effect of insulin on this process is complex, but hypertriglyceridemia is an excellent marker of the insulin-resistant condition. Subjects with increased small dense LDL particles and hypertriglyceridemia also have increased cholesterol content of both VLDL1 and VLDL2 sub fractions. This relatively cholesterol rich VLDL particle may contribute to the atherogenic risk in patients with metabolic syndrome58.

The development of atherosclerosis can be considered to occur in two stages: injury and

response to injury. The primary injurious agents include LDL and other apolipoprotein B

(apo B)-containing lipoproteins. The response to injury makes up a process called inflammation. Macrophages are a key player in atherogenesis58. They first accumulate lipid and then undergo apoptosis; releasing their excess lipid into lipid pools. Macrophages further produce enzymes, such as metalloproteinases, that degrade the extracellular matrix. These latter two changes create unstable plaques that are prone to rupture and to causation of acute ASCVD events.

GLUCOSE INTOLERANCE

The defects in insulin action lead to impaired suppression of glucose production by the liver

and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues, i.e.,

muscle and adipose tissue. To compensate for defects in insulin action, insulin

secretion and/or clearance must be modified to sustain euglycemia. Ultimately, this

compensatory mechanism fails, usually because of defects in insulin secretion, resulting in

progress from IGT to DM.

HYPERTENSION

The relationship between insulin resistance and hypertension is well established59. Under normal physiologic conditions, insulin is a vasodilator with secondary effects on sodium reabsorption in the kidney. However, in the setting of insulin resistance, the vasodilatory effect of insulin is lost but the renal effect on sodium reabsorption is preserved. Insulin also increases the activity of the sympathetic nervous system, an effect that also may be preserved in the setting of the insulin resistance.

AGING

The metabolic syndrome affects about 44% of the population older than age 50. A greater

percentage of women over age 50 have the syndrome than men. The age dependency of the prevalence of metabolic syndrome is seen in most populations around the world.

SEDENTARY LIFESTYLE

Physical inactivity is considered as a predictor of CVD events and related mortality rate28H. Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central), reduced HDL cholesterol, and a trend toward increased triglycerides, high blood pressure, and increased glucose in the genetically susceptible60.

**INSULIN SECRETION, BIOSYNTHESIS, AND ACTION**61.

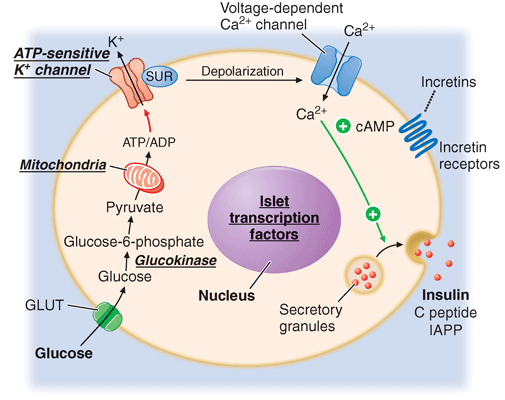
BIOSYNTHESIS:

Insulin is produced in the beta cells of the pancreatic islets. It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the amino-terminal signal peptide, giving rise to proinsulin. Proinsulin is structurally related to insulin-like growth factors I and II, which bind weakly to the insulin receptor. Cleavage of an internal 31-residue fragment from proinsulin generates the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, which are connected by disulfide bonds. The mature insulin molecule and C peptide are stored together and co-secreted from secretory granules in the beta cells. Because C peptide is cleared more slowly than insulin, it is a useful marker of insulin secretion and allows discrimination of endogenous and exogenous sources of insulin in the evaluation of hypoglycemia . Pancreatic beta cells co-secrete islet amyloid polypeptide (IAPP) or amylin, a 37-amino-acid peptide, along with insulin. The role of IAPP in normal physiology is incompletely defined, but it is the major component of the amyloid fibrils found in the islets of patients with type 2 diabetes, and an analogue is sometimes used in treating type 1 and type 2 DM. Human insulin is produced by recombinant DNA technology; structural alterations at one or more amino acid residues modify its physical and pharmacologic characteristics.

SECRETION :

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion. Glucose levels >3.9 mmol/L (70 mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by a facilitative glucose transporter.Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which inhibits the activity of an ATP-sensitive K+ channel. This channel consists of two separate proteins: one is the binding site for certain oral hypoglycemics (e.g., sulfonyl-ureas, meglitinides); the other is an inwardly rectifying K+ channel protein (Kir6.2). Inhibition of this K+ channel induces beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium), and stimulates insulin secretion.

Figure3: Mechanisms of glucose-stimulated insulin secretion and abnormalities in diabetes



INSULIN RESISTANCE

Insulin resistance is defined clinically as the inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake and utilization in an individual as much as it does in a normal population 62. The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, which is caused by an incompletely understood defect in insulin action63. The onset of insulin resistance is heralded by postprandial hyperinsulinemia, followed by fasting hyperinsulinemia and, ultimately, hyperglycemia64.

An early major contributor to the development of insulin resistance is the overabundance of

circulating fatty acids. Plasma albumin-bound free fatty acids (FFAs) are derived

predominantly from adipose tissue triglyceride stores released by lipolytic enzymes lipase.

Fatty acids are also derived from the lipolysis of triglyceride-rich lipoproteins in tissues by

lipoprotein lipase (LPL). The inhibition of lipolysis in adipose tissue is the most sensitive

pathway of insulin action. Thus, when insulin resistance develops, increased lipolysis

produces more fatty acids, which further decrease the antilipolytic effect of insulin.

Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation are seen in liver. The accumulation of lipids in muscle is associated with insulin resistance.

The effects of insulin resistance in adipose tissue provides the most direct evidence for the

mechanism linking insulin resistance to metabolic syndrome. Nevertheless, it is certainly

possible that widespread metabolic disturbance contributes beyond adipose tissue

abnormalities40. The insulin resistance can be a particularly important contributor to the syndrome if it is present in conjunction with obesity64. Based upon the changes in beta-cell mass, phenotype, and function observed as a patient moves toward the development of  T2DM, a stepwise model has been proposed. It is postulated that the third stage in this model correlates to prediabetes in the early phase and to the manifestation of diabetes in the later phases.65

Metabolic changes during the development of type 2 diabetes mellitus: Insulin secretion and insulin sensitivity are related, and as an individual becomes more insulin resistant insulin secretion increases. A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance.65

**TABLE 1. STAGES OF BETA CELL DYSFUNCTION:**65

|  |  |
| --- | --- |
| STAGE | DESCRIPTION |
| Stage 1:Compensation | Associated with higher overall rates of insulin secretion to reduced insulin sensitivity,thereby maintaining normal blood glucose levels. |
| Stage 2: Stable adaptation. | While beta cells attempt to compensate to reduced insulin sensitivity blood glucose still rises b/n 5-6.5 mmol/lt.Beta cell mass is lost and normal function of beta cells is disrupted. |
| Stage 3:Unstable -early decompensation. | During this transient stage glucose levels raise to those levels see in stage 4.Associated with reduced beta cell mass, this stage progresses to stage 4 rapidly. |
| Stage4:Stable decompensation. | Type 2 diabetic patients remain in this stage for rest of their lives while some will progress to stage5. |

**EVALUATION AND CALCULATION OF INSULIN RESISTANCE**

1. DIRECT MEASURES OF INSULIN SENSITIVITY :

HYPERINSULINEMIC EUGLYCEMIC GLUCOSE CLAMP

PROCEDURE :

The glucose clamp technique, originally developed by DeFronzo et al66, is widely accepted as the reference standard for directly determining metabolic insulin sensitivity in humans. After an overnight fast, insulin is infused intravenously at a constant rate that may range from 5 to 120 mU/m2/min (dose per body surface area per minute). This constant insulin infusion results in a new steady state insulin level that is above the fasting level (hyperinsulinemic).

As a consequence, glucose disposal in skeletal muscle and adipose tissue is increased, whereas HGP (hepatic glucose production) is suppressed. Under these conditions, a bedside glucose analyzer is used to frequently monitor blood glucose levels at 5- to 10-min intervals while 20% dextrose is given intravenously at a variable rate to “clamp” blood glucose concentrations in the normal range (euglycemic). An infusion of potassium phosphate is also given to prevent hypokalemia resulting from hyperinsulinemia and increased glucose disposal.

LIMITATIONS :

The main limitations of the glucose clamp approach are that it is time consuming, labor intensive, expensive, and requires an experienced operator to manage the technical difficulties. Thus, for epidemiological studies, large clinical investigations, or routine clinical applications (e.g., following changes in insulin resistance after therapeutic intervention in individual patients) the glucose clamp is not appropriate. In addition, if measuring insulin sensitivity/resistance is not a primary study outcome, then the cost/benefit ratio for the glucose clamp may not be favorable. Another limitation is that the clamp utilizes steady-state insulin levels that may be supra-physiological. This results in a reversal of the normal portal to peripheral insulin gradient. Thus, the glucose clamp may not accurately reflect insulin action and glucose dynamics under physiological conditions that a dynamic test such as an oral meal or oral glucose load may determine.

INSULIN SUPPRESSION TEST :

Procedure The insulin suppression test (IST), another method that directly measures metabolic insulin sensitivity/ resistance, was introduced by Shen et al45 in 1970 and subsequently modified by Harano et al 67.

After an overnight fast, somatostatin analog octreotide (25 mcg bolus, followed by 0.5 mcg/min) is intravenously infused to suppress endogenous secretion of insulin and glucagon. Simultaneously, insulin (25 mU/m2/min) and glucose (240 mg/m2/min) are infused into the same antecubital vein for 3 hours. From the contralateral arm, blood samples for glucose and insulin determinations are taken every 30 min for 2.5 hours and then at 10-min intervals from 150 to 180 min of the IST. The constant infusions of insulin and glucose will determine steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations. The steady-state period is assumed to be from 150 to 180 min after initiation of the IST. SSPI concentrations are generally similar among subjects. Therefore, the SSPG concentration will be higher in insulin-resistant subjects and lower in insulin-sensitive subjects; i.e., SSPG values are inversely related to insulin sensitivity. The IST provides a direct measure of the ability of exogenous insulin to mediate disposal of an intravenous glucose load under steady-state conditions where endogenous insulin secretion is suppressed.

LIMITATIONS :

Many of the limitations of the IST are similar to those described above for the glucose clamp (with the exception that the IST is less technically demanding). Thus, it is impractical to apply the IST in large epidemiological studies or in the clinical care setting. In exquisitely insulin-sensitive individuals, it is possible that subjects may become hypoglycemic during the IST. In individuals with type 2 diabetes, hyperglycemia may lead to glycosuria and underestimation of insulin resistance by SSPG. The infusion of somatostatin during the IST may independently modulate splanchnic blood flow and peripheral glucose clearance. This may potentially affect estimates of insulin resistance determined by SSPG. Finally, SSPG under ideal conditions determines primarily skeletal muscle insulin sensitivity and is not designed to reflect hepatic insulin sensitivity.

2. INDIRECT MEASURES OF INSULIN SENSITIVITY

Minimal Model Analysis of Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT)

PROCEDURE :

The minimal model, developed by Bergman et al68 in 1979, provides an indirect measurement of metabolic insulin sensitivity/resistance on the basis of glucose and insulin data obtained during a frequently sampled intravenous glucose tolerance test (FSIVGTT).

After an overnight fast, an intravenous bolus of glucose (0.3 g/kg body wt) is infused over 2 min starting at time 0. Currently, a modified FSIVGTT is used where exogenous insulin (4 mU/kg/ min) is also infused over 5 min beginning 20 min after the intravenous glucose bolus. Some studies use Tolbutamide instead of insulin in the modified FSIVGTT to stimulate endogenous insulin secretion at this time. Blood samples are taken for plasma glucose and insulin measurements at -20,-10, 0, 2, 3, 4, 5, 6, 8, 10, 12,14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40,50, 60, 70, 80, 90, 100, 120, 140, 160,and 180 min (relative to glucose administration), i.e., standard time points for 3 h after glucose injection.

These data are then subjected to minimal model analysis using the computer program MINMOD to generate an index of “insulin sensitivity” (SI).

LIMITATIONS :

The minimal model approach is simpler than direct methods for determining insulin sensitivity. Nevertheless, it still involves intravenous infusions with multiple blood sampling over a 3 hour period that are nearly as labor intensive as the glucose clamp or IST.

ORAL GLUCOSE TOLERANCE TEST/MEAL TOLERANCE TEST:

The oral glucose tolerance test (OGTT) is a simple test widely used in clinical practice to diagnose glucose intolerance and type 2 Diabetes Mellitus. After overnight fast, blood samples for determinations of glucose and insulin concentrations are taken at 0, 30, 60, and 120 min following a standard oral glucose load (75 g) or a standard meal.

3. SIMPLE SURROGATE INDEXES FOR INSULIN SENSITIVITY/RESISTANCE

Surrogates derived from fasting steady-state conditions

PROCEDURE:

After an overnight fast, a single blood sample is taken for determination of blood glucose and plasma insulin. In healthy humans, the fasting condition represents a basal steady state where glucose is homeostatically maintained in the normal range such that insulin levels are not significantly changing and hepatic glucose production(HGP) is constant; i.e., basal insulin secretion by pancreatic beta cells determines a relatively constant level of insulinemia that will be lower or higher in accordance with insulin sensitivity/resistance such that HGP matches whole body glucose disposal under fasting conditions.

1/FASTING INSULIN:

In healthy subjects, elevations in fasting insulin levels (with normal fasting glucose levels) correspond to increased insulin resistance. Indeed, in nondiabetic subjects, 1/(fasting insulin) is a well-known proxy for insulin sensitivity that decreases as subjects become more insulin resistant (and fasting insulin levels rise).

GLUCOSE/INSULIN RATIO:

A number of studies have used the fasting glucose/insulin ratio (G/I ratio) as an index of insulin resistance. In the case of non-diabetic subjects, the G/I ratio is essentially functionally equivalent to 1/(fasting insulin) since fasting glucose levels are all in the normal range .

HOMEOSTASIS MODEL ASSESSMENT (HOMA) :

HOMA is a model of interactions between glucose and insulin dynamics that is used to predict fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and beta-cell function.

It was first described by Matthews et al. in 1985 69

Homeostasis model of insulin resistance (HOMA-IR) =

{[fasting insulin (U/ml)] X[fasting glucose (mmol/l)]} / 22.5.

The denominator of 22.5 is a normalizing factor; i.e., product of normal fasting plasma insulin of 5 U/ml and normal fasting plasma glucose of 4.5 mmol/l typical of a normal healthy individual.Therefore, for an individual with normal insulin sensitivity, HOMA-IR =1.

HOMA-IR has a reasonable linear correlation with glucose clamp and minimal model estimates of insulin sensitivity/resistance in several studies of distinct populations.

Dr.D.R.Matthews et al69 compared HOMA assessment of insulin resistance with other estimates of insulin resistance. They found that the estimate of insulin resistance obtained by HOMA correlated with estimates obtained by use of euglycemic camp ( p< 0.0001), the fasting insulin concentration ( p< 0.0001) and the hyperglycemic clamp ( p< 0.01).

QUICKI :

It is the reciprocal of HOMA-IR, known as quantitative insulin sensitivity check index (QUICKI) and increasingly used. The quantitative insulin sensitivity check index (QUICKI) is derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose:

QUICKI = 1 / (log(fasting insulin U/mL) + log(fasting glucose mg/dL))

This index correlates well with glucose clamp studies (r = 0.78), and is useful for measuring insulin sensitivity (IS), which is the inverse of insulin resistance70. It also can be obtained from a fasting blood sample, and is the preferred method for certain types of clinical research.

MCAULEY INDEX :

Recently, McAuley et al.proposed another index, which uses fasting insulin and triglyceride values, to be a strong predictor of clamp-derived Insulin Sensitivity71,72.

McAuley Index = Exp [2.63-028 ln (Insulin in Mu/l)-0.31ln (triglyceride in mmol/l).

**GAMMA GLUTAMYL TRANSFERASE**

Gamma-glutamyl transferase (GGT) is a cell-surface protein contributing to the extracellular

catabolism of glutathione (GSH)73. The enzyme is produced in many tissues, but most GGT

in serum is derived from the liver. In the serum, GGT is carried primarily with lipoproteins

and albumi74. Serum levels of GGT are determined by several factors: alcohol intake, body fat content, plasma lipid/lipoproteins and glucose levels, and various medications75,76.

**ASSOCIATION OF GGT WITH INSULIN RESISTANCE AND METABOLIC SYNDROME**

High levels of GGT have been associated in populations with increased risk of

atherosclerotic cardiovascular disease (CVD)77,78. Lee et al79 report that in 3451

Framingham Study participants (mean age 44 years, 52% women) an increased serum

GGT predicted the onset of metabolic syndrome and the occurrence of CVD and death;

moreover, the highest GGT quartile experienced a 67% increase in CVD incidence. In this

study the association of GGT concentrations with CVD and mortality remained significant

after adjustment for traditional cardiac risk factors and C-reactive protein (CRP).

One hypothesis for the relation of GGT levels and CVD holds that GGT itself is

Proatherogenic. GGT has been reported toccur in atherosclerotic plaques80, which might

support this hypothesis. The origins of GGT in plaques could be through influx of

lipoproteins that carry it into lesions. One of the products of GSH hydrolysis produced by

GGT is cysteinyl-glyceine, which can generate superoxide anion radicals through its

interaction with free iron81. This effect could promote atherogenesis via LDL oxidation. At

present the postulated pathogenic pathways remain hypothetical and are yet to be

substantiated.

An alternative hypothesis that appears to be consistent with the findings of Lee et al79 is

that elevations of GGT are a marker of the presence of the metabolic syndrome. Other

workers have reported that high levels of GGT are associated with fatty liver, insulin

resistance, type 2 diabetes, obesity and other metabolic risk factors. There is growing

evidence that the liver, which is the primary source of circulating GGT, is a key target organ

for the development of the metabolic syndrome.

**DIAGNOSIS OF METABOLIC SYNDROME**

The diagnosis of the metabolic syndrome relies on satisfying the criteria listed above by

using tools at the bedside and in the laboratory. The medical history should include

evaluation of symptoms for OSA in all patients and PCOS in premenopausal women.

Family history will help determine risk for CVD and DM. Blood pressure and waist

circumference measurements provide information necessary for the diagnosis.

**LABORATORY EVALUATION**

Fasting lipids and glucose are needed to determine if the metabolic syndrome is present. The

measurement of additional biomarkers associated with insulin resistance can be

individualized. Such tests might include apoB, high-sensitivity CRP, fibrinogen, uric acid,

urinary microalbumin, and liver function tests. A sleep study should be performed if

symptoms of OSA are present. If PCOS is suspected on the basis of clinical features and

anovulation, testosterone, luteinizing hormone, and follicle-stimulating hormone should be

measured.

**MANAGEMENT OF METABOLIC SYNDROME**

Lifestyle modification is the first line treatment (i.e., caloric restriction and physical activity). However, drug treatment is frequently required. Generally, the individual disorders that comprise the metabolic syndrome are treated separately. Diuretics and ACE inhibitors may be used to treat hypertension. Cholesterol lowering drugs may be used to lower LDL cholesterol and triglyceride levels, if they are elevated, and to raise HDL levels if they are low. A 2003 study indicated that cardiovascular exercise was therapeutic in approximately 31% of cases. The most probable benefit was to triglyceride levels, with 43% showing improvement; but fasting plasma glucose and insulin resistance of 91% of test subjects did not improve. Many other studies have supported the value of increased physical activity and restricted caloric intake (exercise and diet) to treat metabolic syndrome.

**IDF RECOMMENDED TREATMENT OF THE INDIVIDUAL COMPONENTS OF THE METABOLIC SYNDROME**

ATHEROGENIC DYSLIPIDAEMIA :

Primary aims for therapy:

Lower TG (as well as lowering ApoB and non-HDL cholesterol<130mg/dl.)

Raise HDL-c levels

Reduce LDL-c levels <100mg/dl.(elevated levels represent a high risk in the metabolic syndrome)

Options : Statins,ezetimibe,niacin derivatives,fibric acid derivatives,omega-3fatty acid derivatives.

Fibrates (PPAR alpha agonists) improve all components of atherogenic dyslipidaemia and appear to reduce the risk for CVD in people with metabolic syndrome. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed that raising HDL-c concentrations using a fibrate in patients with well-established CHD and low LDL-c level will significantly reduce the incidence of major coronary eventsSeveral clinical studies have confirmed the benefits of statin therapy82.

ELEVATED BLOOD PRESSURE :

Hypertension (BP ≥ 140/≥ 90 mm Hg) should be treated37. In patients with established diabetes, antihypertensive therapy should be introduced at BP ≥ 130/≥ 80 mm Hg.

Options:

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs, with some clinical trials (but not all) suggesting they carry advantages over other drugs in people with diabetes. At this time, however, the majority of clinical trials suggest that the risk reduction associated with antihypertensive drugs is the result of blood pressure lowering per se and not due to a particular type of drug.

No particular agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome.

INSULIN RESISTANCE AND HYPERGLYCAEMIA :

There is growing interest in the possibility that drugs that reduce insulin resistance will delay the onset of type 2 diabetes and will reduce CVD risk when metabolic syndrome is present. The Diabetes Prevention Program (DPP) showed that metformin therapy in people with prediabetes will prevent or delay the development of diabetes and recent thiazolidinedione studies have also demonstrated efficacy in delaying or preventing type 2 diabetes in people with impaired glucose tolerance (IGT) and insulin resistance. Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of type 2 diabetes in people with IGT.

**PREVENTION OF METABOLIC SYNDROME**

Various strategies have been proposed to prevent the development of metabolic syndrome. These include increased physical activity (such as walking 30 minutes every day), and a healthy, reduced calorie diet. There are many studies that support the value of a healthy lifestyle as above83. However; one study stated that these measures are effective in only a minority of people, primarily due to a lack of compliance with lifestyle and diet changes. The International Obesity Taskforce states that interventions on a sociopolitical level are required to reduce development of the metabolic syndrome in populations.

A study of 2,375 male subjects over 20 years suggested that daily intake of a pint of milk or equivalent dairy products more than halved the risk of metabolic syndrome84.

**4. MATERIALS AND METHODS**

**Source of data**

Patients attending OPD and admitted in the department of medicine of Victoria hospital, and Bowring and Lady Curzon hospital, attached to Bangalore Medical College and Research Institute

**Methods of collection of data:**

**Study design:**

Cross sectional study

**Study period:**

November 2014 to November 2016

**Place of study:**

Victoria and Bowring and Lady Curzon hospitals attached to BMCRI, Bangalore.

**Sample size:**

100 cases based on the inclusion and exclusion criteria will be taken in to the study

**Inclusion criteria**

Patients aged> 18 years.

Patients fulfilling the criteria of metabolic syndrome - IDF [International Diabetes Federation] guidelines:

* + Waist circumference ≥90 cm in men or ≥80 cm in women{south Asians]
  + Two or more of the followings
* Triglycerides ≥150 mg/dL or treatment for hypertriglyceridemia.
* HDL-C < 40 mg/dL in men or <50 mg/mL in women or treatment for low HDL-C.
* Blood pressure ≥130/85 mmHg or treatment for hypertension.
* Fasting glucose ≥100 mg/dL or treatment for hyperglycemia.

**Exclusion criteria**

* Acute liver disease
* Chronic liver disease and renal disease
* Chronic alcohol consumption
* Pregnancy
* Drugs - antiepileptics, OCPs, trimethoprim, sulphamethoxazole, erythromycin, cimetidine

**Method of data collection**

Data were collected using a pretested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigations were done. An estimation of Gamma Glutamyl Transferase was done for all the patients satisfying the inclusion and exclusion criteria.

Insulin resistance calculation was done for all patients by homeostatic model assessment.

The correlation between level of Gamma Glutamyl Transferase and Insulin Resistance was statistically analyzed.

The purpose of the study was explained to the patient and informed consent was obtained.

**STATISTICAL ANALYSIS**

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean  SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients ,

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis.

SIGNIFICANT FIGURES :

+ Suggestive significance (P value: 0.05<P<0.10)

\* Moderately significant ( P value:0.01<P < 0.05)

\*\* Strongly significant (P value : P<0.01)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

INVESTIGATIONS DONE:

The following investigations were done on the patients;

* Insulin resistance
* Serum Gamma Glutamyl Transferase
* Liver function tests
* Renal function tests
* Fasting lipid profile
* Fasting plasma glucose

ETHICAL CLEARANCE

This study was approved by ethical committee of Bangalore Medical College and Research

Institute, Bangalore

**5. RESULTS**

**Study design**: A cross sectional correlation clinical study

Table 2: Age distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Age in years** | **No. of patients** | **%** |
| 21-30 | 3 | 3.0 |
| 31-40 | 9 | 9.0 |
| 41-50 | 16 | 16.0 |
| 51-60 | 31 | 31.0 |
| 61-70 | 31 | 31.0 |
| 71-80 | 9 | 9.0 |
| >80 | 1 | 1.0 |
| Total | 100 | 100.0 |

Mean ± SD: 57.16±12.26

Graph 1: Age distribution of patients studied

The mean age of the studied population is 57.16±12.26. Clustered around the 5th decade.

Table 3: Gender distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Gender** | **No. of patients** | **%** |
| Female | 46 | 46.0 |
| Male | 54 | 54.0 |
| Total | 100 | 100.0 |

Graph 2. Gender distribution of patients studied

Table 4: Co-morbid conditions distribution of patients studied

|  |  |  |  |
| --- | --- | --- | --- |
| **Co-morbid conditions** | **Gender** | | **Total**  **(n=100)** |
| **Female**  **(n=46)** | **Male**  **(n=54)** |
| DM | 40(87%) | 45(83.3%) | 85(85%) |
| HTN | 32(69.6%) | 44(81.5%) | 76(76%) |
| Dyslipidemia | 31(67.4%) | 28(51.9%) | 59(59%) |

Graph 3. Co-morbid conditions distribution of patients studied

Out of the cases studied 85(85%) were known cases of diabetes and 15(15%) were non diabetics. 76(76%) patients had hypertension and 59(59%) patients had dyslipidemia.

Table 5: DM Duration distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **DM Duration** | **No. of patients** | **%** |
| <1 | 8 | 8.0 |
| 1-5 | 20 | 20.0 |
| 6-10 | 23 | 23.0 |
| 11-15 | 16 | 16.0 |
| 16-20 | 12 | 12.0 |
| >20 | 6 | 6.0 |
| Total | 100 | 100.0 |

Graph 4. DM Duration distribution of patients studied

**DM Duration**

Table 6: HTN Duration distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **HTN Duration** | **No. of patients** | **%** |
| <1 | 5 | 5.0 |
| 1-5 | 40 | 40.0 |
| 6-10 | 26 | 26.0 |
| 11-15 | 4 | 4.0 |
| 16-20 | 1 | 1.0 |
| >20 | 0 | 0.0 |
| Total | 100 | 100.0 |

Graph 5. HTN Duration distribution of patients studied

Table 7: Dyslipidemia duration distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Dyslipidemia duration** | **No. of patients** | **%** |
| <1 | 15 | 15.0 |
| 1-5 | 33 | 33.0 |
| 6-10 | 11 | 11.0 |
| 11-15 | 1 | 1.0 |
| 16-20 | 0 | 0.0 |
| >20 | 0 | 0.0 |
| Total | 100 | 100.0 |

Graph 6. Dyslipidemia duration distribution of patients studied

Table 8: Waist circumference and BMI distribution of patients studied

|  |  |  |  |
| --- | --- | --- | --- |
| **WC/BMI** | **Gender** | | **Total**  **(n=100)** |
| **Female**  **(n=46)** | **Male**  **(n=54)** |
| WC |  |  |  |
| * 80-90 | 16(34.8%) | 0(0%) | 16(16%) |
| * 90-110 | 28(60.9%) | 50(92.6%) | 78(78%) |
| * >110 | 2(4.3%) | 4(7.4%) | 6(6%) |
| BMI (kg/m2) |  |  |  |
| * <18.5 | 0(0%) | 0(0%) | 0(0%) |
| * 18.5-25 | 0(0%) | 1(1.9%) | 1(1%) |
| * 25-30 | 7(15.2%) | 33(61.1%) | 40(40%) |
| * >30 | 39(84.8%) | 20(37%) | 59(59%) |

Graph 7. Waist circumference distribution of patients studied

50 males (92.6%) had waist circumference in the range of 90 – 110 cm and 4 males(7.4%) had waist circumference more than 110cm.Among females, 16(34.8%) patients had waist circumference in the range of 80-90cm, 28(60.9%) patients had in the range of 90 – 110 and 2(4.3%) patients were having waist circumference more than 110cms.

Graph 8. BMI distribution of patients studied

20(37%) male patients had BMI > 30Kg/m2 while, 39(84.8%) female patients had BMI > 30Kg/m2

Table 9: Vital parameters distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Vitals** | **No. of patients**  **(n=100)** | **%** |
| Pulse rate (bpm) |  |  |
| * <70 | 9 | 9.0 |
| * 70-90 | 85 | 85.0 |
| * >90 | 6 | 6.0 |
| SBP (mm Hg) |  |  |
| * <120 | 0 | 0.0 |
| * 120-140 | 30 | 30.0 |
| * >140 | 70 | 70.0 |
| DBP (mg/dl) |  |  |
| * <80 | 11 | 11.0 |
| * 80-100 | 86 | 86.0 |
| * >100 | 3 | 3.0 |

Graph 9. Vital parameters distribution of patients studied.

70(70%) patients had SBP >140mmHg and 86(86%) patients had DBP in the range 80-100mmHg

Table 10: FBS (mg/dl) distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **FBS (mg/dl)** | **No. of patients** | **%** |
| <100 | 7 | 7.0 |
| 100-126 | 9 | 9.0 |
| >126 | 84 | 84.0 |
| Total | 100 | 100.0 |

Graph 10. FBS (mg/dl) distribution of patients studied

84 patients had fasting blood sugar >126mg/dl and 9 patients had FBS in the range of 100-126

Table 11: Creatinine levels distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Creatinine (mg/dl)** | **No. of patients** | **%** |
| <1.1 | 75 | 75.0 |
| >1.1 | 25 | 25.0 |
| Total | 100 | 100.0 |

Graph 11. Creatinine levels distribution of patients studied

Table 12: Lipids distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Lipids** | **No. of patients**  **(n=100)** | **%** |
| Total Cholesterol (mg/dl) |  |  |
| * <200 | 34 | 34.0 |
| * 200-280 | 44 | 44.0 |
| * >280 | 22 | 22.0 |
| LDL (mg/dl) |  |  |
| * <70 | 8 | 8.0 |
| * 70-190 | 86 | 86.0 |
| * >190 | 6 | 6.0 |
| HDL (mg/dl) |  |  |
| * <35 | 61 | 61.0 |
| * 35-60 | 37 | 37.0 |
| * >60 | 2 | 2.0 |
| VLDL (mg/dl) |  |  |
| * <35 | 41 | 41.0 |
| * 35-60 | 52 | 52.0 |
| * >60 | 7 | 7.0 |
| TGL (mg/dl) |  |  |
| * <150 | 25 | 25.0 |
| * 150-500 | 73 | 73.0 |
| * >500 | 2 | 2.0 |

Graph 12. Lipids distribution of patients studied

22(22%) patients had total cholesterol >280mg/dl ; 44(44%) patients were having in the range of 200 – 280 and 34(34%) patients had <200

86(86%) patients had LDL in the range of 70 – 190 and 6 patients had LDL >190 mg/dl

61(61%) patients had HDL <35mg/dl

73(73%) patients had TGL in the range of 150 – 500 mg/dl and 2(2%) patients had >TGL500 mg/dl.

Table 13: Haematological variables distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Variables** | **No. of patients**  **(n=100)** | **%** |
| Hemoglobin (g/dl) |  |  |
| * <12 | 33 | 33.0 |
| * 12-16 | 59 | 59.0 |
| * >16 | 8 | 8.0 |
| WBC |  |  |
| * <6000 | 15 | 15.0 |
| * 6000-12000 | 71 | 71.0 |
| * >12000 | 14 | 14.0 |
| Platelet Count |  |  |
| * <3.5 | 84 | 84.0 |
| * 3.5-5.5 | 16 | 16.0 |
| * >5.5 | 0 | 0.0 |

Graph 13. Haematological variables distribution of patients studied

Table 14: SGOT/SGPT and ALP distribution of patients studied

|  |  |  |
| --- | --- | --- |
|  | **No. of patients**  **(n=100)** | **%** |
| SGOT |  |  |
| * 0 | 0 | 0.0 |
| * 0-42 | 73 | 73.0 |
| * >42 | 27 | 27.0 |
| SGPT |  |  |
| * 0 | 0 | 0.0 |
| * 0-48 | 84 | 84.0 |
| * >48 | 16 | 16.0 |
| ALP |  |  |
| * <25 | 1 | 1.0 |
| * 25-125 | 78 | 78.0 |
| * >125 | 21 | 21.0 |

Graph 14. SGOT/SGPT and ALP distribution of patients studied

84(84%) patients had SGPT <48 and 16 patients had SGPT >48

73(73%) patients had SGOT <42 and 27 (27%) had SGOT>42

78(78%) patients had ALP in the range of 25 – 125 and 21(21%) patents had ALP >125

Table 15: Insulin/GGT and Homa distribution of patients studied

|  |  |  |
| --- | --- | --- |
| **Variables** | **No. of patients**  **(n=100)** | **%** |
| Insulin |  |  |
| * <10 | 46 | 46.0 |
| * 10-15 | 48 | 48.0 |
| * >15 | 6 | 6.0 |
| GGT |  |  |
| * <15 | 11 | 11.0 |
| * 15-21 | 23 | 23.0 |
| * 22-33 | 24 | 24.0 |
| * >33 | 42 | 42.0 |
| HOMA |  |  |
| * <5 | 42 | 42.0 |
| * 5-10 | 52 | 52.0 |
| * >10 | 6 | 6.0 |

Graph 15. Insulin/GGT and Homa distribution of patients studied

48(48%) patients had fasting insulin level in the range of 10-15 and 6(6%) patients had fasting insulin >15

11(11%) patients had GGT <15, 23(23%) patients had GGT 15-21, 24(24%) patients had GGT 22-33, and 42(42%) patients had GGT>33

52(52%) patients had HOMA – IR in the range of 5-10 and 6(6%) patients had > 10

Table 16: Age distribution of patients studied in relation to GGT

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age in years** | **GGT** | | | | **Total** |
| **<15** | **15-21** | **22-33** | **>33** |
| 21-30 | 0(0%) | 2(8.7%) | 0(0%) | 1(2.4%) | 3(3%) |
| 31-40 | 0(0%) | 2(8.7%) | 1(4.2%) | 6(14.3%) | 9(9%) |
| 41-50 | 2(18.2%) | 3(13%) | 5(20.8%) | 6(14.3%) | 16(16%) |
| 51-60 | 4(36.4%) | 4(17.4%) | 6(25%) | 17(40.5%) | 31(31%) |
| 61-70 | 5(45.5%) | 8(34.8%) | 8(33.3%) | 10(23.8%) | 31(31%) |
| 71-80 | 0(0%) | 4(17.4%) | 3(12.5%) | 2(4.8%) | 9(9%) |
| >80 | 0(0%) | 0(0%) | 1(4.2%) | 0(0%) | 1(1%) |
| Total | 11(100%) | 23(100%) | 24(100%) | 42(100%) | 100(100%) |

P=0.406, not significant, Fisher Exact test

Graph 16. Age distribution of patients studied in relation to GGT

Table 17: Gender distribution of patients studied in relation to GGT

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gender** | **GGT** | | | | **Total** |
| **<15** | **15-21** | **22-33** | **>33** |
| Female | 5(45.5%) | 15(65.2%) | 9(37.5%) | 17(40.5%) | 46(46%) |
| Male | 6(54.5%) | 8(34.8%) | 15(62.5%) | 25(59.5%) | 54(54%) |
| Total | 11(100%) | 23(100%) | 24(100%) | 42(100%) | 100(100%) |

P=0.201,Not significant, Chi-Square test

Graph 17. Gender distribution of patients studied in relation to GGT

Table 18: Incidence of DM, Hypertension and Dyslipidemia of patients studied in relation to GGT

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Co-morbid conditions** | **GGT** | | | | **Total**  **(n=100)** | **P value** |
| **<15**  **(n=11)** | **15-21**  **(n=23)** | **22-33**  **(n=24)** | **>33**  **(n=42)** |
| DM | 6(54.5%) | 18(78.3%) | 22(91.7%) | 39(92.9%) | 85(85%) | 0.035\* |
| HTN | 7(63.6%) | 13(56.5%) | 24(100%) | 32(76.2%) | 76(76%) | 0.004\*\* |
| Dyslipidemia | 9(81.8%) | 13(56.5%) | 14(58.3%) | 23(54.8%) | 59(59%) | 0.433 |

Chi-Square test/Fisher Exact test

Graph 18. Incidence of DM, Hypertension and Dyslipidemia of patients studied in relation to GGT

On analysis of incidence of Co-morbid conditions in the quartiles of GGT, among the 11 patients with GGT<15, 6(54.5%) patients had Diabetes, 7(63.6%) had hypertension and 9(81.8%) had dyslipidemia.

Among the 23 patients with GGT in the range of 15-21, 18(78.3%) patients had Diabetes, 13(56.5%) patients had hypertension and 13(56.5%) patients had dyslipidemia.

Among the 24 patients with GGT in the range of 22-33, 22(91.7%) patients had diabetes, 24(100%)patients had hypertension and 14(58.3%) patients had dyslipidemia.

Among the 42 patients with GGT >33, 39(92.9%) patients had diabetes, 32(76.2%) patients had hypertension and 23(54.8%) patients had dyslipidemia.

The incidence of DM and HTN had shown positive correlation with GGT level and the correlation was statistically significant with p=0.035 and 0.004 respectively.

Table 19: Comparison of Clinical variables of patients studied in relation to GGT

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **GGT** | | | | **Total** | **P value** |
| **<15** | **15-21** | **22-33** | **>33** |
| Age in years | 59.82±8.45 | 57.13±13.96 | 60.17±12.15 | 54.76±12.04 | 57.16±12.26 | 0.315 |
| Height (cm) | 1.65±0.10 | 1.63±0.11 | 1.66±0.10 | 1.67±0.11 | 1.65±0.11 | 0.566 |
| Weight (kg) | 87.91±6.38 | 84.61±7.89 | 88.29±7.70 | 85.71±10.85 | 86.32±9.08 | 0.486 |
| WC | 90.82±4.35 | 88.48±4.27 | 95.21±5.86 | 103.31±6.41 | 96.58±8.34 | <0.001\*\* |
| BMI (kg/m2) | 32.06±3.40 | 32.20±4.16 | 32.03±3.55 | 31.06±4.19 | 31.67±3.93 | 0.637 |

ANOVA test

Graph 19. Comparison of Clinical variables of patients studied in relation to GGT

There were no statistically significant difference in Height, Weight and BMI among the quartiles but there was a positive correlation of waist circumference with GGT level which was statistically significant with p<0.001.

Table 20: Comparison of Vitals of patients studied in relation to GGT (ANOVA test)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **GGT** | | | | **Total** | **P value** |
| **<15** | **15-21** | **22-33** | **>33** |
| Pulse rate (bpm) | 81.45±8.05 | 79.57±8.40 | 79.00±7.22 | 79.57±7.25 | 79.64±7.52 | 0.849 |
| SBP (mm Hg) | 145.27±9.48 | 142.26±8.32 | 151.38±8.88 | 148.14±12.96 | 147.25±11.09 | 0.033\* |
| DBP (mm Hg) | 86.73±8.11 | 88.43±7.82 | 90.33±6.18 | 90.05±8.27 | 89.38±7.67 | 0.508 |

Graph 20. Comparison of Vitals of patients studied in relation to GGT

On comparing the vital parameters, SBP had shown positive correlation with GGT level and the correlation was statistically significant with p=0.033

Table 21: Comparison of Blood parameters of patients studied in relation to GGT

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **GGT** | | | | **Total** | **P value** |
| **<15** | **15-21** | **22-33** | **>33** |
| FBS (mg/dl) | 128.09±50.47 | 199.65±49 | 209.33±64.19 | 243.31±76.68 | 212.44±73.61 | <0.001\*\* |
| Urea (mg/dl) | 29.36±8.59 | 31.00±11.48 | 30.04±9.60 | 33.26±11.81 | 31.54±10.88 | 0.578 |
| Creatinine (mg/dl) | 0.77±0.20 | 0.81±0.23 | 0.91±0.22 | 0.91±0.23 | 0.87±0.23 | 0.112 |

ANOVA test

Graph 21. Comparison of Blood parameters of patients studied in relation to GGT

There was positive correlation of FBS with GGT level and the correlation was statistically significant with p <0.001

Table 22: Comparison of Lipid variables of patients studied in relation to GGT

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Lipids** | **GGT** | | | | **Total** | **P value** |
| **<15** | **15-21** | **22-33** | **>33** |
| Total Cholesterol (mg/dl) | 182.73  ±40.63 | 210.09  ±61.79 | 222.04  ±63.42 | 241.50  ±69.85 | 223.14±65.84 | 0.037\* |
| LDL (mg/dl) | 101.09  ±43.70 | 118.13  ±35.85 | 124.54  ±43.69 | 136.71  ±43.59 | 125.60±42.91 | 0.066+ |
| HDL (mg/dl) | 47.36  ±14.06 | 39.09  ±4.79 | 31.96  ±7.30 | 29.79  ±5.28 | 34.38±9.13 | <0.001\*\* |
| VLDL (mg/dl) | 37.45  ±31.84 | 35.65  ±15.11 | 42.58  ±32.69 | 39.36  ±17.23 | 39.07±23.03 | 0.776 |
| TGL (mg/dl) | 142.36±56.72 | 169.35±43.05 | 245.54±207.26 | 207.76±82.41 | 200.80±121.02 | 0.054+ |

Graph 22. Comparison of Lipid variables of patients studied in relation to GGT

On comparison of Lipid variables, there was positive correlation of Total cholesterol with GGT and the correlation was statistically significant with p=0.037

There was negative correlation of HDL with GGT level and the correlation was statistically significant with p<0.001

Table 23: Comparison of Hb, WBC and Platelet count of patients studied in relation to GGT

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **GGT** | | | | **Total** | **P value** |
| **<15** | **15-21** | **22-33** | **>33** |
| Hemoglobin (g/dl) | 13.39±1.31 | 12.63±2.88 | 13.54±2.41 | 12.69±2.04 | 12.96±2.29 | 0.403 |
| WBC | 9773.64  ±4136.69 | 8325.65  ±3123.74 | 9123.33  ±2540.16 | 11139.52  ±14681.17 | 9858.20  ±9799.62 | 0.708 |
| Platelet Count | 2.57±0.67 | 2.62±1.19 | 2.74±0.96 | 2.58±0.73 | 2.63±0.89 | 0.908 |

ANOVA test

Graph 23. Comparison of Hb, WBC and Platelet count of patients studied in relation to GGT

Table 24: Comparison of Insulin and HOMA of patients studied in relation to GGT

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **GGT** | | | | **Total** | **P value** |
| **<15** | **15-21** | **22-33** | **>33** |
| Insulin | 9.05±2.73 | 9.13±2.88 | 9.67±2.53 | 11.46±3.12 | 10.23±3.04 | 0.005\*\* |
| HOMA | 2.81±1.14 | 4.51±1.79 | 4.98±1.93 | 6.98±3.02 | 5.48±2.74 | <0.001\*\* |

ANOVA test

Graph 24. Comparison of Insulin of patients studied in relation to GGT

On comparing the Fasting Insulin level, there was positive correlation of Fasting insulin level with GGT and the correlation was statistically significant with p=0.005.

Graph 25. Comparison of HOMA of patients studied in relation to GGT

On analysing the HOMA-IR, there was positive correlation of HOMA-IR with GGT and the correlation was statistically significant with p<0.001.

**6. DISCUSSION**

There has been a consistent efforts to evaluate biochemical markers to predict an early onset of metabolic syndrome, severity of insulin resistance and subsequently intervene appropriately by means of lifestyle changes and drug therapy , thereby reducing cardiovascular morbidity and mortality. Studies are lacking in adult Indian population

Tests like Homeostatic Model assessment had been proven to be useful in assessing severity of insulin resistance, but the high cost, need of expertise and the need of multiple parameters for calculation have made it impractical to use as a screening and prognosticative test for widespread use. Thus, a prompt, cost effective and easily available biochemical marker is required to predict an early onset, progression and severity of this syndrome.

The purpose of this study is to evaluate the utility of GGT as a measure of insulin resistance in patients with metabolic syndrome.

In our observational correlation clinical study, 100 cases of metabolic syndrome were studied, the mean age of the studied population is 57.16±12.26. Clustered around the 5th decade.

Among the cases, 54(54%) were males and 46(46%) were females.

On analysing as quartiles of GGT, 11(11%) patients had GGT <15, 23(23%) patients had GGT 15-21, 24(24%) patients had GGT 22-33, and 42(42%) patients had GGT>33

Out of the cases studied 85(85%) were known cases of diabetes and 15(15%) were non diabetics. 76(76%) patients had hypertension and 59(59%) patients had dyslipidemia.

On analysis of incidence of co-morbid conditions in the quartiles of GGT, the incidence of DM and HTN had shown positive correlation with GGT level and the correlation was statistically significant with p=0.035 and 0.004 respectively.

In our study, 50 males (92.6%) had waist circumference in the range of 90 – 110 cm and 4 males(7.4%) had waist circumference more than 110cm.Among females, 16(34.8%) patients had waist circumference in the range of 80-90cm, 28(60.9%) patients had in the range of 90 – 110 and 2(4.3%) patients were having waist circumference more than 110cms.

20(37%) male patients had BMI > 30Kg/m2 while, 39(84.8%) female patients had BMI > 30Kg/m2

On analysing the correlation with GGT level, there were no statistically significant difference in Height, Weight and BMI among the quartiles but there was a positive correlation of waist circumference with GGT level which was statistically significant with p<0.001.

In our study, 70(70%) patients had SBP >140mmHg and 86(86%) patients had DBP in the range 80-100mmHg

On comparing the vital parameters with GGT level, SBP had shown positive correlation with GGT level and the correlation was statistically significant with p=0.033

In our study, 84 patients had fasting blood sugar >126mg/dl and 9 patients had FBS in the range of 100-126.

On analysis, there was positive correlation of FBS with GGT level and the correlation was statistically significant with p <0.001.

On evaluation of Lipid parameters, 22(22%) patients had total cholesterol >280mg/dl ; 44(44%) patients were having in the range of 200 – 280 and 34(34%) patients had total cholesterol <200mg/dl.

86(86%) patients had LDL in the range of 70 – 190 and 6 patients had LDL >190 mg/dl.

In our study, 61(61%) patients had HDL <35mg/dl. 73(73%) patients had TGL in the range of 150 – 500 mg/dl and 2(2%) patients had >TGL500 mg/dl.

On comparison of Lipid variables with GGT level, there was positive correlation of Total cholesterol with GGT level and the correlation was statistically significant with p=0.037

There was negative correlation of HDL with GGT level and the correlation was statistically significant with p<0.001.

On analysis of other blood parameters, 75(75%) patients had creatinine level <1.1mg/dl and 25(25%) patients had creatinine level >1.1mg/dl. 84(84%) patients had SGPT <48 and 16 patients had SGPT >48. 73(73%) patients had SGOT <42 and 27 (27%) had SGOT>42. 78(78%) patients had ALP in the range of 25 – 125 and 21(21%) patents had ALP >125.

In our study, 48(48%) patients had fasting insulin level in the range of 10-15 and 6(6%) patients had fasting insulin >15

On comparing the Fasting Insulin with GGT level, there was positive correlation of Fasting insulin with GGT and the correlation was statistically significant with p=0.005.

In our study, 52(52%) patients had HOMA – IR in the range of 5-10 and 6(6%) patients had HOMA-IR > 10

On analysing the correlation of HOMA-IR with GGT level, there was positive correlation of HOMA-IR with GGT and the correlation was statistically significant with p<0.001.

Balogun et al, in their study on 90 patients with type 2 diabetes and 90 nondiabetic

concludes that, the most predominant LFT abnormality in diabetic group was

found to be isolated elevation of GGT85.

B Kasapoglu et al, in their cross-sectional, single-center study with 908 subjects, found that transaminases were in normal ranges in 91.2 percent and GGT was in normal range in 83.4 per cent of metabolic syndrome patients. When the sample is divided into quartiles of the GGT levels, increase in GGT was positively correlated with increased metabolic syndrome prevalence.

They therefore conclude that, elevated liver enzymes, although in normal ranges, especially at upper quartiles, play a central role in early diagnosis of fat overflow to the liver. Regarding the availability and simplicity of these tests in routine clinical practice, they, especially GGT, have potential to be considered in algorithms for metabolic syndrome86.

Onat A et al. in the study on transaminases demonstrates that circulating GGT and transaminase activities are elevated in patients with insulin resistance syndrome87.

In their prospective population-based study on 172 men and 109 women (aged 25-64 years), C Meisinger et al, states that GGT is an important predictor for incident type 2 diabetes in men and women from the general population88.

Girdhar Gopal et al did a study in healthy obese children about the relationship of gamma glutamyl transferase (GGT ) with insulin resistance markers [fasting insulin and Homeostasis Model Assessment of - insulin resistance (HOMA-IR)]. In their study, the serum activity of GGT remained correlated with HOMA-IR even after removing the effect of BMI, weight and age on GGT values. The results showed that GGT is a determinant of HOMA- IR independently of age, BMI and weight. Thus suggested that, GGT can be used as a marker of insulin resistance as it is easier to use in clinical practice than other markers and also help to prevent the development of diabetes89.

Douglas S. Lee et al evaluated 3451 Framingham study participants regarding the relations of GGT with CVD risk factors, and prospectively determined the risk of new-onset metabolic syndrome, incident CVD, and death. On follow-up (mean 19 years), 968 participants developed metabolic syndrome, 535 developed incident CVD, and 362 died. GGT was positively associated with body mass index, blood pressure, LDL cholesterol, triglycerides, and blood glucose in cross-sectional analysis (P<0.005).They found that, the risk of metabolic syndrome increased with higher GGT (multivariable-adjusted hazard ratio [HR] per SD increment log-GGT, 1.26 [95%CI; 1.18 to 1.35]). Douglas S. Lee et al concludes that, an increase in serum GGT predicts onset of metabolic syndrome, incident CVD, and death suggesting that GGT is a marker of metabolic and cardiovascular risk90.

Rantala et al in their cross-sectional, observational study of hypertensive patients and controls regarding the associations between serum gamma-glutamyl transpeptidase activity and the components of the metabolic syndrome, got a highly significant correlation between gamma-glutamyl transpeptidase and the components of the metabolic syndrome. The correlation coefficient were 0.33 between gamma-glutamyl transpeptidase and body mass index, 0.25 between gamma-glutamyl transpeptidase and systolic blood pressure in control men (P = 0.0001), 0.39 between gamma-glutamyl transpeptidase and triglycerides, and 0.32 between gamma-glutamyl transpeptidase and fasting insulin in hypertensive women (P = 0.0001). Rantala et al concludes that, there is a highly significant relationship between gamma-glutamyl transpeptidase and the components of the metabolic syndrome even after adjustment for age, body mass index and alcohol consumption91.

In another study of Sakugawa et al, in 4211 Japanese women to evaluate the association of GGT with Metabolic syndrome and found that, in multivariate analysis, four variables (age ≧ 50 yr, hemoglobin ≧ 14 g/dL, triglyceride ≧ 150 mg/dL, and presence of diabetes) were significantly and independently associated with raised GGT level. There was no significant association between the raised GGT level and the presence of fatty liver. Thus, Sakugawa et al concludes that, Metabolic syndrome seemed to be directly, not indirectly through fatty liver, associated with the raised GGT level in Japanese women92.

**7. CONCLUSION**

In conclusion, a positive correlation was found between GGT levels and Insulin Resistance in the cases studied.

There was a linear increase in HOMA-IR with increasing GGT levels. Hence GGT can probably be used as a surrogate marker of insulin resistance in patients with metabolic syndrome and should probably find a position in algorithms for evaluation of patients with metabolic syndrome .

**8. SUMMARY**

The prevalence of metabolic syndrome varies around the world. It reflects the age and ethnicity of the populations involved in the study and the diagnostic criteria applied. Greater industrialization is associated with rising rates of obesity, diabetes, hypertension which is anticipated to increase prevalence of the metabolic syndrome dramatically, especially as the age of the population increases.

The study was conducted in Victoria hospital and Bowring and Lady Curzon hospital attached to Bangalore medical college and Research Institute. It was an observational correlation study including 100 cases of metabolic syndrome.

The mean age of studied population is 57.16±12.26 with 54% males and 46% females.

In our study, on analysis of co-morbid conditions in the quartiles of GGT, the incidence of DM and HTN had shown positive correlation with GGT level and the correlation was statistically significant with p=0.035 and 0.004 respectively.

There was a positive correlation of waist circumference with GGT level which was statistically significant with p<0.001.

SBP had shown positive correlation with GGT level and the correlation was statistically significant with p=0.033 and there was positive correlation of FBS with GGT level and the correlation was statistically significant with p <0.001.

On comparison of Lipid variables with GGT level, there was positive correlation of Total cholesterol

and negative correlation of HDL with GGT level and the correlation was statistically significant with p=0.037 and p<0.001 respectively.

On comparing the Fasting Insulin with GGT level, there was positive correlation of Fasting insulin with GGT and the correlation was statistically significant with p=0.005.

On analysing the correlation of HOMA-IR with GGT level, there was positive correlation of HOMA-IR with GGT and the correlation was statistically significant with p<0.001.

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**10. ANNEXURES**

**PROFORMA**

NAME : IP/OP NO :

AGE/SEX : ADDRESS :

EDUCATION :

OCCUPATION :

**History of** :

Diabetes :

Yes/no duration :

Treatment history :

Hypertension :

Yes/no duration :

Treatment history :

Dyslipidemia :

Yes/no duration :

Treatment history :

Pregnancy – yes/no

Chronic liver disease – yes/no

Chronic renal disease – yes/no

**Past history**

Chronic drug intake :

Yes/no specify :

Acute CVA - yes/no Acute MI - yes/no

Any other significant past history :

**Personal history**

Smoking

Alcohol

**General physical examination**

Height : cm weight : kg

Bmi : kg/m2 waist circumference - cm

Pulse - bpm BP- mmhg

RR - /’ Temp –

Peripheral signs of atherosclerosis – yes/no

Other significant findings :

**Systemic examination**

CVS:

RS:

CNS:

P/A:

**Investigations:**

CBC:

S.UREA: S.CREATININE:

LFT

LIPID PROFILE

FASTING SERUM INSULIN : mcU/L

FBS : mg/dl PPBS : mg/dl

Insulin Resistance:

Gamma Glutamyl Transferase : U/L

**INFORMED CONSENT**

I have been explained in a language understood by me about the study entitled “THE STUDY OF CORRELATION BETWEEN GAMMA GLUTAMYL TRANSFERASE LEVEL AND INSULIN RESISTANCE IN PATIENTS WITH METABOLIC SYNDROME”

I have been explained about the procedures and investigations that will be done during the study. I have no objections in sharing my medical information and details in case records with the investigator of this study. Personal identity will not be revealed but data may be used for publication/dissertation purpose.

I understand that my participation in this study is entirely voluntary and I am willing to take part in this study

Place: Signature:

Date: Name:

**KEY TO MASTERCHART**

SL NO - Serial number

AGE(YRS) – Age in years

SEX : F – Female

M – Male

DM – Diabetes Mellitus

HTN – Hypertension

DURATION(YR) – Duration in years

HEIGHT(MTS) – Height in metres

WEIGHT(KGS) -Weight in Kilo grams

WC(CM) – Waist circumference in centimetres

BMI– Basal Metabolic Index BP – Blood Pressure

FBS – Fasting Blood Sugar

TC – Total cholesterol

HB – Haemoglobin

WBC – White Blood Cells

PLT – Platelet count

SGOT- serum glutamyl oxaloacetate transferase

SGPT- serum glutamyl pyruvate transferase

TG- triglycerides

GGT – Gamma Glutamyl Transferase

HOMA – IR - Homeostasis Model Assessment - Insulin Resistance