"STUDY OF GAMMA GLUTAMYL TRANSFERASE AS A MARKER IN METABOLIC SYNDROME"

By

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IN

GENERAL MEDICINE

Under the Guidance of

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ABSTRACT

STUDY OF GAMMA GLUTAMYL TRANSFERASE AS A MARKER IN METABOLIC SYNDROME

OBJECTIVES :

1. To study the association of Gamma Glutamyl Transferase levels with metabolic syndrome .
2. To compare and correlate biochemical parameters between controls and cases.

MATERIALS AND METHODS:

This is a case control of study of 110 subjects in R.L.Jalappa hospital both inpatients and outpatient of which included are 55 subjects who satisfy IDF criteria for metabolic syndrome and 55 age and sex matched controls. Blood pressure , waist circumference , Liver function tests including GGT , AST , ALT and ALP , Lipid profile , Fasting plasma glucose , Thyroid profile , Renal function tests and USG abdomen were performed in subjects .

RESULTS :

The mean values of GGT, alanine amino transferase(ALT),aspartate aminotransferase (AST) levels were statistically significantly higher in MS group. The mean values of liver enzymes, in MS group, GGT , AST and ALT respectively, were; 51.89±6.31 , 31.80±17.37 and 37.71±13.52 . In the study sample , increase in GGT was positively correlated with increased MS prevalence. In ROC analysis , GGT is as strongly associated with the IDF diagnostic components as is each individual IDF component, except elevated systolic blood pressure. In covariance analysis, there was significant relationship between elevated GGT levels and MS presence after

adjustment for age, sex and MS diagnostic criteria. In multivariance analysis, in MS group, a high GGT was positively associated with CVD prevalance compared to low GGT group independent of age, sex and smoking habits.

CONCLUSION:

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 syndrome

Key words GGT - liver function tests - metabolic syndrome

ABBREVATIONS

AACE	American Association of clinical Endocrinologists
ALT	Alanine amino transferase
ALP	Alkaline phosphatase
AST	Aspartate amino transferase
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body Mass Index
CAD	Coronary artery disease
CVA	Coronary vascular Accident
CRP	C- reactive protein
CT	Computed Tomography Scan
DM	Diabetes mellitus
FA	Fatty Acids
FBS	Fasting Blood Sugar
FFA	Free Fatty Acids
FGF	Fibroblast derived growth Factor
FPG	Fasting Plasma glucose
GGT	Gamma Glutamyl Transferase
GSH	Glutathione
HBA1C	Glycated haemoglobin
HDL	High density lipoprotein cholestrol
HSL	Harmone sensitive lipase
HTN	Hypertension
IDF	International Diabetes Federation

IFG	Impaired Fasting plasma Glucose
IL-6	Interleukin -6
IFN-ɣ	Interferon -gamma
IR	Insulin Resistance
i.e	that is
IRS	Insulin Resistance Syndrome
LDL	Low density lipoprotein cholesterol
MS	Metabolic Syndrome
Met S	Metabolic Syndrome
NCEP-ATPIII	National cholesterol education program Adult treatment Panel III
NEFA	Non Esterified Fatty acids
NFHS	National Family Health Survrey
NHANES	National health and nutrition examination survey
NAFLDNon	–Alcholic Fatty Liver disease
NIDDM	Non insulin dependent diabetes mellitus
Nil	No history
PAI-1	Plasminogen activator inhibitor-1
PPBS	post prandial blood sugar
SNS	Sympathetic nervous system
T2DM	Type 2 diabetes mellitus
TNF-α	Tumour necrosis factor-α
TSH	Thyroid stimulating harmone
VLDL	Very low density lipoprotein
WHO	World Health Organisation

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INTRODUCTION

The Metabolic Syndrome (MetS) (**'plurimetabolic syndrome', 'syndrome X' , 'deadly quartet', 'insulin resistance syndrome', 'hypertriglyceridemic waist' and 'dysmetabolic syndrome')** is an aggregation of metabolic abnormalities that presage increased risk for the development of atherosclerotic cardiovascular disease (ASCVD)[1].

The constellation of metabolic abnormalities of the metabolic syndrome includes glucose intolerance (type 2 diabetes, impaired glucose tolerance or impaired fasting glycaemia), insulin resistance, central obesity, dyslipidemia and hypertension, all well documented risk factors for atherosclerotic disease [2]. Due to clustering of closely related risk factors for T2DM and heart disease , it is justified to call it as a syndrome [1].

The syndrome has also been associated with easily oxidized , small LDL particles , heightened blood clotting activity (e.g: increased plasminogen activator inhibitor-1) and elevated serum uric acid concentration[2] .

The prevalence of metabolic syndrome in India is 25. 8 %. It is estimated that around 20-25 % of the world's adult population have the MetS and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome[2 , 3].

In developing countries, over the past two decades the lifestyle changes resulting from industrialization and rural-urban migration involving decreased

levels of physical activity and the increased intake of high calorie foods resulted in striking increase in the number of people with the MetS[2] . The metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease .

Metabolic syndrome unequivocally predispose to type 2 diabetes mellitus and is considered as a multi dimensional risk factor for ASCVD[4]. Among the complications , cardiovascular events produce greatest morbidity and mortality.

Others include dyslipidemia , hypertension , systemic inflammation and a thrombotic tendency. Various other conditions like fatty liver , polycystic ovary Syndrome , cholesterol gallstones , sleep apnea , lipodystrophies , Progression to organ failure and development of some cancer types, including primary liver cancer are also associated with metabolic syndrome leading to a considerable interest in several other fields of medicine[5]. Thus , metabolic syndrome ranges from a cluster of unrelated risk factors to a constellation of risk factors linked through a common underlying mechanism [6].

Due to increased risk of Type 2 diabetes mellitus and cardiovascular disease in patients with metabolic syndrome there is increasing importance for the development of targeted preventive approaches[6] .The diagnosis of metabolic syndrome has gained more importance after the identification of its association with increased cardiovascular risk .There has been a consistent effort to identify biochemical markers for predicting the early onset of metabolic syndrome to intervene by life style changes , drug therapy to reduce cardiovascular

morbidity and mortality but studies are lacking in adult Indian population. Markers like adiponectin have been studied as a measure of increased adipose tissue but are not easily available and are cost effective .

Serum GGT , a marker of oxidative stress , is a widely available low-cost parameter and routinely performed as part of liver function tests and can assist in determining the risk of metabolic syndrome in patients[7] .

Gamma-Glutamyl Transferase (GGT) , a second generation enzymatic liver function test, also a sensitive indicator of alcohol ingestion, hepatic inflammation, fatty liver and hepatitis is also associated with an increase in all-cause mortality, as well as chronic heart disease events such as congestive heart failure and components of the metabolic syndrome [8.]

The enzyme is involved in glutathione metabolism and plays critical role in antioxidant defense , detoxification and inflammation processes. It is a novel biomarker of metabolic and cardiovascular risk because increase in serum GGT predicts the onset of metabolic syndrome, incident cardiovascular disease and it is also an independent prognostic factor for coronary artery calcification , coronary complexity and adverse cardiac events in patients with CAD[8,9].

The purpose of this study is to evaluate the utility of GGT as an early diagnostic marker of metabolic syndrome , driving the twin global epidemics of Type 2 diabetes and CVD .

AIMS AND OBJECTIVES

1. To assess the Role of Gamma Glutamyl Transferase as a marker in the diagnosis of metabolic syndrome .
2. To compare and correlate biochemical parameters between controls and cases .

REVIEW OF LITERATURE

HISTORICAL ASPECT:

Metabolic Syndrome started as a concept rather than a diagnosis .

The concept of the metabolic syndrome dates back to atleast 80 years [4].

The metabolic syndrome has its origin in 1920 . Kylin , a Swedish physician, demonstrated the association of high blood pressure (hypertension) , high blood glucose (hyperglycemia) and gout [4,10].

In 1927, Marañón , the founder of modern endocrinology in Spain , described that 'high blood pressure is a pre-diabetic state' and that 'such a concept also applies to obesity', while 'some constitutional predisposition underlies the association of diabetes (adult type), arterial hypertension, obesity and perhaps also gout'.

Insulin resistance (IR) in diabetes was reported by Himsworth in 1939 in a series of Goulstonian lectures to the Royal college of physicians in London. In 1947, Dr. Vague described that to upper body adiposity (android or male-type obesity) as the obesity phenotype that was commonly associated with metabolic abnormalities associated with type 2 diabetes and cardiovascular disease[11].

In 1960, the simultaneous presence of obesity, high blood fat, diabetes and hypertension was first reported as the 'plurimetabolic syndrome'[12] and high risk of coronary artery disease was described in people with this cluster of metabolic abnormalities.

In 1965, Avogaro and Crepaldi presented an abstract at the European Association for the Study of Diabetes annual meeting and described a syndrome comprising hypertension, hyperglycemia, and obesity[13].

The term metabolic syndrome was first coined by Haller and Hanefeld in 1975 [14,15].

In 1977 , Haller[14] used the term " metabolic syndrome " for associations of obesity , diabetes , hyperlipoproteinemia , hyperuricemia and hepatic steatosis when describing the additive effects of risk factors on atherosclerosis . In the same year , Singer used the term for associations of obesity , gout , diabetes mellitus and hypertension with hyperlipoproteinemia[16] .

In 1977 and 1978 , Gerald B . Phillips proposed that risk factors for myocardial infarction comprise to form a " constellation of abnormalities "(i.e glucose intolerance , hyperlipidemia , hypertriglyceridemia , hyperinsulinemia and hypertension) which is associated with heart disease , aging , obesity and other clinical states . He hypothesized that the underlying linking factor was sex hormones , the identification of which could lead to the prevention of cardiovascular disease[17,18] .

In 1988, Dr. Gerald Reaven described syndrome X: insulin resistance, hyperglycemia, hypertension, low high-density lipoprotein (HDL) cholesterol and raised very low-density lipoprotein (VLDL) triglycerides[19.]

In 1989, Kaplan renamed the syndrome "The Deadly Quartet" for the combination of upper body obesity, glucose intolerance, hypertriglyceridemia and hypertension [20.]

Lemieux and colleagues[21] have suggested the importance of abdominal obesity and the so- called hypertriglyceridemic waist phenotype as a central component[21.]

In 1992, Ferranini and colleagues renamed it as "The Insulin Resistance Syndrome" , as clustering of abnormalities were caused by insensitivity to insulin[22.]

Despite the ongoing arguments among various groups , the ultimate importance of this condition is that it helps to identify individuals at high risk of CVD .

DEFINITION

Clinical criteria for Metabolic syndrome have been developed by various expert groups . In 1998 an internationally recognized definition for metabolic syndrome was developed by WHO , to provide a tool for clinicians and researchers .Subsequently, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP: ATP III) , European Group for the Study of Insulin Resistance and American Association of Endocrinology have formulated definitions.

In May 2004, International Diabetes Federation (IDF) [23] established a unified definition for the metabolic syndrome , which is generally accepted for use in clinical practice worldwide along with the one defined by national cholesterol education programme ; adult treatment panel III (NCEP:ATPIII)[24] .

The new IDF definition for metabolic syndrome establishes a comprehensive 'platinum standard' list of additional criteria to be included in epidemiological studies and research and addresses both clinical and research needs, providing an accessible, diagnostic tool suitable for worldwide use .

IDF CRITERIA

The presence of CENTRAL ADIPOSITY defined as waist circumference of ≥90 cm in males and ≥80 cm in females in the Indian population . Along with

central adiposity two of the following four factors should be present to define metabolic syndrome[23]

1. Fasting triglycerides ≥150 mg/dl or specific medication.
2. HDL cholesterol < 40 mg/dl and < 50 mg/dl for men and women , respectively 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 : ATPIII CRITERIA

Three or more of the following criteria [24]

1. Central obesity : Waist circumference ≥ 102 cm(M) , ≥88cm(F).
2. Hypertriglyceridemia : Triglycerides ≥ 150 mg/dl or specific medication.
3. Low HDL cholesterol : <40 mg/dl and <50mg/dl respectively or on specific medication.
4. Hypertension : Blood pressure ≥ 130 mm systolic or ≥ 85 mm diastolic or on specific medication.
5. Fasting plasma glucose ≥100 mg/dl or specific medication or previously diagnosed Type 2 diabetes .

The difference between the two criteria is that the IDF takes central adiposity as an essential factor for defining metabolic syndrome .

WORLD HEALTH ORGANISATION CRITERIA

In 1999 , WHO proposal was designed as a first attempt to define the syndrome[25] . It includes :

Diabetes or impaired fasting glycemia or impaired glucose tolerance or insulin resistance (hyperinsulinemic , euglycemic clamp glucose uptake in lowest 25%)

Plus two or more of the following :

1. Obesity : Body mass index > 30kg/m2 or waist : hip ratio > 0.9(male) or 0.85%(female)
2. Dyslipidemia : TGs≥1.7mmol/L or HDL-C<0.9(male)or <1.0(female) mmol/L
3. Hypertension : BP≥ 140/90 mmHg.
4. Microalbuminuria : albumin excretion ≥20mg/min .

EUROPEAN GROUP FOR THE STUDY OF INSULIN RESISTANCE (EGIR)

Defined metabolic syndrome in 1999 [26].

It includes :

Insulin resistance – hyperinsulinemia : top 25% of fasting insulin values from non-diabetic population .

Plus 2 or more of the following :

1. Central obesity : waist circumference ≥94 cm(male) or ≥80cm (female)
2. Dyslipidemia : TG >2.0 mmol/L or HDL-C<1.0.
3. Hypertension : Blood pressure ≥140/90mm hg and / or on medication .
4. Fasting plasma glucose≥6.1 mmol/L

In 2003 , The **American Association of clinical Endocrinologists** [27](AACE) came with another definition for metabolic syndrome modifying the ATPIII criteria . They have referred to the cluster as the "Insulin resistance syndrome".

American Association of Clinical Endocrinologists (AACE) Clinical Criteria for diagnosis of metabolic syndrome:

RISK FACTOR COMPONENTS	**CUTPOINTS FOR ABNORMALITY**
Overweight/obesity	> BMI _25 kg/m^2
Elevated triglycerides	150 mg/dL (1.69 mmol/L)
Low HDL cholesterol	
Men	40 mg/dL (1.04 mmol/L)
Women	>150 mg/dL (1.69 mmol/L)
Elevated blood pressure	130 / 85 mm Hg
2-Hour postglucose challenge	>140 mg/dL
Fasting glucose	Between 110 and 126 mg/dL
Other risk factors	
o Family history of type 2 diabetes, o Hypertension or CVD o Polycystic ovary syndrome o Sedentary lifestyle o Advancing age o Ethnic groups having high risk for o type 2 diabetes or CVD	

By the AACE's definition, once a person develops type 2 diabetes mellitus , the term insulin resistance syndrome no longer applies.

These criteria appear to be a hybrid of those of ATPIII and WHO criteria . no defined number of risk factors is specified and diagnosis is left to clinical judgment.

TABLE- 1 : DIAGNOSTIC CRITERIA PROPOSED FOR THE DIAGNOSIS OF METABOLIC SYNDROME[24]

Clinical measures	WHO (1998) [5]	EGIR (1999) [6]	ATPIII (2001) [7]	AACE (2003) [8]	IDF (2005) [9]
Insulin resistance	IGT, IFG, T2DM, or lowered insulin Sensitivity[a] **plus any 2 of the following**	Plasma insulin >75th percentile **plus any 2 of the following**	**None, but any 3 of the following 5 features**	IGT or IFG **plus any of thefollowing based on the clinical judgment**	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI > 30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women	BMI ≥ 25 kg/m^2	Increased WC (population specific) **plus any 2 of the following**
Lipids	TGs ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TGs ≥150 mg/dL or on TGs Rx. HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)[b]
Other	Microalbuminuria: Urinary excretion rate of >20 mg/min or albumin: creatinine ratio of >30 mg/g.			Other features of insulin resistance[c]	

a. Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

b. In 2003, the American Diabetes Association (ADA) changed the criteria for IFG tolerance from >110mg/dl to >100mg/dl [10].

c. Includes family history of type 2 diabetes mellitus, polycystic ovary syndrome, sedentary lifestyle, advancing age, and ethnic groups susceptible to type 2 diabetes mellitus.

BMI: Body mass index; HDL-C: High density lipoprotein cholesterol; IFG: Impaired fasting glucose; IGT:Iimpaired glucose tolerance; Rx: Receiving treatment;

TGs:Ttriglycerides; T2DM: Type 2 diabetes mellitus; WC: Waist circumference.

EPIDEMIOLOGY

The prevalence of metabolic syndrome varies around the world , in part reflecting the age and ethnicity of the populations studied and diagnostic criteria applied .

In general the prevalence increases with age . The highest recorded prevalence worldwide is in native Americans , with nearly 60% of women ages 45-49 and 45% of men ages 45-49 meeting National cholesterol Education Program and Adult Treatment Panel III criteria .

Based on the data from National Health and Nutrition Examination Survey (NHANES) the age adjusted prevalence of metabolic syndrome in the United states adults who did not have diabetes is 28% for men and 30% for women.

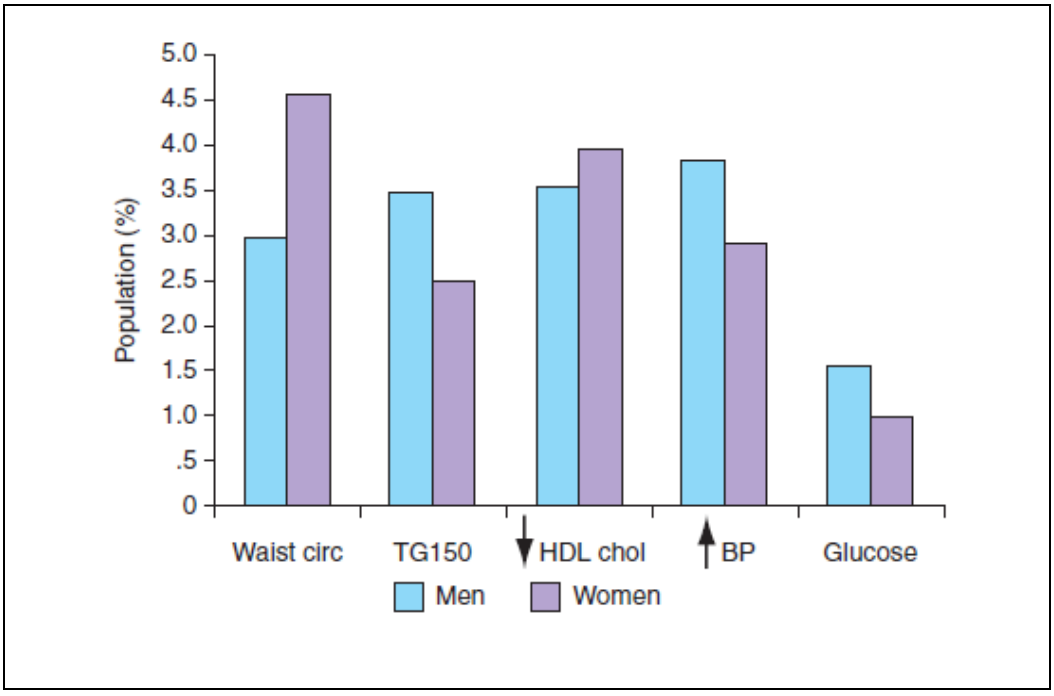


Chart 1 : Prevalence of the metabolic syndrome components, from NHANES [28]

In the United States , metabolic syndrome is less common in African – American men and more common in Mexican-American women , where as fasting triglycerides >150 mg/dl and hypertension are more likely in men.

In urban Indian population there is high prevalence of obesity and insulin resistance . A study from Chennai reported 18.7% prevalence of IRS in upper socio-economic strata in south India , while it was 6.5% in the low socio-economic strata[29,30] . Higher prevalence of METS in women as compared with men is seen in urban south Indian population[29] .

Approximately 20-25% of urban south Asians have evidence of metabolic syndrome. Further-more , IR was reported to be present in nearly 30 percent of children and adolescents in India , more so in girls[31].

According to a recent study on south Indians , the prevalence of the METS was estimated to be 23.2%,18.3% and 25.8% according to WHO , ATP III and IDF definitions respectively[32].

High prevalence of cardiovascular risk factors and the MET S is seen in intra-country rural-to-urban migrant population belonging to low socio-economic stratum residing in urban shins[31] .

The metabolic syndrome was present in 31.6% of Indian population , prevalence was 22.9% in men and 39.9% in women , the age-adjusted prevalence was 24.9% , 18.4% in men and 30.9% in women with significant age related increase in its prevalence [33].

India is currently experiencing an increasing obesity epidemic[34]. This is in contrast to the 1990's where the National Nutrition Monitoring Bureau documented the prevalence of obesity in Indian women to be 4.1%[35] and the National Family

Health Survey (NFHS) reported obesity prevalence rates ranging between 3.5% to 4.1%.[36,37]

Today over 20% of men and 30% of women in urban areas have generalized obesity and nearly 40% of females have abdominal obesity [35.] It is further predicted to increase by 89% in males and 82% in females[38] .

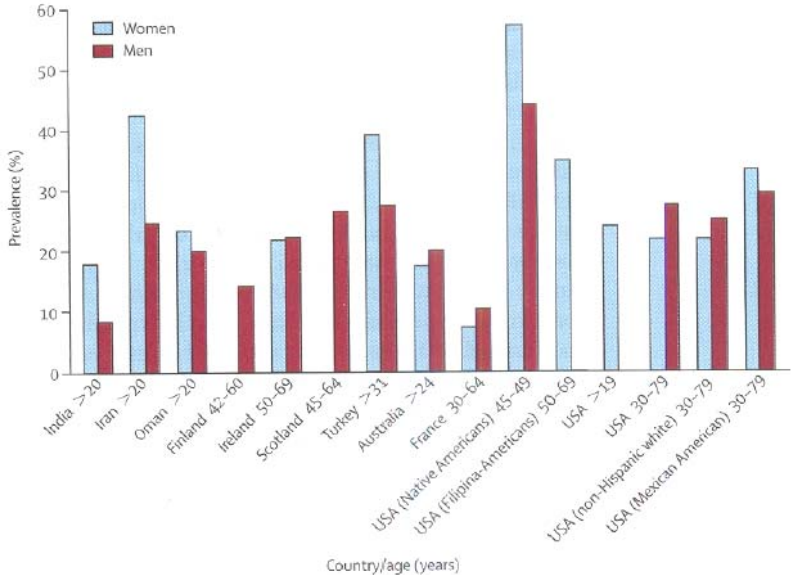


Chart 2 : PREVALANCE OF METABOLIC SYNDROME ACCORDING TO NCEP-ATPIII CRITERIA[39]

COMPONENTS OF METABOLIC SYNDROME

NCEP-ATP III[24] identified six components of the metabolic syndrome that relate to CVD:

1. Abdominal obesity
2. Atherogenic dyslipidemia
3. Raised blood pressure
4. Insulin resistance - glucose intolerance
5. Proinflammatory state
6. Prothrombotic state

These components of the metabolic syndrome constitute a particular combination of what ATP III terms:

- Underlying risk factors
- Major risk factors
- Emerging risk factors.

Underlying risk factors for CVD are obesity (especially abdominal obesity), physical inactivity and atherogenic diet.

Major risk factor are cigarette smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, family history of premature coronary heart disease (CHD) and aging .

Emerging risk factors include elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, proinflammatory state and prothrombotic state.

RISK FACTORS[40,41]

1. **Overweight / Obesity**

Central adiposity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between waist circumference and increasing adiposity. It presents clinically as increased waist circumference. However, despite the importance of obesity, patients who are normal weight may also be insulin-resistant and have the syndrome.

2.Atherogenic dyslipidemia

It manifests in routine lipoprotein analysis by raised triglycerides and low concentrations of HDL cholesterol. A more detailed analysis usually reveals other lipoprotein abnormalities, eg, increased remnant lipoproteins, elevated apolipoprotein B, small LDL particles, and small HDL particles. All of these abnormalities have been implicated as being independently atherogenic.

3. Lipodystrophy

Lipodystrophic disorders in general are associated with the metabolic syndrome. Both genetic (e.g., Berardinelli-Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired (e.g., HIV-related lipodystrophy in patients treated with highly active antiretroviral therapy) forms of lipodystrophy may give rise to severe insulin resistance and many of the components of the metabolic syndrome.[1]

4. Sedentary Lifestyle

Physical inactivity is a predictor of CVD events and related mortality rate. 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 susceptible. Compared with individuals who watched television or videos or used the computer <1 h daily, those who carried out those behaviour for >4 h daily had a twofold increased risk of the metabolic syndrome.

5. Aging

The metabolic syndrome affects 44% of the U.S. population older than age 50. A greater percentage of women over age 50 have the syndrome than men. The age dependency of the syndrome's prevalence is seen in most populations around the world.

6. Diabetes Mellitus

DM is included in both the NCEP and International Diabetes Foundation (IDF) definitions of the metabolic syndrome. It is estimated that the great majority (~75%) of patients with Type 2 diabetes or impaired glucose tolerance (IGT) have the metabolic syndrome. The presence of the metabolic syndrome in these populations relates to a higher prevalence of CVD compared with patients with Type 2 diabetes or IGT without the syndrome.

7. Coronary Heart Disease

The approximate prevalence of the metabolic syndrome in patients with coronary heart disease (CHD) is 50% with a prevalence of 37% in patients with premature coronary artery disease (>age 45), particularly in women. With appropriate cardiac rehabilitation and changes in lifestyle (e.g., nutrition, physical activity, weight reduction and in some cases, pharmacologic agents), the prevalence of the syndrome can be reduced.

8. A proinflammatory state

It is recognized clinically by elevations of C-reactive protein (CRP), commonly present in persons with metabolic syndrome. Multiple mechanisms seemingly underlie elevations of CRP. One cause is obesity, because excess adipose tissue releases inflammatory cytokines that may elicit higher CRP levels.

9. A prothrombotic state

It is characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, that associates with the metabolic syndrome. Fibrinogen, an acute-phase reactant like CRP, rises in response to a high-cytokine state. Thus, prothrombotic and proinflammatory states may be metabolically interconnected.

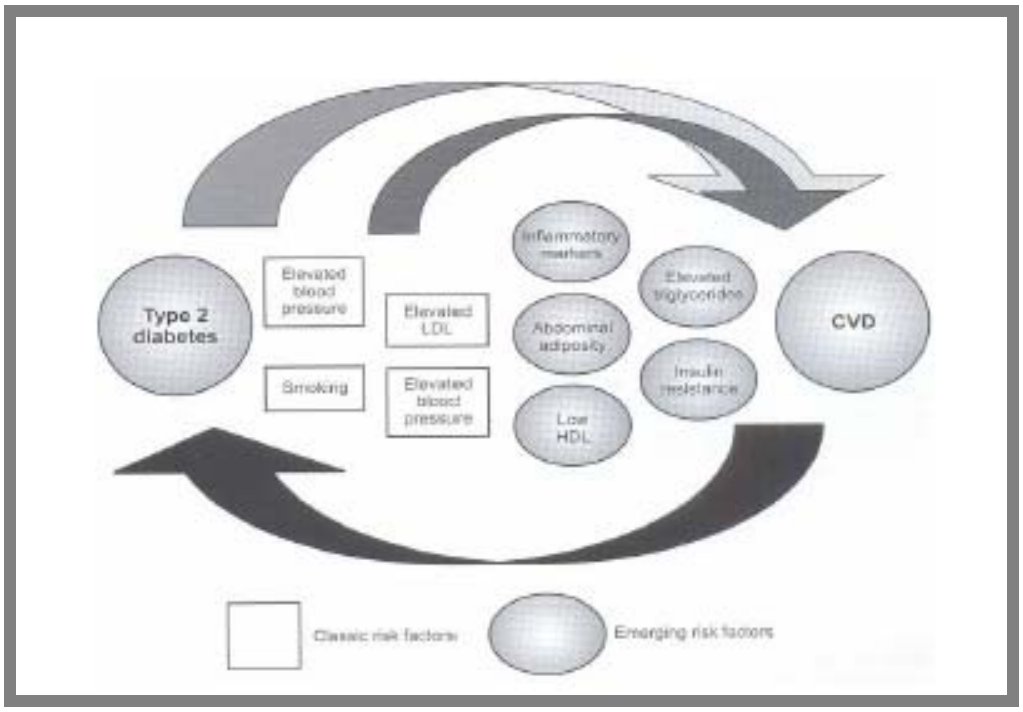


Figure 1 : RISK FACTORS FOR METABOLIC SYNDROME [42]

ETIO-PATHOGENESIS

The metabolic syndrome has three potential etiological categories : Obesity and disorders of adipose tissue , insulin resistance and a constellation of independent factors (e.g, molecules of hepatic, vascular and immunological origin) that mediate specific components of the metabolic syndrome . Other factors- aging , proinflammatory state and hormonal changes – have been implicated as contributors[40,41] .

OBESITY :

Abdominal obesity and insulin resistance along with other conditions like physical inactivity are the predominant risk factors for metabolic syndrome[40] . Obesity is an excess of body fat . It is measured as BMI or WC .

Abdominal (or central obesity) obesity correlates more strongly with insulin resistance and the metabolic syndrome .It is a marker of " dysfunction adipose" tissue and is of central importance in clinical diagnosis .

The prevalence of obesity worldwide is reaching epidemics and is responsible for high prevalence of metabolic syndrome[4].

The prevalence of metabolic syndrome rises in parallel with increasing obesity[43] .

Obesity contributes to hypertension , high serum cholesterol , low HDL cholesterol , and hyperglycemia , and associates with high CVD risk[40] .

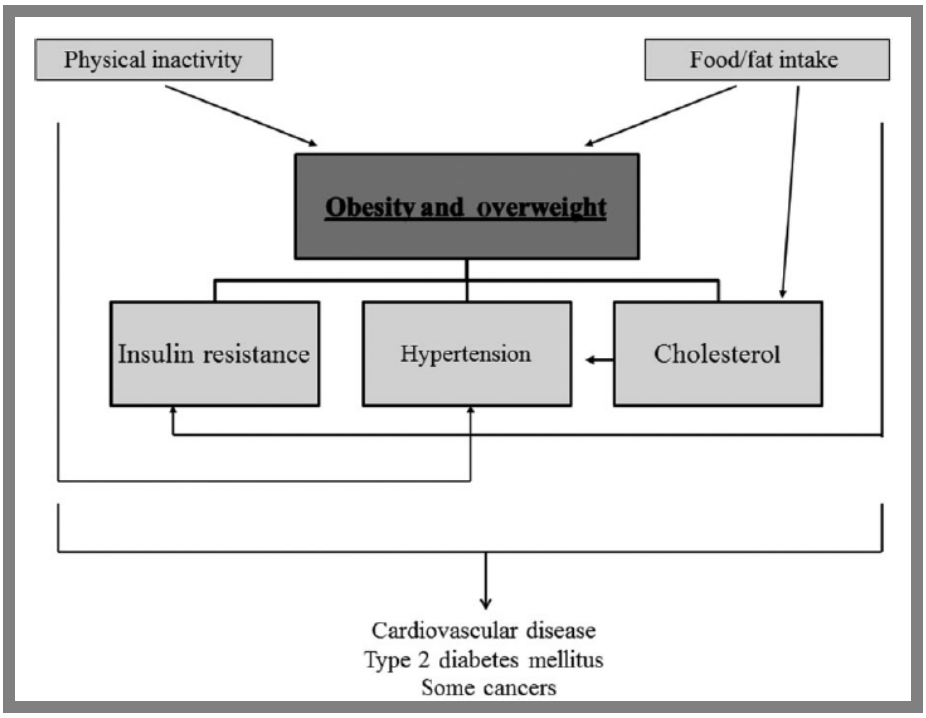


Figure 2 : Interplay between the risk factors for metabolic syndrome. Overweight and obesity are central to the risk of metabolic syndrome (MetS), both predisposing to insulin resistance, hypertension and dyslipidaemia, all of which are risk factors of MetS[40.]

The mechanisms where by obesity results in metabolic syndrome are being extensively studied . Excess adipose tissue releases several products that appear to worsen metabolic syndrome[44]. Non esterified fatty acids (NEFA) is the most important fuel source that contribute to the insulin-resistant state among individuals with obesity . It relates to hepatic carbohydrate and lipid metabolism.

Adipose tissue triglycerides undergoes lipolysis and releases NEFA into the circulation during the fasting state . Hormone sensitive lipase (HSL) is the major enzyme involved in lipolysis , its activity is enhanced by catecholamines and suppressed by insulin . During fasting , when insulin levels are low , ipolysis is as high as NEFA release .NEFA is the major source during fasting .

If NEFA supply exceeds needs for energy utilization , they flux into liver , muscle and accumulate impairing liver metabolism and enhances insulin resistance [44.]

Hepatic insulin resistance is associated with decreased apolipoprotein B degradation and increased production of triacylglycerol-rich lipoproteins. This change plus other metabolic alterations predisposes to the metabolic syndrome . Beyond storage of fatty acids , excess adipose tissue also releases other products like cytokines , PAI-1(plasminogen activator inhibitor-1) , and adiponectin that apparently exacerbate the risk factors .

Adipose tissue releases numerous cytokines , including pro-inflammatory molecules such as IL-6 and tumor necrosis factor alpha (TNF-α)[45]. This excess release of cytokines is secondary to infiltration of adipose tissue with activated macrophages resulting in a high level of circulating cytokines [46] . These can have several systemic effects like enhancement of insulin resistance in muscle , production of acute phase reactants C-reactive protein(CRP) and exacerbation of inflammation in arteriosclerotic lesions. These cytokines play an important role in the causation of the pro-inflammatory state of metabolic syndrome .

Excess amounts of PAI-1 released from adipose tissue in response to obesity also predisposes to pro-thrombotic state[47] .

The protein adiponectin , released from adipose tissue is reduced in obese individuals. The reduced Adiponectin levels can therefore be one of the key factors responsible for atherogenic and diabetogenic metabolic risk factor profile [48-51].

Adipose tissue further secretes leptin an appetite suppressant , levels of which are high in obesity and do not suppress the appetite of obese individuals a condition called LEPTIN RESISTANCE. Leptin can have systemic actions as well as actions in hypothalamus , one such systemic action is to enhance fatty-acid oxidation by the liver, preventing steatosis[52].

Due to association between abdominal adiposity and the presence of the features of metabolic syndrome, the measurement of waist circumference has been proposed as a crude anthropometric correlate of abdominal and visceral adiposity.

Relative increases in visceral versus subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the greater prevalence of the syndrome in those populations compared with African-American men in whom subcutaneous fat predominates.

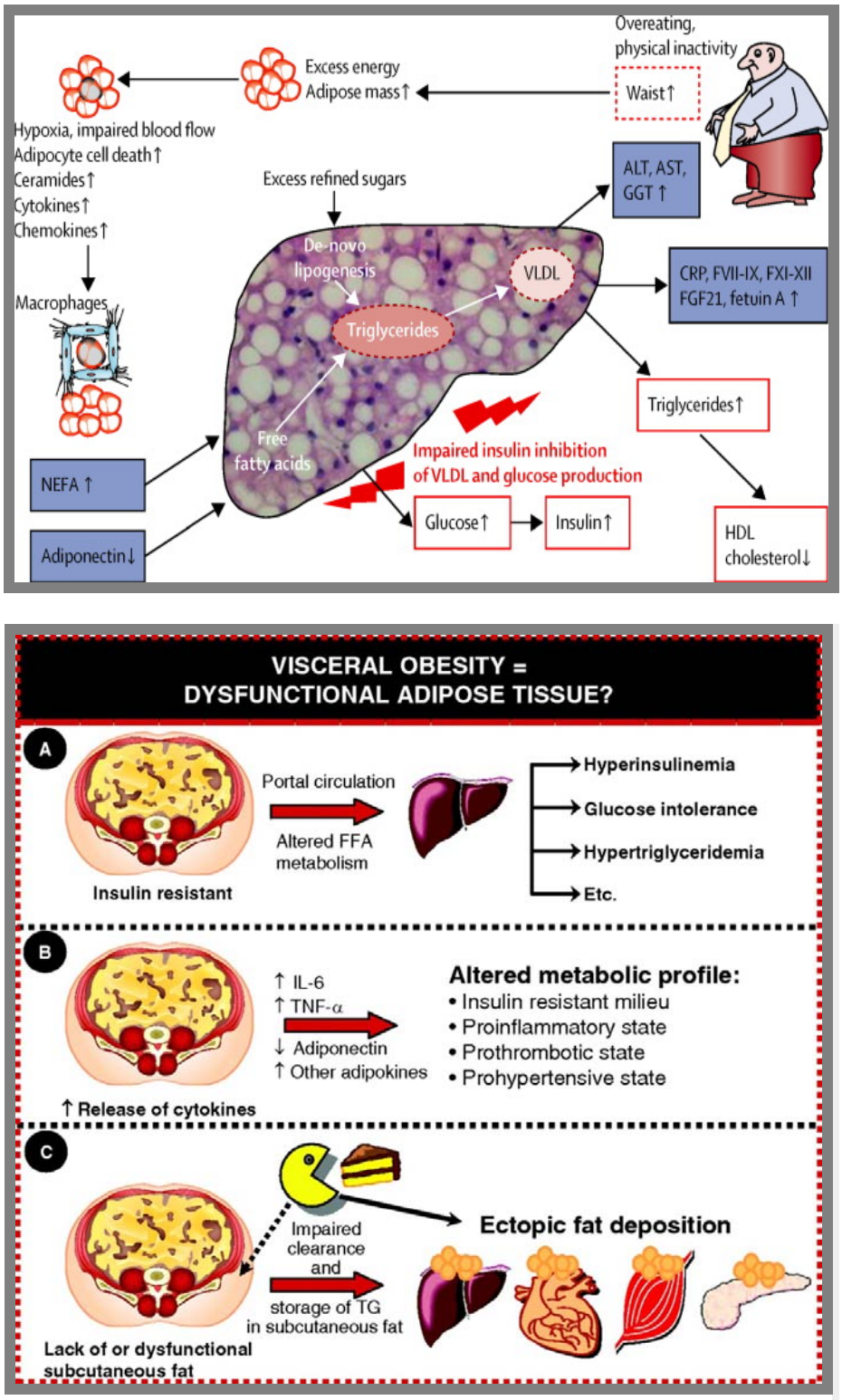


Figure 3: Proposed mechanisms by which visceral obesity, as the most dangerous form of obesity, could be linked to the athero-thrombotic-inflammatory abnormalities of insulin reistance [44.]

INSULIN RESISTANCE

The most widely accepted and unifying hypothesis to describe the pathophysiology of metabolic syndrome is insulin resistance . It plays a greater priority than obesity in pathogenesis[53,54] and directly causes other metabolic risk factors along with its accomplice hyperinsulinemia .The onset of insulin resistance is heralded by post prandial hyperinsulinemia followed by fasting hyperinsulinemia and ultimately hyperglycemia.

It is defined as a pathophysiological condition in which a normal insulin concentration does not adequately produce a normal insulin response in the peripheral target tissues such as adipose tissue , muscle and liver.

At any given level of body fat a broad range of insulin sensitivities exists , though Insulin resistance rises with increasing body fat content[55] . Most people with categorical obesity (body mass index [BMI] >30 kg/m^2) have postprandial hyperinsulinemia and relatively low insulin sensitivity, but variation in insulin sensitivities exists even within the obese population[56] . Overweight persons (BMI 25 to 29.9 kg/m^2) likewise exhibit a spectrum of insulin sensitivities, suggesting an inherited component to insulin resistance[55].

In some populations (eg, South Asians) insulin resistance occurs commonly even with BMI <25 kg/m^2 and contributes to a high prevalence of type 2 diabetes and premature CVD. South Asians and others who manifest insulin resistance with only mild-to-moderate overweight can be said to have primary insulin resistance.

Even with primary insulin resistance weight gain seems to enhance insulin resistance and metabolic syndrome. Thus, dissociation of obesity and primary insulin resistance in patients with metabolic syndrome is difficult.

Abundant circulating free fatty acids derived predominantly from adipose tissue triglyceride stores by lipolytic enzyme lipase and in tissues by lipolysis of triglyceride rich lipoproteins by lipoprotein lipase contributes predominantly to the development of insulin resistance . Excessive fatty acids enhance substrate availability and cause insulin resistance by modifying downstream signaling. They impair insulin mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle.

Insulin mediates both anti-lipolysis and stimulation of LPL in adipose tissue and insulin resistance produces more fatty acids by increasing lipolysis and also decrease the anti lipolytic effect of insulin.

Excess NEFA is diverted to liver promoting fatty liver and atherogenic dyslipidemia , when insulin resistant muscle is overloaded with lipid from high plasma NEFA levels. Thus , insulin resistance in muscle predisposes to glucose intolerance , worsened by hepatic gluconeogenesis in insulin-resistant liver and effects of insulin resistance in adipose tissue and muscle provides the direct evidence for the mechanism linking resistance to insulin to metabolic syndrome.

INCREASED WAIST-CIRCUMFERENCE

Waist circumference is an important component for the diagnosis of metabolic syndrome[57]. But measuring waist circumference does not reliably distinguish increases in subcutaneous adipose tissue vs visceral fat; this distinction requires CT or MRI. With increase in visceral adipose tissue , adipose tissue-derived FFAs are directed to the liver. in contrast increase in abdominal

subcutaneous fat releases lipolysis products into systemic circulation and avoid more direct effects on hepatic metabolism.

DYSLIPIDEMIA

In general, FFA flux to the liver is associated with increased production of apoB-containing, triglyceride-rich very low density lipoproteins (VLDLs). The effect of insulin on this process is complex, but hypertriglyceridemia is an excellent marker of the insulin-resistant condition[58].

The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL cholesterol , as a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridemia , a decrease in the HDL cholesterol content is a consequence of reduced cholesteryl- ester content of the lipoprotein core in combination with cholesteryl ester transfer protein–mediated alterations in triglyceride, making the particle small and dense. This change in lipoprotein composition also results in increased clearance of HDL from the circulation. The relationships of these changes in HDL to insulin resistance are probably indirect, and occurs in concert with the changes in triglyceride-rich lipoprotein metabolism.

In addition to HDL, low-density lipoproteins (LDLs) are modified in composition. With fasting serum triglycerides >2.0 mM (~180 mg/dL), there is almost always a predominance of small dense LDLs. Small dense LDLs are more atherogenic. They are toxic to the endothelium and they transit through the endothelial basement membrane and adhere to glycosaminoglycans. They also have increased susceptibility to oxidation and are selectively bound to scavenger receptors on monocyte-derived macrophages.

Subjects with increased small dense LDL particles and hypertriglyceridemia also have increased cholesterol content of both VLDL-1 and VLDL-2 subfractions.

This relatively cholesterol-rich VLDL particle contributes to the atherogenic risk in patients with metabolic syndrome.

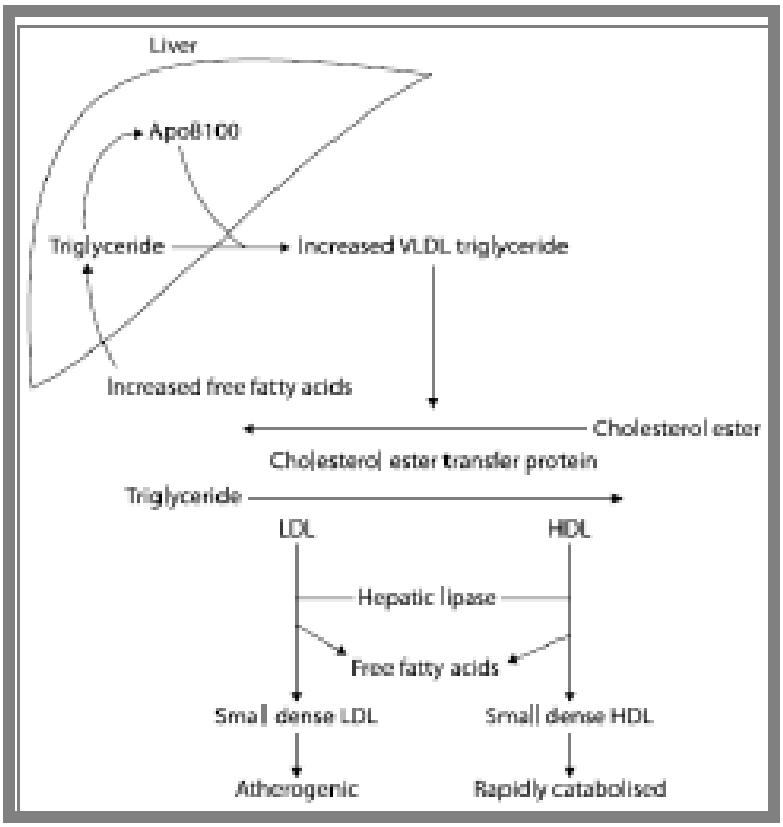
Infiltration of plasma LDL into the arterial intima is the first step in the pathogenesis of atherosclerosis. The rate of infiltration of LDL depends on two factors: (1) the concentration of LDL in the circulation and (2) the permeability of the arterial wall[59]. Several mechanisms have been proposed for transport of LDL into the sub-endothelium : vesicular ferrying through endothelial cells, passive sieving through the endothelial pores and passage between cells.

Not all that enters the arterial wall stays there , some escapes by reversal of the same process . A portion of LDL becomes entrapped into the extracellular matrix[60] and is modified by several types like aggregation , fusion of lipoproteins , proteolysis , lipolytic degradation such as hydrolysis of cholesterol esters , phospholipids and triglyceride, oxidation and glycation[61]. When LDL is modified in various ways it acquires inflammatory potential leading to the activation of various types of cells ; endothelial cells , monocyte / macrophages and smooth muscle cells[60,62].

Key changes of inflammation are endothelial dysfunction , adherence to circulating monocytes , movement of monocytes into the arterial wall and their activation , proliferation of smooth muscle cells and enhanced fibrosis. Macrophages play a key role in atherogenesis[62] . 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 two changes create unstable plaques that are prone to rupture and to cause acute ASCVD events .

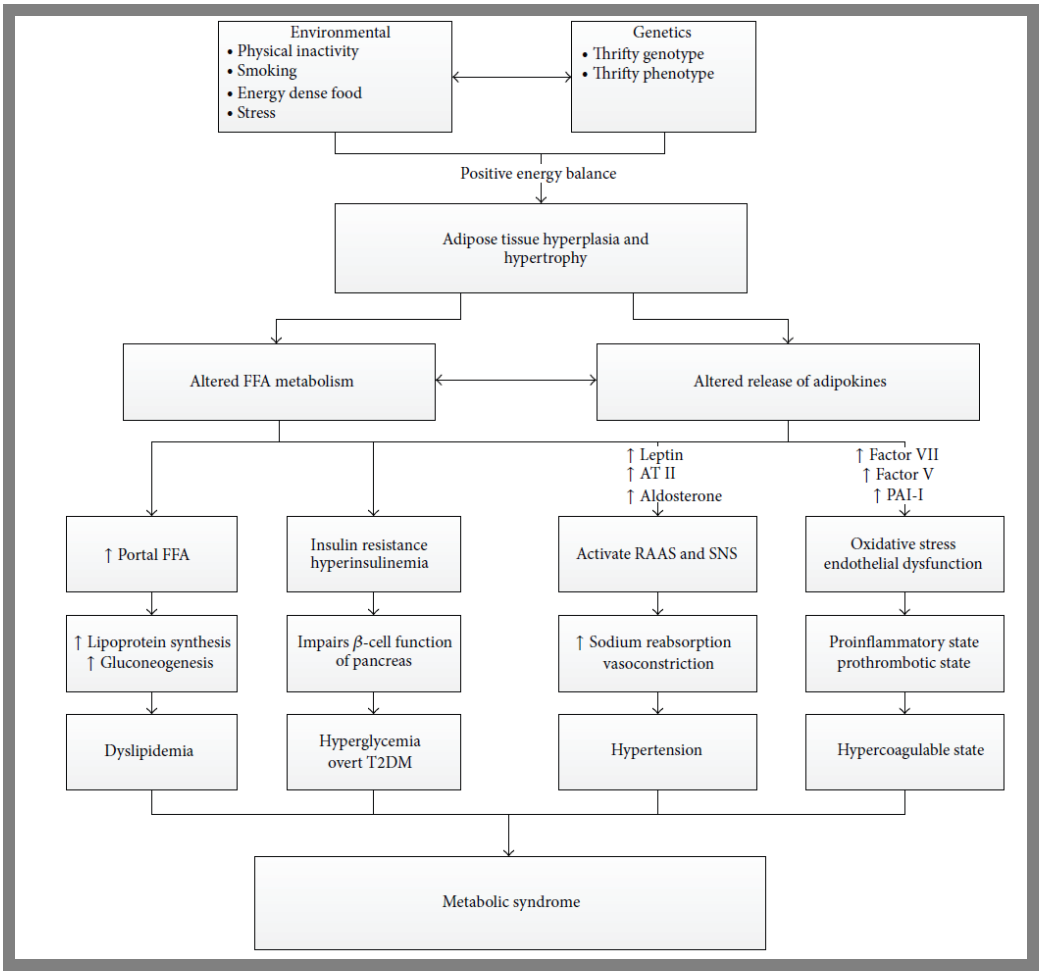
Figure 4 : Formation of VLDL from liver [43]



GLUCOSE INTOLERENCE

The defects in insulin action leads to impaired suppression of glucose by the liver , kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues like muscle and adipose tissue[58]. 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 IFG and / or IGT to DM.

TABLE 2: SCHEMATIC PRESENTATION OF METABOLIC SYNDROME



PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME[58]

In the liver excess free fatty acids (FFAs) , released from an expanded adipose tissue mass result in an increased production of glucose and triglycerides and secretion of VLDLs[58] along with reduction in HDL cholesterol and increased density of low density lipoproteins (LDLs).They also reduce insulin sensitivity in muscle by inhibiting insulin mediated glucose uptake.

Other associated defects include increase in circulating glucose due to reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride. Hyperinsulinemia occurs due to increase in circulating glucose , to some extent FFA, increased pancreatic insulin secretion and result in enhanced sodium reabsorption and increased sympathetic nervous system (SNS) activity and contribute to hypertension .Excessive FFAs also produce pro inflammatory state which super imposes and contributes to insulin resistance.

Adipocytes and Monocyte derived macrophages enhance secretion of IL-6 and tumour necrosis factor-alpha (TNF-α) resulting in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFA. IL-6 , cytokines and TNF-α enhances hepatic glucose production by liver and also hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor-1(PAI-1) resulting in a prothrombotic state . Cytokines also stimulate hepatic production of C-reactive protein (CRP).reduced production of Adiponectin , an anti-inflammatory and insulin sensitizing cytokine is also associated with metabolic syndrome .

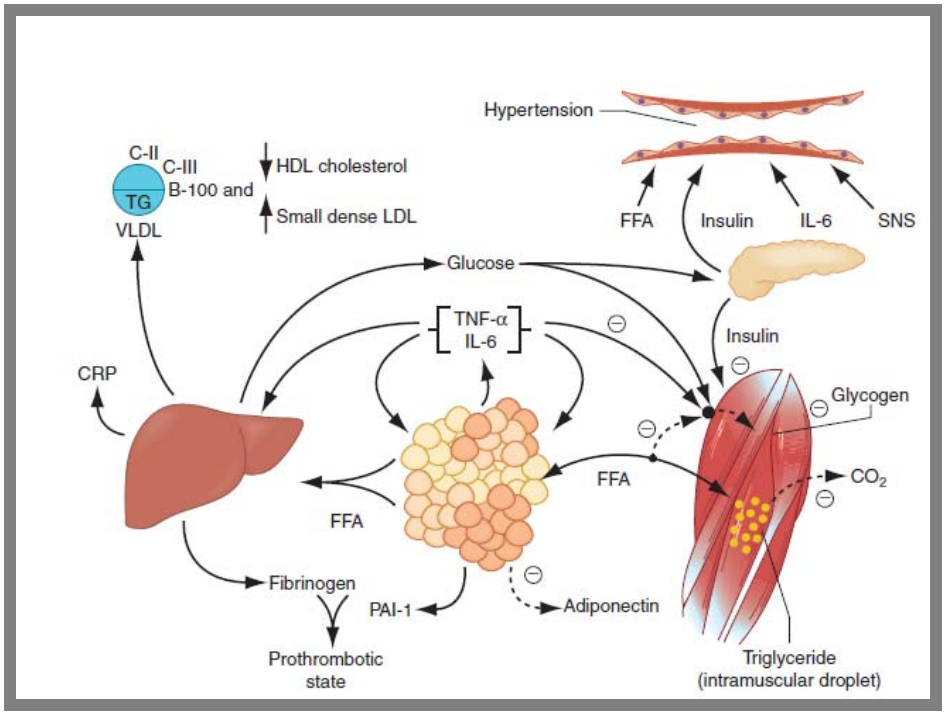


Figure 5: PATHOPHYSIOLOGY OF METABOLIC SYNDROME[58]

GGT AND METABOLIC SYNDROME :

Serum γ-glutamyltranspeptidase (GGT) , a glycoprotein with a molecular weight of 68000 Da consisting of two proteins, the larger chain with a molecular weight of 46 000 Da and the smaller one with a molecular weight of 22 000 Da[63,] regarded as a biomarker of hepatobiliary disease and alcohol consumption/abuse.

It is present in the cell membranes of many organ tissues including the kidney, lung, Pancreas[64] and vascular endothelium as well as in the extracellular fluid attached to α and β Lipoproteins[65] and albumin carrier molecules [66] .

Most GGT in serum is derived from the liver. It is a sensitive indicator of hepatic cell inflammation and hepatic intracellular triglyceride accumulation as seen in

obesity[67], nonalcoholic fatty liver disease (NAFLD)[68], non–insulin dependent diabetes mellitus (NIDDM)[69] and insulin resistance[70.]

GGT is the enzyme responsible for the extracellular catabolism of glutathione and mediates the transmembrane transfer of glutathione, a major component of intracellular antioxidant-protective mechanisms[71 .]

GGT hydrolysis glutathione and produces cysteinyl- glycine, a Powerful reductant of Fe3+, which simultaneously generate Fe2+ and a free thiyl radical , leading to LDL oxidation and contributes to other processes of atherosclerosis, such as metalloproteinase activation, cell proliferation and apoptosis[72].

Increased levels of GGT can also be used as a marker of insulin resistance[73]. Its activity has also been shown to increase in response to oxidative stress [74.]

GGT also accelerates the production of reactive oxygen species and glutathione-dependent low density lipoprotein(LDL) oxidation in the presence of iron ions[75,76.]

It is expressed in the atheromatous core of coronary plaques, where it co-localizes with oxidized LDL and foam cells[77.]

GGT is also pro-inflammatory and mediates inter-conversion of the glutathione-containing inflammatory mediator leukotriene C4 into leukotriene D4[78].

Higher serum GGT is associated with development of cardiovascular disease (CVD) risk factors including diabetes, hypertension, dyslipidemia and the metabolic syndrome[79,80.]

Raised serum GGT levels predict the development of noninsulin dependent diabetes mellitus (NIDDM, type 2 diabetes) in men, independently of serum glucose, body mass index and other predictors of type 2 diabetes[81].

In individuals with metabolic syndrome excess fat in the liver enhances oxidative stress, leading to overconsumption of GSH with a compensatory increase in GGT synthesis[82.]

As GGT measures a single specific entity and offer additional information over presently used determinants , can be easily standardized with both high sensitivity and specificity and can be readily tested automatically in most regions it can be considered as a unique biomarker for cardiac and metabolic risk evaluation[83.]

Hence , higher than expected GGT levels in otherwise healthy individuals should alert the Physician to study those patients in more detail to prevent unnecessary cardiac-related events and deaths in future years.

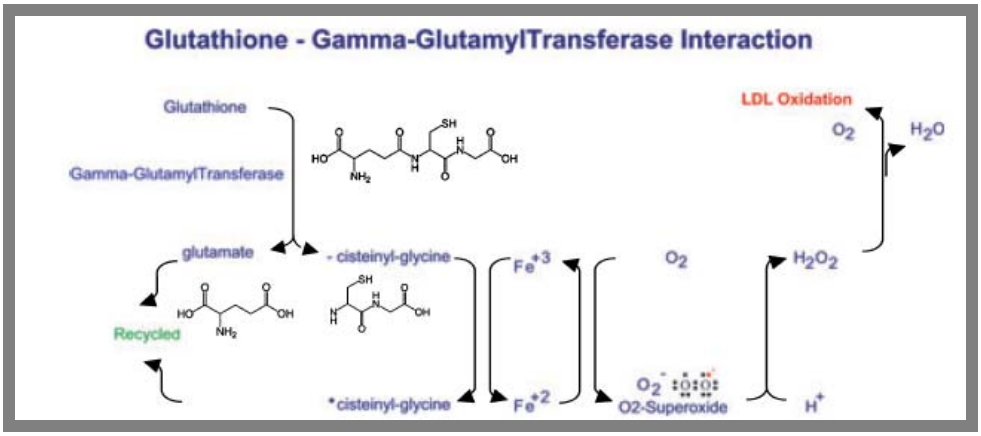


Figure 6 : Steps in the gamma-glutamyl transferase enzyme reaction and its relationship to the oxidation of low-density lipoprotein (LDL) cholesterol[63]

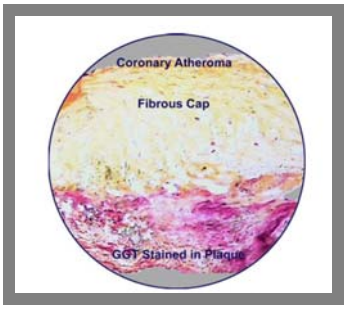


Figure 7 : Photomicrograph of a coronary atheroma (20_ magnification) identifying active enzyme within the plaque by an enzyme histochemical reaction to human gamma-glutamyl transferase (GGT), stained red with the diazonium salt fast garnet GBC, as the chromogen[63].

MANAGEMENT

LIFE STYLE MODIFICATIONS

As obesity is the major driving force behind the metabolic syndrome it is a primary target of therapy by reducing the body weight by 10 percent per year with a goal to achieve a BMI < 25kg/m^2 and by reducing caloric intake .

Emphasis should be kept on reducing consumption of saturated and trans saturated fatty acids and cholesterol , reduced intake of simple sugars and ample intake of fruits , vegetables and whole grains .

DYSLIPIDEMIA

The primary target is to reduce LDL-C . The most effective drugs for reducing these lipoproteins are statins which is a therapeutic intervention used in most trials.

ELEVATED BLOOD PRESSURE

As per Joint national committee (JNC-7) life style theraphy is the first line for management of blood pressure .when lifestyle changes donot reduce BP to< 140/90mmHg drug theraphy with Angiotensin-converting enzyme should be first-line of therapy in patients with metabolic syndrome.

ELEVATED PLASMA GLUCOSE

Life style intervention in patients with IFG by weight reduction , dietary fat restriction and increased physical activity to reduce incidence of T2DM.

MATERIALS AND METHODS

The study samples were collected from out patient and in-patient Department of Medicine, R.L.Jalappa Hospital and Sri Devaraj URS Medical college, Tamaka ,Kolar. The study subjects included both male and female Met S patients and age and sex matched non Met S individuals in the age group of 18-50 years of age .

The study is undertaken over a period of 1 year .

A total of 110 patients were enrolled in the study of which 55 had MS and 55 were controlled individuals .

The applied selection criteria were as follows:

INCLUSION CRITERIA :

Cases for the study are included based on International diabetic federation (IDF) diagnostic criteria for metabolic syndrome between age group 18-50 years :

Central obesity as defined by waist circumference ≥90 cms for men and ≥ 80 cms for women in Indian population.

Plus any two of the following 4 factors:

1. Raised Triglyceride level ≥150mg/dl or specific treatment for this abnormality.
2. Reduced HDL cholesterol <40 mg/dl or specific treatment for this lipid abnormality.
3. Raised B.P systolic ≥130 mm Hg and diastolic ≥85 mm Hg or on treatment for previously diagnosed hypertension.

4. Raised Fasting Plasma Glucose ≥ 100 mg/dl or previously diagnosed type-2 diabetes mellitus.

Controls: Age and sex matched healthy individuals with no comorbidities who give informed consent for the study will be included.

Exclusion Criteria

1. Hypothyroidism.
2. Malignant diseases.
3. Severe renal insufficiency.
4. Acute and chronic liver disease.
5. Chronic alcohol consumption
6. Drugs- antiepileptics , oral contraceptives, erythromycin, cimetidine.
7. Pregnant women .

STUDY DESIGN :

A hospital based cross-sectional study .

SAMPLE SIZE :

It was calculated using open Epi version 2 software.

Sample size was calculated using the standard deviation and variance for GGT levels in Metabolic Syndrome at 95% confidence interval and 80% power.

Sample size was estimated to be approximately a minimum of 55 cases and controls.

An equal number of age group and sex matched normal controls shall be recruited to compare the GGT levels.

Hence the study will be done on a minimum total of 110 patients inclusive of both groups.

STUDY PROTOCOL

METHOD OF DATA COLLECTION AND ANALYSIS OF SAMPLES

Ethical clearance obtained from Sri Devaraj Urs University Ethics Committee.

Before collection of data or blood sample, each patient was explained the details of the study including rationale, expected benefits, risk profile, confidentiality safeguards and study protocol. Only those patients who were willing to follow the study protocol and gave their written consent were included in the study.

A detailed clinical history, physical examination and relevant investigations were undertaken.

History of duration of diabetes, hypertension, dyslipidemia was taken.

Treatment history of diabetes, hypertension, dyslipidemia was taken.

Appropriate blood samples were collected from Met S patients and age and sex matched non-MetS individuals for estimation of serum GGT, cholesterol, triglyceride, HDL and plasma glucose fasting blood sample were drawn into serum (without anticoagulant) gel containing yellow colour capped BD Vacutainer tubes. All samples were immediately centrifuged and stored at 2-8^{o}C until analysis for the relevant biochemical parameters. All analyses were performed within 3 hours of sample collection.

1. Serum Cholesterol was measured by XL600 autoanalyzer using CHOD-PAP principle.
2. Serum Triglyceride was measured by XL600 autoanalyzer using Glycerol Kinase principle.
3. Serum HDL was measured by ERBA V2 semi-autoanalyzer using PEG Precipitation principle.
4. Serum GGT level was measured by XL600 DRY CHEMISTRY autoanalyzer using Gamma Glutamyl 3 carboxy -4- nitranilide principle . This

GGT method is an adaptation of the methodology recommended by the International Federation of Clinical Chemistry (IFCC).This method uses the substrate L gamma-glutamyl-3-carboxy-4-nitranilide with glycylglycine .GGT catalyzes the transfer of the glutamyl moiety from gamma-glutamyl-3carboxy-4-nitranilide (GCNA) to glycylglycine thereby releasing 5-amino-2nitrobenzoate which absorbs at 450nm. This change is proportion to the gamma-glutamyl transferase activity and is measured using a bichromatic(450,600nm) rate technique .

The GGT flex reagent catridge is required to perform the GGT test.This test is performed on the dimension clinical chemistry system after the method is verified. Sampling , reagent delivery , mixing , processing and printing of results are automatically performed by the dimension system.

Reference range for normal GGT values in our lab are 11-43U/I.

Figure 8: DRY CHEMISTRY AUTO ANALYZER FOR ESTIMATING GGT:

5. Plasma glucose was measured by XL600 autoanalyzer using GOD-POD principle.
6. Patient's recent-most blood/plasma/serum values of the afore-mentioned biochemical parameters were noted, if already available, provided they were done on the same day.

7. Patients relevant anthropometric data were collected. The serum levels of GGT, Cholesterol, Triglyceride, HDL and fasting plasma glucose levels of the two groups were compared for presence or absence of statistically significant differences.

- BMI calculated as:-wt in kg/height in m^2.
- Blood pressure is recorded after atleast 5 mins of rest in both arms both sitting and supine position.
- Waist circumference - measured in a horizontal plane midway between the inferior margin of ribs and superior border of iliac crest while the person is standing and during expiration.

Figure 9 : MEASURING WAIST CIRCUMFERENCE IN A PERSON WITH IDF CRITERIA FOR METABOLIC SYNDROME:

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and SD. Independent t test was used as test of significance to identify the mean difference between two groups. p value <0.05 was considered as statistically significant. ROC curve was plotted to find the area under curve and sensitivity and specificity of GGT in Metabolic syndrome.

Descriptive statistics

All quantitative data like age, vital signs and investigation were presented as mean and standard deviation with 95% confidence intervals.

All qualitative data like sex, symptoms, baseline medical characteristics, clinical examination findings were presented as frequency and percentages.

Analytical statistics

Correlation and regression statistics are applied to assess the association of GGT levels in MS and comparison with control groups.

Validity measures such as sensitivity and specificity are computed for GGT in diagnosis of metabolic syndrome.

The study required following investigation :

1. Liver function tests (GGT, Alanine amino transferase , Aspartate amino transferase , Alkaline phosphatase).
2. Fasting lipid profile (LDL cholesterol ,HDL cholesterol ,Triglycerides ,Total cholesterol).

3. Fasting plasma glucose, Post prandial blood glucose ,HBA1C
4. Thyroid profile.(TSH).
5. Renal function tests.(blood urea and serum creatinine),
6. USG abdomen.

RESULTS

A case control study on 55 Metabolic syndrome patients (cases group) and 55 non metabolic syndrome subjects (control group) was undertaken to study the role of Gamma glutamyl transferase in the diagnosis of metabolic syndrome.

The study group (cases and controls) was matched with age , gender to compare important variables .

Table 3 : Age distribution of subjects

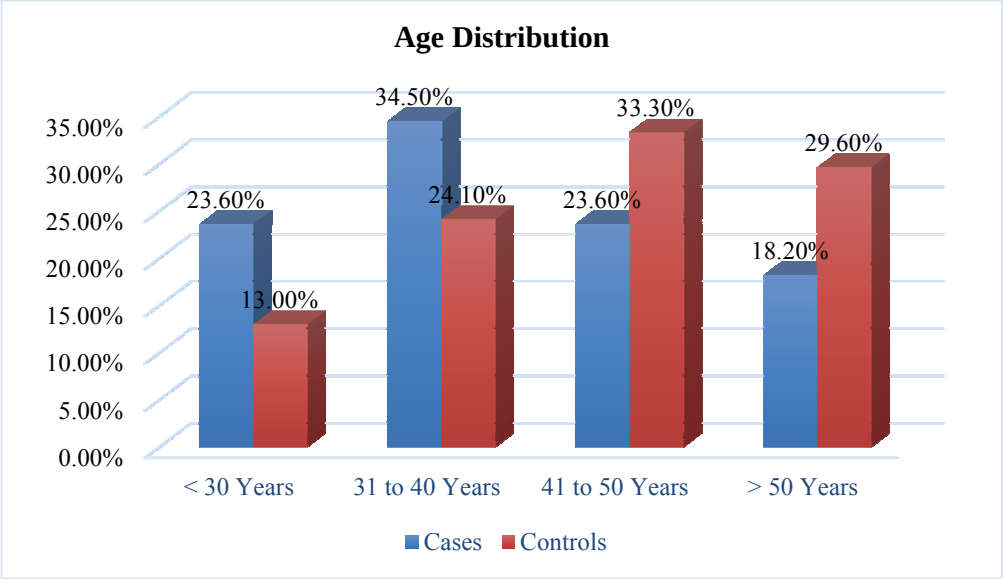
		GROUP				P value
		Cases		Controls		
		Count	Percent	Count	Percent	
Age	< 30 Years	13	23.6%	7	13.0%	0.164
	31 to 40 Years	19	34.5%	13	24.1%	
	41 to 50 Years	13	23.6%	18	33.3%	
	> 50 Years	10	18.2%	16	29.6%	

In the study there was no significant difference in Age distribution between two groups. Majority of subjects in both groups were above 30 years age group.

Maximum number of subjects with metabolic syndrome are in the age group between 31-40 years .

There was no significant difference in gender between two groups.

This ensures that Age and gender were matched in cases and controls.



Graph 3 : Bar diagram showing age distribution of subjects

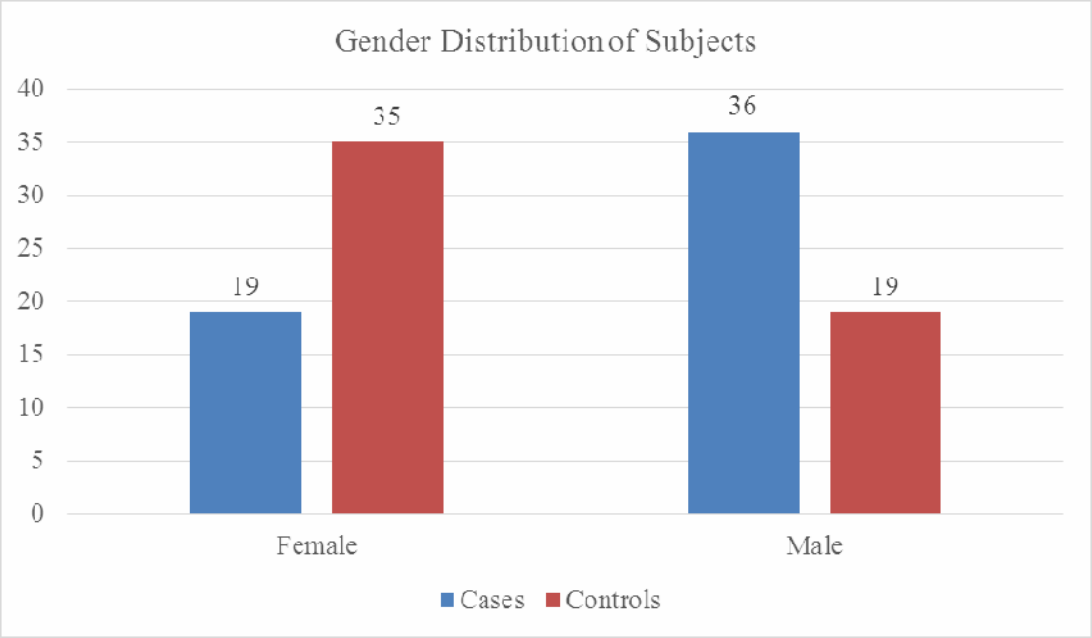
Table 4 : MEAN AGE OF SUBJECTS :

	Group	N	Mean	Std. Deviation
Age(yrs)	**Cases**	55	39.49	11.119
	Controls	54	43.96	10.174

Mean Age of Cases was 39.49 ± 11.11 Years and Controls was 43.96 ± 10.17 years.

Table5 : Gender distribution between cases and controls

		Group		Total
		Cases	Controls	
Gender	**Female**	19	35	**54**
	Male	36	19	**55**
Total		**55**	**54**	**109**

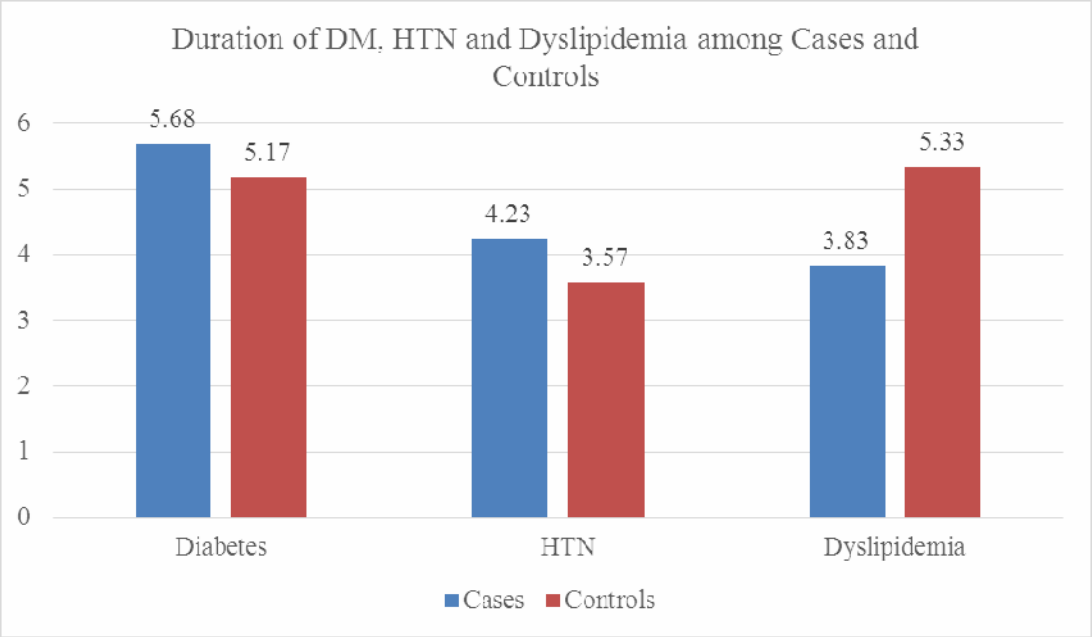


Graph 4 : Gender Distribution of Subjects

Table 6 : Duration of DM, HTN and Dyslipidemia among Cases and Controls

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
Diabetes	5.68	3.58	5.17	1.34	**0.635**
HTN	4.23	2.82	3.57	1.51	**0.558**
Dyslipidemia	3.83	2.71	5.33	1.03	**0.194**

There was no significant difference in mean duration of DM, HTN and Dyslipidemia between cases and controls.



Graph 6 : Bar diagram showing Duration of DM, HTN and Dyslipidemia among Cases and Controls

Table 7 : Mean SBP and DBP between Cases and Controls

	Group	N	Mean	Std. Deviation	P value
SBP	**Cases**	55	133.58	15.762	**<0.001***
	Controls	54	120.26	7.554	
DBP	**Cases**	55	84.91	8.776	**<0.001***
	Controls	54	74.44	5.545	

There was significant difference in Mean SBP and DBP between cases and Controls in the study i.e. Cases had higher SBP and DBP.

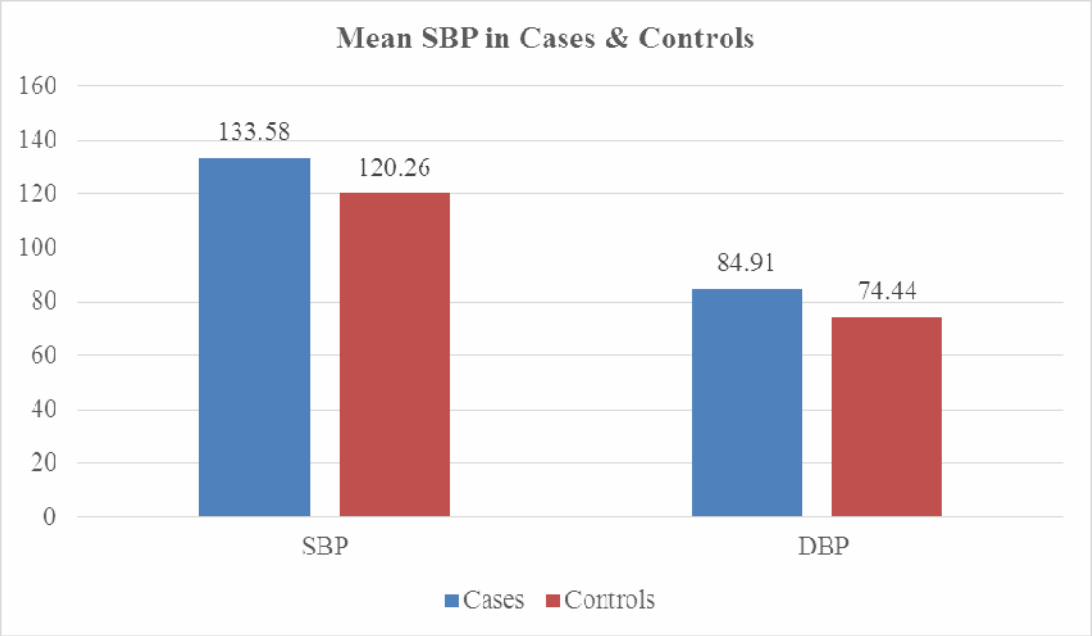
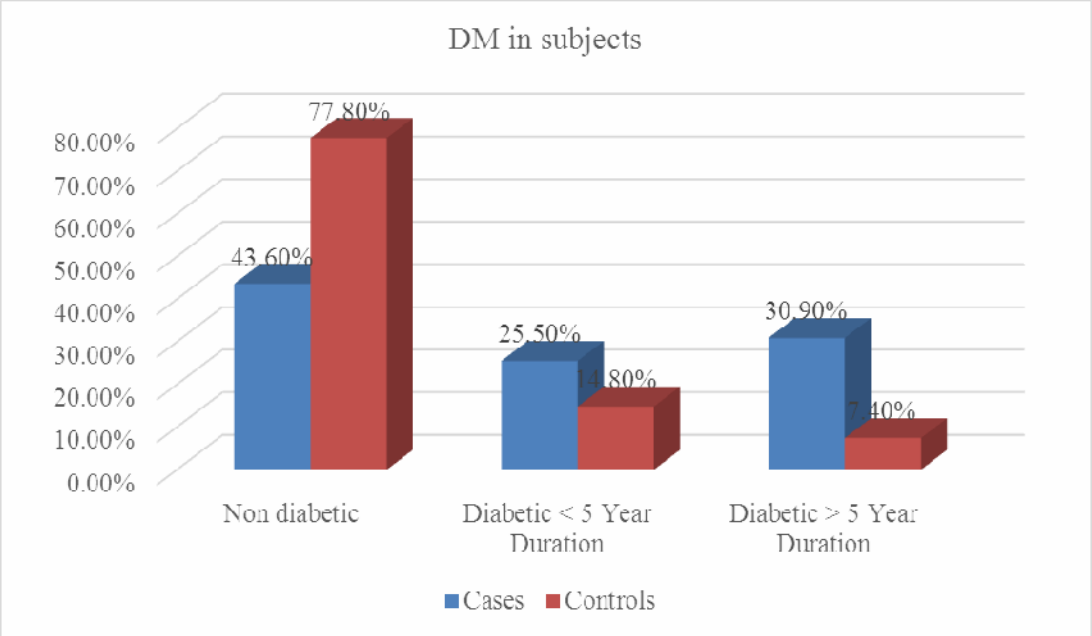


Figure 1: Mean SBP and DBP in Cases and Controls

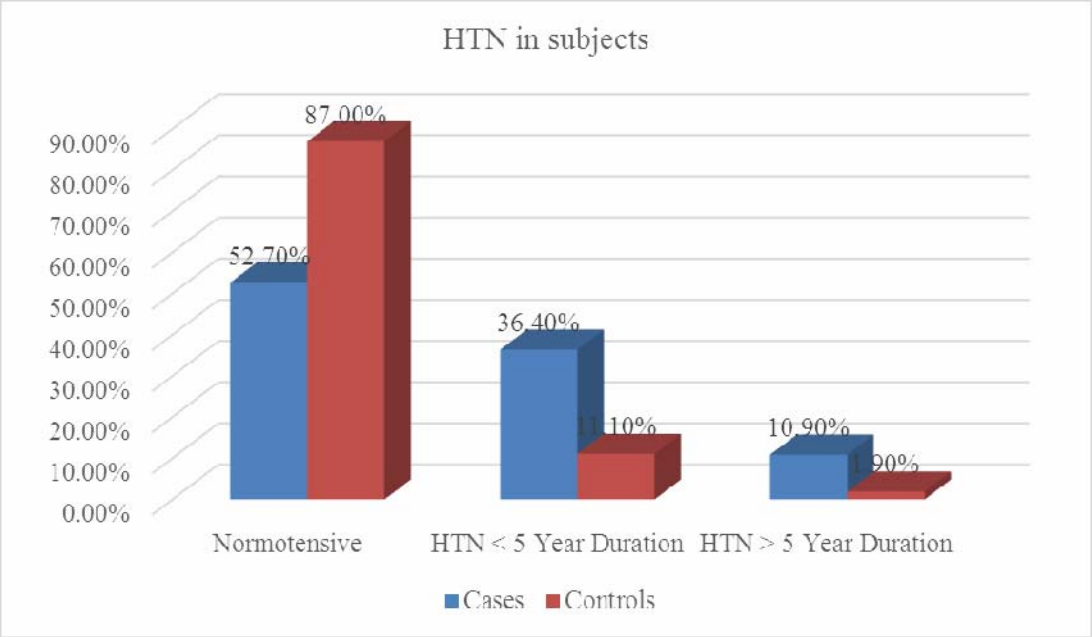
Table 2: Past History of DM, HTN and Dyslipidemia

		Group				P value
		Cases		Controls		
		Count	Percent	Count	Percent	
Diabetes History	Non diabetic	24	43.6%	42	77.8%	**0.001***
	Diabetic < 5 Year Duration	14	25.5%	8	14.8%	
	Diabetic > 5 Year Duration	17	30.9%	4	7.4%	
HTN History	Normotensive	29	52.7%	47	87.0%	**<0.001***
	HTN < 5 Year Duration	20	36.4%	6	11.1%	
	HTN > 5 Year Duration	6	10.9%	1	1.9%	
Dyslipidemia History	No Dyslipidemia	26	47.3%	48	88.9%	**<0.001***
	Dyslipidemia < 5 Year Duration	24	43.6%	4	7.4%	
	Dyslipidemia > 5 Year Duration	5	9.1%	2	3.7%	

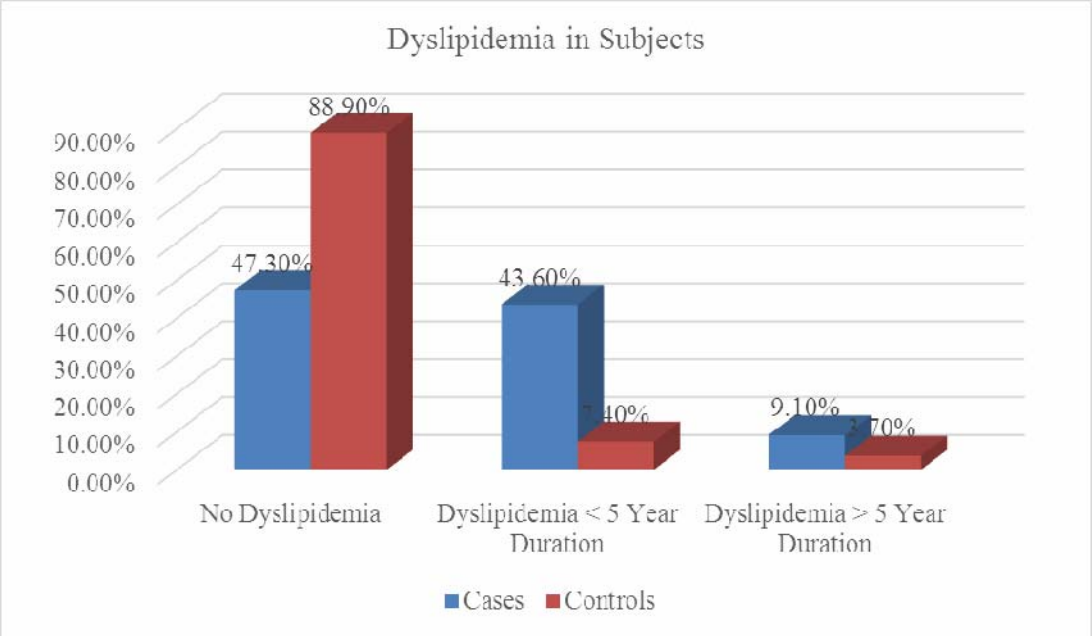
Diabetic history was present in 56.4% of cases and 22.2% of controls. Hypertension history was present in 47.3% of cases and 13% of controls. Dyslipidemia history was present in 52.7% of cases and 11.1% of controls. There was significant difference in past history among cases and controls.



Graph 7: Bar diagram showing Diabetes History in Subjects



Graph 8 : Bar diagram showing HTN in subjects

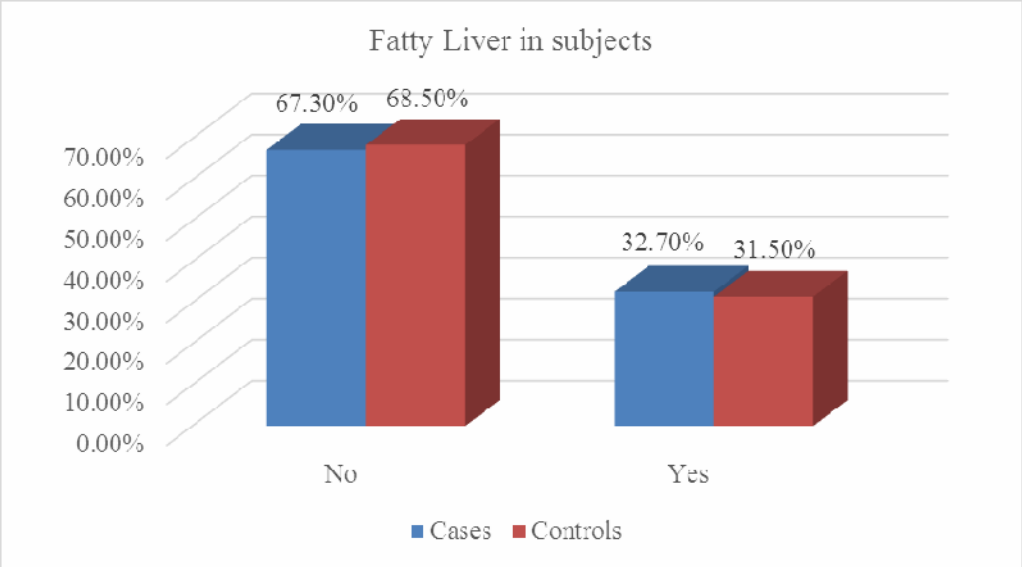


Graph 9 : Bar diagram showing Dyslipidemia history in Subjects

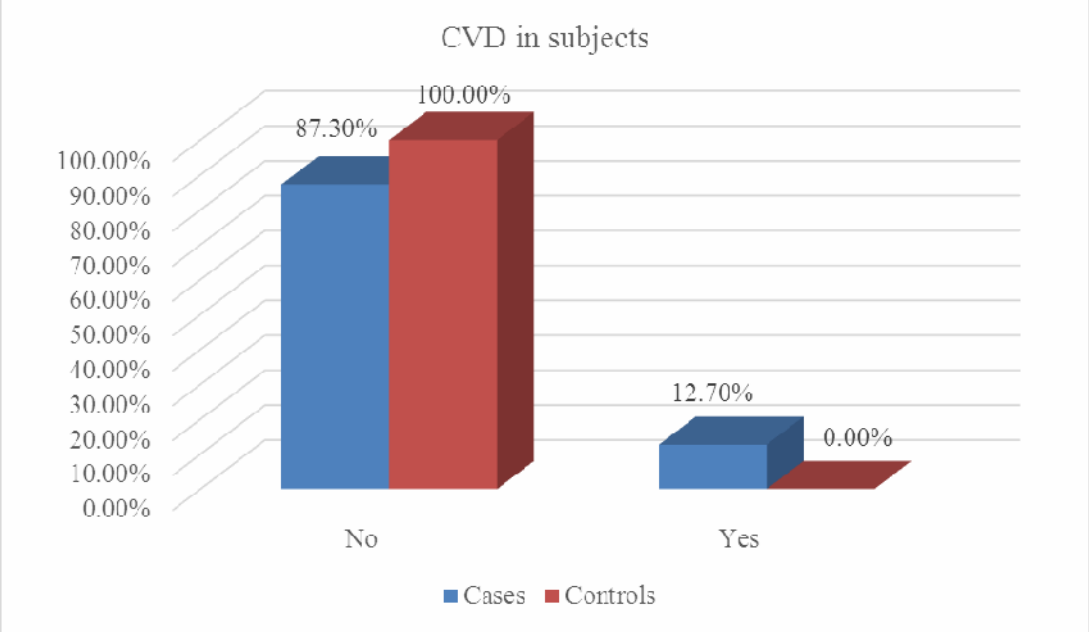
Table 9 : Comorbidities in Subjects

		Group				P value
		Cases		Controls		
		Count	Percent	Count	Percent	
Fatty Liver	**No**	37	67.3%	37	68.5%	**0.889**
	Yes	18	32.7%	17	31.5%	
CVD	**No**	48	87.3%	54	100.0%	**0.007***
	Yes	7	12.7%	0	0.0%	
CVA	**No**	53	96.4%	54	100.0%	**0.157**
	Yes	2	3.6%	0	0.0%	

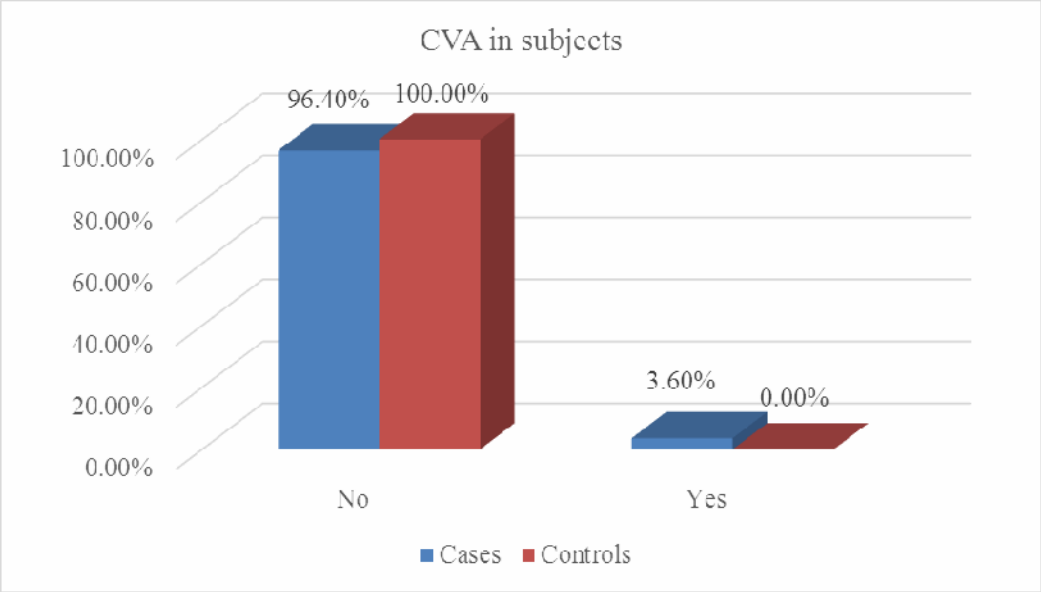
CVD was present in 12.7% of cases and none of the controls had CVD. 3.6% of cases had CVA and none of the controls had CVA. There was significant association between cases CVD.



Graph 10 : Bar diagram showing Fatty liver in subjects



Graph 11 : Bar diagram showing CAD in subjects

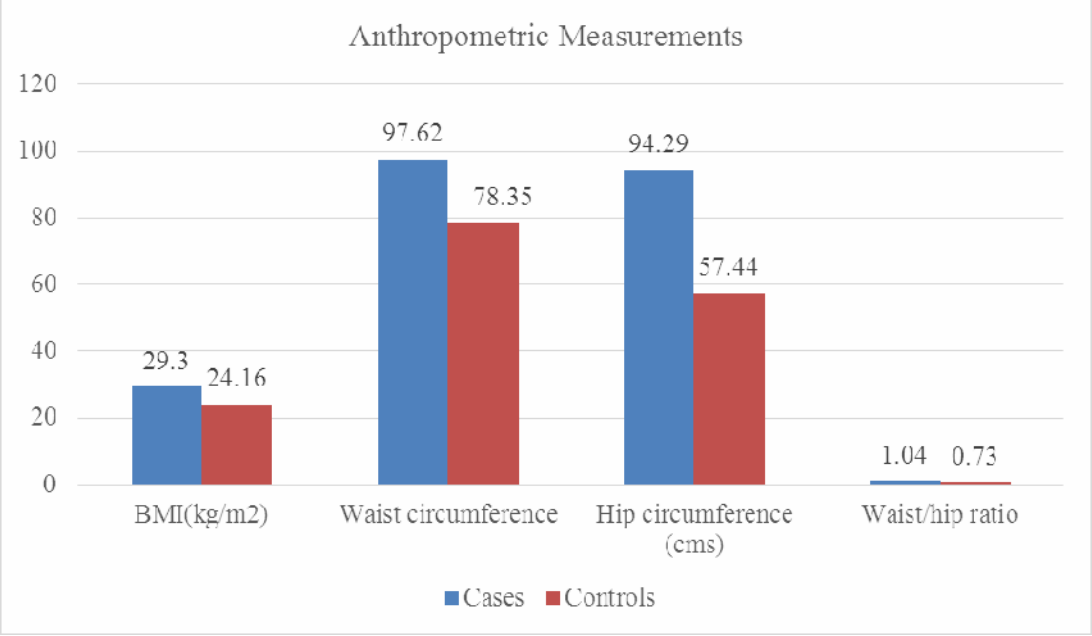


Graph 12 : Bar diagram showing CVA in subjects

Table 10 : Anthropometric Measurements between two groups

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
BMI(kg/m2)	29.30	2.57	24.16	.90	**<0.001***
Waist circumference	97.62	5.31	78.35	3.02	**<0.001***
Hip circumference (cms)	94.29	6.70	57.44	4.58	**<0.001***
Waist/hip ratio	1.04	0.07	0.73	0.05	**<0.001***

Mean BMI, waist circumference, Hip circumference and WHR are shown in above table. There was significant difference in all the mean values between two groups. i.e. all the anthropometric parameters were higher in cases than in controls.

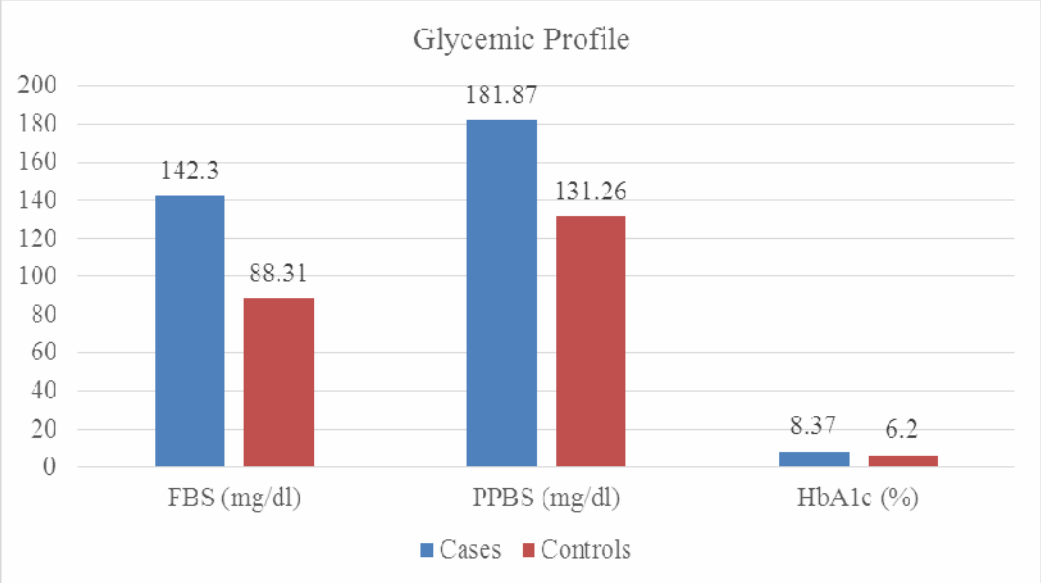


Graph 13 : Bar diagram showing Mean of Anthropometric Measurements

Table 11: Glycemic Profile between two groups

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
FBS(mg/dl)	142.30	59.98	88.31	10.32	**<0.001***
PPBS(mg/dl)	181.87	65.02	131.26	13.49	**<0.001***
HbA1c (%)	8.37	2.53	6.20	.57	**<0.001***

There was significant difference between Mean FBS, PPBS and HbA1c in cases and controls. I.e. Glycemic parameters in cases was higher than that of controls.

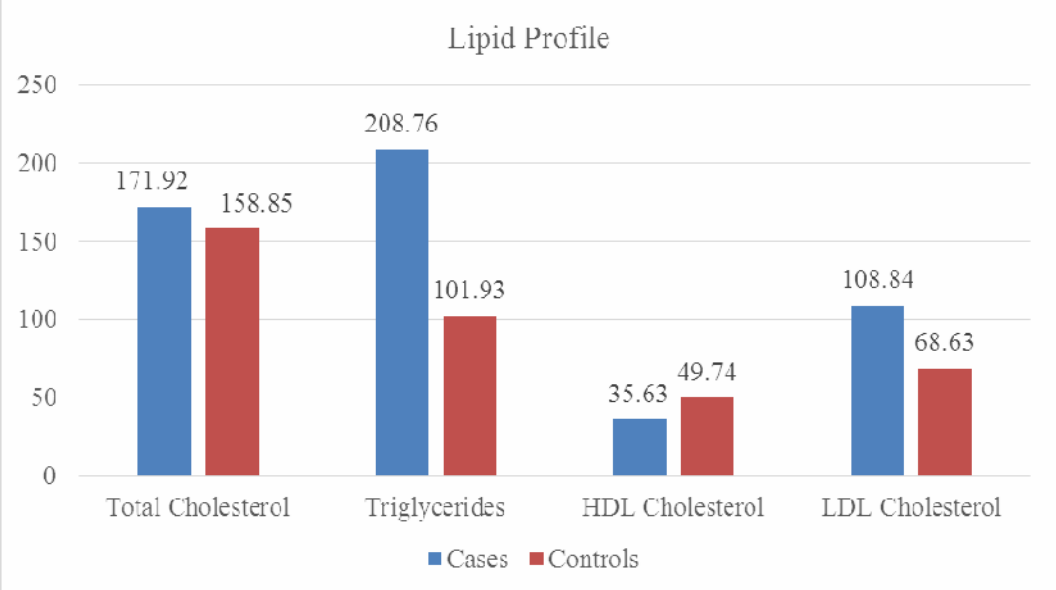


Graph 14 : Bar diagram showing Mean Values of Glycemic Profile between two groups

Table 12: Lipid Profile of Subjects

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
Total Cholesterol	171.92	48.00	158.85	19.31	**0.066**
Triglycerides	208.76	92.85	101.93	20.77	**<0.001***
HDL Cholesterol	35.63	8.74	49.74	6.29	**<0.001***
LDL Cholesterol	108.84	39.07	68.63	14.94	**<0.001***

There was significant difference in Mean TG, HDL and LDL cholesterol between two groups. I.e. TG & LDL was increased and HDL was decreased significantly in Cases. No significant difference was noticed between two groups for Total cholesterol.



Graph 15 : Bar diagram showing Lipid Profile between two groups

Table 13 : Liver Function Tests between two groups

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
GGT	51.89	6.31	38.09	8.10	**<0.001***
AST	31.80	17.37	25.59	5.23	**0.013***
ALT	37.71	13.52	28.50	5.03	**<0.001***
ALP	167.42	66.34	82.61	19.02	**<0.001***

In the study Mean GGT, AST, ALT and ALP levels were significantly higher in cases than in controls.

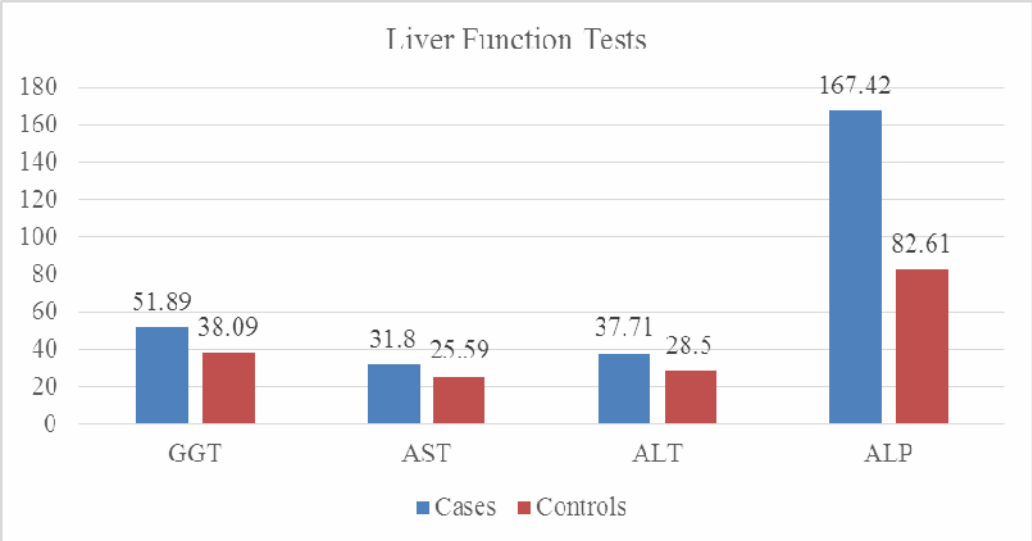


Figure 2: Bar diagram showing Liver function tests between two groups

Table 14 : Comparison of GGT with Comorbidities in cases

		GGT				P value
		Normal		Raised		
		Count	%	Count	%	
DM	Non diabetic	1	25.0%	23	45.1%	**0.653**
	Diabetic < 5 Year Duration	1	25.0%	13	25.5%	
	Diabetic > 5 Year Duration	2	50.0%	15	29.4%	
HTN	Normotensive	3	75.0%	26	51.0%	**0.598**
	HTN < 5 Year Duration	1	25.0%	19	37.3%	
	HTN > 5 Year Duration	0	0.0%	6	11.8%	
Dyslipidemia	No Dyslipidemia	4	100.0%	22	43.1%	**0.90**
	Dyslipidemia < 5 Year Duration	0	0.0%	24	47.1%	
	Dyslipidemia > 5 Year Duration	0	0.0%	5	9.8%	
Fatty Liver	No	2	50.0%	35	68.6%	**0.445**
	Yes	2	50.0%	16	31.4%	
CVD	No	3	75.0%	45	88.2%	**0.444**
	Yes	1	25.0%	6	11.8%	
CVA	No	4	100.0%	49	96.1%	**0.687**
	Yes	0	0.0%	2	3.9%	

There was no significant association between GGT and Comorbidities in Cases.

Table 15: Comparison of GGT with Comorbidities in Controls

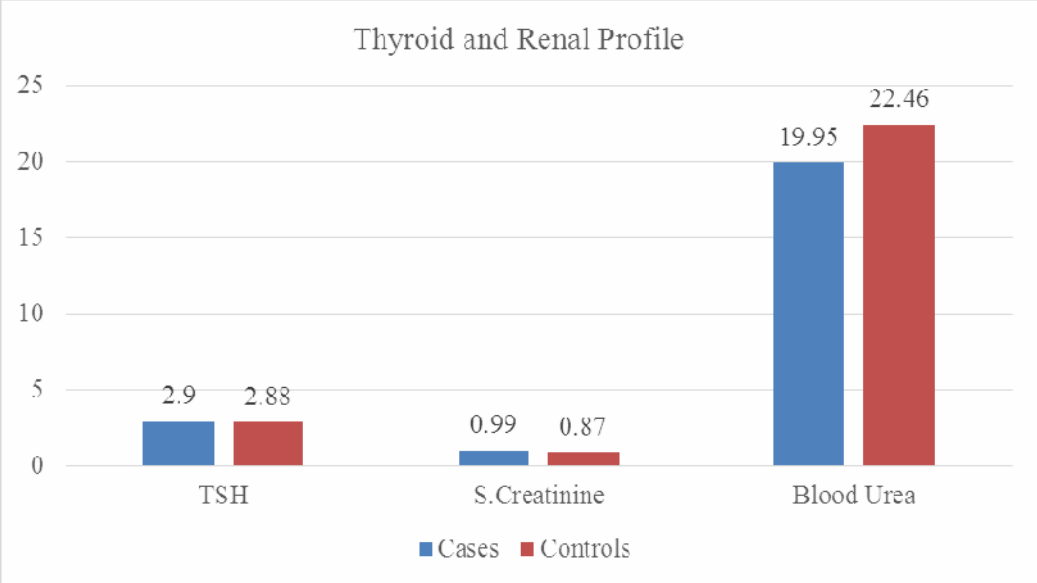
		GGT				P value
		Normal		Raised		
		Count	%	Count	%	
DM	Non diabetic	19	63.3%	23	95.8%	**0.016***
	Diabetic < 5 Year Duration	7	23.3%	1	4.2%	
	Diabetic > 5 Year Duration	4	13.3%	0	0.0%	
HTN	Normotensive	28	93.3%	19	79.2%	**0.252**
	HTN < 5 Year Duration	2	6.7%	4	16.7%	
	HTN > 5 Year Duration	0	0.0%	1	4.2%	
Dyslipidemia	No Dyslipidemia	26	86.7%	22	91.7%	**0.430**
	Dyslipidemia < 5 Year Duration	2	6.7%	2	8.3%	
	Dyslipidemia > 5 Year Duration	2	6.7%	0	0.0%	
Fatty Liver	No	18	60.0%	19	79.2%	**0.132**
	Yes	12	40.0%	5	20.8%	
CVD	No	30	100.0%	24	100.0%	-
	Yes	0	0.0%	0	0.0%	
CVA	No	30	100.0%	24	100.0%	-
	Yes	0	0.0%	0	0.0%	

There was no significant association between GGT and Comorbidities in Controls.

Table 16: Thyroid Profile and Renal profile between two groups

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
TSH	2.90	0.77	2.88	0.85	**0.917**
S.Creatinine	0.99	0.33	0.87	0.42	**0.107**
Blood Urea	19.95	4.53	22.46	5.65	**0.012***

There was significant difference in Mean Blood urea levels between cases & Controls. Whereas no statistical significance was observed for TSH and Serum Creatinine.

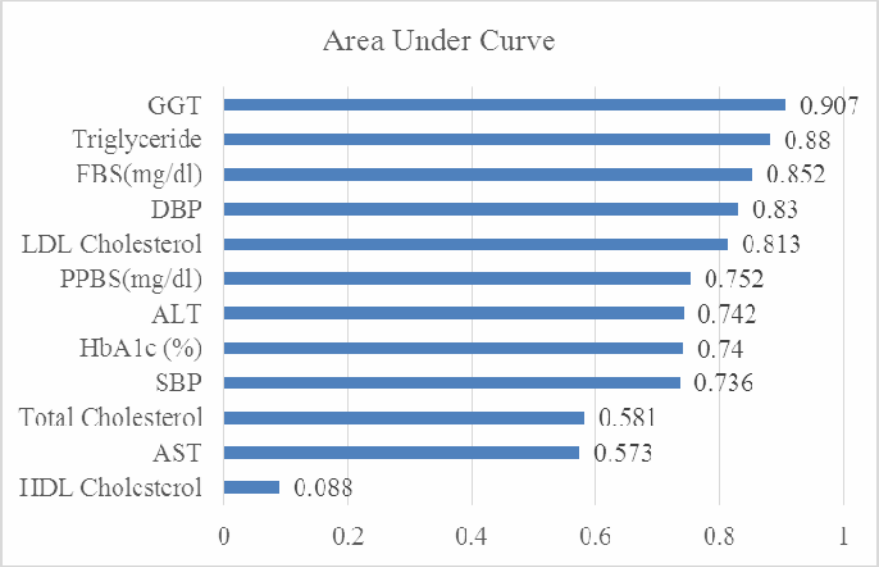


Graph16 : Bar diagram showing Thyroid and Renal Profile of subjects

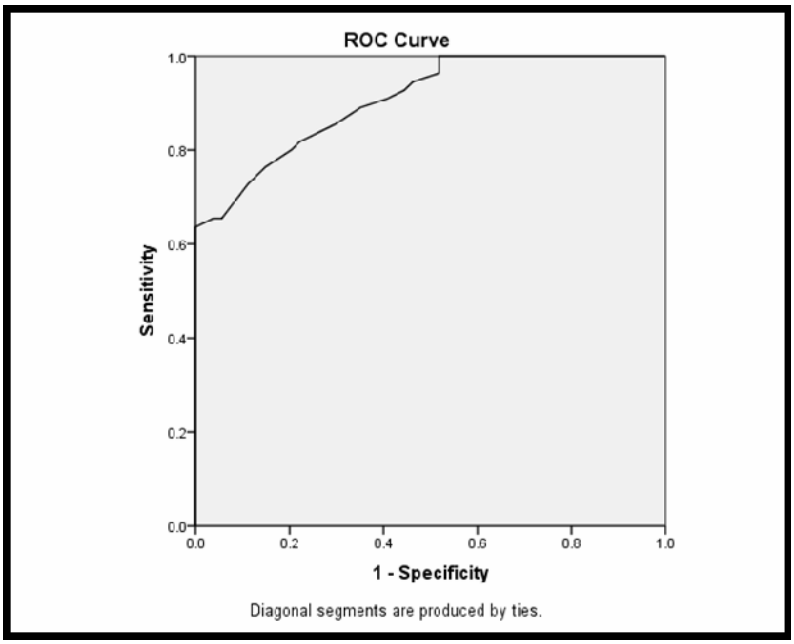
Table 17: Receiver operating characteristic (ROC) analysis of metabolic syndrome components and liver function tests (LFTs)

Test Result Variable(s)	Area Under the Curve	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
GGT	0.907	<0.0001*	0.855	0.959
AST	0.573	0.188	0.456	0.690
ALT	0.742	<0.0001*	0.642	0.842
SBP	0.736	<0.0001*	0.641	0.831
DBP	0.830	<0.0001*	0.751	0.909
FBS(mg/dl)	0.852	<0.0001*	0.781	0.923
PPBS(mg/dl)	0.752	<0.0001*	0.651	0.853
HbA1c (%)	0.740	<0.0001*	0.641	0.839
Total Cholesterol	0.581	0.142	0.467	0.696
Triglyceride	0.880	<0.0001*	0.806	0.954
HDL Cholesterol	0.088	<0.0001*	0.028	0.148
LDL Cholesterol	0.813	<0.0001*	0.722	0.905

Area under the curve for various markers for metabolic syndrome are shown in the above table. It was observed that among the Liver functions tests, Blood pressure, Glycemic profile and Lipid profile parameters. GGT (Gamma Glutamyl Transferase) has the highest Area under curve, hence suggesting that it is a better marker for metabolic syndrome. Second closest marker was Triglyceride, followed by FBS.



Graph 17 : Bar diagram showing Area Under Curve in Cases with respect to Various Metabolic syndrome parameters



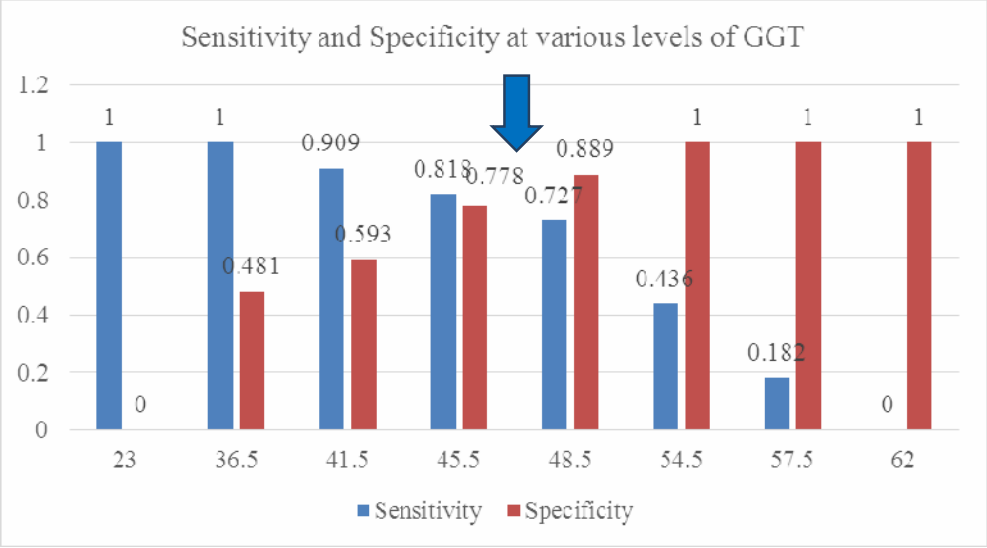
Graph 18 : ROC curve of GGT in Metabolic Syndrome Cases

ROC curve showing Area under the curve for GGT in Metabolic syndrome cases. It shows various points of sensitivity and specificity for GGT. Among all the parameters studied the ROC plot is close to the upper left corner for GGT. Hence it has the highest overall accuracy to predict metabolic syndrome.

Table 18: Sensitivity and specificity of diagnosing MS for some GGT values

GGT Value	Sensitivity	Specificity
23	1.000	0.000
36.5	1.000	0.481
41.5	0.909	0.593
45.5	0.818	0.778
48.5	0.727	0.889
54.5	0.436	1.000
57.5	0.182	1.000
62	0.000	1.000

Various sensitivity and specificity values are shown for different GGT levels. Levels of GGT at 23 has 1% sensitivity and 0% Specificity was notices and GGT value of 62 had 0% sensitivity and 100% specificity. GGT at 45.5 had higher sensitivity and specificity compared to other values. Hence the cut off value in the study was 45.5.

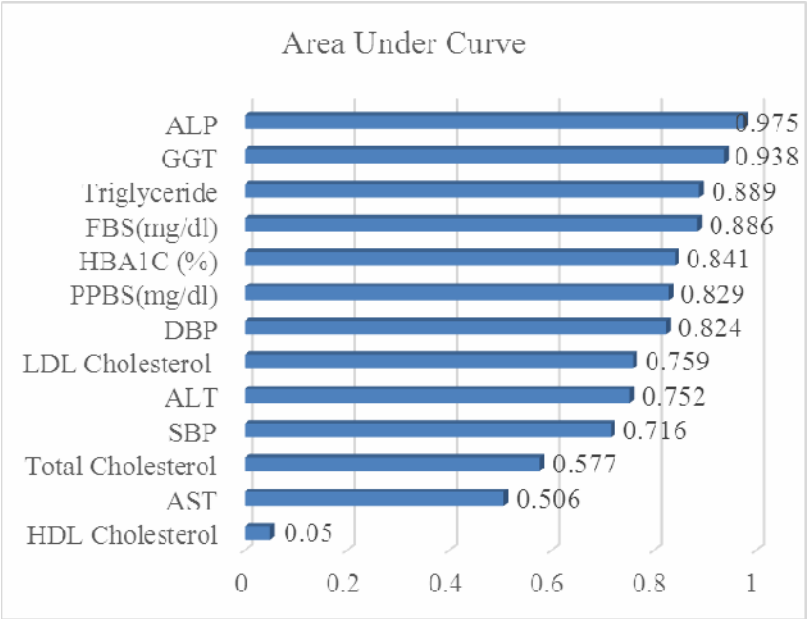


Graph 19 : Bar diagram showing Sensitivity and Specificity at various levels of GGT

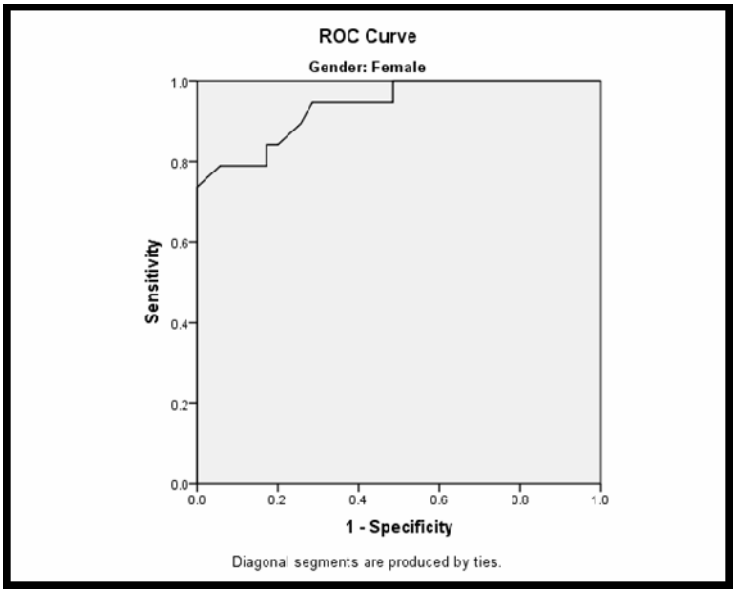
Table 19: Receiver operating characteristic (ROC) analysis of metabolic syndrome components and liver function tests (LFTs) in Females

Test Result Variable(s)	Area	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
GGT	0.938	<0.0001*	0.872	1.000
Triglyceride	0.889	<0.0001*	0.767	1.000
FBS(mg/dl)	0.886	<0.0001*	0.796	0.975
HBA1C(%)	0.841	<0.0001*	0.717	0.964
PPBS(mg/dl)	0.829	<0.0001*	0.687	0.970
DBP	0.824	<0.0001*	0.702	0.946
LDL Cholesterol	0.759	0.002*	0.596	0.923
ALT	0.752	0.002*	0.603	0.901
SBP	0.716	0.009*	0.561	0.871
Total Cholesterol	0.577	0.356	0.390	0.763
AST	0.506	0.942	0.304	0.708
HDL Cholesterol	0.050	<0.0001*	0.000	0.106

Area under the curve for various markers for metabolic syndrome in Females are shown in the above table. It was observed that among the Liver functions tests, Blood pressure, Glycemic profile and Lipid profile parameters, GGT (Gamma Glutamyl Transferase) has the highest Area under curve, hence suggesting that it is a better marker for metabolic syndrome in Females. Second closest marker was Triglyceride, followed by FBS.



Graph 20 : Bar diagram showing area under the curve for Cases with respect to Various Metabolic syndrome parameters in Females



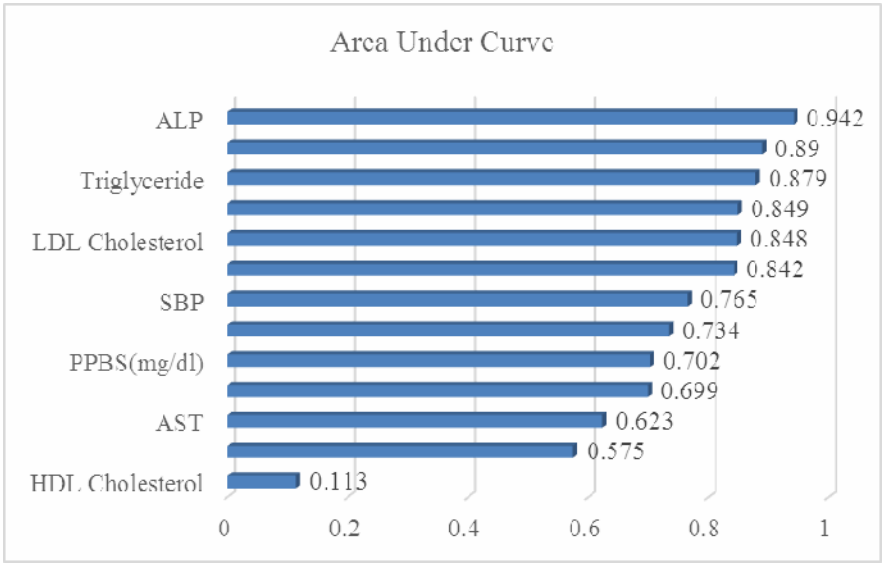
Graph 21 : ROC curve of GGT in Metabolic Syndrome Cases in Females

ROC curve showing Area under the curve for GGT in Female Metabolic syndrome cases. It shows various points of sensitivity and specificity for GGT among Females. Among all the parameters studied the ROC plot is close to the upper left corner for GGT. Hence it has the highest overall accuracy to predict metabolic syndrome in Females.

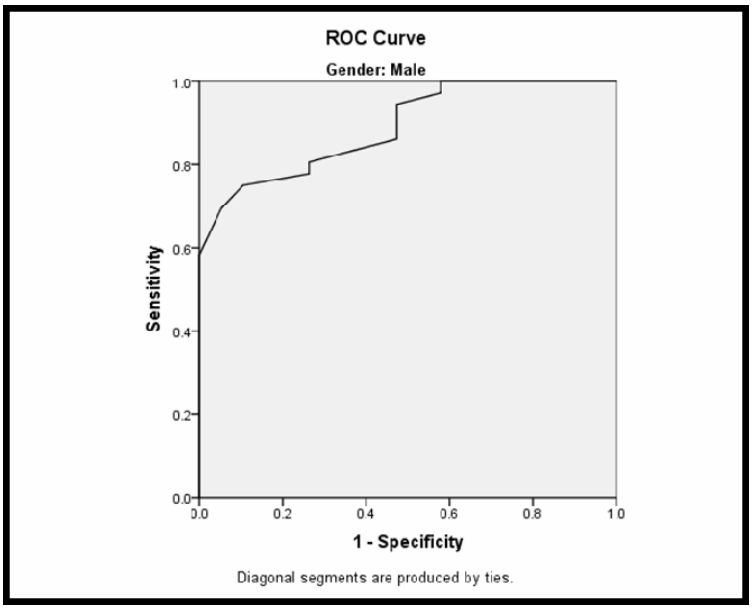
Table 20 : Receiver operating characteristic (ROC) analysis of metabolic syndrome components and liver function tests (LFTs) in Males

Test Result Variable(s)	Area	P value	95% Confidence Interval	
			Lower Bound	Upper Bound
GGT	0.890	<0.0001*	0.807	0.972
Triglyceride	0.879	<0.0001*	0.785	0.973
DBP	0.849	<0.0001*	0.750	0.949
LDL Cholesterol	0.848	<0.0001*	0.738	0.958
FBS(mg/dl)	0.842	<0.0001*	0.739	0.945
SBP	0.765	0.001*	0.643	0.887
ALT	0.734	0.005*	0.601	0.867
PPBS(mg/dl)	0.702	0.015*	0.564	0.839
HbA1c (%)	0.699	0.016*	0.563	0.835
AST	0.623	0.137	0.477	0.769
Total Cholesterol	0.575	0.362	0.426	0.724
HDL Cholesterol	0.113	<0.0001*	0.023	0.203

Area under the curve for various markers for metabolic syndrome among males are shown in the above table. It was observed that among the Liver functions tests, Blood pressure, Glycemic profile and Lipid profile parameters GGT (Gamma Glutamyl Transferase) has the highest Area under curve, hence suggesting that it is a better marker for metabolic syndrome in males. Second closest marker was Triglyceride, followed by DBP.



Graph 22 : Bar diagram showing area under the curve for Cases with respect to Various Metabolic syndrome parameters in Males



Graph 23 : ROC curve of GGT in Metabolic Syndrome Cases in Males

ROC curve showing Area under the curve for GGT in Males with Metabolic syndrome . It shows various points of sensitivity and specificity for GGT among Males. Among all the parameters studied the ROC plot is close to the upper left corner for GGT. Hence it has the highest overall accuracy to predict metabolic syndrome in males.

Table 21 : Logistic Regression to find the independent risk factor for increased GGT among the subjects

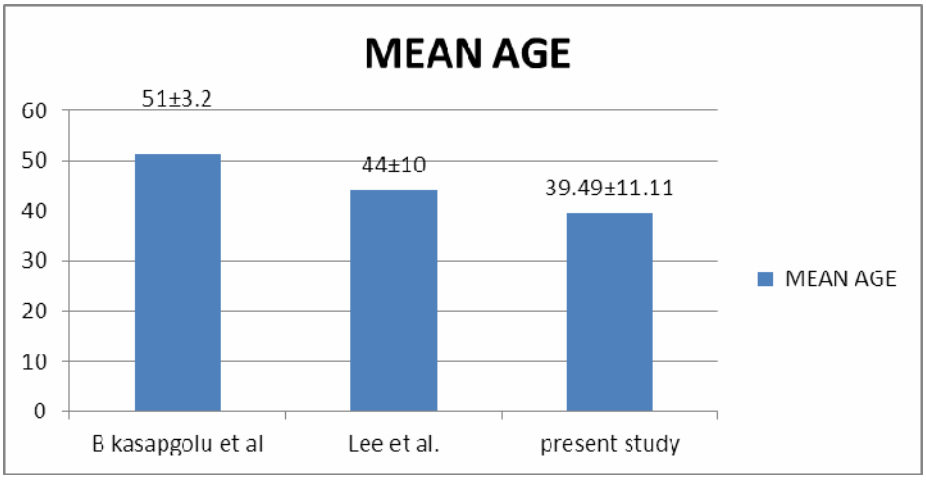
	Adjusted OR	P value	95% C.I.for EXP(B)	
			Lower	Upper
Age 31 to 40 years	0.376	0.348	0.049	2.901
Age 41 to 50 Years	0.481	0.467	0.067	3.458
Age > 50 Years	0.170	0.106	0.020	1.459
Male	0.455	0.228	0.126	1.637
SBP >130 mg/dl	378.072	0.998	0.000	-
DBP > 80 mg/dl	118.081	0.003*	5.281	2640.113
BMI	2.455	0.272	0.494	12.192
Waist Circumference > 90 in Males, > 80 in Females	0.148	0.036*	0.025	0.886
FBS > 100 mg/dl	2.085	0.368	0.421	10.323
PPBS > 140 mg/dl	0.377	0.255	0.070	2.023
HbA1c > 6.5%	0.543	0.393	0.134	2.204
TC > 200 mg/dl	0.392	0.500	0.026	5.966
TG > 150 mg/dl	0.710	0.788	0.059	8.596
HDL < 40 mg /dl	62.028	0.001*	4.987	771.511
LDL > 90 mg/dl	1.991	0.443	0.342	11.580

Logistic regression was carried out to find the independent risk factor for increase in GGT. It was observed that Increased Diastolic blood pressure, Increased Waist circumference and decreased HDL were independent risk factors for increase in GGT in the study.

DISCUSSION

The metabolic syndrome is a cluster of cardio-metabolic conditions and is now considered to be the driving force behind a CVD epidemic . A need for the early diagnosis of metabolic syndrome is essential to prevent and decrease morbidity and mortality due to cardiovascular disease ,but studies are lacking in Indian population. The role of GGT as a diagnostic marker of metabolic syndrome is critically evaluated in this study .

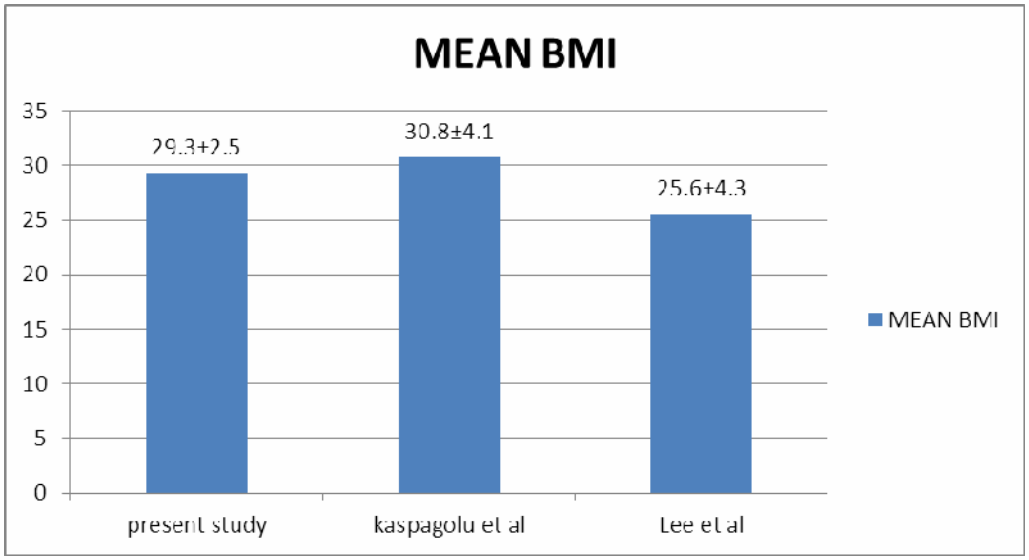
In our study , 110 subjects were recruited comprising 55 cases of metabolic syndrome and 55 age and sex matched controls . The mean age in the study group was 39.49±11.11 and 43.96±10.17 years in the control group . There was no significant difference in age distribution between two groups . Majority of subjects in both groups were clustered between third and fourth decade of life with 34.5% belonging to this category . There was no significant difference in gender between both groups . In a study done by B Kasapgolu et al[7]. the mean age was 51.3±3.2 and in other study by Lee et al[84]. the mean age in the study group is 44±10.



Graph 24 : COMPARISION OF MEAN AGE WITH OTHER STUDY.

The mean BMI was 29.30±2.57 in the study group and 24.16±0.90 in the control group. The mean waist-hip ratio is 1.04±0.07 in the study group and 0.73±0.05 in controls .The mean waist circumference is 97.62±5.31 and 78.35±3.02 in cases and controls. In a study done by B Kasapgolu et al[7] almost similar results were obtained . The mean waist circumference and BMI are 104.1±9.8 and 30.8±4.1 . In Framingham heart study by Lee et al[84] mean BMI was 25.6±4.3 . The above observations indicate obesity and increased central adiposity are pivotal to pathogenesis of metabolic syndrome.

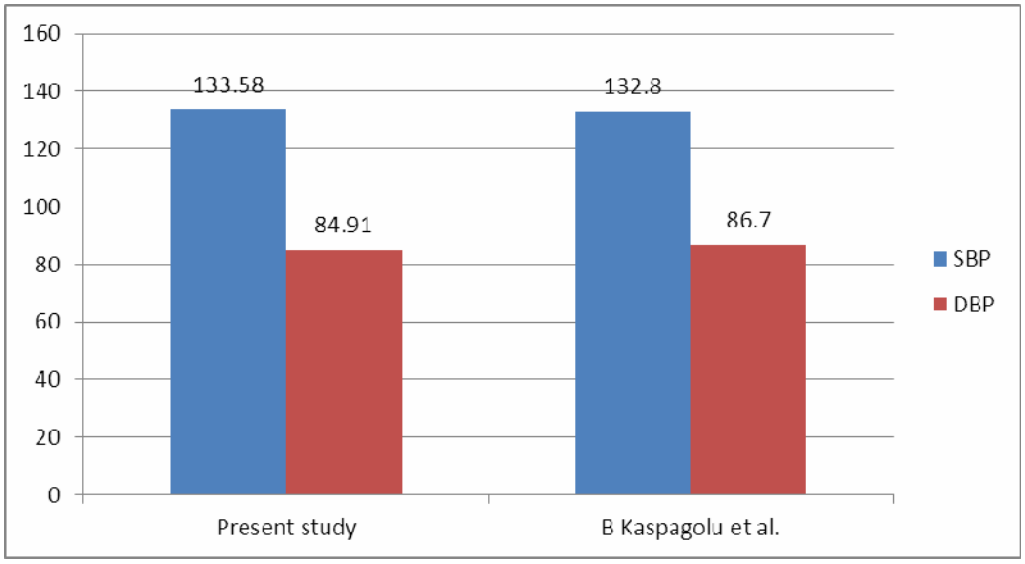
Graph -25 : COMPARISION OF MEAN BMI WITH OTHER STUDY



The mean duration of hypertension was 4.23±2.82 years in the study group . The mean SBP in cases was 133.58±15.76 mmHg and 120.26±7.55 mm Hg. The mean DBP was 84.91±8.78 mmHg and 74.44±5.54 mm Hg in cases and controls groups. A total of 31 out of 55 patients satisfied the IDF criteria of SBP> 130 mmHg . Around 47.3% of cases have history of hypertension . This results suggest elevated systolic blood pressure is an important contributing factor for metabolic syndrome.

In the reference study done by B Kasapgolu et al[7]. and Lee et al[84]. similar results were found .SBP and DBP being 138.2±11.7 and 86.7±7.2mm Hg in a study by B Kasapgolu et al[7]. and 122±16 and 76±10 mm Hg in a study by Lee et al [84].the mean SBP value being slightly lower than the present study . In another study by AO Rantala et al[81]. higher values were observed with SBP being 160±20.3 and DBP being 98.2±10.2 mm Hg , being significantly different from our study

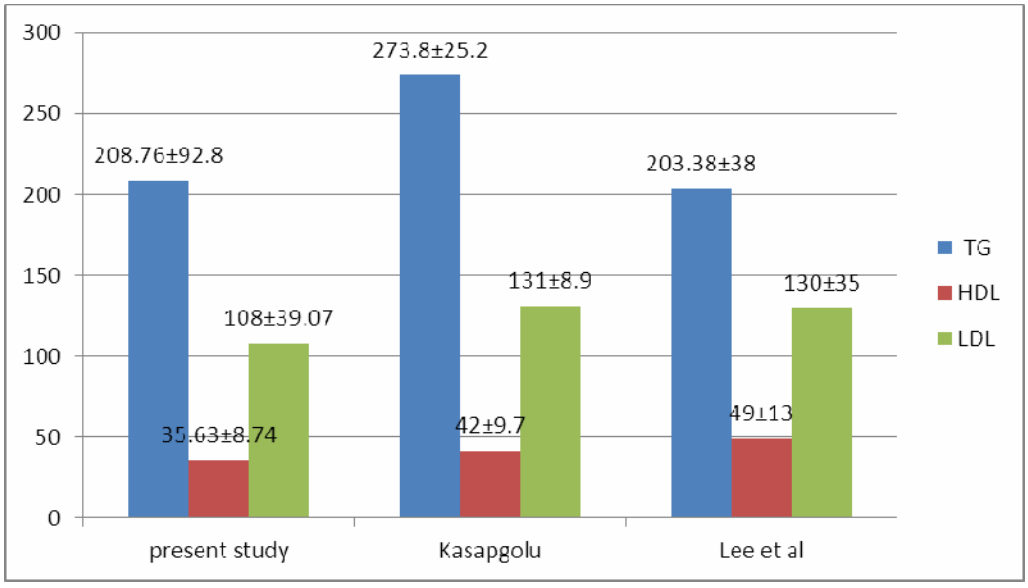
Graph 26 :COMPARISION OF MEAN SBP AND DBP WITH OTHER STUDIES



The mean duration of dyslipidemia was 3.83±2.71 years in the study group . The mean total cholesterol is 171.92±48 , triglycerides 208.76±92.85 , HDL 35.63 ±8.74 and LDL being 108.84±39.07 . In our study there is significant difference in Mean TG, HDL and LDL cholesterol between two groups. I.e. TG & LDL was increased and HDL was decreased significantly in Cases. No significant difference was noticed between two groups for Total cholesterol. Dyslipidemia history was present in 52.7% of cases .

The values in our study with respect to lipid profile were lower than the study by B Kasapgolu et al [7.] where in mean TG was 273.8±25.2 , LDL 131.4±8.9 and HDL being 42±9[7] . In a study by Lee et al[84]. mean cholesterol was 203±38 , TG 205±80 , HDL 49±13 and LDL being 130±35 .where in values of total cholesterol , HDL and LDL were higher than the present study. This difference can be due to variations in diet and familial metabolic parameters in particular geographic distributions . Hypertriglyceridemia and high LDL level was found in maximum number of cases in study group and levels of HDL were found to be low . A similar finding was noted in both the reference studies .

Graph 27 : COMPARISION OF MEAN TG, HDL AND LDL WITH THE OTHER STUDIES



The mean duration of diabetes was 5.68±3.58 in the study group . 56.4% of study group and 22.2% of controls have history of diabetes in the past .In the present study , mean FPG is 142.30±59.98 , PPBS 181.87±65.02 , HBA1C 8.37±2.53 in cases and 88.31±10.32 , 131.26±13.49 and 6.20±0.57 in the control group. Glycemic parameters in cases were higher than controls suggesting high

prevalence of type 2 diabetes in patients with metabolic syndrome. In studies by B Kasapgolu et al[7]. mean FBS was 107±11.7 mg/dl and in study by Lee et al[84]. also mean FBS was 144.06 ± 51.70, which is comparable with our study and infact shows to be quite significant

With respect to burden of cardiovascular disease , 7 out of 55 patients i.e 12.7% of the study population were suffering from cardiovascular disease .In all these patients higher levels of GGT were noted i.e values are higher compared to the subjects without cardiovascular disease , suggesting a direct correlation of GGT levels with increased cardiovascular risk . In Framingham Heart study by Lee et al[84]. In metabolic syndrome group higher GGT levels associated were cross-sectionally related to CVD risk and higher GGT levels predicted CVD , mortality and metabolic syndrome. This study also stated GGT , a routinely available metabolic marker and indicative of oxidative stress, as a significant predictor of CVD and mortality events . In the study by B.Kasapgolu et al[7]. a high GGT was positively associated with CVD prevalence in MS group, compared to low GGT group independent of age and sex . Thus metabolic syndrome is accompanied by an increase in relative risk for ASCVD[85-87] in populations at risk. The risk is essentially doubled in prospective epidemiologic studies . In a study by Lakka et al[86]. metabolic syndrome was associated with cardiovascular disease and all- cause mortality even in the absence of base line CVD and diabetes . Most individuals with metabolic syndrome can be considered to be at a higher life time risk for ASCVD , but this entity alone is inadequate to guide clinical management for short-term risk reductions . Presence of significant subclinical atherosclerosis can identify the high risk status besides

the metabolic disorder . So early identification , treatment and prevention of metabolic syndrome is essential .

Several studies have shown association of GGT with metabolic syndrome and cardiovascular disease risk factors. GGT , a cell surface protein which contributes to extracellular glutathione catabolism is derived predominantly by liver and is carried primarily with lipoproteins and albumin. In Framingham heart study by Lee et al[84]. in 3451 participants , increased serum GGT predicted the onset of metabolic syndrome and the occurrence of CVD and death . an increase in CVD incidence by 67% is seen in highest GGT quartile . After adjustment for traditional risk factors and CRP , the association of GGT concentrations with CVD and mortality remained significant . Devers et al[88]. also suggested association of higher serum GGT with development of CVD risk factors including diabetes , hypertension and metabolic syndrome. Ruttmann et al[89]. showed that GGT activity is independently associated with cardiovascular mortality. In a study by Rantala et al[81]. GGT co-related significantly with the components of metabolic syndrome after adjustment for age , body mass index , gender and alcohol consumption. As per B kasapoglu et al[7] increase in GGT is positively correlated with increased MS prevalence and is strongly associated with IDF diagnostic components of metabolic syndrome. This study also showed positive association with CVD prevalence in MS group with high GGT compared to the low GGT group .

One hypothesis in favour of GGT levels and CVD is that GGT itself is proatherogenic and it occurs in atherosclerotic plaques .through influx of lipoproteins GGT is carried into plaques and cysteinyl-glyceine produced by

hydrolysis of GSH generate superoxide anion radicals through its interaction with free iron which can promote atherogenesis via LDL oxidation.

As per Lee et al[84] elevations of GGT are a marker for the presence of the metabolic syndrome because liver , which is the primary source for circulating GGT is the key target organ for development of metabolic syndrome .

In the present study fatty liver was present in 32.7% of the study group , among which 16 individuals have raised GGT values . An elevation of GGT was closely related to hepatic steatosis[90] as it is strongly associated with the metabolic syndrome[91]. According to Ortega et al[92]. fatty liver causes hepatocellular damage that stimulate synthesis of GGT and also excess fat in the liver enhances oxidative stress , leading to over consumption of GSH with a compensatory increase in GGT synthesis but elevations of GGT alone are not the only biomarker of hepatic steatosis. Elevated transaminases are also associated with metabolic syndrome and risk of CVD . In the present study all major components of metabolic syndrome are linked to elevations of serum GGT and higher GGT levels occurred in obese persons , particularly those with abdominal obesity and are accompanied by more insulin resistance and greater risk of developing type 2 diabetes and hypertension. These findings are similar to that in D.E.S.I.R cohort study by Andre et al[93].

But GGT levels did not correlate with cerebrovascular disease which is against the study done by Wannamethee et al[94]. where elevated GGT is associated with significantly increased risk of stroke , fatal CHD events and CVD mortality independent of established CVD risk factors.

In the study of Khubchandani et al. [95] on 25 diabetic subjects compared with 25 normal individuals , serum GGT levels were significantly higher in diabetics in comparision of normal individuals . It can be due to oxidative stress in diabetics which leads to increase in serum GGT level. In our study around 54.9% of diabetics i.e around 28 individuals have raised GGT levels.

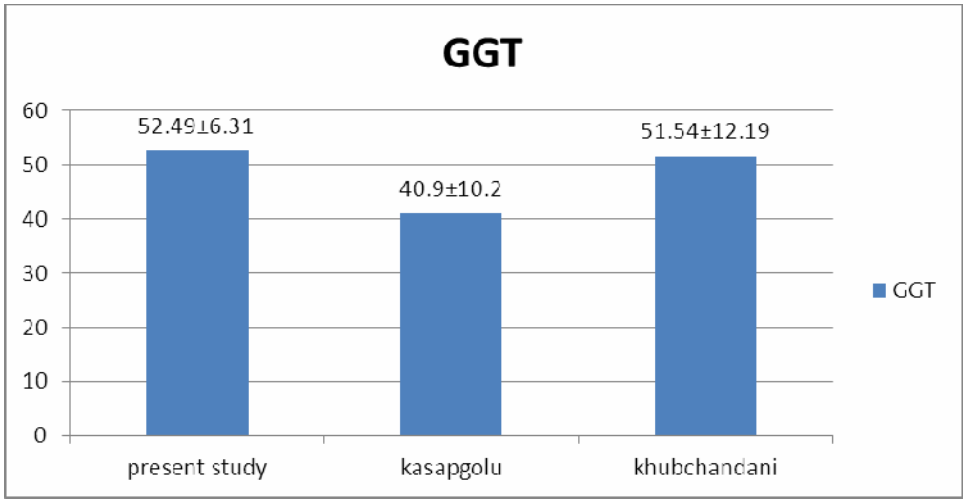
Validity measures were computed taking reference values of GGT for sensitivity and specificity .In our study values are shown for different GGT levels. The Levels of GGT at 23 has 1% sensitivity and 0% Specificity and GGT value of 62 had 0% sensitivity and 100% specificity. GGT at 45.5 has higher sensitivity and specificity compared to other values .Hence the cut-off value of GGT in our study is 45.5.

Receiver operating characterstic (ROC) analysis of components of metabolic syndrome and liver function tests were performed and among all the parameters in the curve GGT has highest area under curve suggesting it as a better marker for metabolic syndrome followed by triglycerides and FBS .

In females , among all the parameters studied the ROC plot is close to the upper left corner for GGT and has the highest overall accuracy to predict metabolic syndrome . Even in males among all parameters studied GGT has highest overall accuracy to predict metabolic syndrome . These results suggests that GGT values are predictive of metabolic syndrome.

In this study mean value of GGT was 52.49±6.31 , and in a study by B Kasapgolu et al[7]. mean GGT is 40.9±10.2 and mean GGT being 51.54±12.19 , in study by Khubchandani et al[95.]

Graph 28 : COMPARISION OF MEAN GGT WITH OTHER STUDY



With respect to other liver function tests , mean AST in the study group was 31.80±17.37 and ALT 37.71±13.52 and 25.59±5.23 and 28.50±5.03 in the control group. The levels of ALP are 167.42±66.34 in the study group and 82.61±19.02 in the control group . indicating higher levels of transaminases in patients with metabolic syndrome group when compared to controls even though in the normal range . These results are similar to that of Lee et al . and Kasapoglu et al[7]. where in mean values of AST and ALT were 21.1±11.7 , 25.6±17.7 and 21.1±9.1 , 26.8±9.3 in the study group and 18.1±7.8 , 19.4±8.7 and 17.7±6.3, 19.2±4.5 in the control group.

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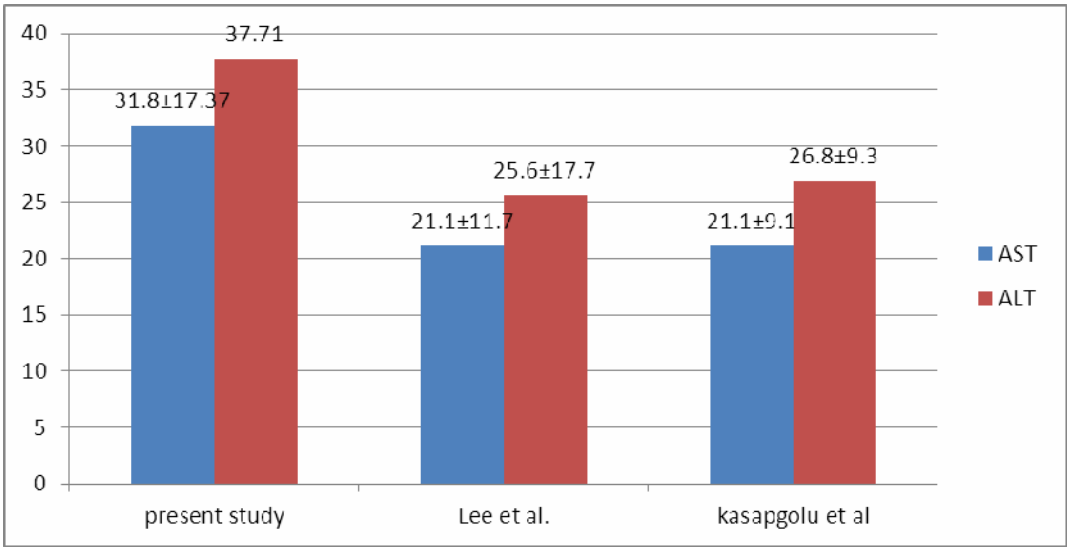

Graph 29 : COMPARISION OF MEAN AST AND ALT WITH OTHER STUDIES

In a study of Balogun et al[96]. the GGT and ALT values were significantly higher (52.9IU/I and 24.3 U/I) in the diabetic group compared to the controls (34.4IU/I and 9.2 IU/I) and the predominant LFT abnormality in diabetic group was found to be isolated elevation of GGT .

GGT is an important predictor for incident type 2 diabetes in men and women as per C.Meisinger et al[97] . and association being independent of other predictors of type 2 diabetes including alcohol and BMI .

Bruckert et al[98]. analyzed the potential relationships between serum levels of AST , ALT and GGT and cardiovascular and metabolic risk factors and concluded that cardiovascular and metabolic features characterizing the plurimetabolic syndrome including serum uric acid levels ,are associated with significant elevation of hepatic enzymes.

In the study done by Onat et al[99].circulating GGT and transaminases activities are elevated in patients with metabolic syndrome.

Nanniperi et al[100]. revealed elevated ALT and AST are positively associated with obesity and inversely associated with physical activity and high ALT and AST was associated with higher prevalence of metabolic syndrome and T2DM .

Wannamethee et al[94]. proposed that elevated levels of ALT and GGT within the normal ranges are independent predictors for T2DM and elevated GGT is associated with fourfold increase in risk compared to threefold increase for elevated ALT.

Rantala et al[81]. concluded that there is significant association between GGT and components of metabolic syndrome after adjustment for age , BMI and alcohol consumption. This population based study assessed the relationship

between GGT and the concept of 'metabolic syndrome' or the 'insulin resistance syndrome'.

In study of Sakugawa et al[101]. the serum GGT level was found to be correlated with components of Met S . This study also correlated serum GGT levels with metabolic syndrome (hypertension, diabetes mellitus and dyslipidemia) and risk factors for metabolic syndrome .In this srudy GGT elevation was independently associated with hypertriglyceridemia and diabetes mellitus but not associated with ultrasonographic evidence of fatty liver . 30 % of the study group had features of NAFLD on ultrasound imaging in this study indicating higher prevalence of NAFLD in MS patients contributing to its pathogenesis .

In KERCADRS , a prospective cohort study by Yousefzadeh et al[102]. area under curve for GGT is 0.722 and in ROC curve analysis the optimum cut-off value for GGT is 20.15IU with sensitivity and specificity of 71.6% and 66.1%. being a sensitive indicator for diagnosing and predicting MS . In the present study area under curve for GGT is 0.907 and in ROC curve GGT at 45.5 has higher sensitivity and specificity.

In the present study , it was found that GGT levels were in the upper limit of normal or higher in patients with metabolic syndrome cases compared to age and sex matched controls. Logistic regression was carried out to find the independent risk for increase in GGT , increase waist circumference and decrease in HDL were independent risk factors for increase in GGT in the study .GGT levels were higher in all patients suffering from CVD compared to subjects without CVD . As GGT has highest area under ROC curve and as it has overall highest accuracy to predict metabolic syndrome patients compared to other parameters it is better marker for metabolic syndrome .

CONCLUSION

This study has critically evaluated the utility of GGT as a diagnostic marker for metabolic syndrome , with good results . An elevated level of GGT was found to be associated with metabolic syndrome and is a strong predictor of cardiovascular risk .GGT correlated well with all the parameters of MS especially with hypertriglyceridemia with which it was the highest . GGT was found to be significantly higher in patients with cardiovascular disease .It was also noted that there was a clustering of patients in the range of upper limit of normal values for GGT indicating the possible need for considering even such values in the context of metabolic syndrome and CVD risk. Considering the CVD risk primary prevention may be emphasized in patients of metabolic syndrome with high GGT values .Hence GGT particularly has a position in algorithms for the evaluation of metabolic syndrome and CVD assesement

SUMMARY

In this dissertation under taken in R.L Jalappa hospital , the primary objective was to assess the utility of Gamma Glutamyl Transferase as a diagnostic marker of metabolic syndrome and compute its sensitivity and specificity .

One Hundred and Ten (110) patients were recruited including 55 cases of metabolic syndrome selected as per IDF criteria for MS and 55 age and sex matched controls. GGT levels were obtained for all the patients along with other metabolic parameters and all patients were assessed for preexisting cardiovascular disease.

All the data obtained was entered into Microsoft excel sheet and analysis was done using SPSS22 version software . ROC curve was plotted to find the area under curve and sensitivity and specificity of GGT in diagnosis of Metabolic syndrome .

In the study group Mean Age is 39.49±11.11 and there were 19 females and 36 males of metabolic syndrome .

Mean duration of diabetes was 5.68±3.58 and mean duration of HTN was 3.87±2.71 among the study group. Mean SBP and DBP was 133.58±15.76 and 84.91±8.77 in the study group. History of diabetes was present in 56.4% and 47.3% has history of hypertension and 52.7% has past history of dyslipidemia.

About 54.9% of diabetics and 49% of hypertensives and 56.9% of individuals with dyslipidemia have raised GGT values .

Around 42.7% have evidence of Fatty liver on ultrasound . About 12.7% has history of cardiovascular disease and 3.7% has history of cerebrovascular accident .

Mean BMI was 29.30±2.57 , waist circumference was 97.62±5.31 , Hip circumference was 94.29±6.70 and waist-hip ratio was 1.04±0.07 .

Mean FBS , PPBS and HBA1C was 142.30±59.98 , 181.87±65.02 and 8.37±2.53 in the study group and all the glycemic parameters are higher in metabolic syndrome group.

Mean TG , HDL and LDL cholesterol was 208.76±92.85 , 35.63±8.74 and 108.84±39.07 .

In the

study mean GGT was 51.89±6.31. Sensitivity and specificity values were calculated for different values of GGT and highest sensitivity and specificity was observed at GGT values of 45.5 which is taken as a cut-off value .

ROC curve was plotted for various parameters of metabolic syndrome and among all the parameters GGT has highest area under curve proving it as a better marker for metabolic syndrome.

Logistic regression was carried out to find the independent risk factors for increase in GGT and it was observed that increased diastolic blood pressure , waist circumference and decreased HDL cholesterol were independent risk factors for increase in GGT .

Considering all the observations made in the study Gamma glutamyl transferase which is simple and easily available Liver function test has potential

to be considered in algorithms for evaluation of patients with Metabolic syndrome.

Hence higher GGT values in otherwise healthy individuals should alert the physicians to evaluate those patients to prevent complications in future years .

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ANNEXURES

PROFORMA

Case No :

Name: Mr/Mrs OP No:

Age: IP No:

Gender: Ward:

Date: Occupation:

Weight:

Address :

Chief history :

History of presenting illness :

PAST HISTORY:

Hypertension yes/no if yes , duration:

Diabetes yes/no if yes , duration:

CV diseases yes/no if yes , duration:

CVAccident yes/no if yes , duration:

Liver diseases yes/no if yes , duration:

Drug ingestion yes/no if yes , duration & details:

Others :

FAMILY HISTORY:

Diabetes : yes/no if yes , duration:

Hypertension : yes/no if yes , duration:

OCCUPATIONAL HISTORY:

PERSONAL HISTORY:

Economic status :

Diet: vegetarian / mixed

Smoking : yes/no if yes, duration:

Alcohol : yes/no if yes , duration:

MENSTRUAL HISTORY : Regular/irregular/not applicable.

GENERAL PHYSICAL EXAMINATION:

Ht: Wt: BMI:

Waist circumference :

Hip circumference :

Waist: Hip ratio:

Blood pressure : Pulse rate :

SYSTEMIC EXAMINATION :

CVS :

RS :

CNS :

PER ABDOMEN :

INVESTIGATIONS :

BLOOD :

FBS: mg/dl

PPBS : mg/dl

HBA1c: %

LIPID PROFILE

1.TOTAL CHOLESTEROL: mg/dl

2.TRIGLYCERIDES: mg/dl

3.HDLc: mg/dl

4.LDL: mg/dl

LIVER FUNCTION TESTS :

1 . AST –

2. ALT-

3. ALP-

4. GGT-

USG ABDOMEN –

TSH –

Renal function tests :

1. Blood urea
2. Serum creatinine

INFORMED CONSENT FORM

STUDY OF GAMMA GLUTAMYL TRANSFERASE AS A MARKER IN METABOLIC SYNDROME.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1.

2.

3.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____(Day/month/year)

ಮಾಹಿತಿಯುಕ್ತ ಸಮ್ಮತಿಯ ನಮೂನೆ

ಸಮೂಹ ಕಠೋರತೆಯ ಅಂಕವಿಧಾನಗಳು ಪೂರ್ವ ಸೂಚಕ ಮೌಲ್ಯದ ಹೋಲಿಕೆ

ನ್ಯುಮೋನಿಯಾ ಸ್ವಾಧೀನಪಡಿಸಿಕೊಂಡಿತು .

ಸಮುದಾಯಸ್ವಾಧೀನಪಡಿಸಿಕೊಂಡಿತುನ್ಯುಮೋನಿಯಾ (ಸಿಎಪಿ) ಅಭಿವೃದ್ಧಿಶೀಲದೇಶಗಳಲ್ಲಿ 30% ರಿಂದ 20 % ರಷ್ಟುಪ್ರಕರಣಗಳಲ್ಲಿಸಾಮಾನ್ಯವ್ಯಾಧಿ . ಇದು ಸೂಕ್ತ ಪೂರ್ವ ಸೂಚಕ ಅಂಶಗಳಲ್ಲಿ ಜ್ಞಾನ ತೀವ್ರ ನಿಗಾ ಚಿಕಿತ್ಸೆಯ ಅಗತ್ಯ ಹೆಚ್ಚಿನ ಅಪಾಯ ರೋಗಿಗಳ ಆರಂಭಿಕ ಗುರುತಿನ ಉಪಯುಕ್ತ ಇರಬ ಹುದುಭರವಸೆಯಿದೆ . ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪುತ್ತೀರಿವೇಳೆ ನೀವು ಅಥವಾ ನೀವು ಅಥವಾ ಎರಡೂ ಜವಾಬ್ದಾರಿ ವ್ಯಕ್ತಿಯಿಂ ದಮಾಹಿತಿ (ಪ್ರತಿ proforma ಮಾಹಿತಿ) ಸಂಗ್ರಹಿಸುತ್ತದೆ.ನಿಮ್ಮ ಆಸ್ಪತ್ರೆ ದಾಖಲೆಯಿಂದ ಚಿಕಿತ್ಸೆ ಮತ್ತು ಸೂಕ್ತವಿವರಗಳನ್ನು ಸಂಗ್ರಹಿಸುತ್ತದೆ ಸಂಗ್ರಹಿಸಿದ ಈ ಮಾಹಿತಿ ಮಾತ್ರ ಪ್ರೌಢಪ್ರ ಬಂಧದಲ್ಲಿ ಮತ್ತು ಪ್ರಕಟಣೆ ಬಳಸಲಾಗುತ್ತದೆ . ಈ ಅಧ್ಯಯನ ವುಸಾಂಸ್ಥಿಕನೈ ತಿಕಸ ಮಿತಿಯು ವಿಮರ್ಶಿಸುತ್ತದೆಮಾಡಲಾಗಿದೆ . ನೀವು ಭಾಗವಹಿಸಲು ಇಚ್ಛಿಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುತ್ತಾನೆ ಆರೈಕೆ ಬದಲಾಗುವುದಿಲ್ಲ . ನೀವು ಸ್ವಯಂ ಪ್ರೇರಣೆಯಿಂದ ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿಕೊಂಡಲ್ಲಿ ಹೆಬ್ಬೆಟ್ಟಿನ ಗುರುತು ಸೈನ್ / ಒದಗಿಸುವಅಗತ್ಯವಿದೆ

ನಾನು ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನ ದಿಂದಹಿಂತೆಗೆದುಕೊಳ್ಳುವಂತೆ ಮತ್ತು ಈ ನನ್ನ ಮುಂದಿನ ಆರೈಕೆ ಬದಲಾಗುವುದಿಲ್ಲ ಉಚಿತ ಉಳಿಯಲು ಎಂದು ಅರ್ಥ . ನಾನು ಓದಲು ಅಥವಾನನಗೆ ಓದಲು ಮಾಡಲಾಗಿದೆ ಮತ್ತು ಅಧ್ಯಯನ ದಉದ್ದೇಶ , ಬಳಸಲಾಗುವವಿಧಾನ , ಅಧ್ಯಯನ ಮತ್ತು ಅಧ್ಯಯನ ದಸಮಯದಲ್ಲಿ ಸಂಗ್ರಹಿಸಿದ ಮತ್ತು ಬಹಿರಂಗ ನಡೆಯಲಿದೆ ಮಾಹಿತಿಯನ್ನು ಪ್ರಕೃತಿಯಲ್ಲಿ ನನ್ನ ಒಳಗೊಳ್ಳುವಿಕೆ ಸಂಬಂಧಿಸಿದ ಅಪಾಯ ಮತ್ತು ಲಾಭಗಳನ್ನು ಅರ್ಥ . ನಾನು ಅಧ್ಯಯನ ಮತ್ತು ನನ್ನ ಪ್ರಶ್ನೆಗಳಿಗೆ ವಿವಿಧ ಅಂಶಗಳನ್ನು ನನ್ನ ತೃಪ್ತಿ ಉತ್ತರಿಸುವ ಬಗ್ಗೆ ನನ್ನ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಅವಕಾಶಹೊಂದಿದ್ದರು . ನಾನು , ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಮತ್ತು ಪ್ರೌಢಪ್ರ ಬಂಧದಲ್ಲಿ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯ ಸಂಗ್ರಹಣೆಮತ್ತು ಡಿಸ್ಕ್ಲೋಸರ್ ಅಧಿಕೃತಗೊಳಿಸಲು ಒಪ್ಪುತ್ತೀರಿ ರುಜುಮಾಡಿರುವ

ವಿಷಯದ ಹೆಸರು

KEY TO MASTER CHART

BMI- Body mass index

HTN-Hypertension

DM-Diabetes mellitus

SBP-Systolic blood pressure

DBP- Diastolic blood pressure

BP- Blood pressure

CHOL-Cholestrol

TGL-Triglycerides

USG- Ultrasonography

MASTER CHART

s.no	Name	age(yrs)	sex	hosp.no	B.P(mm/hg)	SBP	DBP	height(mts)	weight(kgs)	BMI(kg/m2)	waist circumference	hip cicumference (cms)	waist/hip ratio	alcohol	diabetes	HTN	dyslipidemia	FBS(mg/dl)	PPBS(mg/dl)	HBA1C(%)	total CHOL.	TGL	HDL CHOL	LDL CHOL	GGT(µ/L)	AST	ALT	ALP	USG(FATTY LIVER)	TSH	S.CREAT	BU	CVD	CVA
1	ashwath narayana	60	M	204291	160/100	160	100	1.7	85	29.41	106	100	1.06	NO	0	2	5	86	124	6.2	104	407	40.7	38.1	56	52	48	302	YES	2.2	0.6	16	NO	NO
2	sheshadri	36	M	204297	120/86	120	86	1.79	88	27.46	94	92	1.02	NO	0	0	1	92	118	5.6	200	211	35.2	100	58	48	52	98	NO	3.8	1.1	20	NO	NO
3	gayathri	40	F	204254	116/84	116	84	1.61	82	32.03	92	86	1.06	NO	1	0	1	152	182	11.6	144.5	140	27.9	89.7	45	24	32	112	NO	4.1	1.2	24	NO	NO
4	prathima	33	F	204261	150/80	150	80	1.67	80	31.25	95	94	1.01	NO	2	1	1	211.9	182	7.8	187.3	284	34.1	109.6	54	64	62	148	yes	3.3	0.8	20	NO	NO
5	ashok	27	M	204310	120/80	120	80	1.67	84	30.11	86	92	0.93	NO	0	0	0	90	90	5.8	200.9	212	35.2	133.8	49	18	16	124	yes	2.28	1.1	14	NO	NO
6	bharathamma	37	F	201055	140/86	140	86	1.64	85	31.6	88	96	0.91	NO	2	3	3	133.6	160	11.8	163.2	141	44.3	100	53	28	32	89	no	3.5	1.6	21	NO	NO
7	srinivas	25	M	204327	128/86	128	86	1.73	88	29.4	108	96	1.13	NO	0	0	0	86	121	6.1	241	160	40.5	170	57	40	24	111	no	4.2	0.7	23	NO	NO
8	lakshmi	35	F	203054	140/90	140	90	1.7	84	29.06	96	88	1.09	NO	0	1	1	92	141	7.1	84.7	158	17.3	51.4	44	54	43	152	no	2.2	0.9	27	NO	NO
9	venkata chalapati	43	M	204332	120/70	120	70	1.61	81	31.24	98	92	1.07	NO	6	0	0	262.7	310	9.2	109.8	184	34.6	51.7	39	32	40	167	no	3.4	1	29	NO	NO
10	muni raja	30	M	204334	130/90	130	90	1.68	79	27.99	93	94	0.98	NO	0	0	0	92	138	6.1	158.1	190	38.5	95.8	54	10	12	145	yes	3.22	1.4	24	NO	NO
11	balakrishna	60	M	204256	150/86	150	86	1.76	89	28.73	106	100	1.06	NO	10	5	5	146	190	8.3	199.7	211.8	35.5	131.1	53	48	46	162	yes	3.3	1.8	12	NO	NO
12	rathnaiah	46	M	204281	140/90	140	90	1.49	82	36.93	98	94	1.04	NO	6	4	4	138	194	10.4	159.5	90.1	43.9	99.7	46	33	43	206	no	2.8	0.3	18	NO	NO
13	vasantha	32	F	204271	120/80	120	80	1.7	78	26.98	98	90	1.08	NO	0	0	0	87	146	7.1	138.4	106.4	31.2	82.6	51	16	18	122	no	1.9	0.9	27	NO	NO
14	srirama reddy	52	M	204260	150/80	150	80	1.73	86	28.73	104	100	1.04	NO	10	5	5	268	321	11.1	127.7	422	33	171	49	28	32	88	yes	2.85	1.9	24	YES	NO
15	amarnatha	36	M	201049	126/84	126	84	1.73	85	28.4	102	96	1.06	NO	1	0	1	172	284	9.1	159.5	90	29.9	99.7	57	24	40	96	no	1.6	1.4	19	NO	NO
16	raja reddy	31	M	201064	130/90	130	90	1.7	86	19.75	98	100	0.98	NO	1	0	1	198	246	8.7	140	109	43	21.8	49	32	12	140	yes	2.78	1.9	29	NO	NO
17	nagaraj reddy	27	M	201050	110/70	110	70	1.76	87	28.08	94	82	1.15	NO	0	0	0	72	110	7.6	89.7	74	64	55	58	17	15	156	no	2.39	0.8	20	NO	NO
18	venkataronamma	28	F	199051	130/90	130	90	1.79	82	25.6	106	100	1.06	NO	0	0	0	101	148	7.1	177	321	24	64.7	58	58	72	188	no	1.8	0.4	18	NO	NO
19	suresh babu	29	M	201171	140/90	140	90	1.64	83	30.85	98	86	1.14	NO	2	0	0	142	209	5.1	135	208	33.5	94.5	59	24	34	124	yes	4.2	1.1	14	NO	NO
20	bayanna	57	M	201232	110/70	110	70	1.7	86	29.75	100	101	0.99	NO	10	0	0	143	243	7.9	226.6	100	23.5	147.6	54	34	40	162	no	3.03	1.1	21	NO	NO
21	vasantha R	46	F	115665	150/90	150	90	1.7	88	30.44	98	98	1	NO	6	2	0	246.4	146	10.1	179.1	91.1	39.9	51.7	47	14	32	154	no	2.54	0.8	11	NO	NO
22	srinivas L	34	M	204274	140/90	140	90	1.67	90	32.27	102	98	1.04	NO	2	3	0	375.4	179	13.1	276.1	188	40.9	149.5	38	72	60	288	yes	2.94	0.88	12	NO	NO
23	vijay kumar	29	M	204285	128/82	128	82	1.64	84	31.23	100	103	0.97	NO	0	0	0	90	101	5.6	263.1	246	43.5	106.7	37	24	34	244	no	3.02	0.95	22	NO	NO
24	prakash	32	M	204289	140/90	140	90	1.61	88	33.94	100	104	0.96	NO	0	1	0	87	122	6	173	260	54.3	192.6	54	32	34	232	yes	2.54	1.23	24	YES	NO
25	gajendra K	34	M	204426	140/90	140	90	1.67	80	28.68	104	100	1.04	NO	2	0	0	149	201	9.1	171	181	34.3	191.1	40	56	48	289	no	3.97	1.26	19	NO	NO
26	kodandapani	55	M	204264	150/100	150	100	1.79	88	27.46	106	100	1.06	NO	13	10	10	121.4	199.9	12	225	190	25.1	98.4	53	48	46	121	no	3.35	0.97	10	NO	NO
27	basavaraj	32	M	204303	112/70	112	70	1.82	87	26.26	100	102	0.98	NO	0	0	0	98	109	5	127	217	35.2	105	59	32	24	141	no	2.25	0.83	22	NO	NO
28	janardhan	45	M	204296	120/80	120	80	1.79	82	25.59	96	98	0.98	NO	0	0	0	78	122	5.1	121	117.4	37.3	149.9	52	17	18	98	no	3.5	0.84	20	NO	NO
29	devakumar	55	M	204294	140/90	140	90	1.67	84	30.11	99	90	1.1	NO	6	4	2	148.4	228.5	12.7	242	45.9	58.4	49.2	44	15	16	78	no	3.04	0.76	16	NO	NO
30	krishnappa	56	M	204267	160/100	160	100	1.7	86	29.75	96	94	1.02	NO	8	8	8	162.4	200	9.8	85	280	25.7	116	59	25	35	121	no	3.6	0.85	19	NO	NO
31	ram reddy	58	M	204282	150/100	150	100	1.73	82	27.39	98	96	1.02	NO	12	10	8	199.4	298	11.1	150.5	232.3	37.6	132.3	48	38	36	164	no	2.52	0.65	17	NO	NO
32	farida banu	41	F	204300	120/80	120	80	1.73	85	28.4	100	102	0.98	NO	7	0	0	138	187	7.1	141.2	59	47.3	57.7	37	12	26	368	yes	1.54	1.1	18	YES	NO
33	narayana swamy	39	M	204268	110/70	110	70	1.7	88	30.44	93	87	1.06	NO	0	0	0	98	146	5.5	157.4	224	30.5	112.5	54	18	46	188	no	2.32	1.24	11	NO	NO
34	ramesh	40	M	204305	150/90	150	90	1.7	86	29.75	92	90	1.02	NO	2	2	1	168	189	9.1	183	240	33.2	113.4	48	24	42	178	yes	4	1.14	14	YES	NO

MASTER CHART

35	narayana swamy	35	M	204292	140/90	140	90	1.7	92	31.83	96	98	0.98	NO	0	1	1	99	108	6.1	108	270	27.2	86.2	56	34	42	169	no	2.51	0.92	19	NO	NO
36	geetha bai	26	F	204258	120/80	120	80	1.76	86	27.76	102	98	1.04	NO	0	0	0	87	111	5.9	147	242	29.7	124	55	72	63	158	no	3.1	0.8	22	NO	NO
37	somasekhar	37	M	204279	118/76	118	76	1.61	87	33.56	96	99	0.97	NO	1	0	0	167	199	12	170	437	30.7	71.2	59	12	24	286	no	4.1	1.3	24	NO	NO
38	Rani	55	F	204265	140/90	140	90	1.67	86	30.83	96	84	1.14	NO	4	4	2	187	289	13.8	199	218	24.9	97.7	56	24	34	133	no	3.6	0.64	23	NO	NO
39	noushad pasha	26	M	204329	110/70	110	70	1.67	82	29.4	96	92	1.04	NO	0	0	0	89	134	5.8	161	293	35.5	75.5	55	42	42	146	yes	2.96	0.85	20	YES	NO
40	changamma	50	F	185508	154/86	154	86	1.7	75	25.95	86	89	0.97	NO	5	6	5	200	299	11.8	98	222	25.7	131	61	12	42	204	no	2.4	0.9	21	YES	NO
41	savithramma	48	F	1020915	160/96	160	96	1.73	88	29.4	92	80	1.15	NO	10	10	8	221	324	8.6	230	244	25	87.4	57	32	24	222	yes	3.46	0.8	22	NO	NO
42	shazia khunum	23	F	135222	120/80	120	80	1.73	78	26.06	100	106	0.94	NO	0	0	0	99	156	7.4	98	249	25.1	131.3	52	12	58	122	no	1.54	0.6	26	NO	NO
43	venkatlakshmi	45	F	133498	128/84	128	84	1.7	92	31.83	108	100	1.08	NO	7	0	0	198	289	12	230	248.8	38.5	47.8	56	68	55	268	no	2.33	1.12	21	NO	NO
44	Muniraju	38	M	134432	140/90	140	90	1.64	88	32.71	96	98	0.98	NO	0	2	2	98.9	145	6.2	195.8	204.4	37.7	121.7	45	64	48	144	YES	3.84	1.2	20	NO	NO
45	panduranga	41	M	132371	159/94	159	94	1.67	82	29.4	98	99	0.98	NO	7	5	5	112	206.5	8.6	205.4	173.3	35.2	138.3	55	34	48	98	NO	3.77	0.67	18	NO	YES
46	manjunath	46	M	134803	138/86	138	86	1.67	78	27.96	99	84	1.18	NO	8	2	5	159	135.2	9.2	225.1	166.7	45.4	153.5	49	12	42	96	NO	3.56	0.8	24	NO	NO
47	balaram	21	M	134805	110/70	110	70	1.64	79	29.37	96	84	1.14	NO	0	0	0	101	134	6.1	227.6	200.97	39	146.5	43	18	34	124	NO	2.8	0.79	19	NO	NO
48	nagarathnama	35	F	134827	158/92	158	92	1.61	78	30.09	86	96	0.9	NO	0	3	3	108	144.4	6.1	217	418	35.4	137	54	24	32	324	YES	2.32	0.6	16	NO	NO
49	fareedha	20	F	134792	110/70	110	70	1.7	82	28.37	92	92	1	NO	0	0	0	96	112	5.8	171.8	172	28.4	118	56	12	40	186	NO	2.64	0.78	17	NO	NO
50	savithramma	36	F	132984	120/70	120	70	1.73	86	28.73	92	84	1.1	NO	3	0	3	147	209	11.8	218.4	228	39	130	58	8	24	156	NO	3.51	1.2	18	NO	NO
51	venkatappa	48	M	133837	138/88	138	88	1.76	94	30.34	94	82	1.15	NO	0	4	4	102	148.6	6	229.8	448.6	26	116	57	26	43	172	YES	2.19	0.9	21	NO	NO
52	venkatronappa	47	M	133361	120/84	120	84	1.73	82	27.39	98	90	1.09	NO	10	0	9	129	200.4	12.8	129.4	187.5	35	131.9	55	33	54	111	NO	2.21	1.13	19	NO	YES
53	lakshmamma	50	F	125329	148/94	148	94	1.73	86	28.73	106	102	1.04	NO	5	5	5	201	144.8	8.7	167	180.3	44.9	161	59	48	46	256	NO	1.98	0.78	21	NO	NO
54	nagaraj shetty	60	M	123546	156/98	156	98	1.7	88	30.44	96	84	1.14	NO	7	7	0	206.5	300	9	227.8	131	39	146.5	47	12	35	121	YES	0.98	0.97	29	YES	NO
55	shylaja	25	F	127124	120/78	120	78	1.7	76	26.29	100	104	0.96	NO	0	0	2	94.4	128.4	5.9	158.4	156	39.6	100	56	39	34	156	NO	3.46	1.2	22	NO	NO
56	gangamma	38	F	131616	130/80	130	80	1.62	66	25.2	78	62	0.8	NO	0	0	0	76	121	5.2	167	124	54	87	48	23	32	87	NO	1.29	0.8	22	NO	NO
57	kamala bai	42	F	48412	110/70	110	70	1.53	58	24.7	75	50	0.67	NO	0	0	0	87	126	6.1	154	134	53	89	25	19	21	78	YES	2.34	0.9	18	NO	NO
58	narayanappa	50	M	121545	126/84	126	84	1.54	56	23.5	70	53	0.75	NO	7	0	0	89	173	7	134	129	46	56	28	24	24	96	NO	3.12	1.1	28	NO	NO
59	shantha kumari	36	F	33810	116/80	116	80	1.62	64	24.5	81	63	0.78	NO	0	0	0	74	127	5.8	147	143	42	67	50	31	35	67	YES	4.21	0.6	27	NO	NO
60	achamma	45	F	1020618	124/82	124	82	1.65	64	23.5	79	51	0.65	NO	5	0	4	88	153	6.9	164	87	46	78	34	29	19	103	NO	4.11	1.4	18	NO	NO
62	kempamma	48	F	116969	130/80	130	80	1.67	66	23.6	77	52	0.67	NO	0	0	0	68	174	5.8	155	98	49	54	45	19	28	102	NO	2.12	1.8	12	NO	NO
63	thara	32	F	122286	110/74	110	74	1.64	66	24.4	76	59	0.77	NO	0	0	0	85	138	6.3	143	79	53	65	43	34	26	110	YES	3.22	0.4	27	NO	NO
64	jyothamma	38	F	1004488	128/84	128	84	1.63	61	22.8	82	66	0.81	NO	0	0	0	76	133	6.8	132	32	55	76	24	22	34	67	NO	2.33	1.9	26	NO	NO
65	nagarathnama	42	F	98655	120/80	120	80	1.66	64	23.3	80	58	0.73	NO	3	0	0	98	137	7.4	123	67	61	43	26	31	23	53	NO	1.76	0.4	29	NO	NO
66	venkateshappa	50	M	116578	110/70	110	70	1.69	70	24.4	78	60	0.77	NO	0	0	0	102	144	5.7	164	86	48	54	28	27	21	89	YES	2.22	0.9	31	NO	NO
67	venkataramana R	55	M	117514	116/68	116	68	1.68	64	22.8	75	50	0.67	NO	0	0	5	87	147	6.4	148	97	46	65	34	22	36	102	NO	3.51	1	27	NO	NO
68	lakshmamma	52	F	192917	124/70	124	70	1.7	67	23.2	81	53	0.65	NO	0	0	0	104	152	5.8	137	78	53	32	43	29	32	98	NO	3.73	1.9	34	NO	NO
69	arathi	23	F	120013	130/70	130	70	1.71	69	23.5	83	57	0.69	NO	0	0	0	86	123	6.7	158	102	51	54	32	19	28	112	NO	3.91	1.6	27	NO	NO
70	rathnama	40	F	120048	128/84	128	84	1.69	69	24.1	76	59	0.78	NO	4	0	0	108	167	5.8	143	113	47	76	36	31	22	56	YES	3.33	1.4	31	NO	NO
71	shafiulla	48	M	118514	120/78	120	78	1.67	68	24.5	79	58	0.74	NO	0	0	0	95	132	6.2	139	124	49	87	38	27	34	65	NO	3.12	0.5	29	NO	NO
72	lakshmamma	55	F	126670	128/80	128	80	1.72	70	23.8	78	56	0.72	NO	0	0	0	94	146	6	148	132	44	98	39	18	38	54	NO	3.41	0.2	24	NO	NO
73	vanitha	25	F	126672	130/70	130	70	1.7	70	24.1	77	58	0.75	NO	0	0	0	87	128	6.9	167	106	48	67	43	31	33	78	NO	4.22	1.3	28	NO	NO

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74	narayanamma	52	F	135537	122/72	122	72	1.55	55	22.8	80	54	0.67	NO	4	0	0	93	119	5.7	69	75	38	78	25	22	21	64	YES	3.81	1	18	NO	NO
75	krishnappa	60	M	135961	110/68	110	68	1.57	59	23.8	75	59	0.78	NO	6	0	6	75	108	6.1	175	98	44	68	28	28	27	87	NO	3.99	0.5	12	NO	NO
76	mallikarjuna	45	M	163652	132/78	132	78	1.64	66	24.7	81	60	0.74	NO	0	0	0	84	128	6.6	166	103	47	56	49	17	29	98	NO	3.2	0.68	23	NO	NO
77	shaziya taj	29	F	160151	112/72	112	72	1.63	69	25.8	84	56	0.67	NO	0	0	0	86	133	6.1	148	117	45	47	36	34	33	102	YES	2.9	0.82	19	NO	NO
78	lalitha	40	F	156037	110/70	110	70	1.67	72	25.7	83	65	0.78	NO	0	0	0	83	128	5.2	183	120	53	59	38	25	26	108	NO	2.7	0.75	21	NO	NO
79	azeema bee	55	F	144647	130//70	130	70	1.68	70	24.8	82	60	0.73	NO	7	0	0	98	119	6.7	174	125	52	58	35	27	34	88	YES	2.5	0.74	16	NO	NO
80	madhu kumar	29	M	163750	120/76	120	76	1.66	65	23.7	80	54	0.68	NO	0	0	0	92	130	6	165	105	39	67	47	31	31	76	NO	2.3	0.65	23	NO	NO
81	thipamma	48	F	157289	116/72	116	72	1.64	61	22.5	77	55	0.71	NO	0	0	5	89	127	5.7	186	110	43	69	40	18	28	68	YES	2.1	0.6	27	NO	NO
82	kasthuri	60	F	152117	120/78	120	78	1.6	58	22.7	76	52	0.69	NO	5	0	0	86	118	7.3	164	103	47	57	32	33	24	64	NO	2.4	0.78	17	NO	NO
83	nagaraj	45	M	143142	130/78	130	78	1.58	59	23.6	75	55	0.73	NO	0	4	0	105	113	5.8	148	87	51	56	45	27	34	58	NO	2.6	1.12	13	NO	NO
84	yashodamma	36	F	163767	120/80	120	80	1.55	57	23.8	81	55	0.68	NO	0	0	0	107	121	6.2	158	98	56	58	35	21	29	87	NO	2.8	0.81	27	NO	NO
85	basavaraj	38	M	144173	110/70	110	70	1.57	61	24.7	76	51	0.67	NO	0	0	0	108	125	5.9	168	79	63	76	31	28	34	66	NO	3.5	0.75	5.9	NO	NO
85	praveen	21	M	64168	108/68	108	68	1.61	64	24.6	74	56	0.75	NO	0	3	0	76	137	6.1	157	88	58	75	27	18	23	59	YES	4.1	0.65	13	NO	NO
87	mala	30	F	163719	110/70	110	70	1.67	72	25.8	77	59	0.77	NO	0	0	0	87	138	5.7	145	105	59	86	44	24	22	102	NO	1.6	0.58	26	NO	NO
88	shanthamma	33	F	163671	120/80	120	80	1.54	58	24.6	79	62	0.79	NO	0	0	0	79	124	6.3	177	107	43	97	32	32	35	104	NO	2.8	0.96	25	NO	NO
89	saraswathamma	58	F	136235	114/72	114	72	1.53	56	23.9	78	65	0.83	NO	0	0	0	73	125	6	167	85	48	85	26	29	21	112	YES	4.2	0.57	29	NO	NO
90	muniyappa	38	M	142726	122/72	122	72	1.66	66	24.1	81	71	0.87	NO	0	2	0	86	132	6.3	168	96	38	75	45	31	28	65	NO	3.7	0.45	28	NO	NO
91	krishnamurthy	46	M	160629	130/80	130	80	1.73	75	25.2	80	61	0.76	NO	0	6	0	84	121	5.9	186	70	56	69	47	22	35	66	YES	3.9	0.59	17	NO	NO
92	shakunthala	48	F	163822	120/68	120	68	1.72	73	24.7	78	62	0.79	NO	4	0	0	82	134	6.8	158	132	54	98	49	27	22	78	NO	3.3	0.39	19	NO	NO
93	suma	21	F	163774	110/70	110	70	1.69	71	24.8	75	61	0.81	NO	0	0	0	79	125	5.7	160	125	47	87	51	19	29	58	NO	3.1	0.45	26	NO	NO
94	khadhar pasha	58	M	162922	120/80	120	80	1.71	72	24.6	76	52	0.68	NO	0	5	0	83	139	6.4	176	117	55	94	48	20	26	74	NO	2.6	0.67	23	NO	NO
95	subramani	36	M	143155	122/78	122	78	1.75	74	24.1	74	58	0.79	NO	0	2	0	74	124	5.2	178	129	49	58	44	24	33	67	NO	2.8	1.2	20	NO	NO
96	mariyamma	44	F	141338	130/70	130	70	1.66	66	23.8	78	59	0.75	NO	0	0	0	79	127	6.3	169	79	45	59	46	31	23	89	NO	2.4	0.95	25	NO	NO
97	rajamma	58	F	204405	128/70	128	70	1.58	59	23.6	79	54	0.68	NO	0	0	0	83	130	7.3	170	83	42	84	32	27	27	113	NO	0.85	1.9	22	NO	NO
98	prabhavathi	45	F	152105	120/70	120	70	1.62	62	23.8	81	63	0.78	NO	0	0	7	93	125	6.3	178	97	56	78	30	30	32	115	YES	0.67	1.7	24	NO	NO
99	chowdamma	52	F	204707	130/90	130	90	1.64	66	24.7	81	60	0.74	NO	0	0	0	84	128	6.6	166	103	47	56	49	17	29	98	NO	3.2	0.68	21	NO	NO
100	venkatesh	48	M	202956	110/72	110	72	1.63	69	25.8	84	56	0.67	NO	5	0	0	86	133	7.3	148	117	45	47	36	34	33	102	YES	2.9	0.53	28	NO	NO
101	narayana swamy	51	M	204349	116/68	116	68	1.67	72	25.7	83	65	0.78	NO	0	0	0	83	128	5.2	183	120	53	59	38	25	26	108	NO	2.7	0.8	24	NO	NO
102	sarojamma	52	F	204052	120/80	120	80	1.68	70	24.8	82	60	0.73	NO	7	0	0	98	119	6.7	174	125	52	58	35	27	34	88	YES	2.5	0.74	21	NO	NO
103	krishnappa	52	M	204652	130/70	130	70	1.66	65	23.7	80	54	0.68	NO	0	0	0	92	130	6	165	105	39	67	47	31	31	76	NO	2.3	0.65	23	NO	NO
104	nagamma	39	F	204061	118/68	118	68	1.64	61	22.5	77	55	0.71	NO	0	0	5	89	127	5.7	186	110	43	69	40	18	28	68	YES	2.1	0.6	17	NO	NO
105	shylaja	45	F	158383	120/80	120	80	1.6	58	22.7	76	52	0.69	NO	5	0	0	86	118	7.3	164	103	47	57	32	33	24	64	NO	2.4	0.78	25	NO	NO
106	pavithra	46	F	144430	120/70	110	70	1.58	59	23.6	75	55	0.73	NO	0	0	0	105	113	5.8	148	87	51	56	45	27	34	58	NO	2.6	1.12	19	NO	NO
107	chandramma	55	F	204505	130/70	130	70	1.55	57	23.8	81	55	0.68	NO	0	0	0	107	121	6.2	158	98	56	58	35	21	29	87	NO	2.8	0.81	17	NO	NO
108	mangamma	56	F	205283	120/76	120	76	1.57	61	24.7	76	51	0.67	NO	0	0	0	108	125	5.9	168	79	63	76	51	28	34	66	NO	3.5	0.75	19	NO	NO
109	srinivasan	38	M	204274	110/68	110	68	1.61	64	24.6	74	56	0.75	NO	0	3	0	76	137	6.1	157	88	58	75	27	18	23	59	YES	4.1	0.75	24	NO	NO
110	selva kumar	48	M	175724	114/72	114	72	1.67	72	25.8	77	59	0.77	NO	0	0	0	87	138	5.7	145	105	59	86	44	22	22	102	NO	1.6	0.6	18	NO	NO