A STUDY OF LIPOPROTEIN (a) AND BIOCHEMICAL PARAMETERS OF METABOLIC SYNDROME AMONG YOUNGER POPULATION

Dissertation

Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the requirements for the award of the degree of

M.D BIOCHEMISTRY

Branch XIII

APRIL 2015

CERTIFICATE

This is to certify that the dissertation entitled "**A study of lipoprotein (a) and biochemical parameters of metabolic syndrome among younger population"** is a bonafide work done by **Dr. B. Poonguzhali** in partial fulfilment of the university rules and regulations for award of **M.D Biochemistry [Branch-XIII]** under my guidance and supervision during the academic year 2012-2015.

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DECLARATION

I Dr. B.Poonguzhali here by submit the dissertation titled "**A study of lipoprotein (a) and biochemical parameters of metabolic syndrome among younger population"** done in partial fulfilment for the award of the degree **M.D Biochemistry [Branch-XIII]** in Sree Mookambika Institute of Medical Sciences, Kulasekharam. This is an original work done by me under the guidance and supervision of Dr.R.Nagendran, M.D.

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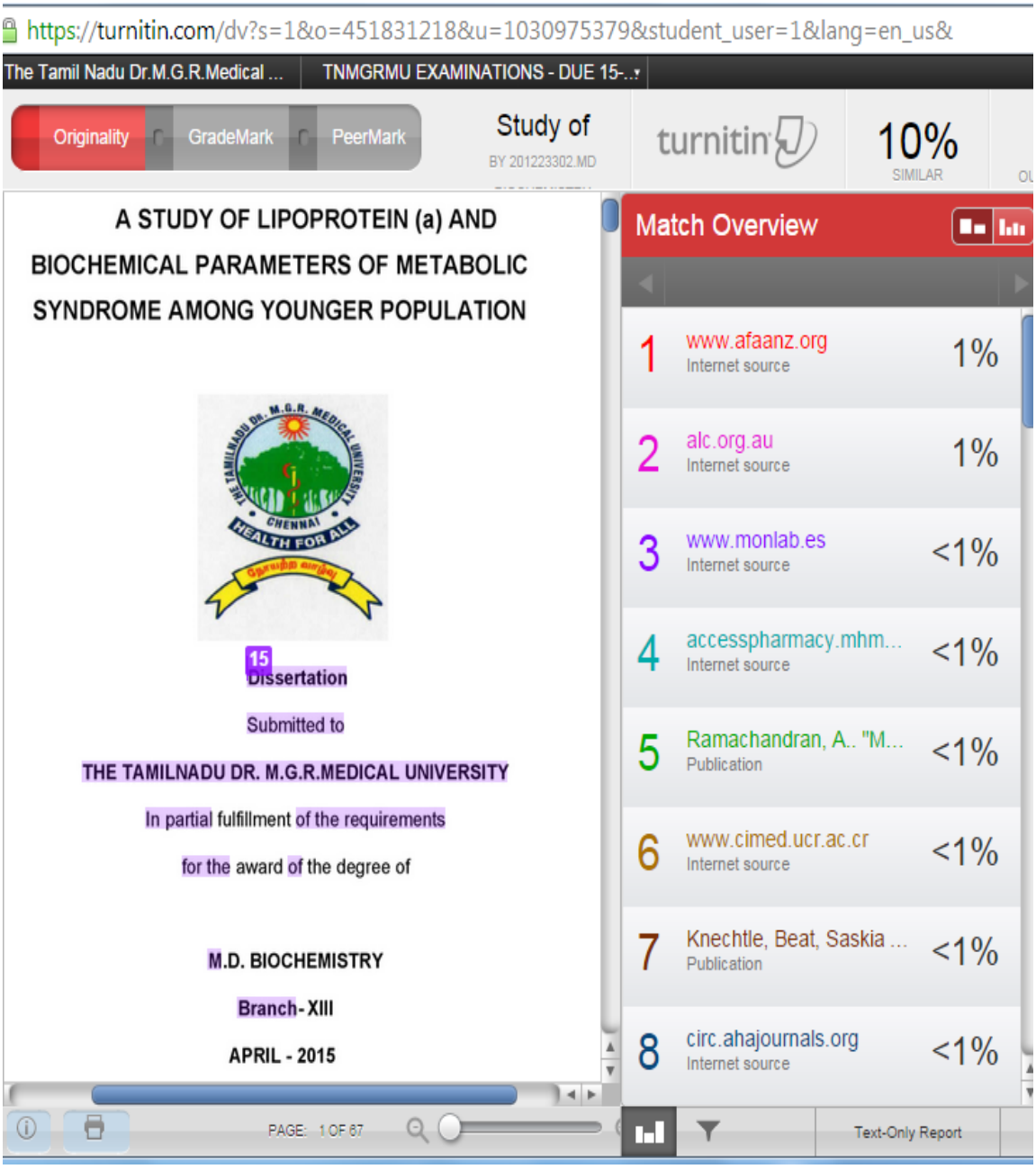
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LIST OF ABBREVIATIONS

MS, Met S	-	Metabolic syndrome
WHO	-	World Health Organisation
NCEP ATP III	-	National Cholesterol Education Programme Adult Treatment Panel III
IDF	-	International Diabetes Federation
CVD	-	Cardio Vascular Disease
HDL	-	High Density Lipoprotein
LDL	-	Low Density Lipoprotein
VLDL	-	Very Low Density Lipoprotein
Lp(a)	-	Lipoprotein (a)
NHANES	-	National Health and Nutrition Examination Survey
FFA	-	Free Fatty Acids
SNS	-	Sympathetic nervous system
PAI	-	Plasminogen Activator Inhibitor
IL	-	Interleukins
TNF	-	Tumour Necrosis Factor
CRP	-	C Reactive Protein
FOS	-	Framingham Offspring Study
FRS	-	Framingham Risk Score
ABC	-	ATP-binding cassette protein
LCAT	-	Lecithin Cholesterol Acyl Transferase

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TITLE: STUDY OF LIPOPROTEIN(A) AND BIOCHEMICAL PARAMETERS OF METABOLIC SYNDROME AMONG YOUNGER POPULATION.

INTRODUCTION

Metabolic syndrome is defined as the combination of obesity, hyperglycemia/diabetes, hypertension and dyslipidemia. Metabolic syndrome is attracting more commercial interest, due to components of the MS enhances the chance for cardio vascular disease and also the total morbidity and mortality in our population. Lipoprotein (a) has emerged nowadays as a powerful genetic risk factor for CAD.

AIMS AND OBJECTIVES

Our aim is to know the prevalence of metabolic syndrome among younger population and to study the relationship between Lipoprotein (a) and metabolic syndrome.

MATERIALS AND METHODS

Patients and bystanders (136 persons) who attended the medicine OPD of Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamilnadu for routine medical check up formed the subjects for the present cross-sectional study. The following parameters were collected: age, gender, religion, waist circumference, blood pressure and fasting clinical chemistry parameters (Blood glucose, serum triglycerides, HDL and lipoprotein (a)).Blood glucose is estimated by GOD-POD method, Serum triglycerides by GPO-PAP method, HDL by direct detergent method and lipoprotein (a) by latex turbidimetry method.

RESULTS

In our study population, prevalence of metabolic syndrome is 47.1% (64 persons) according to the Modified NCEP ATP III Criteria and according to the IDF Criteria; prevalence is 44.9% (61 persons). Prevalence of metabolic syndrome (By Modified NCEP ATP III Criteria or IDF Criteria) with the age category has significant correlation according to the p-value 0.000 (<0.01). Amount of lipoprotein (a) is present in the metabolic syndrome category, by Modified NECP ATP III Criteria with the mean and standard deviation of 55.65 ± 18.30 and IDF Criteria with the mean and standard deviation of 56.07 ± 18.10. Metabolic syndrome category by either Modified NECP ATP III Criteria or IDF Criteria has significant correlation with lipoprotein (a) according to their p-value 0.000 (<0.01).

CONCLUSION

Prevalence of metabolic syndrome with age category has significant correlation. Prevalence is maximum at the age group of 35-39 years followed by the age group of 30-34 years and then 24-29 years. Lipoprotein (a) level has significant correlation with the metabolic syndrome. It has significantly correlated with the individual components of metabolic syndrome and age category also (p value <0.01).

Key words: Metabolic syndrome, Lipoprotein (a), coronary artery disease.

INTRODUCTION

A combination of decreasing demands and increased intake of food and physical inactivity has led to increasing prevalence of obesity, hyper glycaemia/diabetes, hypertension and dyslipidemia. A combination of all the above features is called metabolic syndrome. [1] Increasing prevalence of metabolic syndrome in various countries in South Asia, due to rapid nutritional and lifestyle transition in urbanized areas.[2]

Metabolic syndrome is attracting more commercial interest, due to components of the MS enhances the chance for cardio vascular disease and also the total morbidity and mortality in our population.[3] Different guidelines issued by World Health Organization (WHO), National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) and International Diabetes Federation (IDF) have been proposed to identify metabolic syndrome in clinical practice.[4]

According to WHO estimation 2003, 16.7 million people in the world die due to CVD each year and 80% deaths occur in low and middle income countries.[5] Asian Indians considered to be a "high risk population" for both metabolic syndrome and CVD.[6] In India, prevalence of metabolic syndrome is varying between 10% to 50% depending on age and sex.[7] Persons affected with metabolic syndrome have a 30-40% chance of developing diabetes and CVD within 20 years, it depends on number of individual components present.[3] Primordial prevention is the best one to protect the adult CVD epidemic.[8] For effective prevention of CVD and Type2 diabetes mellitus, components of the MS and obesity recognized early in the lifetime is important.[9]

South Asians have high numbers of diabetes and highest numbers of premature CAD in the world, both occur about 10 years early compared to other populations. This increased risk is due to South Asian dyslipidemia. It is characterized by high levels of apolipoprotein B, lipoprotein (a), triglycerides in the serum and low levels of apolipoprotein A_1 and HDL cholesterol.[10]

Lipoprotein (a) has emerged nowadays as a powerful genetic risk factor for CAD.[11] Nowadays Clinical interest in Lp(a) has increased more times, because the studies has explained the relationship between plasma Lp(a) concentrations (reported as $\geq$ 30mg/dL) and coronary and cerebro vascular disease, peripheral artery disease, and also the early origin of atherosclerosis in children and adolescents. The scarcity of studies about the epidemiological behaviour of Lp(a) in our country, the main aim of our research is to study the relationship between Lp(a) and the metabolic syndrome and its components in younger population .[12]

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

1. To know the prevalence of metabolic syndrome among younger population.
2. To study the relationship between Lipoprotein (a) and metabolic syndrome.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

EVALUATION OF THE METABOLIC SYNDROME

In his 1988 lecture Reaven described about the metabolic syndrome. He explained that insulin resistance was the main trigger of the syndrome. He named this syndrome as syndrome "X".[1] He described the following parameters as the components of syndrome "X"- insulin resistance, hyperglycaemia, hyperinsulinemia, increased VLDL triglyceride, decreased HDL and hypertension. [13] Reaven had mentioned insulin resistance as the central causal factor for the metabolic syndrome, but the more recent definitions including International Diabetes Federation (2006) suggested the obesity as the central factor for defining the syndrome if at least two other elements of hypertension, dyslipidemia and hyperglycaemia are present. So, nowadays insulin resistance is not the part of the syndrome.[1]

As early as 250 years ago, even before the metabolic syndrome description, the Italian anatomist Margagni identified the link between visceral obesity, atherosclerosis, HTA (arterial hypertension), frequent respiratory disorders during sleep and the high levels of uric acid in the blood.[14]

In the year 1920, Nicolae Paulescu, talking about the obesity and diabetes, and he said "most frequently, the obese people become glycosuric, as if the two affections (obesity and fat diabetes) represent two consequent phases of the same pathological process".[15]

In 1927, Maranon, described that arterial hypertension is a pre-diabetical stage and this is also similarly applied to obesity. Maranon also explained the fact that food is essential for treating and preventing these disturbances. He is a founder of modern endocrinology in the Spain. [15]

In the mid 20th century, the French physician Vague was the first to identify 'android obesity' (upper body adiposity) as the condition most often associated with diabetes and cardiovascular disease.

The often – simultaneous presence of obesity, the high level of blood lipids, diabetes mellitus and arterial hypertension was first mentioned under the name of Plurimetabolic syndrome in the 1960.

In the 1970, Moga, Orha, Haragus supported the fact among connection between the Metabolic syndrome components at present and correlating that to the cardiovascular diseases.[13]

The Metabolic syndrome was called by various names in time : the X syndrome, the X plus syndrome, the Plurimetabolic syndrome, the X metabolic syndrome, the insulin resistance- dyslipidemia syndrome, the cardiovascular metabolic syndrome, the syndrome of atherogenic factors' agglomeration, the atherogenic metabolic syndrome, the deadly quartet. Recently, the MetS is used to replace the term of metabolic syndrome.[16]

DEFINITIONS OF METABOLIC SYNDROME: There are various definitions and cut-off points for defining the metabolic syndrome had proposed.

WHO CRITERIA (1999)[17]

According to this metabolic syndrome is defined as the presence of

Diabetes (or) Impaired glucose tolerance (or) Insulin resistance and ≥ 2 of the following parameters:

(i) BMI > 30Kg/m^2

WHR > 0.9 for men, > 0.85 for women.

(ii) TG ≥150 mg/dl (1.7mmol/l) (or)

HDL-C <35 mg/dl (0.9mmol/l) for men,

<39 mg/dl (1.0mmol/l) for women

(iii)BP ≥ 140/90 mmHg or medication

(iv)Microalbuminuria

Albumin excretion ≥ 20μgm/min (or)

Albumin: Creatinine ratio ≥ 30 mg/g

WHO-World Health Organization

BMI- Body mass index

WHR-Waist hip ratio

TG-Triglycerides

HDL-C- High density lipoprotein cholesterol

BP- Blood pressure

* defined as the top quartile of fasting insulin in the non diabetic population.

MODIFIED WHO CRITERIA (MICROALBUMINURIA WAS EXCLUDED) 18

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(iii) BP ≥ 140/90 mmHg or medication

WHO-World Health Organization

BMI- Body mass index

WHR-Waist hip ratio

TG-Triglycerides

HDL-C- High density lipoprotein cholesterol

BP- Blood pressure

EGIR 1999[18]

According to this, metabolic syndrome is defined as the Insulin resistance * or Hyperinsulinemia (only non diabetic subjects) plus 2 or more of the following parameters:

I.	Central obesity : waist circumference	≥ 94cm (M)
		≥ 80cm (F)
II.	Dyslipidemia : Triglycerides	> 2mmol/l (or)
	HDL-C	< 1 mmol/l

III. Hypertension: Blood pressure ≥ 140/90 mm Hg and / or Medication

IV. Fasting plasma glucose ≥ 6.1mmol/l

EGIR – European group for the study of insulin resistance

HDL-C - High density lipoprotein cholesterol

M – Male

F – Female

* defined as the top quartile of fasting insulin in the non diabetic population.

NCEP- ATP III CRITERIA[19, 20]

According to this, metabolic syndrome is defined as the presence of ≥ three of the following parameters:

i. Waist circumference > 102cm in men,
> 88cm in women

ii. SBP > 130 mm Hg and /or
DBP > 85 mm Hg or
medical treatment of previously diagnosed hypertension.

iii. TG > 150 mg/dl (1.7mmol/l)

iv. HDL-C < 40mg/dl (1.0 mmol/l) in men,
<50mg/dl (1.3 mmol/l) in women

v. Fasting plasma glucose > 100mg/dl (5.6 mmol/l) changed in 2005 from 110 mg/dl (6.1 mmol/l).

NCEP– National Cholesterol Education Program

ATP III- Adult treatment panel III

SBP – Systolic blood pressure

DBP – Diastolic blood pressure

TG – Triglycerides

HDL–C – High density lipoprotein cholesterol

MODIFIED NCEP- ATP III CRITERIA [10, 21]

According to this, metabolic syndrome is defined as the presence of ≥ three of the following parameters:

i.	Waist circumference	≥ 90cm in men,
		≥ 80cm in women
ii.	SBP	≥130 mm Hg and /or
	DBP	≥ 85 mm Hg or
	medical treatment of previously diagnosed hypertension.	
iii.	TG	≥ 150 mg/dl (1.7mmol/l)
iv.	HDL-C	< 40mg/dl (1.0 mmol/l) in men,
		<50mg/dl (1.3 mmol/l) in women
v.	Fasting plasma glucose	≥ 100mg/dl (5.6 mmol/l)

NCEP– National Cholesterol Education Program

ATP III- Adult treatment panel III

SBP – Systolic blood pressure

DBP – Diastolic blood pressure

TG – Triglycerides

HDL – C – High density lipoprotein cholesterol

IDF CRITERIA [22]

According to this, Metabolic syndrome is defined as the presence of central obesity (waist circumference* with ethnicity specific values) plus any two of the following parameters:

i. TG ≥ 150mg/dl or specific treatment for this lipid abnormality

ii. HDL-C < 40mg/dl (men)
<50mg/dl (women)
or specific treatment for this lipid abnormality

iii. SBP ≥130 mm Hg and /or
DBP ≥ 85 mm Hg or
medical treatment of previously diagnosed hypertension

iv. Fasting plasma glucose ≥100mg/dl or previously diagnosed type 2 diabetes mellitus. If >100 mg/dl, OGTT is strongly recommended but is not necessary to define presence of the syndrome

IDF – International Diabetes Federation

SBP – Systolic blood pressure

DBP – Diastolic blood pressure

TG – Triglycerides

HDL – C – High density lipoprotein cholesterol

* ETHNIC SPECIFIC VALUES FOR WAIST CIRCUMFERENCE

1. Europids In the USA, the ATP III values (102 cm male; 88cm females) are likely to continue to be used for clinical purposes.	Male ≥94cm Female ≥ 80cm
2. South Asians Based on a Chinese, Malay and Asian-Indian population	Male ≥90cm Female ≥ 80cm
3. Chinese	Male ≥90cm Female ≥ 80cm
4. Japanese	Male ≥90cm Female ≥ 80cm
5. Ethnic south and central Americans	Use south Asian recommendations until more specific data are available
6. Sub-Saharan Africans	Use European data until more specific data are available
7. Eastern Mediterranean and middle East (Arab) populations	Use European data until more specific data are available

AACE CRITERIA[23]

AACE indroduces a clinical criteria for metabolic syndrome. This criteria seems to be a combination of WHO and ATP III MS but here, diagnosis is based on the clinical judgement. In patients without Impaired Fasting Glucose (IFG) i.e Fasting blood glucose concentration >110 and < 126 mg/dl, glucose challenge test is recommended, when an abnormality is clinically suspected. Any abnormal finding in 2 hour post glucose will improve diagnosis of type 2 diabetes mellitus.

American Association of Clinical Endocrinologists (AACE) criteria for defining the Insulin Resistance Syndrome.

Risk factor components	Cut off for abnormality
Overweight/ obesity	> BMI 25kg/m^2
Elevated Triglycerides	> 150 mg/dl (1.69 mmol/l)
Low HDL Cholesterol	
Men	<40 mg/dl (1.04 mmol/l)
Women	< 50 mg/dl (1.29 mmol/l)
Elevated blood pressure	> 130/85 mm Hg
Fasting glucose mg/dl	Between 110 and 126
2 hour post glucose challenge	> 140mg/dl

Other risk factors

- Family history of type 2 diabetes
- Hypertension or Cardiovascular Disease
- Polycystic Ovary syndrome
- Gestational diabetes
- Acanthosis Nigricans
- Sedentary life style
- Advancing age
- Ethnic groups having high risk for type 2 diabetes mellitus or cardiovascular disease

    - ❖ Diagnosis depends on clinical judgement based on risk factors.

EPIDEMIOLOGY

Data from many world regions suggest that more than 1 in 5 adults have metabolic syndrome. It is estimated that 20% to 25% of adults worldwide have Metabolic Syndrome. Obesity is widely recognized as one of the biggest health threats of the 21st century.

In a recent review and pooling of literature, it was estimated that 23.2% of the world's adult population in 2005 was overweight (24% of men and 22.4% of women). Additionally, 9.8% of the adult population worldwide was obese (7.7% of men and 11.9% of women). The number of adults projected to be overweight by 2030 is 1.35 billion with 573 million projected to be obese.[24]

The third NHANES survey showed the prevalence of MS among US adults. The age adjusted prevalence of the Metabolic Syndrome was 23.7%. The prevalence

increased from 6.7% in younger participants (20-29 years) to 43.5% (60-69 years) and 42% (70 years) for older participants. Mexican Americans had highest prevalence of the MS (31.9%) and among them women had 26% higher prevalence than men. However, among African Americans compared to Mexican Americans, women had 57% higher prevalence than men.[25]

According to ATP III and IDF definitions, the overall prevalence of MetS was 12.5% and 17.9% respectively in working East African adults (Ethiopia). Using ATP III criteria, the prevalence of metabolic syndrome was 10% in men and 16.2% in women. Application of the IDF criteria resulted in a metabolic syndrome prevalence of 14% in men and 24% in women. The most common MetS components among women were reduced high density lipoprotein cholesterol (HDL-C) 23.2% and abdominal obesity (19.6%); whilst reduced HDL –C concentrations (23.4%) and high blood pressure (21.8%) were most common among men.[26]

The metabolic syndrome ratio in the adult turkey population was 17.91%, while these ratios for diabetes mellitus and hypertension were 4.16% and 13.66% respectively. The prevalence of hypertension, metabolic syndrome and obesity were higher in females than males, whereas diabetes mellitus was higher in males than females.[27]

It was estimated that 20%-25% of south Asians have developed metabolic syndrome and many more may be prone to it. In urban Indian adults aged (20-50 yrs), prevalence of metabolic syndrome was reported to be 41.1%.[3]

Nowadays, obesity is increasing epidemically in India. National Nutrition Monitoring Bureau depicted the obesity prevalence in Indian women to be 8% and men

7%. This is increased compared to the 1990 survey, where the NNMB depicted the obesity prevalence in Indian women to be 4.1% and men 2.7%[28] and the National Family Health Survey documented prevalence rates of obesity ranging between 3.5% to 4.1%.[29]

Today, over 20% of men in urban areas have generalised obesity and about women, 40% have abdominal obesity and 30% have generalised obesity.[30] It is documented that the obesity prevalence in India increased by 89% in males and 82% in females between the years of 2002 and 2010.[31]

A study from urban eastern India found the prevalence of metabolic syndrome was 43.2% (n=509) and prevalence was higher in females 52.2% (n=307), compared to males 34.2% (n=202).[39]

One of the tribal population of India, Bhutia shows higher prevalence of metabolic syndrome with no significant rural-urban difference (42.15% in urbanized areas, 42.69% in rural areas).[32]

Mohan et al study report shows 18.7% prevalence of insulin resistance syndrome in upper socioeconomic class in south India and 6.5% in the lower socioeconomic class. The data also shows prevalence of insulin resistance and the prevalence of type 2 diabetes are same in rural and urban areas.[33]

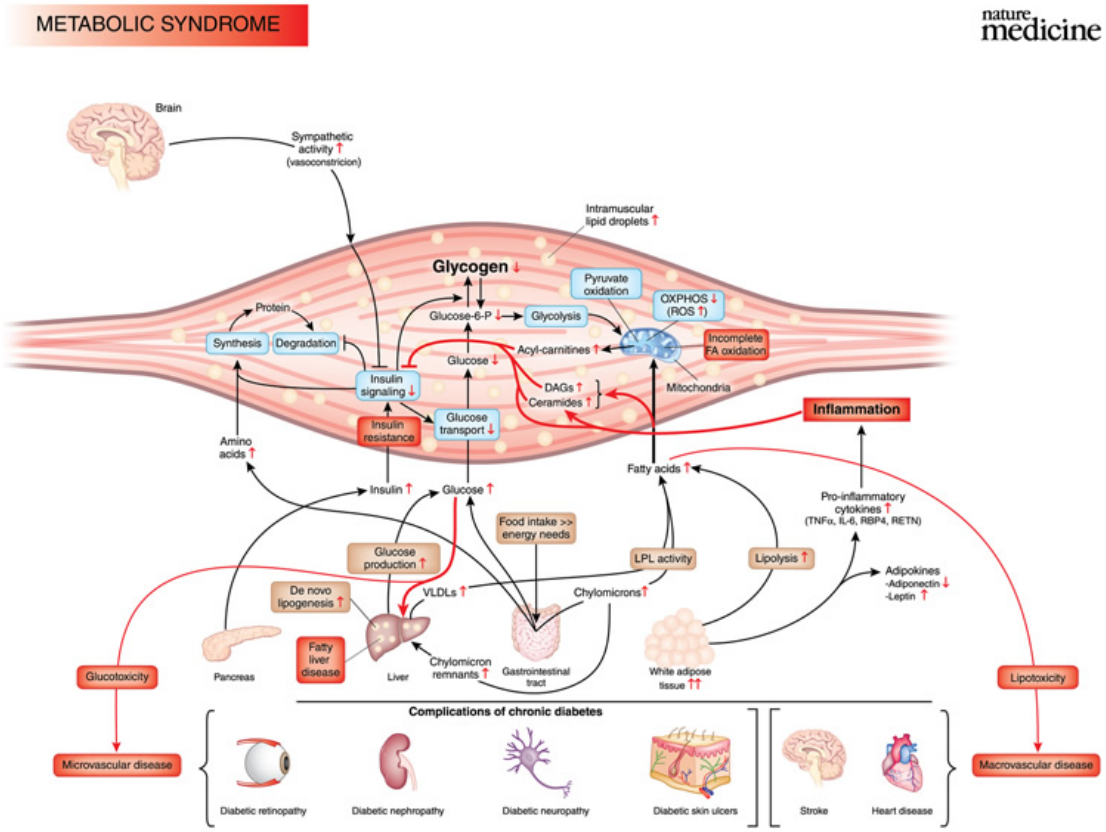
In study done in Chennai, prevalence of metabolic syndrome was 46.3% and also prevalence of MS increased in males (45%) than the females (42.2%). Among the study subjects, 93.2% had one abnormal parameter.[34]

RISK FACTOR CLUSTERING AND PATHOGENESIS

The pathogenesis of the metabolic syndrome is multi factorial. The major underlying risk factors are obesity and insulin resistance. Risk associated with obesity is best identified by increased waist circumference (abdominal obesity), insulin resistance can be secondary to obesity but can have genetic components as well. Insulin resistance persons with mild to moderate overweight also said to have primary insulin resistance. In these persons also weight gain enhances the insulin resistance and metabolic syndrome. so, it is difficult to dissociates the primary insulin resistance and obesity in MS patients.

Several factors further exacerbate the metabolic syndrome: advancing age, endocrine dysfunction, physical inactivity, and genetic aberrations altering the individual risk factors. The increasing trend of metabolic syndrome prevalence in the world is mainly due to obesity exacerbated by the sedentary lifestyles.

Free fatty acids are produced abundantly from an expanded adipose tissue mass. In the liver, it produces an increased production of triglycerides, glucose and secretion of VLDL. FFA also causes the reduction in high density lipoprotein cholesterol and an increased density of low density lipoproteins. It reduces insulin sensitivity in muscle by the mechanism of inhibiting the insulin mediated glucose uptake. Other associated defects with this include increased lipid accumulation in triglyceride and a reduction in glucose partitioning to glycogen. Increasing the circulating glucose levels and also some FFA enhance the production of insulin by pancreas resulting in hyperinsulinemia. It may increases the reabsorption of sodium and sympathetic nervous system (SNS) activity. Through this mechanism, it contribute to development of the hypertension.



PATHOGENESIS OF METABOLIC SYNDROME

Insulin resistance produced by the excessive FFA levels is superimposed by the para and endocrine effect of pro inflammatory state. Adipose tissue produces variety of cells including adipocytes, monocyte-derived macrophages, interleukin-6 and tumour necrosis factor alpha. Among them, IL-6 and TNF-α results in more insulin resistance and lipolysis of triglyceride stores in adipose tissue to circulating FFA. Increased levels of IL-6 and other cytokines in the circulation may enhance glucose and VLDL production by the liver and insulin resistance in the muscle. Along with production of PAI-1 by adipose tissue, Cytokines and FFA also increase the production of fibrinogen and PAI-1 by the liver. This will end in a pro-thrombotic state. Reduced levels of adiponectin production (insulin sensitizing and anti-inflammatory cytokine) also lead to the development and pathophysiology of metabolic syndrome.

COMPONENTS OF THE METABOLIC SYNDROME [35, 36]

ATP III identified six components of the metabolic syndrome related to cardiovascular disease.

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance ± glucose intolerance
- Proinflammatory state
- Prothrombotic state

These metabolic syndrome components divide into 3 categories

  - Underlying
  - Major
  - Emerging risk factors.

- **Underlying** risk factors for cardiovascular disease are physical inactivity, obesity (especially abdominal obesity) and atherogenic diet; the **major** risk factors are hypertension, Low HDL cholesterol, elevated LDL cholesterol, family history of premature Coronary heart disease (CHD), cigarette smoking and ageing; and the **emerging** risk factors include insulin resistance, glucose intolerance, small LDL particles, elevated triglycerides, Prothrombotic state and Proinflammatory state. The later five components are called as **metabolic risk factors** for present purposes.

ABDOMINAL OBESITY

It is the form of obesity, strongly associated with the MS. It clinically presents as increased waist circumference.[35] Individuals with abdominal obesity, who are not obese on the basis of height and weight, also can be insulin resistant.[37]

Distinction between large waist circumferences due to increases in visceral fat mass or subcutaneous adipose tissue is still debated one. Computed tomography or magnetic resonance imaging helps to identifying the distinction between these two.[38]

A study provided evidence that visceral adipose tissue has a stronger association with MS than abdominal subcutaneous adipose tissue independent of metabolic syndrome criteria and measurement site.[39]

When there is increases in visceral adipose tissue, expecting more amount of free fatty acids to the liver through the splanchnic circulation, whereas increases in the level of abdominal subcutaneous fat enhances the lipolysis products into systemic circulation and avoid direct effects on hepatic metabolism that means lipid synthesis, glucose production and secretion of prothrombotic proteins (fibrinogen and PAI -1).[40]

These differences in free fatty acid flux explains the increasing waist circumference and prevalence of MS in Asians (predominance of visceral fat) compared to African- American men (predominance of subcutaneous fat).[41, 42]

ATHEROGENIC DYSLIPIDEMIA

It manifests in routine analysis of lipoprotein levels by increased triglycerides and low HDL levels, but detailed analysis only explains the other lipoprotein abnormalities, eg. elevated apolipoprotein B, increased remnant lipoproteins, small

LDL and small HDL particles. All the above abnormalities are individually leads to atherogenic dyslipidemia.[43]

Increased flux of FFA to the liver causes enhanced production of VLDL in general. Action of insulin in the above process is complex one. In normal conditions, insulin inhibits the VLDL secretion into the systemic circulation but in the case of insulin resistance, increase in FFA flux to the liver increases hepatic triglyceride synthesis.[44]Along with this, it also decreases the lipoprotein lipase concentrations in peripheral tissues mainly adipose tissue. This will result in hypertriglyceridemia. Hypertriglyceridemia in insulin resistance is mainly due to increased VLDL secretion and some extent by decreased lipoprotein lipase concentrations.

The second lipid alteration present in the metabolic syndrome is a decreased HDL- cholesterol levels. In the presence of hypertriglyceridemia, increased triglyceride content and reduced content of the cholesteryl ester in the core of lipoprotein causes the formation of small and dense particles.Due to this change in composition of lipoprotein, results in enhanced HDL clearance from the circulation. [45, 46]

In addition to HDL, the LDL composition is also altered in a same way. In fact, with fasting serum triglyceride more than 2mmol/l, almost nearly equal to all patients have a predominance of small dense LDL.[47] This type of change in LDL composition is leads to the relative reduction of esterified cholesterol, unesterified cholesterol and phospholipid with either an increase or no change in LDL triglyceride.[48]

Small dense LDL is more atherogenic compared to buoyant LDL because

1. It is more toxic to the endothelium.
2. It is more able to transit through the endothelial basement membrane.

3. It adheres well to the glycosaminoglycans.
4. It has increased susceptibility to oxidation.
5. It is more selectively bound to scavenger receptors on monocyte derived macrophages. [49]

ELEVATED BLOOD PRESSURE

It highly associates with the obesity and occurs mainly in persons with insulin resistance. Hypertension is multifactorial in origin. For example, increasing arterial stiffness significantly contributes to systolic hypertension in the elderly.

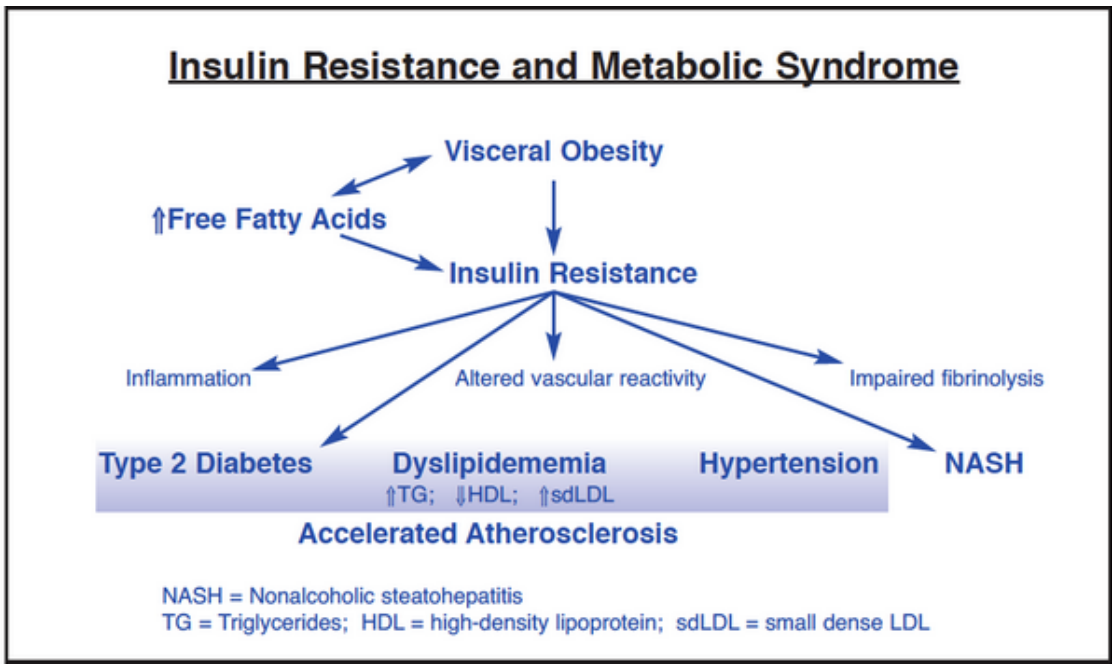
The relation between insulin resistance and hypertension is well established. Insulin resistance involves glucose but not lipid or potassium metabolism, is located in peripheral tissues, but not the liver, is limited to non oxidative pathways of intracellular glucose disposal, and is directly correlated with the severity of hypertension.[50] The relationship between hypertension and insulin resistance relates to several different mechanisms. Insulin has the vasodilator activity and secondary effect of reabsorption of sodium in the kidney. It also increases the sympathetic nervous system activity.In case of insulin resistance, vasodilator property is lost and effect of reabsorption of sodium in the kidney. [51, 52, 53] and sympathetic nervous system activity are preserved. [54, 55, 56]

INSULIN RESISTANCE

It is first identified as the central causal factor for metabolic syndrome. That's why MS is otherwise called insulin resistance syndrome. Even though the mechanism of action is uncertain, it mainly correlates with the risk of cardio vascular disease. Insulin resistance ends in glucose intolerance that leads to diabetes mellitus which also acts as an individual CVD risk factor.

Most accepted and unifying hypothesis to describe pathophysiology of metabolic syndrome is insulin resistance. Insulin resistance can be defined as a condition of decreased responsiveness of these target tissues to normal levels of circulating insulin, that is, a state of decreased insulin sensitivity. [57]

Insulin resistance arises from both genetically determined and acquired metabolic defects.



In a genetically predisposed individuals, increased amount of circulating FFA levels leads to the development of insulin resistance. In the adipose tissue, by the action of the enzyme hormone sensitive lipase (cyclic AMP dependant) triglycerides converted to free fatty acids. Although the synthesis, manner of secretion, and mechanism of endothelial finding of lipoprotein lipase appear similar in all tissues, the factors that control gene expression and post translational events related to processing vary from tissue to tissue.[58]

Insulin inhibits the action of lipolysis in adipose tissue. In case of insulin resistance, this inhibition is lost. So, increased amount of lipolysis and more production of free fatty acids occurred in those conditions. Then, excessive FFA inhibits the action of insulin. It is mainly by the mechanism of modifying downstream signalling and increased substrate availability. [59]

Elevated FFA inhibits insulin signalling. It causes decreases in insulin mediated glucose transport in muscle (mediated by a decrease in translocation of GLUT-4). It results in muscle glucose transport suppression and decreased glycogen synthesis and glycolysis in muscle.[60, 61]

PRO-INFLAMMATORY STATE

It is mainly identified clinically in persons with metabolic syndrome by the increased levels of C-reactive protein. Multiple factors cause elevation of C-reactive protein levels. Obesity is among one of them.

Chronic inflammation may represent a triggering factor in the origin of the metabolic syndrome: stimuli such as over nutrition, physical inactivity, and ageing would result in cytokine hyper secretion and eventually lead to insulin resistance and diabetes in genetically or metabolically predisposed individuals. Alternatively, resistance to the anti-inflammatory actions of insulin would result in enhanced circulating levels of proinflammatory cytokines resulting in persistent low grade inflammation. A generally enhanced adipose tissue derived cytokine expression may be another plausible mechanism for the inflammation/metabolic syndrome relationship. The role of adipokines (adipose tissue specific or enriched hormones secreted by adipose tissue) in the metabolic syndrome is still debated [62, 63]

Adipokines involved in the inflammation (TNF α, IL-6, IL-8, IL-1β, IL-10, Nerve growth factor, Transforming growth factor-β) and acute-phase response (haptoglobin, plasminogen activator inhibitor-1, serum Amyloid A). In case of obesity, adipose tissue produces increased amount of these proteins. Through this mechanism, it connects with insulin resistance and MS.

The increases in the levels of inflammatory cytokines including

- IL- 6
- TNF α
- Resistin
- CRP

reflect over production by the expanded adipose tissue mass. [64]

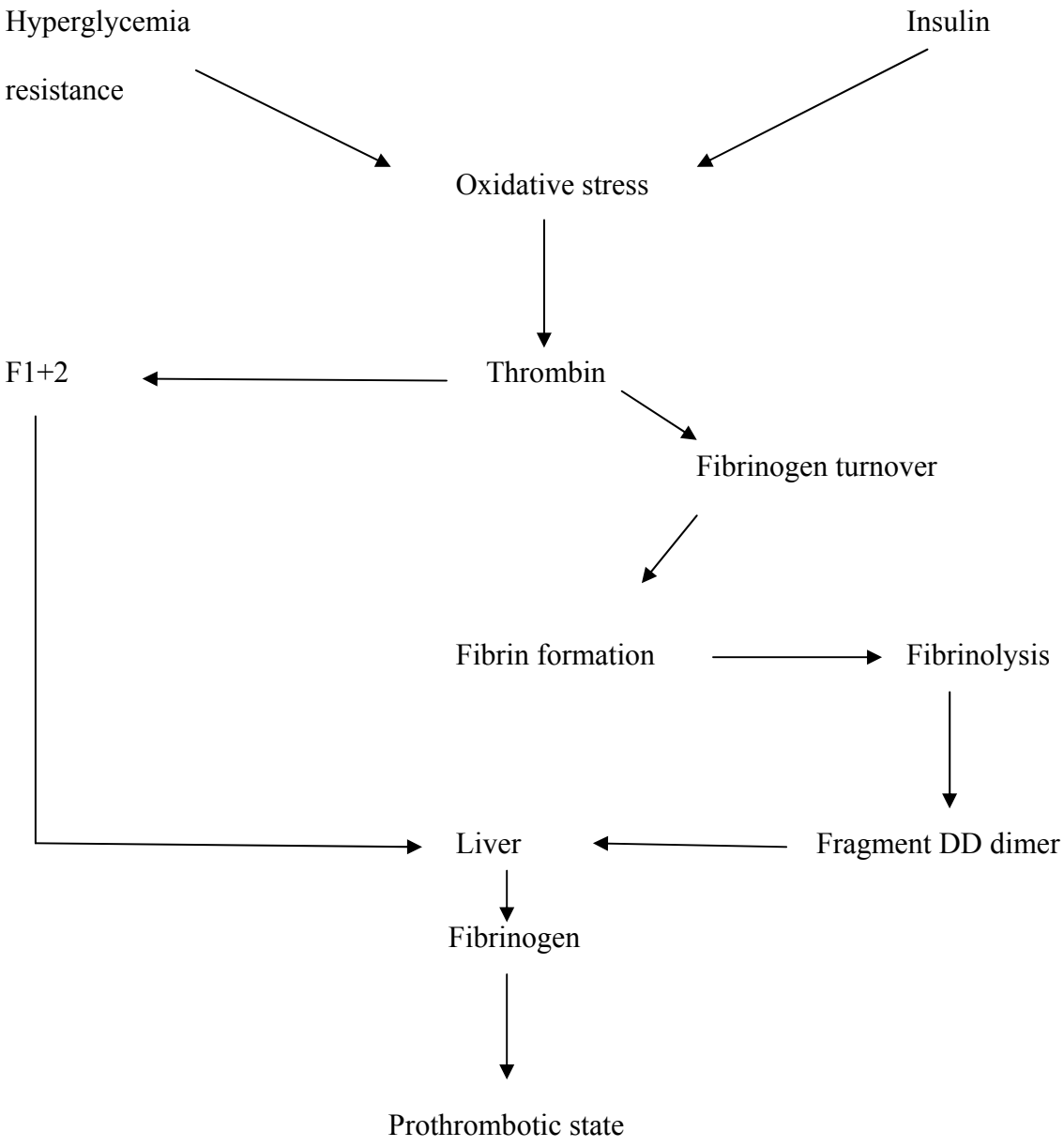
Evidence suggests that monocyte-derived macrophages reside in adipose tissue and might be at least in part of the source of the generation of proinflammatory cytokines locally and in the systemic circulation.[65] There is increasing evidence that insulin resistance in the liver, muscle, and adipose tissue is not only associated with the abundance of proinflammatory cytokines (and relative deficiency of the anti-inflammatory cytokine adiponectin), but is a direct result of this burden.[66]

Concentrations of CRP levels vary within ethnic groups and by ethnic origin.[67] For example, concentrations of CRP levels higher in the Asian Indians compared to the European whites because of insulin resistance and greater central obesity in our peoples.[68]

PROTHROMBOTIC STATE

It is characterized by increased plasma plasminogen activator inhibitor (PAI)-1 and fibrinogen, also 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 inter connected.

Jones RL and colleagues proposed a hypothetical pathway leading to increased plasma fibrinogen level in diabetes.



Hyperglycemia and insulin resistance and the consequent oxidative stress may give rise to increase thrombin formation. This process causes increased production of prothrombin further leading to prothrombin fragmentation (F1+2) and increased turnover of fibrinogen with increased production of fibrin and consequently increased release of fragment-D. Both F1+2 and fragment D regulate production of fibrinogen in the liver, increased release of them in the circulation may produce an increase in circulating fibrinogen.

CLINICAL OUTCOMES OF METABOLIC SYNDROME [69, 70]

ATP III viewed cardio vascular disease as the primary clinical outcome of MS. The people affected by the MS have increased chance of getting Type 2 diabetes mellitus and CVD. There are two types of risk in people with MS, including short term and long term risk. Short term means people affected by MS have increased chance for CVD events in the period of less than ten years and drug therapy required for these people. Long term means people having less short term risk but increased long term risk and life style modification is enough for these patients.

Cardio vascular disease and all cause mortality are increased in men with the metabolic syndrome, even in the absence of base line CVD and diabetes. According to the Framingham cohort study, 50% of the population attributable risk for the diabetes mellitus is mainly due to metabolic syndrome.[35]

CLINICAL FEATURES AND ASSOCIATED DISEASES

SYMPTOMS AND SIGNS

The metabolic syndrome is typically unassociated with symptoms. On physical examination, waist circumference may be expanded and blood pressure elevated. The presence of one or either of these signs should alert the clinician to search for other biochemical abnormalities that may be associated with the metabolic syndrome. Less frequently, lipoatrophy or acanthosis nigricans is found on examination, because these physical findings are typically associated with severe insulin resistance, other components of the metabolic syndrome should be expected.

CARDIO VASCULAR DISEASE

The relative risk for new onset cardio vascular disease in patients with the metabolic syndrome, in the absence of diabetes, averages between 1.5 and 3 fold. In an 8 year follow up of middle aged men and women in the Framingham offspring study (FOS), the population attributable risk for patients with the metabolic syndrome to develop cardio vascular disease was 34% in men and 16% in women. In the same study, both the metabolic syndrome and diabetes predicted ischemic stroke with greater risk for patients with the metabolic syndrome than for diabetes alone (19% Vs 7%), particularly in women (27% Vs 5%). Patients with metabolic syndrome are also at increased risk for peripheral vascular disease.

TYPE 2 DIABETES

Overall, the risk for type 2 diabetes in patients with the metabolic syndrome is increased three to five fold. It is widely accepted that insulin resistance is an early

finding, evident before the onset of hyperglycaemia and predictive of the subsequent development of diabetes. The study done by Peter et al showed that Relative risk for T2DM is similar in (6.90%) men and women with the MS.[167]. According to the Framingham cohort study, 50% of the population attributable risk for the diabetes mellitus is mainly due to metabolic syndrome.[35] Non-diabetic patients with MS are at a very high risk for the development of diabetes. Risk is particularly high when glucose dysregulation is present (impaired fasting glucose or impaired glucose tolerance).

OTHER ASSOCIATED CONDITIONS

In addition to the features specifically associated with metabolic syndrome, insulin resistance is accompanied by other metabolic alterations. These included elevations in the levels of apo B and C III, homocysteine, uric acid, prothrombotic factors (fibrinogen, PAI-1), asymmetric dimethylarginine, serum viscosity, pro-inflammatory cytokines, CRP, white blood cell count and microalbuminuria. Beyond cardio vascular disease and type 2 diabetes, individuals with metabolic syndrome seemingly are susceptible to other conditions, notably, non-alcoholic fatty liver disease (NAFLD) and/or non alcoholic steatohepatitis (NASH), polycystic ovary syndrome (PCOD), cholesterol gall stones, asthma, obstructive sleep apnea (sleep disturbances) and some forms of cancer.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) [71, 72]

NAFLD is a spectrum. It has 3 forms of disease (mild, moderate and severe).Mild one is simple fatty liver. Moderate one is non-alcoholic steatohepatitis. Severe form is cirrhosis. Most extreme form is non-alcoholic fatty liver disease. This

condition progresses to the hepato cellular carcinoma or liver failure. Treatment and prognosis are different for every condition.

NAFLD is usually clinically silent, and its impact has mostly under estimated. It has minimal and nonspecific symptoms like right upper quadrant discomfort and fatigue. Diagnosis is made on incidently by radio graphic findings of fatty liver or increased amino transferase levels.

Non-alcoholic fatty liver disease is closely associated with insulin resistant, obesity and metabolic syndrome. Treatment for this condition is treating each component of the metabolic syndrome and weight loss.

POLYCYSTIC OVARY SYNDROME (PCOS) [73, 74]

Polycystic ovary syndrome is clinically defined as oligomenorrhoea associated with hyperandrogenism. It has been described poetically as “the thief of womanhood” because women with PCOS seek medical attention for infertility and hirsutism. Many patients with polycystic ovary syndrome also have features of the metabolic syndrome, including insulin resistance, obesity and dyslipidemia suggesting an increased risk for cardio vascular disease. PCOS is highly associated with the metabolic syndrome, with prevalence between 40 and 50%. Women with PCOS are 2 to 4 times more chance to get MS than the women without PCOS.

Insulin resistance is the main causative factor in PCOS affected with metabolic syndrome. So, screening for IGT is recommended in adolescent age group itself. First line of treatment for PCOS patients is modification of life style and weight reduction through enhanced physical activity. More studies are needed to describe the role of Insulin sensitizing drugs in PCOS patients with metabolic syndrome.

OBSTRUCTIVE SLEEP APNEA (OSA) [75]

The combination of metabolic syndrome and obstructive sleep apnea (OSA) has been referred to as “syndrome Z”. There are many factors to promote the MS in OSA patients.Those including alterations in the hypothalamic-pituitary axis, triggering of oxidative stress, elevations of many inflammatory mediators (TNF-α, CRP and IL-6), dysregulation of adipokines levels and sleep deprivation. Knowledge about these factors help to prevent the development of metabolic syndrome in OSA patients.

The number of apneas and hypopneas per hour of sleep is termed the apnea-hypopnea index (AHI).The diagnosis of OSA can be made when the AHI is more than 5 in a patient with excessive day time sleepiness.

Continuous positive airway pressure (CPAP) treatment in OSA patients improves insulin sensitivity.

HYPERURICEMIA [76, 77]

Incidence of hyperuricemia in males was 19.07%, which is much higher than that in females 3.42%. The pathogenic mechanism may be due to estrogen promoting uric acid excretion, so it may be more important for men to prevent hyperuricemia. Hyperuricemia is associated with MS components such as dyslipidemia, hyperglycemia, obesity, and hypertension. Hyperinsulinemia also decreases the excretion of uric acid in the proximal convoluted tubule of the kidney and produces hyperuricemia.

Microalbuminuria may also be caused by altered endothelial pathophysiology in the insulin resistant state.

MANAGEMENT OF METABOLIC SYNDROME

RISK ASSESSMENT

Many approaches are available for estimating the ten year risk for CVD. According to the Framingham Heart Study, adding abdominal obesity, triglycerides and fasting glucose to Framingham risk algorithm yields little or no increase power of prediction; however, in the Quebec Cardiovascular Study, concentrations of fasting insulin, triglycerides, apo B, small dense LDL and WC all proved important determinants.[78]

The PROCAM (Prospective cardio vascular Munster study) risk algorithm also includes a family history of premature coronary heart disease and triglycerides.[79] Increased C-reactive protein levels have high risk for CHD beyond standard criteria.[80,81]

According to the Chinese Multi-provincial Cohort Study, original Framingham study over estimate the coronary heart disease risk in Chinese population. Recalibration is required to correct this over estimation. It also advised to other population with no established cohort, to follow the recalibration method.[82]

Metabolic syndrome is common in Indian patients with angiographically documented CAD; most patients with Metabolic syndrome have 10-year risk of >10% as estimated by FRS (Framingham Risk Score). Though Metabolic syndrome is uniformly prevalent across all age groups, using the FRS may underestimate the cardio vascular risk in Indian patients despite documented coronary artery disease. These findings have significant implications for Asian patients with coronary artery disease in whom onset of CAD is often at a younger age than their western counterparts. These

shall be continued health care emphasis on detection of metabolic syndrome and identification of targeted preventive strategies. [83]

The FRS may actually underestimate the overall risk in younger patients, who are likely to have a longer life expectancy as well as in patients with metabolic syndrome. Since CAD often develops at a younger age in the developing world, more data are needed on the relationship between metabolic syndrome and FRS in the resident Indian population.

MANAGEMENT OF UNDERLYING RISK FACTORS

OBESITY

It has various definitions according to different population. Management of obesity also follow the certain principles.

Weight reduction is the best option to reduce all metabolic syndrome risk factors. It is mainly achieved by modification of behaviour and enhanced physical activity. Through this mechanism, it decreases the energy intake and increases the energy expenditure. The first is that “crash diets” and “extreme diets” are seldom effective in producing long term weight reduction. Such diets include very low caloric diet and high fat/low carbohydrate diets more effective and healthful for long term weight loss are reduced energy diets.[84, 85]

Reduced intake of calories, 500-1000 calories per day is adviced to reach a weight loss of 0.5-1 Kg per week. The target of reduction of body weight is 7 to 10% over one year. Along with this, maintenance of increased physical activity and modification of behaviour on long term basis also important. The emphasis in behavioural modification should include improvements in eating habits (examples.

setting goals, planning meals, reading labels, eating regular meals, reducing portion sizes, self monitoring, and avoiding eating binges). Although knowledge and education are critical, they are insufficient and thus professional support (Eg. Nutrition counselling) is often very helpful.

Weight reduction drugs have not been particularly effective for treatment of obesity, bariatric surgery is the best option to treat the morbid obesity patients.[86] After one year follow up in patients undergoing surgery, 95% of them have free from symptoms. [87]

In consideration of the safety and advantage of laproscopic bariatric surgery and its dramatic effect on the metabolic syndrome, laproscopic bariatric surgery might be used more freely in the treatment of the metabolic syndrome. Current indications for surgery in morbidly obese patients include body mass index greater than 40 or greater than 35 if co-morbidities are present; however, for patients with moderate obesity (BMI between30 to 35) and the metabolic syndrome, laproscopic bariatric surgery might be included in the choices of treatments.[88]

In addition to resolving the metabolic syndrome, significant weight reduction after obesity surgery is also very effective in the reduction of uric acid levels and elevated liver function. The significant reduction of white blood cell count after obesity surgery reflects the improvement of a proinflammatory state in severely obese patients.

PHYSICAL INACTIVITY[89, 90, 91]

Physical activity can be characterized by any movement that requires skeletal muscles and therefore increases energy expenditure over resting metabolic rate.

Forms of exercise include

- Aerobic activity
- Resistance exercise

Aerobic exercise consists of rhythmic, repeated and continuous movements of the same large muscle for at least 10 minutes at a time. When it is performed at sufficient intensity and frequency for several months, maximal oxygen uptake improves by 15% - 20% in previously sedentary individuals (Eg. walking, jagging, bicycling and swimming).

Resistance exercise consists of activities that use muscular strength to move a weight or move against a resistive load. By increasing muscle mass and endurance, resistant exercise training can produce more rapid changes in functional status and body composition than aerobic training. It also improves insulin sensitivity to a similar extent as aerobic exercise (Eg. weight lifting and exercise using weight machines).

Based on the above data, moderate intensity activity has an important role to play in the modification of risk factors for cardio vascular disease and the metabolic syndrome.

ATHEROGENIC AND DIABETOGENIC DIETS[92, 93, 94, 95]

Persons affected by metabolic syndrome must follow the following diet: low consumption of simple sugars, reduced intakes of trans fats, saturated fats and cholesterol, and high amount of vegetables, fruits and whole grains should be taken. Amount of unsaturated fats and carbohydrate intake is still debated. Some investigators advised to low fat diet (to promote weight reduction), others advised to take high intake

of monounsaturated fat (decreases postprandial hyperglycemia and serum TG levels, increases the HDL-C levels).

A healthy diet also includes whole grains, fat-free or low fat dairy products and protein foods such as lean meats, poultry without skin, seafood, processed soy products, nuts, seeds, beans and peas. Choose and prepare foods with little sodium (salt).

Data suggesting that phytochemical-abundant dietary patterns such as Mediterranean diet, may be beneficial for treating metabolic syndrome, because of their impact on insulin signalling.

Epidemiological studies, particularly in males, suggest that moderate wine intake may protect against the development and complications of metabolic syndrome, an effect that is at least partially attributable to polyphenols, such as resveratrol, found in red wines.

MANAGEMENT OF METABOLIC RISK FACTORS

ATHEROGENIC DYSLIPIDEMIA [96, 97, 98, 99, 100]

This condition consists of increased triglycerides, apo B and small LDL particles and low HDL cholesterol. 3-hydroxy 3-methyl glutaryl- coenzyme A reductase inhibitors (statins) reduce risk for major cardiovascular disease events in high risk patients with the metabolic syndrome by reducing all apo B containing lipoproteins. Statins are frequently combined with fibric acid derivatives, to reduce the triglyceride and cholesterol levels. Fibrates + statins combination is the popular one, but it has higher risk for myopathy. Rhabdomyolysis is a known, rare serious side

effect of statin monotherapy and of statin-fibrate combination therapy. It is mainly noted for the fibrate Gemfibrozil because this combination produces high statin concentrations in the blood.

Fenofibrate + Statin combination is less likely to cause myopathy. Low dose of nicotinic acid + Statin is an alternative combination to Fibrate + Statin therapy.

Bile acid sequestrants like Cholestryamine produce moderate reductions in LDL cholesterol. These are second line drugs in atherogenic dyslipidemia and additive in LDL cholesterol lowering in combination with other cholesterol lowering drugs. They lack systemic toxicity.[101]

Low HDL cholesterol is common among patients managed for dyslipidemia and represents an important and under treated source of elevated cardio metabolic risk. Nicotinic acid, the most powerful agent currently available for the correction of low HDL cholesterol, has been shown in well-designed clinical trials to inhibit the progression of atherosclerosis and to reduce cardiovascular event rates in patients at high risk of adverse cardiovascular outcome.[102]

Some studies suggest that omega-3 poly unsaturated fatty acids supplementation is also effective when added in combination with other lipid-lowering drugs. Omega-3 fatty acids reduce plasma triglyceride levels by several mechanisms. It can also influence the levels of other lipids and lipoproteins including HDL-C and LDL-C.[103]

BLOOD PRESSURE[104, 105, 106]

Treatment for patients with hypertension and MS includes two types of therapy, pharmacological and non-pharmacological therapy. Non-pharmacological therapy

includes alcohol and calorie restriction, smoking cessation, sodium restriction, increased physical activity and weight reduction.

Pharmacological therapy includes ACE inhibitors, ARB and central sympatholytic agents. Renin Angiotensin Activating system blockers (ACE inhibitors, ARB) is the first line of drugs because of their effect of increases the insulin sensitivity and sympathetic inhibitory effect. Central sympatholytic agents like Imidazoline drugs, are also inhibits the sympathetic nervous system activity.

ACE inhibitors provide Cardio protective and Reno protective benefits beyond their effect on blood pressure: the ARBs also reno protective and cardio protective. Long acting calcium channel blockers are recommended in hypertensive patients with metabolic syndrome because it produces improvement in insulin resistance. Spironolactone along with ACE inhibitor or ARB therapy is the drug of choice for diabetic nephropathy patients.

Patients with MS require strict blood pressure control. If type 2 diabetes mellitus is present, in 2/3 of them target blood pressure values could be achieved only with two or more antihypertensive drugs.

Treatment with Irbesartan + hydrochlorothiazide fixed-dose combinations provides good blood pressure control in > 2/3 rds of HT patients with metabolic syndrome. Lipid and blood pressure targets are reached in a high percentage of patients with hypertension and cardio vascular disease treated with a combination of Amlodipine + Atorvastatin.

INSULIN RESISTANCE AND HYPERGLYCAEMIA[107, 108, 109, 110]

According to previous reports, Metformin or thiazolidinediones decreases the type 2 diabetes mellitus risk in IFG/IGT patients but life style intervention is important to decreases the risk.

Czech Diabetes Society provides the latest recommendations, to protect the patients suffered by type 2 diabetes mellitus, against coronary and cerebrovascular disease is mainly to target all cardiovascular risk factors including Dyslipidemia, obesity, hypertension and other symptoms of metabolic syndrome.

The target HbA_1C levels in patients with the low cardiovascular risk should be below 4.5% but to target HbA_1C below 6% is enough for the patients with a history of limited life expectancy, severe hypoglycaemia, extensive co morbid conditions or advanced micro and macro vascular complications or those with long duration diabetes.

Life style changes are the main aspect of therapy. Metformin is the drug of choice. If mono therapy does not provide satisfactory result, combination with other oral hypoglycemic agents or insulin provided.

It is possible to use a range of different combinations, metformin is administered with sulphonylurea derivatives (advantage-low price), with a glitazone (advantage-no risk of hypoglycaemia), with incretins,acarbose,with glinides, anti obesity agents or insulin. The next step is triple combination of hypoglycaemic agents.

Therapy also includes dietary and lifestyle changes, and education for prevention of complications, particularly prevention of diabetic foot and atherosclerosis.

The use of lipid-altering, antihypertensive and hypoglycaemic drugs can modify insulin sensitivity and body weight. Metformin and thiazolidinediones improve insulin sensitivity but have discrepant effects on body weight; metfomin reduces weight whereas thiazolidinediones increase it. The increase in weight in patients treated with insulin secretagogues (sulphonyl ureas and repaglinide or nateglinide) and insulin results mostly from improved glyceamic control and increase in caloric intake as a result of hypoglycaemia.

With the exception of nicotinic acid, lipid altering drugs do not affect insulin sensitivity or weight, whereas the effect of antihypertensive drugs is more complex. Beta adrenergic blockers and thiazide diuretics might decrease insulin sensitivity but less so at low doses, whereas ACE inhibitors and angiotensin II receptors antagonists have variable effects.

By uncertain mechanisms, ACE inhibitors and angiotensin II receptors antagonists seem to decrease the incidence of type 2 diabetes.

PROTHROMBOTIC STATE

Metabolic syndrome is accompanied by elevation in Prothrombotic factors (fibrinogen, plasminogen activator inhibitor 1 and possibly other coagulation factors). The only available clinical approach to an increased risk for arterial thrombosis in patients with metabolic syndrome is low dose asprin or other antiplatelet drugs. These drugs are universally recommended unless contraindicated in patients with established cardiovascular disease. In other people with the metabolic syndrome, asprin prophylaxis is a therapeutic option when the risk for cardiovascular disease events is judged to be relatively high.

Assessment of prothrombotic state typically found in subjects with metabolic syndrome is not so easy in routine medical laboratory. The level of fibrinogen can be easily determined automatically, however, coagulation factors such as plasminogen activator inhibitor 1 are generally not routinely measured.

Weight loss due to lifestyle modifications such as low caloric diet, physical activity, and adequate pharmacologic interventions influencing simultaneously single components of the metabolic syndrome (antihypertension, antidiabetic, hypolipemic and antithrombotic agents) are effective methods to decrease the impact of prothrombotic state in metabolic syndrome and it can prevent the development of atherothrombosis and its clinical manifestations.

PROINFLAMMATORY STATE

This state is characterized by increased levels of cytokines and acute phase reactants. Among this increased levels of CRP concentrations is the main indicator of proinflammatory state and it has high risk for diabetes and CVD.[111]

Life style therapies, mainly weight reduction, decreases the C-reactive protein levels and also the inflammatory state. Some study demonstrates that during weight loss, after gastric restrictive surgery, inflammatory mediators remain elevated for atleast 3 months postoperatively, suggesting initially an ongoing inflammatory state. However, 2 year after surgery,the inflammatory mediators reach near normal values.[112]

No specific anti-inflammatory drugs are available to treat the proinflammatory state. However, several drugs used to treat other metabolic risk factors- statins, fibrates and thiazolidinediones have been reported to reduce concentrations of C- reactive proteins.[113]

THERAPEUTIC STRATEGY FOR METABOLIC SYNDROME:

primary goals of therapy (recommended) →secondary goals (informed by clinical judgement)

RISK FACTOR (10 yr risk for coronary heart disease)	**Lower to moderate risk (<10%)**	**Moderately high risk (10-20%)**	**High risk (>20%)***
Metabolic syndrome as a whole	Reduce lifetime risk for ASCVD and diabetes	Reduce both lifetime and short - term risk	Reduce short- term risk
Obesity	10% reduction in body weight (preference to lifestyle therapy) →BMI <25%	10% reduction in body weight (consider weight loss drugs) →BMI <25%	10% reduction in body weight(consider weight loss drugs) →BMI <25%
Atherogenic diet	Maximal anti-atherogenic diet	Maximal anti-atherogenic diet	Maximal anti-atherogenic diet
Physical inactivity	Exercise 30 min/day→60 min/day	Exercise 30 min/day→60 min/day	Exercise 30 min/day→60 min/day
Atherogenic dyslipidemia : ↑LDL cholesterol (non-HDL cholesterol)	LDL cholesterol (non-HDL cholesterol)<130 (160) mg/dl→100 (130) mg/dl (with lifestyle)	LDL cholesterol (non-HDL cholesterol)<130 (160) mg/dl (with drugs if necessary)→100 (130) mg/dl	LDL cholesterol (non-HDL cholesterol)<100 (130) mg/dl→70 (100) mg/dl (in CHD patients)
Atherogenic dyslipidemia: ↓ HDL cholesterol	Raise HDL (lifestyle therapy)	Raise HDL (lifestyle therapy)	Raise HDL (consider drug therapy)

Blood pressure	BP <140/90 mmHg (with drugs if necessary)→130/80 (with lifestyle therapies)	BP <140/90 mmHg (with drugs if necessary)→130/80 (with lifestyle therapies)	BP <140/90 mmHg (with drugs if necessary)→130/80 (with drugs in diabetes and chronic renal failure)
Elevated fasting blood sugar (prediabetes)	FBG<100 mg/dl (with lifestyle therapy)	FBG<100 mg/dl (with lifestyle therapy)	FBG<100 mg/dl (consider insulin sensitizer)
Elevated fasting blood sugar (diabetes)	$HbA1_C$ 6-7%	$HbA1_C$ 6-7%	$HbA1_C$ 6-7%
Prothrombotic state	No drug	Consider anti platelet drug (aspirin)	Anti platelet drug (aspirin)
Proinflammatory state	Complete smoking cessation	Complete smoking cessation	Complete smoking cessation

*High risk patients include those ASCVD, diabetes, and those multiple risk factors and 10-yr risk for coronary heart disease greater than 20%.

LIPOPROTEINS AND ITS METABOLISM

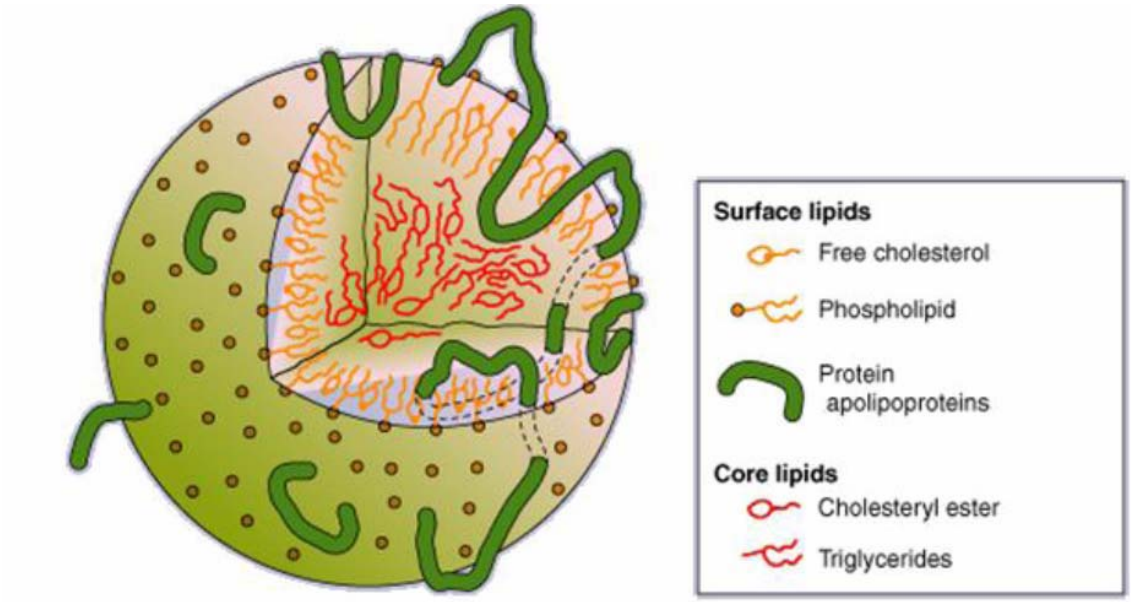
Lipoproteins are complexes of lipids and proteins that are essential for the transport of cholesterol, triglycerides and fat-soluble vitamins.[114]

COMPOSITION OF LIPOPROTEIN

Lipoproteins are complex macromolecular spherical complexes that contain hydrophobic non- polar lipids (triglycerides, cholesteryl esters and fat soluble vitamins) surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins that interact with body fluids .[114,115,116,117] Free cholesterol molecules are dispersed

throughout the lipoprotein shell to stabilize it in a way that allows it to maintain its spherical shape.[117] The association of the core lipids with the phospholipids is noncovalent, occurring primarily through hydrogen bonding and van der Waal's forces. This binding is loose enough to allow ready exchange of lipids among the plasma lipoproteins and between cell membranes and lipoprotein, yet strong enough to allow the various classes and subclasses of lipoproteins to be isolated by a variety of analytical techniques.[116]

Structure of Lipoprotein



The lipoproteins are essential mainly for the transport of water insoluble lipids through the aqueous blood plasma.[115] Lipoproteins play an essential role in the absorption of dietary cholesterol, long chain fatty acids and fat soluble vitamins, the transport of triglycerides, cholesterol and fat soluble vitamins from the liver to the peripheral tissues and the transport of cholesterol from the peripheral tissues to the liver.[114]

CLASSIFICATION OF LIPOPROTEINS

The plasma lipoproteins are divided into five major subclasses based on their relative density as determined by ultracentrifugation.[114, 115]

i. Chylomicrons

ii. Very low density lipoproteins

iii. Low density lipoproteins

iv. Intermediate density lipoproteins

v. High density lipoproteins

Each lipoprotein class comprises a family of particles that vary slightly in density, size and migration during electrophoresis and protein composition. The density of lipoprotein is determined by the amount of lipids per particle. HDL is the smallest and the most dense lipoprotein while chylomicrons and VLDL are the largest and least dense lipoproteins. Most plasma triglycerides are transported by chylomicrons and VLDL while cholesteryl esters are transported by LDL and HDL.[114]

The physico-chemical properties are summarized in the table below: [118]

Lipoproteins	**Chylomicrons**	**VLDL**	**IDL**	**LDL**	**HDL**
Density(g/ml)	<0.95	0.95-1.006	1.006-1.019	1.019 - 1.063	1.063-1.210
Electrophoretic Mobility	Origin	pre-β	Between β and pre-β	Beta β	Alpha α
Molecular weight (Daltons)	0.4-30X10^9	5-10x10^6	3.94.8X10^6	2.75X10^6	1.83.6 X 10^5
Diameter (nm)	>70	25-70	22-24	19-23	4-10

Lipid Protein ratio	99:1	90:10	85:15	80:20	50:50
Major lipids	Exogenous TG	Endogenous TG	Endogenous TG & Cholesterol esters	Cholesterol esters	Phospho lipids
Major Proteins	A1, B48, CI, CII, CIII	B100, CI, CII, CIII, E	B-100,E	B-100	AI,AII
Triglycerides	80-95	55-80	20-50	5-15	5-10
Cholesterol	2-7	5-15	20-40	40-50	15-25
Phospholipids	3-9	10-20	15-25	20-25	20-30
Proteins	1-2	7-10	11	21	50

APOLIPOPROTEINS (APOPROTEINS)

The proteins or polypeptides associated with lipoproteins are called as apolipoproteins.[114, 115,116,117]

Ten principle apoproteins are characterized.[117] One or more apoproteins are present in each lipoprotein. The major apolipoproteins of HDL is designated A. The main apolipoprotein of LDL is ApoB100, which is also found in VLDL. Chylomicrons contain a truncated form of apoB (B-48), which is synthesized in the intestine while apoB100 is synthesized in the liver. ApoC-I, C-II and C-III are freely transferable between several lipoproteins. Apo E is found in VLDL, HDL, chylomicrons and chylomicron remnants.[115]

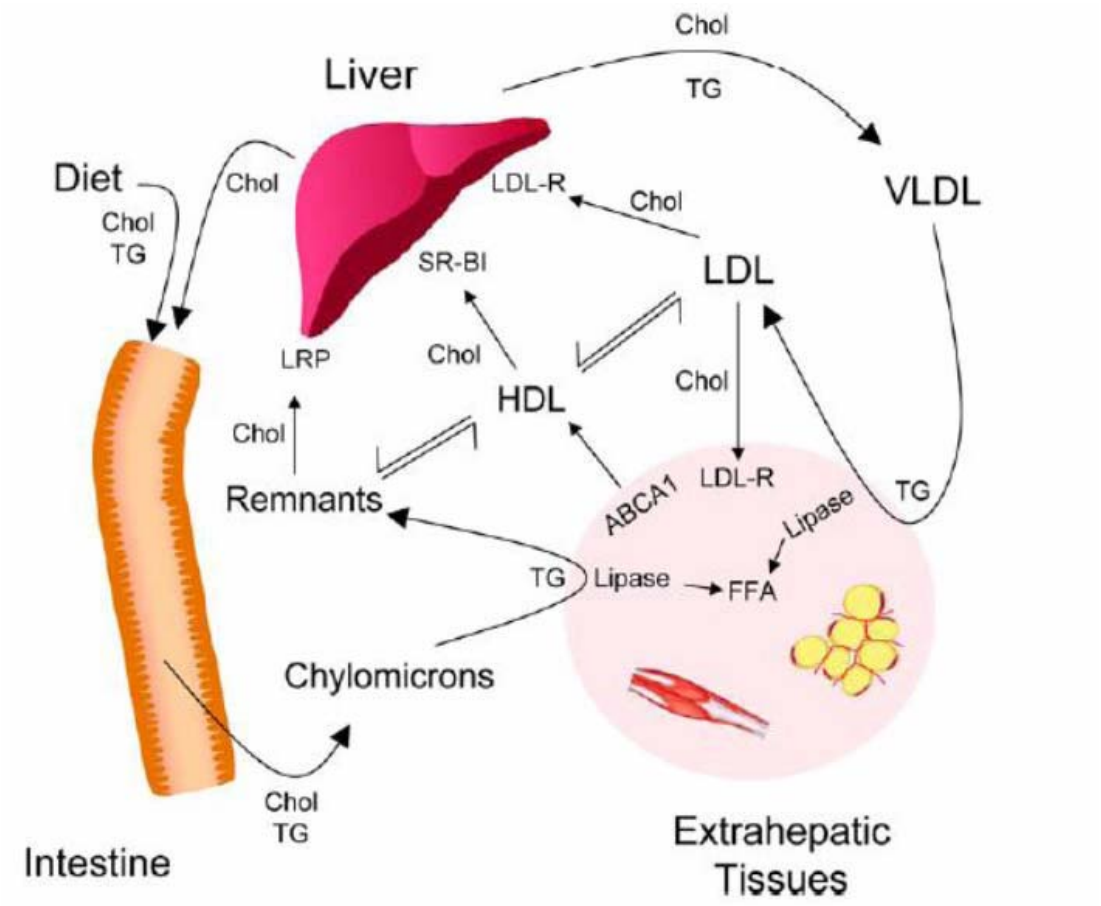
Apolipoproteins collectively have three major functions[116]

1. Activating important enzymes in the lipoprotein metabolic pathways.

2. Maintaining the structural integrity of the lipoprotein complex.

3. Facilitating the uptake of lipoprotein into cells through their recognition by specific cell surface receptors.

Lipoprotein Metabolism

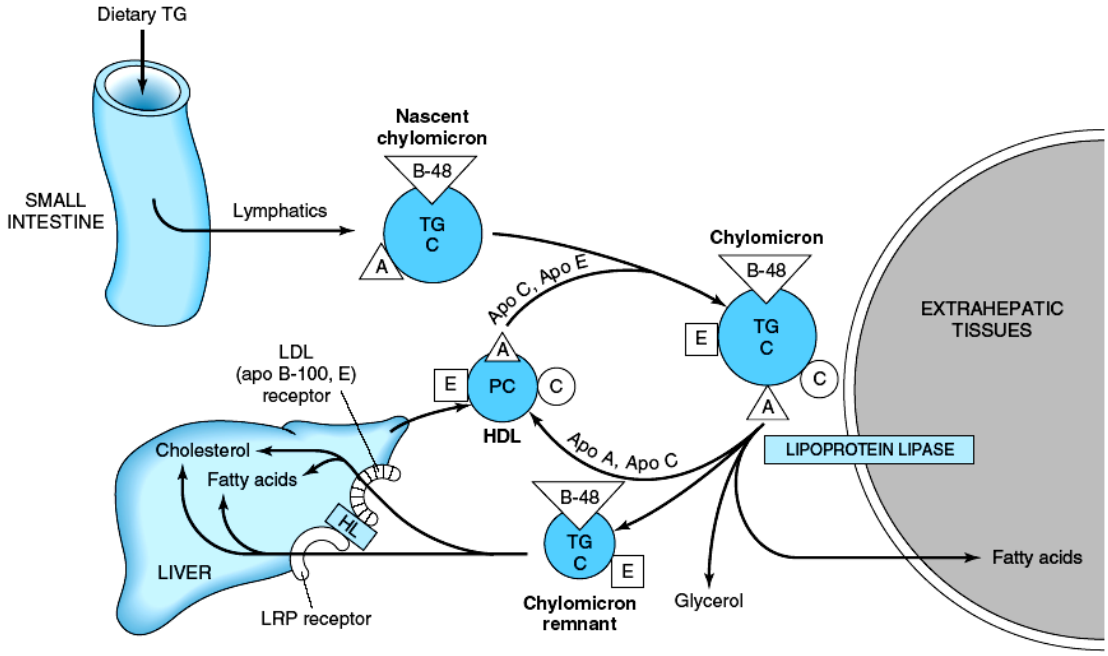


Chylomicrons deliver triglycerides derived from the intestine into blood. Following triglyceride lipolysis to free fatty acids (FFAs) by peripheral tissues, chylomicron remnant particles are cleared by the liver via LDL receptor (LDL-R) related protein (LRP). The liver uses endogenously synthesized triglyceride and cholesterol as well as lipids derived from chylomicron remnants to synthesize VLDL. Triglyceride-rich VLDL is converted by lipolysis to intermediate density lipoprotein (IDL; not shown) and then cholesterol-rich LDL. Peripheral tissues and liver take up LDL-derived cholesterol via the LDL receptor. HDL accepts cholesterol from peripheral tissue for transport back to the liver. The protein components of lipoproteins play key roles as structural elements, enzymes, enzyme cofactors, and ligands for cell surface receptors. For example, apoB is a ligand for the LDL receptor whereas apoA-I interacts with the scavenger receptor SR-BI. Recent mass spectrometric studies demonstrate that lipoproteins carry a diverse array of lower abundance proteins, raising the possibility that lipoproteins play previously unsuspected role in vascular disease and inflammation [64]

EXOGENOUS PATHWAY (DIETARY LIPIDS)

Dietary lipids are hydrolyzed by lipases within the intestinal lumen and emulsified with bile acids to form micelles. Dietary cholesterol, fatty acids and fatsoluble vitamins are absorbed from the proximal small intestine. Cholesterol and retinol are esterified, long chain fatty acids are incorporated into triglycerides and they are packaged with B48, phospholipids and cholesterol in the golgi apparatus to form chylomicrons. The nascent chylomicrons are carried via the intestinal villi to intestinal lymph and delivered via the thoracic duct directly into systemic circulation. Shortly after entering circulation, the particles acquire C apolipoproteins and apo E from circulating HDL. Apo CII present on the chylomicrons now activates the enzyme Lipoprotein lipase (LPL), anchored to the proteoglycans present on the capillary endothelial surfaces of adipose tissue, heart and skeletal muscle. The LPL rapidly hydrolyses the triglycerides to free fatty acids, which are taken up by muscle cells as an energy source or into adipose cells for storage by re-esterification into triglycerides. Some of the fatty acids bind albumin and is transported to other tissues. The chylomicron particle progressively shrinks in size as the hydrophobic core is hydrolyzed and the hydrophilic lipids and the apoproteins on the particle surface are transferred to HDL, creating chylomicron remnants. The chylomicron remnants are rapidly taken up by liver by endocytosis for which the apoE acts as a ligand for the receptor. It is then hydrolyzed by the lysosomes. The cholesterol released can form bile acids, be incorporated into newly synthesized lipoprotein or be stored as cholesteryl esters. It can also down-regulate HMG Co-A reductase, the rate- limiting enzyme in cholesterol synthesis.[114,115]

Exogenous pathway – metabolic fate of Chylomicrons [119]

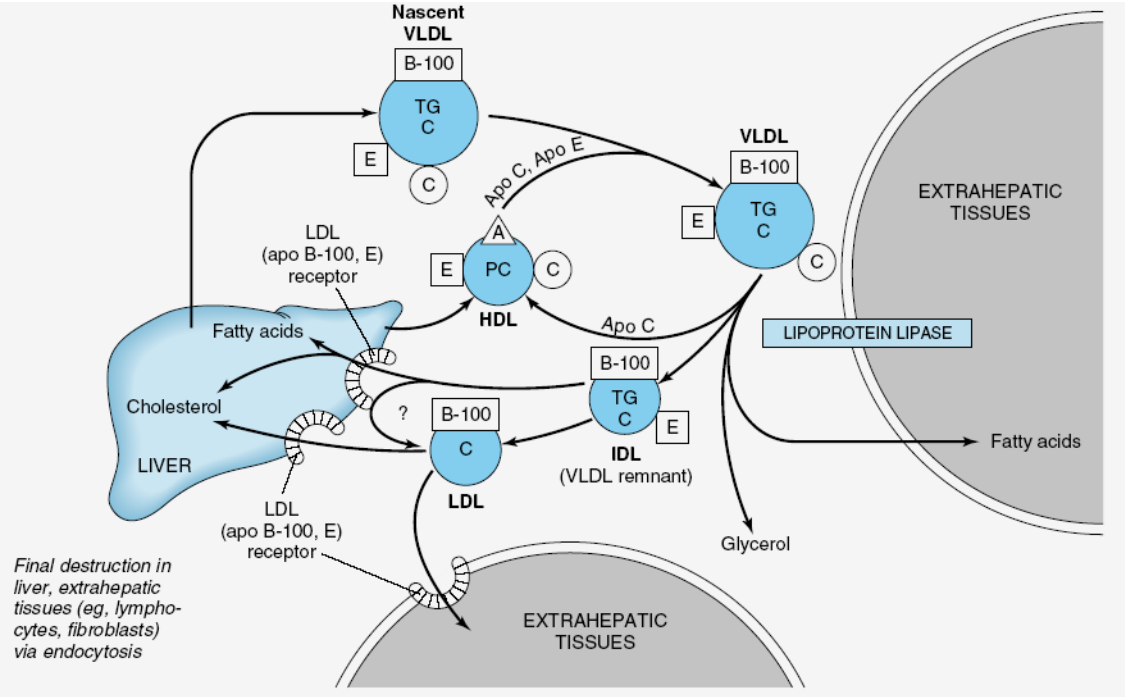


ENDOGENOUS PATHWAY (HEPATIC LIPIDS)

The endogenous pathway of lipoprotein metabolism refers to the hepatic secretion of apoB-containing lipoprotein and its metabolism. The hepatocytes synthesize triglycerides from fatty acids and carbohydrates. Cholesterol is acquired from receptor mediated uptake of chylomicron remnants and also de-novo synthesis of cholesterol by up-regulation of HMG Co-A reductase. The triglycerides and cholesterol along with apoproteins is packaged into secretory vesicles in the golgi apparatus, which requires microsomal transfer protein (MTP) [114], exocytosed into the extracellular space and introduced into circulation through the fenestrae of hepatic sinusoidal endothelium in the form of nascent VLDL. This triglyceride rich particle (55% by mass) contains apoB100, apoE and small amounts of C apoproteins on its surface. After secretion into the plasma, VLDL acquires multiple copies of apoE and C apolipoproteins by transfer

from HDL. In circulation, the triglycerides in VLDL are hydrolyzed by LPL, especially in muscle and adipose tissue. During the hydrolysis, the C apolipoproteins are transferred back to HDL. VLDL particles are thus converted to VLDL remnants, some of which are taken up by the liver and the rest are converted to smaller, denser particles called IDL. The IDLs contain roughly equal amounts of cholesterol and triglycerides. The liver removes approximately 40-60% of IDL by LDL receptor mediated endocytosis via binding to apoE. The remainder of IDL is remodelled by hepatic lipase (HL) to form LDL. During this process, most of the triglycerides in the particle is hydrolyzed, all apolipoproteins except apoB100 are transferred to other lipoproteins. The cholesterol in LDL accounts for over half of the plasma cholesterol in most individuals. Approximately 70% of circulating LDL is cleared by LDL receptor mediated endocytosis in the liver.[114]

Endogenous pathway-Metabolic fate of VLDL and production of LDL



LOW-DENSITY LIPOPROTEIN RECEPTOR PATHWAY

LDL receptors are specific receptors present in coated pits on plasma membranes that recognize and bind apoB100 of LDL. When LDL binds to the receptor, it is internalized by endocytosis. The acidic milieu of the endosome dissociates the receptor from the LDL and the receptor returns to the cell surface while LDL migrates to the lysosome. Here, apoB100 is degraded to small peptides and amino acids. Cholesteryl esters are hydrolyzed and the cholesterol is utilized for the synthesis cell membrane, steroid hormone and bile acids where appropriate. Oversupply of free cholesterol leads to: i. Inhibition of HMG Co-A reductase. ii. Increased cholesteryl ester formation by ACAT and iii. Inhibition of new LDL synthesis. LDL remains in circulation for about 3 days. LDL is also taken up by extrahepatic tissue (Eg. macrophages) through the scavenger receptors or non-receptor mediated pinocytosis. Macrophages that become engorged with cholesteryl esters are called “foam cells" which are the earliest lesions of atherosclerosis. Two thirds of the LDL is normally removed by LDL receptors and the remainder by scavenger cell system.[114]

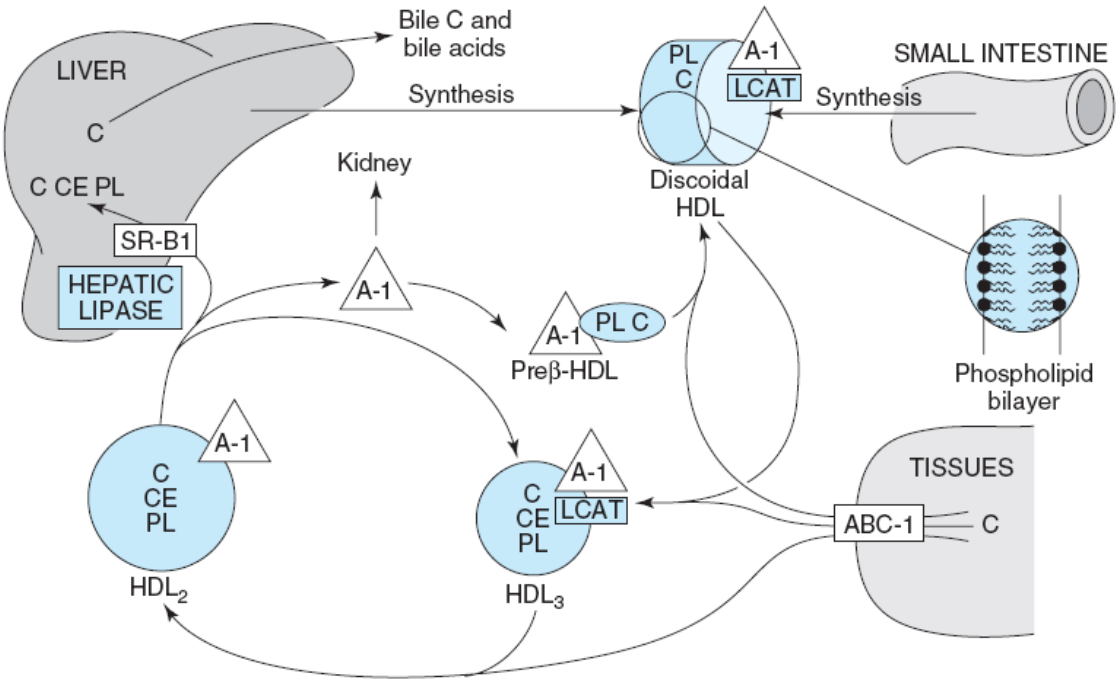
HIGH DENSITY LIPOPROTEIN REVERSE CHOLESTEROL TRANSFER PATHWAY

This pathway transports excess cholesterol from the periphery back to the liver for excretion. HDL is secreted from the liver and the intestine as disk shaped nascent particles that consist primarily of phospholipids and apoA1. Newly secreted apoA-1 rapidly acquires phospholipids and unesterified cholesterol from its site of synthesis via efflux promoted by the membrane protein ATP-binding cassette protein A1 (ABCA1) resulting in the formation of discoidal HDL particles which further acquire unesterified cholesterol from the periphery. The acquired cholesterol is esterified by Lecithin-

Cholesterol Acyl Transferase (LCAT), a plasma enzyme associated with HDL and the more hydrophobic cholesteryl esters moves to the core of the HDL particles. The HDL particles progressively becomes spherical and adds on to further lipids and apoproteins transferred from the surfaces of chylomicrons and VLDL during lipolysis. HDL cholesterol can be selectively taken up by the liver via selective transfer of lipids to cells. HDL apoE can also be recognized by the hepatic remnant receptors. HDL cholesteryl esters can also be transferred to apoB containing lipoproteins in exchange for triglyceride by the Cholesterol Ester Transfer Protein (CETP).[114,116]

HDL particles undergo extensive remodelling in the plasma by a variety of lipid transfer proteins and lipases. Phospholipid transfer protein transfers phospholipids from other lipoproteins to HDL. After CETP- mediated lipid exchange, the triglyceride enriched HDL becomes a much better substrate for Hepatic lipase (HL) which hydrolyses the triglycerides and phospholipids to generate smaller HDL particles that are catabolised faster.[114]

HDL reverse cholesterol pathway - Metabolism of HDL[120]



LIPOPROTEIN (a)

Lipoprotein (a) is also called as the sinking pre-β-lipoprotein is similar to LDL in its protein composition.[121] Lp(a) is a complex particle in human plasma that is assembled from one LDL molecule that carries all the lipid and one glycoprotein [apo(a)], which has a high degree of homology to plasminogen.[122,123]

HISTORICAL ASPECTS

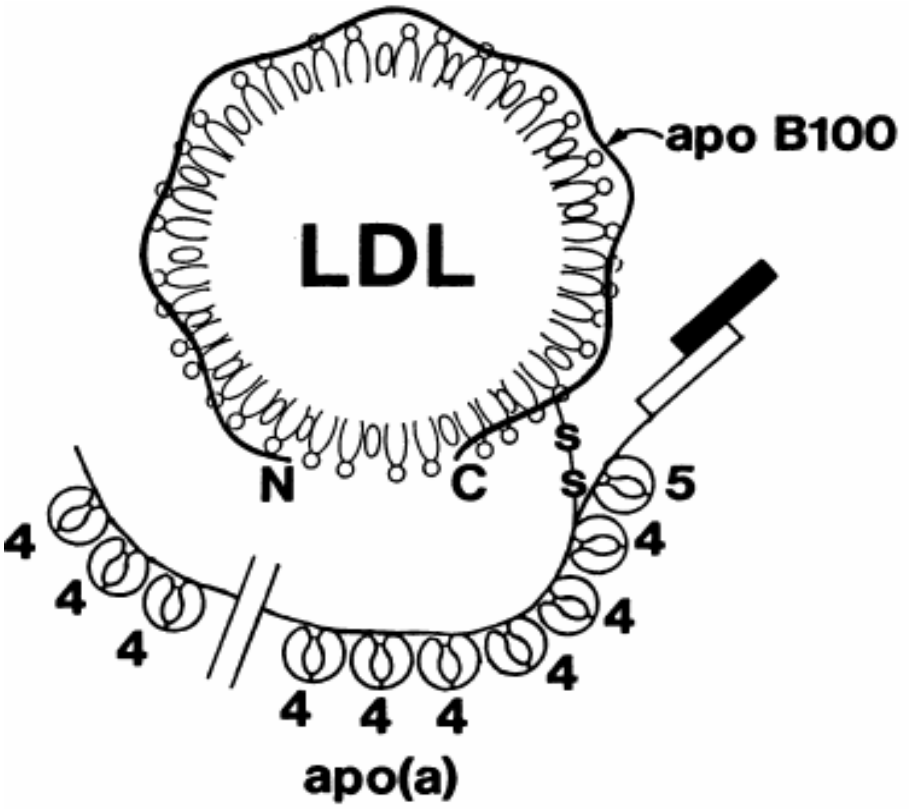
Lp(a), was discovered by Ka¨re Berg [124,125,126](1963) in Norway in a immunochemical study designed to detect antigenic variations in human LDL.[122] Lp(a) was purified to homogeneity and characterized in some detail in the early 1970s. Lp(a) was rediscovered several times and designated "Pre-beta-1 lipoprotein".[124,125,127] Harvie and Schultz reported that their preparations of Lp(a) had a rather broad sedimentation coefficient distribution, and suggested heterogenicity of Lp(a). The first systematic

study on Lp(a) heterogeneity was carried out in 1984 by Fless et al., who not only confirmed the findings of Harvey and Schultz but also found that Lp(a) exhibits both inter- and intra-individual density heterogeneity, and that this heterogeneity is accounted for by differences in lipid and protein composition. Scanu et al. and Fless et al. in 1990 first established that the protein moiety of Lp(a), namely the apo B-apo(a) complex contrary to apoB100, is water soluble.[128]

A breakthrough in Lp(a) research was the cloning and sequencing of apo(a) by MC Lean et al(1986), which revealed a high degree of homology of apo(a) with plasminogen.[127] Discovery of the genetic size polymorphism of apo(a) by Utermann et al. (1987) has provided major insights into the genetic control of plasma Lp(a) concentrations.[128] As early as 1967 Renninger et al. recognized a positive association of Lp(a) lipoprotein with myocardial infarction.[129] The clinical interest in Lp(a) arose when Dahlen and co-workers recognized a higher frequency of Lp(a) positive subjects among men with coronary heart disease as compared with the controls.[125,127]

STRUCTURE OF Lp(a)

Lp(a) is LDL-like particle formed by the association of the highly polymorphic glycosylated apolipoprotein(a) (apo(a)) with apolipoprotein B100 (apo B100), the classic protein moiety of LDL. The apo(a) is attached to apo B100 through a single disulphide link between apo B100 Cys 3734 and apo(a) kringle(K) IV type 9 Cys[122]; additional noncovalent interactions play accessory roles in promoting, mediating and reinforcing the association between the apolipoproteins. Under microscopic analysis of Lp(a) particles, apo(a) assumes a belt-like structure; both apo(a) ends are attached at two distant sites to a spherical LDL.[130]



Schematic model of the structure of human plasma Lp(a). Lp(a) is made up of an LDL-like structure in which apo B100, the protein moiety of authentic LDL, is covalently linked to a glycoprotein, apo(a), which is the specific marker of Lp(a) and exhibits a striking similarity to plasminogen. The dominant structural motif of apo(a) is the "kringle," a three-disulfide, triple loop structure named for its resemblance to a Danish pretzel. K4 is repeated 13-37 times, whereas there is only one kV. It is now established that the size of each apo(a) isoform is under strict genetic control and determined by the number of kringles that it contains. Usually, there is 1 mol of apo(a) and I mol of apo B100 in each Lp(a) particle. However, species of Lp(a) having one copy of apo B100 and 2 mol of apo(a) have been reported)[128]

STRUCTURE OF Apo(a)

Apo(a) is a high molecular weight glycoprotein with a high carbohydrate content and displaying remarkable size heterogeneity. Several molecular weight forms have been described with masses ranging from 280000 to 700000 daltons. The genetic basis for this polymorphism is due to six different apo(a) phenotypes. It has been

postulated that apo(a) phenotypes are controlled by a series of autosomal alleles at a single locus.[131] The complete primary amino acid sequence of an apo(a) of unknown phenotype has been recently derived by sequencing cloned human apo(a) cDNA. Initial protein sequencing studies had revealed a high degree of homology between peptides from apo(a) and human plasminogen.[123,131] The latter is a single-chain protein of *Mr* 92000 containing several distinct structural regions: an N-terminal sequence of 76 amino acids is followed by five tandemly arranged kringle domains having approximately 40%-50% homology with each other. Each kringle contains 78-80 amino acids and includes six Cys residues with disulfide bridges between the first and sixth, second and fourth, and third and fifth cysteines in each kringle sequence, giving it a characteristic triple-loop structure. Sequencing of apo(a) at the protein level had revealed a high degree of homology with plasminogen.[131] Plasminogen is a plasma serine protease of the fibrinolytic system.[126] Apo(a) contains one copy each of sequences homologous to the kringle V and protease regions from plasminogen.[123,131] Apo(a) is much larger than plasminogen. This is due to the amplification of one of the plasminogen like K IV in apo(a). There are ten distinct classes (subtypes) of Kringle IV that differs from each other in amino acid sequence copy. Subtypes 1 and 3 to 10 are present in a single copy. Subtype 2 is present in variable numbers (3 to >40). This is responsible for the size heterogeneity of apo(a) . In contrast to plasminogen, apo(a) has a high carbohydrate content. During protein sequencing studies, a carbohydrate-rich peptide was isolated in high yield, which could be separated from the other apo(a) peptides by gel filtration alone. This peptide Tl was 55 amino acids in length. This peptide represents the sequence connecting two kringle IV-like domains. Seven probable glycosylation sites could be identified in peptide Tl: one N-linked

oligosaccharide within the kringle and six O-linked oligosaccharides (four Thr and two Ser) in the connecting sequence.[131]

Structural Comparison between Human Plasma Apo(a) and Plasminogen[132]

Parameter	Apo(a)	Plasminogen
Molecular weight	280,000-800,000	- 90,000
Signal sequence	19 residues*	19 residues**
NH2 terminus	Glu-Gln-Ser-His-Val-Val...	Glu-Pro-Leu-Asp-Asp-Tyr.
Kringle 1	Absent	1
Kringle 2	Absent	1
Kringle 3	Absent	1
Kringle 4	13-37***	1
Kringle 5	1	1
Activation site	Ser-Ile 4308-4309	Arg-Val 561-562
Catalytic triad	Ser-His-Asp	Ser-His-Asp
Amino acids in mature protein	4529	
Carbohydrate(%)	28	
Sialic acid(%)	21	

* *Apo(a): -Met-Glu-His-Lys-Glu-Val-Val-Leu-Leu-Leu-Leu-Leu-Phe-Leu-Lys-Ser-Ala-Ala-Pro*

** *Plasminogen: -Met-Glu-His-Lys-Glu-Val-Val-Leu-Leu-Leu-Leu-Leu-Phe-Leu-Lys-Ser-Gly-Gln-Gly-. ..*

*** *Isoforms with higher or lower K4 number are possible*

CHARACTERISTICS OF Lp(a)

Lp(a)	
Electrophoretic mobility (agarose)	Pre – beta
Buoyant density(g/ml)	1.040-1.131
Isoelectric Point(pl)	4.9
Molecular mass (Daltons)	$3.8\text{-}4.66 \times 10^6$
Molecular diameter(A_0)	250
Plasma concentration (mg/dl)	0.1 to 120
Protein(g/ml)	800000-1350000
Free cholesteryl ester (mol/mol)	750
Cholesteryl ester (mol/mol)	2000
Triglycerides (mol/mol)	350
Phospholipids (mol/mol)	1110
Fractional catabolic rate (per day)	0.26-0.306
Plasma t1/2 days	3.32-3.93
Synthetic rate (mg/kg/day)	4.60+/-3.64(0.54-11.39)

METABOLISM OF Lp (a)

Apo(a) transcripts have recently been found in adrenal glands, lungs, pituitary, brain and testes, circulating apo(a) is mainly synthesized by the liver as a precursor with lower molecular mass which is processed into the mature form and then secreted into the blood stream.[130]

Rapidly after secretion, free apo(a) binds to circulating LDLs to generate complete Lp(a) particles. The association between apo(a) and apo B occurs extracellularly following secretion rather than inside cellular compartments since coprecipitation of apo B and apo(a) was only observed in the culture medium and not in cell lysates.[123,130] Specific kringle-4 domains in apo(a), mainly T-6 and T-7, bind in a first step to circulating LDL, followed by the stabilization of the newly formed Lp(a) complex by a disulfide bridge.[133] The apo(a)/ Lp(a) secretion from hepatocytes is regulated at various levels including postranslationally by apo(a) isoform-dependent prolonged retention in the endoplasmic reticulum.[134]

About 90% of Lp(a) concentration is under genetic regulation.[130] Lp(a) levels are particularly affected by apo(a) synthetic rate, which is subject to strong genetic regulation. The greatest part of the variability in Lp(a) levels (over 40%) is accounted for by quantitative polymorphism in the internal sequence of the apo(a) gene; qualitative polymorphisms in the sequence of the promoter play only a minor role (from 10 to 14%)0.[130] Despite this genetic regulation, some metabolic abnormalities which may have an effect on Lp(a) levels in the plasma are the diabetes, liver and renal failure, acute-phase response, hormonal homeostasis and defects in the LDL-receptor gene have all been shown to influence the still enigmatic metabolism of this lipoprotein.[130]

Lp(a) plasma levels are known to be elevated in patients with: Nephrotic syndrome, end stage renal disease, Continuous Ambulatory Peritoneal Dialysis, hemodialysis, IDDM, hypothyroidism.[135]

Several rare disorders such as LCAT, LPL deficiency, as well as liver disease and abetalipoproteinemia are associated with low plasma levels or lack of Lp(a).[134]

The sites and mechanism of Lp(a) removal from plasma are only poorly understood.[134] There are conflicting observations regarding the catabolic pathways of Lp(a). Because of its resemblance to LDL, it was initially postulated that Lp(a) degradation was mediated by the LDL receptor (LDL-R) (50) via apoB-100 in the Lp(a). LDL-receptor seems to play only a minor role in Lp(a) elimination.[123] Evidence is now accruing in favor of a nonspecific receptor pathway, both in human skin fibroblast cultures, human monocyte-derived macrophages, plasminogen receptor and the asialoglycoprotein receptor have been implicated. Recent observations suggest that the VLDL-receptor which is primarily expressed in skeletal muscle may be of significance for Lp(a) binding and degradation.[123] In line with the fact that chronic renal failure is associated with increased Lp(a) plasma levels, it was suggested that the kidneys may be important for Lp(a) catabolism.[123,136] Circulating Lp(a) interacts specifically with kidney cells, or possibly other tissues, causing cleavage of 2/33/4 of the N-terminal part of apo(a) by a collagenase-type protease. Part of these apo(a) fragments are found as excretory products of Lp(a) in urine, but there are indications that they, in fact, represent the biologically active form of apo(a) and are possibly responsible for the atherogenicity of Lp(a).[137] The fractional rates of catabolism for both apo B and apo(a) from Lp(a) were identical, and considerably lower than that observed for LDL, in line with the notion that the in vivo mechanisms of Lp(a)

clearance are different from the LDL receptor and eliminate the bulk of Lp(a) as an integral particle from the circulation.[123,138]

GENETICS OF Lp(a)

Lp(a) is a quantitative genetic trait. The distribution of Lp(a) in the population is highly skewed and very broad.[139] The apo(a) gene is located in the long arm of chromosome 6 (6q26-27) where it is closely linked to the plasminogen gene.[130,136]

Sequencing of cloned human apo(a) complementary DNA revealed that apo(a) contains 10 different kringle IV subtypes, designed as types 1–10. The high quantitative polymorphism in the sequence encoding the plasminogen kingle IV type 2 domain explains the high degree of individual allelic size polymorphism of the protein as, to date, more than 34 size alleles have been identified in the apo(a) locus, encoding as many detectable isoforms in plasma.[130] Although the size of the apo(a) particle usually determines its rate of hepatic synthesis and secretion, there is profound interindividual variation in the Lp(a) levels for a given apo(a) size, suggesting that factors beyond gene size predict plasma levels. Interest is now focused on other apo(a) gene variations to explain this. Several polymorphisms in the apo(a) gene have been reported. Of these, a C/T variation in the promoter region of the apo(a) gene and a pentanucleotide repeat (TTTTAn) _1 kb upstream of the apo(a) gene have been studied in this regard.[140]

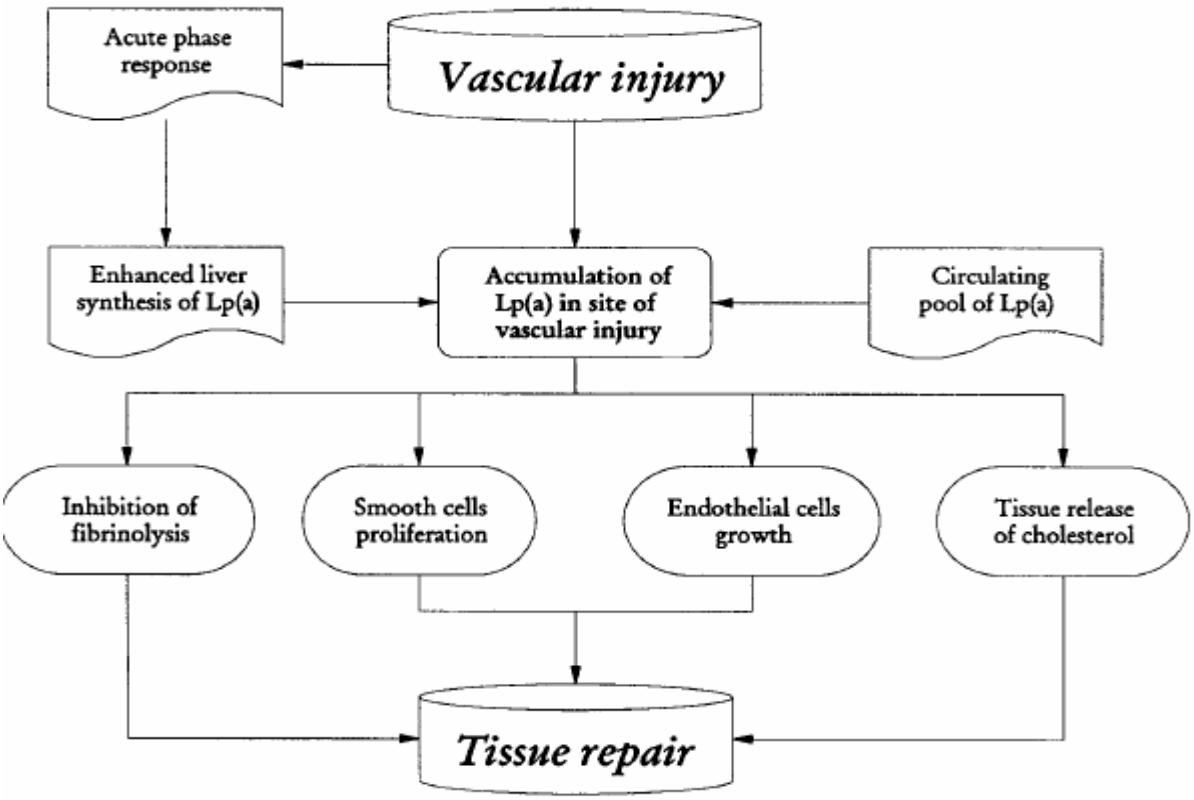
FUNCTIONS OF Lp(a)

The physiological functions of Lp(a) is unknown.[141]

Lp(a) promotes tissue repair

It now seems that Lp(a) offers an evolutionary advantage to humans by promoting or accelerating the healing of wounds and the repair of tissue injuries and

vascular lesions. Lp(a) behaves as an acute-phase reactant. The sequence of the apo(a) gene contains several interleukin 6 (IL-6)-responsive elements that enhance transcription of the gene. IL-6 generates a marked, dose-dependent enhancement of apo(a) mRNA synthesis that leads to the accumulation of Lp(a) particles in hepatocyte culture, and several prospective clinical trials demonstrated significant rises in plasma Lp(a) after inducing different forms of acute phase response in vivo. Due to the additional presence of apo(a), Lp(a) can be recognized by a broad variety of receptors at the surface of endothelial cells, macrophages, fibroblasts, exposed sub-endothelial matrix, stabilized fibrin and platelets. Defensin, a peptide released from activated or senescent neutrophils, enhances the binding of Lp(a) to endothelial cells by approximately four-fold and to smooth muscle cells by six-fold.[130] The large amount of apo(a) bound to the fibrin surface, the platelets and endothelial cells, inhibits the clot lysis mechanism. The growth factor like properties of Lp(a) also promotes vascular repair and cell regeneration.



The role of Lp(a) in tissue repairing mechanism

Lp(a) inhibits fibrinolysis.[130,141]

Lp(a) clearly inhibits plasminogen activation by t-PA in the presence of fibrin. Kinetic analysis of the data suggests that the inhibitory mechanism is uncompetitive. But there is no evidence to support the binding of Lp(a) directly to the enzyme-substrate complex (t-PA and plasminogen). However, if we consider that the active catalytic complex is comprised of enzyme-substrate-activator (t-PA-plasminogen-fibrin), and that Lp(a) binds to the activator, thereby making it unavailable for binding to the catalytic complex, we are left with the much less active enzyme-substrate complex (t-PAplasminogen).

Another group of investigators have demonstrated that Lp(a) can inhibit the fibrinolytic activity of plasma generated by addition of streptokinase, but the

concentrations of Lp(a) required were significantly higher than noted in experiments with t-PA. It appears that streptokinase binds to Lp(a) and thereby inhibits streptokinase mediated plasminogen activation competitively as well as uncompetitively.[142] The finding that Lp(a) also binds to glycoprotein IIb further supports the important role of Lp(a) in fibrinolysis.[143]

Lp(a) inhibits cancer growth and spread:

OReilly et al explained that angiostatin, a 38 kDa fragment produced by cancer mediated proteolysis of plasminogen, inhibits the angiogenesis of tumours and metastasis (through plasminogen kringle domains I –IV) and inhibits endothelial cell migration (through plasminogen kringle domain V). Apo(a) portion of Lp(a) has high homologous to plasminogen residues. So, Lp(a) also decreasing the growth and spread of cancer like angiostatin. The concentration of Lp(a) is commonly reported to be elevated in cancer patients further supporting that Lp(a) has a biological role in the fight against cancer.[130]

RELATIONSHIP BETWEEN Lp(a) AND METABOLIC SYNDROME

Lp(a) AND ATHEROGENIC DYSLIPIDEMIA[141]

Numerous epidemiological studies have shown that Lp(a) in plasma is a risk factor for a variety of cardiovascular diseases, including silent CAD, acute MI, asymptomatic carotid atherosclerosis,[128,144] peripheral artery occlusive disease (PAOD), stroke and abdominal aortic aneurysm.[145] The Framingham study reported that Lp(a) levels above 30mg/dl similar risk to TC > 240 mg /dl or HDL-C <35 mg/dl.

A few mechanisms have been proposed for the putative role of Lp(a) in IHD. Its incorporation into plaque and high affinity binding to glycosaminoglycans and

fibronectin suggest a direct atherogenic action in combination with elevated cholesterol. Lp(a) has less resistance to oxidation than does the LDL particle and can be actively taken up by scavenger receptors, leading to the formation of foam cells, smooth muscle cell proliferation, and plaque inflammation and instability. Further, Lp(a) may impair fibrinolytic activity by competing with plasminogen for fibrin binding, by competing with tissue-type plasminogen activator for fibrin binding or by direct binding to fibrin.[143,144,146]

Lp(a) enters into and leaves the arterial wall by mechanisms similar to LDL and appears to accumulate more at sites of arterial injury than LDL. Its similarity to LDL may also contribute to the development of atherosclerosis. Lp(a) has also been shown to bind proinflammatory oxidized phospholipids recently associated with coronary artery disease. Oxidized Lp(a) is also implicated in the causation of endothelial dysfunction.[144] Lp(a) has been shown to be critical in the initiation of atherogenesis through induction of chemotactic activity to circulating monocytes and enhancement of expression of intercellular adhesion molecule-1. An endothelial cell-activating effect of Lp(a) is potent surface expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule (ICAM)-1 and E-selectin. This may be a main event in the initiation process of atherogenic disease.[147]

Lp(a) AND DIABETES

In diabetes, conflicting reports are available regarding prognostic significance of Lp(a) levels. A few studies record that it may be elevated in insulin-dependent diabetes mellitus. Particularly, patients with microalbuminuria and proliferative retinopathy show higher Lp(a) levels. Similarly, Lp(a) has been correlated to CAD in diabetics in some studies, while other trials do not show any such correlation. South

Indian non-insulin-dependent diabetes mellitus (NIDDM) patients with high Lp(a) levels, however, show good correlation with CAD.

Lp(a) AND PROTHROMBOTIC STATE

Mechanisms by which Lp(a) may contribute to thrombus formation include inactivation of tissue factor pathway inhibitor, thus promoting coagulation, and attenuation of fibrinolysis through inhibition of plasminogen activation. It has been also shown that Lp(a) competes for the binding of plasminogen to the plasminogen receptor on endothelial cells and macrophages. All of these actions by Lp(a), occurring in vivo, create a prothrombotic state. Moreover, owing to its preferential uptake and degradation by macrophages, Lp(a) could colocalize with fibrin at intimal tissue sites resulting in a complex which is also atherogenic.[127,128]

Apo(a) contains multiple tandem repeats of plasminogen-like kringle 4 (61% - 75% homology) followed by a single copy of kringle 5 and of the protease domain(~ 94% homology). Some of the plasminogen-like kringle 4 copies endow apo(a) with the ability to compete with plasminogen for binding to cells and fibrin. However, the substitution of the Arg-Val in plasminogen cleavage site by Ser-Ile in apo(a) impairs the generation of plasmin like activity by activators. Thus, the competitive binding of Lp(a) for lysine residues of fibrin and cell membrane proteins results in decreased plasmin formation and favour the deposition of fibrin and lipids within the vascular wall. Lp(a) was also shown to attenuate clot lysis in plasma and patients with elevated levels of Lp(a) were found to manifest significantly reduced endogenous clot lysis in plasma ex vivo.[127]

Lp(a) MEASUREMENT

Immunometric analysis includes ELISA, DELPHIA, immunonephelometry, and turbidimetry. Commercially available assays include an immunoturbidimetric test, which can be run on automated chemistry analyzers.[148] Most of these assays, except ELISA are based on the use of polyclonal antibodies from various animal species. An ELISA method in which, Lp(a) particles are captured using monoclonal antiLp(a) antibody , and a horseradish peroxidase enzyme conjugated polyclonal antiLp(a) antibody as the detection antibody has been described and is commercially available.[126] In another approach, both the capture and detection antibodies are specific for apo(a).

The structural heterogenicity of Lp(a) as a consequence of the apo(a) size heterogenicity has important implications for the accurate measurement of Lp(a). Antibodies are raised against either Lp(a) or apo(a) in the intact Lp(a) molecule since disassociation of apo(a) from apo B-100 decreases its immuno reactivity. If antibodies are raised against K-IV repeats, it would lead to heterogeneity due to variation in their numbers. A recent report suggests that patients suffering from coronary artery disease (CAD) excrete significantly higher amounts of apo(a) into the urine than controls and that urinary apo(a) is a valuable predictor of CAD. Using urinary apo(a) as a marker for CAD has the advantage of easier sampling compared to plasma samples.[135]

Owing to the lack of standardization, each laboratory must determine its own reference interval. This should be done with a suitably large population and should be done in consultation with cardiologists who will be using the results. The reference interval is method specific, and if changing methods, a new interval must be established.[148]

It is not known whether risk is associated simply with an elevated number of Lp(a) particles in the circulation as measured using an anti apo-B antibody or else related to the presence apo(a) size polyforms. It is likely that both factors influence risk. Lp(a) concentrations can also be expressed in terms of particle number, the mass of apo (a), apoB 100 or Lp(a) cholesterol. Which approach will best predict the risk of CHD is yet to be determined. At present Lp(a) values are expressed in terms of total Lp(a) mass. Currently a value of about 30 mg/dl of total Lp(a) particle mass is used as a cut off [148], above which elevated levels of Lp(a) are associated with increased risk of CHD. An International Federation of Clinical Chemistry (IFCC) committee has been set to work towards standardizing Lp(a). Apo(a) protein, mRNA and DNA size polymorphism studies demonstrate that the number of K-IV repeats in the gene and the resulting size of the protein are inversely correlated with Lp(a) levels in the plasma in all populations studied so far.[139,145] Because there is profound inter individual variation of Lp(a) levels for a given apo(a) size, suggesting that factors beyond gene size predict plasma levels, interest has focused on other apo(a) gene variations. Several apo(a) gene polymorphisms have been reported. A pentanucleotide sequence repeat polymorphism (TTTTA) at position-1373 before the translation initiation codon of the apo(a) gene and a C/T variation in the promoter region of apo(a) gene may be some of the factors associated with variable plasma Lp(a) concentration. The TTTTA polymorphism could account for about 10–14% of the inter-individual variations of Lp(a) levels in Caucasians.[135,139]

! Increased levels of Lp(a) are observed in blacks. Despite the higher levels of Lp(a) in blacks, they appear to have a lower death rate from coronary heart disease than white men.[125,135]

OTHER FACTORS AFFECTING PLASMA LEVELS OF Lp(a)

Lp(a) levels, do not alter with the age. Sex, anthropometric parameters, environmental factors, other coronary risk factors and other lipoproteins are not significantly altering the Lp(a) levels[135,145] but alcohol consumption, hypothyroidism and hormones (growth hormone, estrogens) affects the Lp(a) levels. Several renal diseases, familial hypercholesterolemia, rheumatoid arthritis and drugs such as cyclosporin, danazol, and stanazolol increases the Lp(a) levels.

Lp(a) levels are not readily amenable by dietary restriction also. Moderate drinking of alcohol lowers plasma Niacin and hormone replacement therapy decreases the Lp(a) levels.. The high heritability of plasma Lp(a) concentrations and their lack of responsiveness to environmental influences suggest a potential value of Lp(a) as a stable risk factor for vascular disease.

MATERIALS & METHODS

MATERIALS AND METHODS

SOURCES OF DATA

Patients and bystanders who attended the medicine OPD of Sree Mookambika Institute of Medical Sciences, Kulasekharam, Tamilnadu for routine medical check up formed the subjects for the present cross-sectional study. The total of 136 subjects that came to the hospital during January 2014 to April 2014 was enrolled into the study.

DIAGNOSTIC CRITERIA

Metabolic syndrome was diagnosed according to the NCEP-ATP III criteria (Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults – Adult Treatment Panel III) and IDF criteria.

INCLUSION CRITERIA

1. Patients and bystanders attending medicine OPD of Sree Mookambika Institute of Medical Sciences.
2. Age between 24-39 years.

EXCLUSION CRITERIA

1. Subjects having following conditions to be excluded.

   Pregnancy, Congenital diseases, Severely ill patients.

2. Those who are not willing to participate.

METHOD OF COLLECTION OF DATA

Informed consent was taken from the all subjects. A pre-structured and pretested proforma was used to collect the data. Baseline data including age, gender,

religion, detailed medical history, clinical examinations and relevant investigations were included as part of the methodology.

The following parameters were collected: age, gender, religion, waist circumference, blood pressure and fasting clinical chemistry parameters. Waist circumference was measured using a non-stretchable fibre measuring tape. The subjects were asked to stand erect in a relaxed position with both feet together on a flat surface. Waist circumference was taken at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mmHg using the mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 min apart and the mean of the two was taken as blood pressure. Blood samples were collected from each participant after a 9-hour overnight fasting and employing standard infection prevention procedures. The collected blood samples were used to determine the concentrations of HDL-cholesterol, triglyceride, lipoprotein (a) and fasting glucose.

1. ESTIMATION OF LIPOPROTEIN (a) BY LATEX TURBIDIMETRY

CLINICAL SIGNIFICANCE

Lp(a) is a low density lipoprotein-like particle containing apolipoprotein B-100 disulphide-linked to one large glycoprotein called apolipoprotein (a). Many investigators have confirmed that a high Lp(a) concentration represents an indicator of risk for cardiovascular disease, especially when serum LDL-cholesterol or Apo B are elevated. The quantification of Lp(a) in serum or plasma is important for identification of individuals at risk for developing atherosclerosis.

PRINCIPLE OF THE METHOD

The Lp(a)-turbilatex is a quantitative turbidimetric test for the measurement of Lp(a) in human serum or plasma.

Latex particles coated with antibodies anti-Lp(a) are agglutinated when mixed with samples containing Lp(a). The agglutination causes an absorbance change, dependent upon the Lp(a) contents of sample that can be quantified by comparison from a calibrator of known Lp(a) concentration.

REAGENTS

Diluent (R1)	Glycine buffer50 mmol/L, pH 9.0. Sodium azide 0.95 g/L
Latex (R2)	Latex particles coated with mouse monoclonal anti-human Lp(a), pH 8.2. Sodium azide 0.95 g/L.
Optional	Ref.:1107022 Lp(a) calibrator Ref.:1107024 Lp(a) Control

PROCEDURE

1. Bring the working reagent and the photometer (cuvette holder) to 37ºC.
2. Assay conditions:

   Wavelength: 570 nm (540-600)

   Temperature: 37ºC

   Cuvette ligth path: 1 cm
3. Adjust the instrument to zero with distilled water.

4. Pipette into a cuvette

R1: Diluent (µl)	400
R2: Latex (µl)	100
Calibrator or sample (µl)	7

5. Mix and read the absorbance immediately (A1) and after 4 minutes (A2) of the sample addition.

REFERENCE VALUES

Normal values up to 30 mg/dl.

2. ESTIMATION OF BLOOD GLUCOSE

- Gesan Mono reagent LR (Liquid Reagent) 6 x 50 ml kit used.
- Colorimetric enzymatic method GOD-POD.

PRINCIPLE

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GOD}} H_2O_2 + \text{Gluconic acid}$$

$$2H_2O_2 + \text{phenol} + \text{4 aminophenazone} \xrightarrow{\text{POD}} \text{Quinonimine (coloured compound)} + 4H_2O_2.$$

Glucose is oxidized, in presence of glucose oxidase (GOD), into gluconic acid and hydrogen peroxide. This one reacts, by peroxidase (POD), with 4 aminophenazone and phenol giving a coloured compound whose colour intensity is directly proportional to the glucose concentration in the tested sample.

REAGENTS

R_1	Phosphate buffer pH 7.4	100.0 mmol/l
	Phenol	9.0 mmol/l
	GOD ≥	25000 U/l
	POD ≥	1500 U/l
	4 aminophenazone	2.3 mmol/l

SAMPLE

- Serum heparinised plasma or EDTA plasma used.
- Diluted urine 1:10
- Do not use samples with hemolysis
- Specimens should be separated from cells as soon as possible after collection to avoid loss due to glycolysis
- The glucose is stable in the samples upto 3 days at 2-8^{o} C, after the addition of a glycolytic inhibitor as sodium fluoride, potassium fluoride..

PROCEDURE

Wavelength	510 (500-550) nm
Working temperature	37^{o}C
Optical path	1 cm
Reaction	"End point"

Bring the reagents at 15-25^{o}C before use them.

MONOREAGENT PROCEDURE "SAMPLE STARTER"

	Blank	Standard	Sample
Working reagent	1000 µl	1000µl	1000µl
Distilled water	10µl	_	_
Sample	_	_	10µl
Standard	_	10µl	_

Mix, then incubate 10 minutes at 37°C. Measure the absorbance of sample (EC) and standard (ESTD) against the reagent blank.

CALCULATION

Glucose (mg/dl) ◦(mmol/l) =EC/ESTD x concentration of standard

Conversion factor

Glucose (mg/dl) x 0.05551 = glucose (mmol/l)

REFERENCE VALUES

Serum-plasma 70-105 mg/dl (3.9-5.8 mmol/l)

Urine <0.5g /24h (<28 mmol/24h)

REAGENTS PREPARATIONS

Reagent is liquid and ready to use.

Storage and Stability:

- Store the kit at 2-8ºC. Do not freeze the reagents.

- After opening, the reagent is stable 90 days if recapped immediately and protected from contamination, evaporation, direct light and stored at the correct temperature.

Precaution:

Reagents contain sodium azide (0.095%) as preservative. Avoid swallowing and contacting with skin, eyes and mucous membranes.

3. ESTIMATION OF SERUM TRIGLYCERIDES

- Gesan triglycerides monoreagent LR Liquid (6x50 ml) Reagent Kit for measurement of triglycerides in serum or plasma.
- Colorimetric enzymatic method Glycerol phosphate oxidase - peroxidase method..

PRINCIPLE

Glycerol released from hydrolysis of triglycerides by lipoprotein lipase is converted by glycerol kinase into glycerol-3-phosphate, which is oxidized by glycerol phosphate oxidase to dihydroxyacetone phosphate and hydrogen peroxide. In the presence of peroxidase, hydrogen peroxide oxidizes phenolic chromogen to a red coloured compound/

$$\text{Triglycerides} + H_2O \xrightarrow{\text{Lipoprotein lipase}} \text{Glycerol} + \text{Fatty acid}$$

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{Glycerol kinase}} \text{Glycerol 3 phosphate} + \text{ADP}$$

$$\text{Glycerol 3 phosphate} + O_2 \xrightarrow{\text{Glycerol 3 phosphate oxidase}} \text{Dihydroxy acetone phosphate} + H_2O_2$$

H_2O_2 + 4 Aminophenazone +p-chlorophenol $\xrightarrow{\text{Peroxidase}}$ Red colour Quinoneimine

Intensity of coloured compound is proportional to the concentration of triglycerides in the sample.

REAGENTS

R_1

PIPES buffer	100.0 mmol/l
Phenol	16.0 mmol/l
Lipoprotein lipase	≥4000 U/l
Glycerol kinase	≥2000 U/l
Peroxidase	≥2500 U/l
ATP	0.8 mmol/l
4 Aminophenazone	1.4 mmol/l
Glycerol 3 phosphate oxidase	≥2000 U/l

REAGENTS PREPARATION

Reagent is liquid and ready to use. Keep out the reagents from refrigerator only for the use and recap them immediately.

STORAGE

- Store the kit at 2-8^{o}C.
- After opening, the vials R_1 is stable 90 days if recapped immediately & protected from evaporation, direct light and contamination and stored at the correct temperature.

SPECIMEN COLLECTION AND PREPARATION

- Serum-heparinized plasma or EDTA plasma
- In the samples, stored at 2-8^{o}C and at -20^{o}C, the triglycerides are stable, respectively, upto 3 days and 12 months.
- It's advisable, in presence of strongly lipemic, jaundiced or turbid serum, to prepare a blank of the sample using saline solution.

PROCEDURE

Wavelength	510 (500-550) nm
Working temperature	37^{o}C
Optical path	1 cm
Reaction	"End point" (increasing)

Bring the reagents at 15-25^{o}C before use.

MONO REAGENT PROCEDURE "SAMPLE STARTER"

	Blank	Standard	Sample
Working reagent	1000 µl	1000 µl	1000 µl
Distilled water	10 µl	_	_
Sample	_	_	10 µl
Standard	_	10 µl	_

Mix, then incubate for 5 minutes at 37^{o}C. Measure the absorbance of sample (EC) and standard (ESTD) against the reagent blank.

CALCULATION

Triglycerides (mg/dl) or (mmol/l) = EC/ESTD X Concentration of standard

Conversion factor

Triglycerides (mg/dl) x 0.01126 = Triglycerides (mmol/l)

REFERENCE VALUES (to 37^{o}C)

	Serum – Plasma
Men	60-165 mg/dl (0.68-1.86 mmol/l)
Women	40-140 mg/dl (0.45-1.58 mmol/l)

It has been noticed that the values obtained using the plasma as sample are, from 2% to 4% lower than values obtained using the serum.

4. ESTIMATION OF SERUM HDL-CHOLESTEROL

- Bio systems kit
- Direct detergent method

PRINCIPLE

The chlolesterol from LDL, VLDL and chylomicrons is broken down by the cholesterol oxidase in an enzymatic accelerated non-colour forming reaction. The detergent present in the reagent B, solubilizes cholesterol from HDL in the sample. The HDL cholesterol is then spectrophotometrically measured by means of the coupled reactions described below.

$$\text{Cholesterol esters} + H_2O \xrightarrow{\text{Cholesterol esterase}} \text{Cholesterol} + \text{Fatty acid}$$

$$\text{Cholesterol} + \tfrac{1}{2}\, O_2 + H_2O \xrightarrow{\text{Cholesterol oxidase}} \text{Cholestenone} + H_2O_2$$

$$2\, H_2O_2 + \text{4 amino antipyrine} + \text{DSBmT} \xrightarrow{\text{Peroxidase}} \text{Quinoneimine (Red colour)} + 4\, H_2O$$

REAGENT CONTENTS AND COMPOSITION

A. Reagent 1 x 60 ml. Good's buffer, cholesterol oxidase < 1 U/ml, peroxidise < 1 U/ml, N,N-bis (4 sulfobutyl)-m-toluidine (DSBmT) 1 mmol/l, accelerator 1mmol/l.
B. Reagent 1 x 20 ml. Good's buffer, cholesterol esterase <1.5 U/ml, 4 amino antipyrine 1 mmol/l, ascorbate oxidase < 3.0 KU/l, detergent.

STORAGE

Store at 2 – 8°C.

Indications for deterioration: Presence of particulate material, Turbidity.

AUXILIARY REAGENTS

Serum HDL/LDL calibrator (Biosystems code.11693)

Human serum. Concentration is given on the label. The concentration value is traceable to the CDC Reference Measurement Procedure (Centers for disease control and prevention). Reconstitute with 1.0 ml of distilled water. Stable for 1 week at 2-8°C or for 2 months at -18°C when frozen in aliquots.

REAGENT PREPARATION

Reagents are provided ready to use.

SAMPLES

Serum collected by standard procedures. HDL cholesterol in serum or plasma is stable for 7 days at 2-8^{o}C. EDTA, lithium or sodium, heparin may be used as anticoagulants.

PROCEDURE

1. Bring the reagents and the photometer to 37^{o}C.
2. Pipette into a cuvette

Reagent A	750 µl
Serum /calibrator	7 µl

3. Mix and insert the cuvette into the photometer. Start the stopwatch. After 5 minutes, read the absorbance (A_1) at 600/700 nm against distilled water.
4. Pipette into a cuvette

Reagent B	250 µl

Mix.

5. After 5 minutes, read the absorbance (A_2) at 600/700 nm.

CALCULATIONS

The cholesterol HDL concentration is calculated using the following general formula.

C sample = ($A_2 - A_1$) sample/ ($A_2 - A_1$) calibrator X C calibrator

REFERENCE VALUES

HDL cholesterol concentrations vary considerably with age and sex. The following cut-off point has been recommended for identifying individuals at high risk of coronary artery disease.

Up to 35 mg/dl = 0.91 mmol/l	High risk
>60 mg/dl = >1.56 mmol/l	Low risk

STATISTICAL ANALYSIS

Data collected were entered in excel. Analysis was done by SPSS version 18.Simple proportion, Percentage, Mean, Standard deviation, and Pearson correlation co-efficient were calculated. Appropriate test of significance like chi-square test and "t" test were done. Values of $p < 0.05$ were considered statistically significant.

RESULTS

5. RESULTS

5.1 GENERAL CHARACTERISTICS OF THE STUDY POPULATION

5.1.1 Age Distribution

Age	Number	Percentage
24 - 29 Years	43	31.6
30 - 34 Years	28	20.6
35 - 39 Years	65	47.8
Total	136	100

Descriptive Statistics					
	Number	**Minimum**	**Maximum**	**Mean**	**Std. Deviation**
AGE	136	24	39	32.60	5.04

There were 136 persons taken for this study. Out of them, maximum number of persons 65 (47.8%) comes under the category of 35-39 years, followed by 43 (31.6%) persons comes under the category of 24-29 years, and then 28 (20.6%) persons comes under the category of 30-34 years. The youngest age of the person participated in this study is 24 years and the oldest is 39 years with the mean age of 32.6 years.

5.1.2 Sex Distribution

Sex	Number	Percentage
Male	78	57.4
Female	58	42.6
Total	136	100

Out of 136 persons participated in this study, maximum number of persons 78 (57.4%) are males, followed by females 58 (42.6%).

5.1.3 Religion

Religion	Number	Percentage
Hindu	82	60.3
Christian	42	30.9
Muslim	12	8.8
Total	136	100

According to religion wise, 82 (60.3%) persons coming under Hindu, followed by 42 (30.9%) persons of Christians, and 12 (8.8%) persons of Muslims.

5.2 PARAMETERS OF METABOLIC SYNDROME INCLUDING Lp(a)

5.2.1 DESCRIPTION OF PARAMETERS

Descriptive Statistics					
	Number	Minimum	Maximum	Mean	Std. Deviation
WC	136	78	104	91.92	5.46
SBP	136	100	160	131.56	11.77
DBP	136	70	100	84.07	7.11
FBS	136	82	170	106.82	13.32
TGL	136	112	204	155.71	22.18
HDL	136	25	54	40.50	6.88
Lp(a)	136	13.12	90.91	43.36	21.77

According to the parameters of metabolic syndrome, minimum waist circumference is 78 cm and maximum is 104 cm with the mean and standard deviation of 91.92 ± 5.46. Minimum systolic BP is 100 mmHg and maximum is 160 mmHg with the mean and standard deviation of 131.56 ± 11.77, followed by diastolic BP, minimum is 70 mmHg and maximum is 100 mmHg with the mean and standard deviation of 84.07 ± 7.11.About fasting blood sugar, minimum is 82 mg/dl and maximum is 170 mg/dl with the mean and standard deviation of 106.82 ± 13.32. In lipids, minimum

triglyceride is 112 mg/dl and maximum is 204 mg/dl with the mean and standard deviation of 155.71 ± 22.18, followed by High density lipoprotein cholesterol, minimum is 25 and maximum is 54 with the mean and standard deviation of 40.50 ± 6.88. According to the lipoprotein (a) values, minimum is 13.12 and maximum is 90.91 with the mean and standard deviation of 43.36 ± 21.77.

5.2.2 PREVALENCE OF ABNORMAL PARAMETERS

	Number	**Percentage**
Obesity	103	75.7
History of Anti- HTN Treatment	32	23.5
Abnormal SBP	51	37.5
Abnormal DBP	52	38.2
Hypertensive	61	44.9
History of Anti- DM Treatment	38	27.9
Abnormal FBS	47	34.6
Diabetic	50	36.8
History of Anti- lipid Treatment	21	15.4
High TGL	62	45.6
Abnormal TGL	64	47.1
Low HDL	41	30.1
Abnormal HDL	50	36.8
Increased Lp(a)	90	66.2

In our study population, maximum number of persons 103 (75.7%) have affected by obesity (Increased waist circumference) followed by 64 (47.1%) have abnormal triglyceride levels. Among the abnormal triglyceride levels, 62 (45.6%) have high triglyceride levels and 21 (15.4%) have history of lipid lowering drug treatment. Next maximum 61 (44.9%) persons affected by hypertension and then 50 (36.8%)

affected by diabetes and abnormal high density lipoprotein cholesterol levels. Among hypertensive patients 52 (38.2%) having abnormal diastolic blood pressure and 51 (37.5%) have abnormal systolic blood pressure levels. Among diabetic patients 47 (34.6%) having abnormal fasting blood sugar levels and 38 (27.9%) have history of anti diabetic treatment. Among abnormal high density lipoprotein cholesterol 41 (30.1%) having low high density cholesterol levels and 21 (15.4%) have history of lipid lowering drug treatment. Finally in total number of 136 persons, 90 (66.2%) persons have increased lipoprotein (a) levels.

5.3 PREVALENCE OF INDIVIDUAL METABOLIC SYNDROME PARAMETERS AMONG AGE AND SEX CATEGORIES

5.3.1 OBESITY

5.3.1.1 Obesity and Age

Age Category	OBESE		Total
	Yes	No	
24 - 29 Years	21 (48.8%)	22 (51.2%)	43 (100%)
30 - 34 Years	21 (75.0%)	7 (25.0%)	28 (100%)
35 - 39 Years	61 (93.8%)	4 (6.2%)	65 (100%)
Total	103 (75.7%)	33 (24.3%)	136 (100%)

Chi^2 Value – 28.539 df – 2 p-Value – 0.000 (Significant)

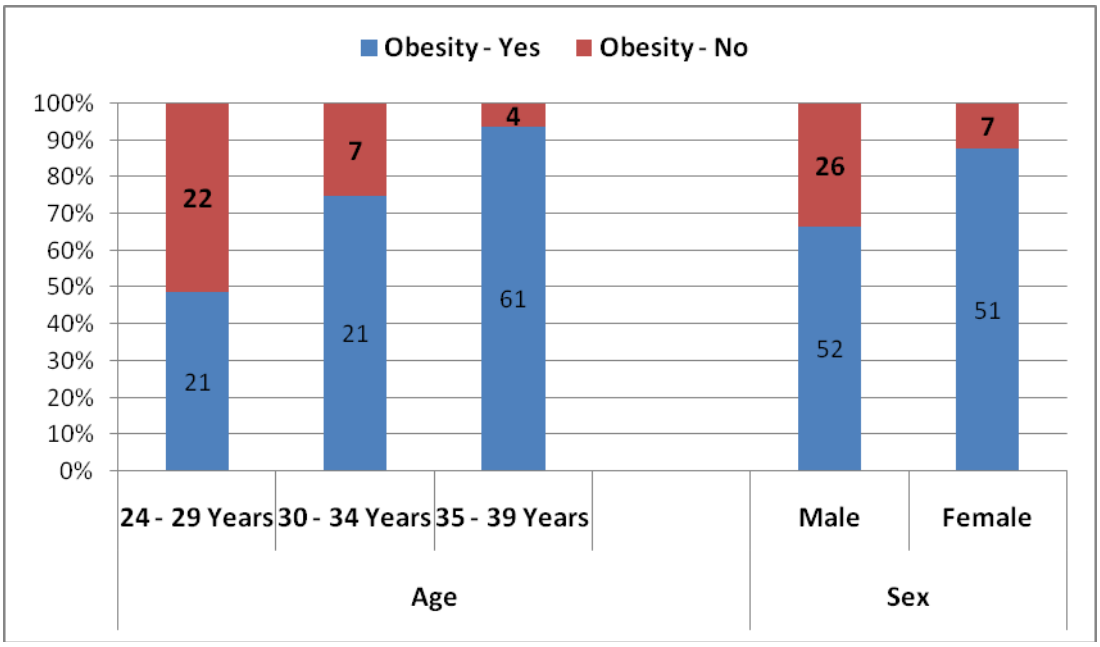
In our study, maximum number of persons 61 (93.8%) have affected by obesity comes under the age group of 35-39 years, followed by 21(75%) persons of 30-34 years and 21 (48.8%) persons of 24-29 years. So, prevalence of obesity with the age category has significant correlation according to the p-value 0.000 (<0.01).

5.3.1.2 Obesity and Sex

Sex Category	OBESE		Total
	Yes	No	
Male	52 (66.7%)	26 (33.3%)	78 (100%)
Female	51 (87.9%)	7 (12.1%)	58 (100%)
Total	103 (75.7%)	33 (24.3%)	136 (100%)

Chi^2 Value – 8.185 df – 1 p-Value – 0.004 (Significant)

According to the sex category, maximum percentage of females 51 (87.9%) have affected by obesity than males 52 (66.7%).prevalence of obesity with the sex category also have significant correlation according to the p-value 0.004 (<0.01).



5.3.2 HYPERTENSION

5.3.2.1 Hypertension and Age

Age Category	HYPERTENSION		Total
	Yes	No	
24 - 29 Years	0 (0.0%)	43 (100%)	43 (100%)
30 - 34 Years	11 (39.3%)	17 (60.7%)	28 (100%)
35 - 39 Years	50 (76.9%)	15 (23.1%)	65 (100%)
Total	61 (44.9%)	75 (55.1%)	136 (100%)

Chi^2 Value – 62.351 df – 2 p-Value – 0.000 (Significant)

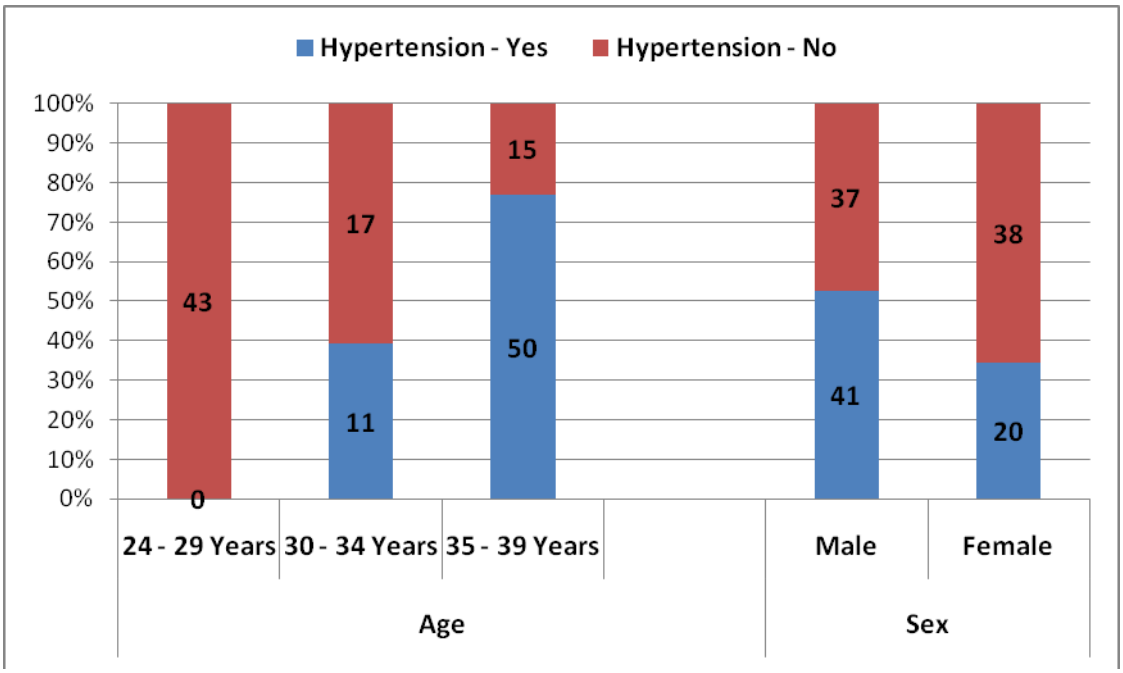
In our study, maximum number of persons 50 (76.9%) affected by hypertension, comes under the age group of 35-39 years, followed by 11 (39.3%) persons in the age group of 30-34 years. Nobody affected by hypertension, in the age group of 24-29 years. Prevalence of hypertension with the age category has significant correlation according to the p-value 0.000 (<0.01).

5.3.2.2 Hypertension and Sex

Sex Category	HYPERTENSION		Total
	Yes	No	
Male	41 (52.6%)	37 (47.4%)	78 (100%)
Female	20 (34.5%)	38 (65.5%)	58 (100%)
Total	61 (44.9%)	75 (55.1%)	136 (100%)

Chi^2 Value – 4.397 df – 1 p-Value – 0.036 (Significant)

According to hypertension and sex category, maximum number of males 41 (52.6%) were affected by hypertension than the females 20(34.5%). Prevalence of hypertension with the age category has significant correlation according to the p-value 0.036 (<0.05).



5.3.3 DIABETS MELLITUS

5.3.3.1 Diabetes Mellitus and Age

Age Category	DIABETES MELLITUS		Total
	Yes	No	
24 - 29 Years	9(20.9%)	34(79.1%)	43 (100%)
30 - 34 Years	11(39.2%)	17(60.8%)	28 (100%)
35 - 39 Years	30(46.2%)	35(53.8%)	65 (100%)
Total	50(36.7%)	86(63.3%)	136 (100%)

Chi^2 Value – 13.347 df – 2 p-Value – 0.001 (Significant)

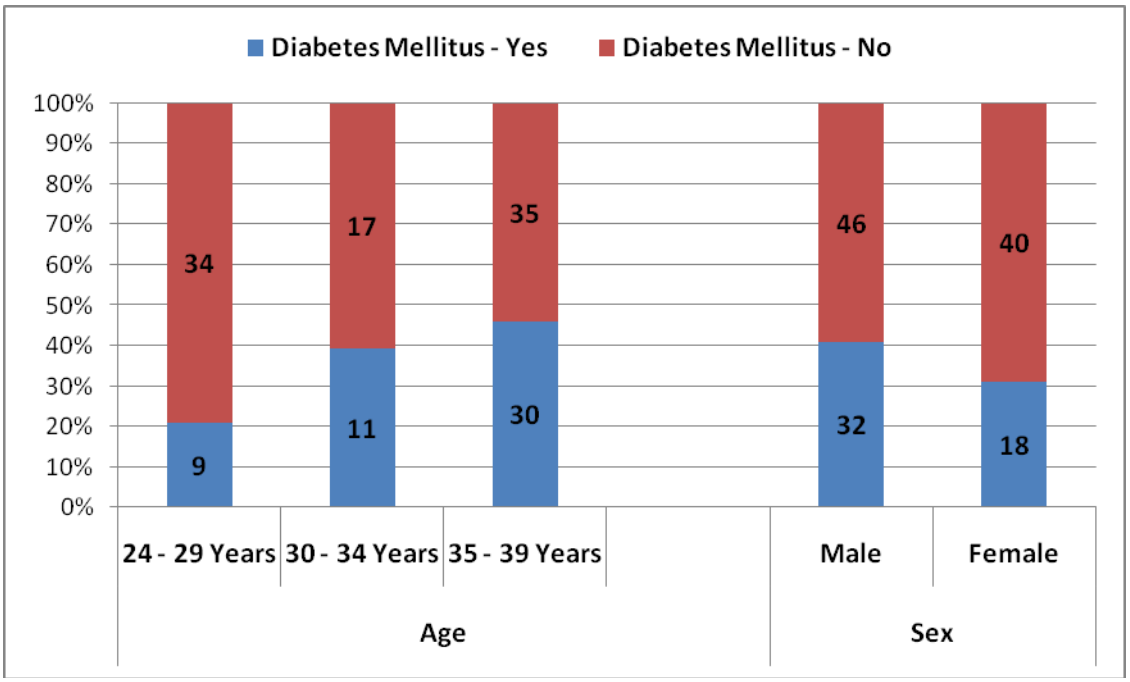
In our study, maximum number of persons 30 (46.2%) have affected by diabetes mellitus comes under the age group of 35-39 years, followed by 11 (39.2%) persons of 30-34 years and 9 (20.9%) persons of 24-29 years. So, prevalence of diabetes mellitus with the age category has significant correlation according to the p-value 0.000 (<0.01).

5.3.3.2 Diabetes Mellitus and Sex

Sex Category	DIABETES MELLITUS		Total
	Yes	No	
Male	32(41.0%)	46(59.0%)	78 (100%)
Female	18(31.0%)	40(69.0%)	58 (100%)
Total	50(36.8%)	86(63.2%)	136 (100%)

Chi^2 Value –1.428 df – 1 p-Value – 0.232 (Significant)

According to diabetes mellitus and sex category, maximum number of males 32 (41.0%) were affected by diabetes mellitus than the females 18(31.0%).Prevalence of diabetes mellitus with the age category has significant correlation according to the p-value 0.232 (<0.05).



5.3.4 ABNORMAL TGL

5.3.4.1 Abnormal TGL and Age

Age Category	ABNORMAL TGL		Total
	Yes	No	
24 - 29 Years	1 (2.3%)	42(97.7%)	43 (100%)
30 - 34 Years	19(67.9%)	9(32.1%)	28 (100%)
35 - 39 Years	44(67.7%)	21(32.3%)	65 (100%)
Total	64(47.1%)	72(52.9%)	136 (100%)

Chi^2 Value – 50.507 df – 2 p-Value – 0.000 (Significant)

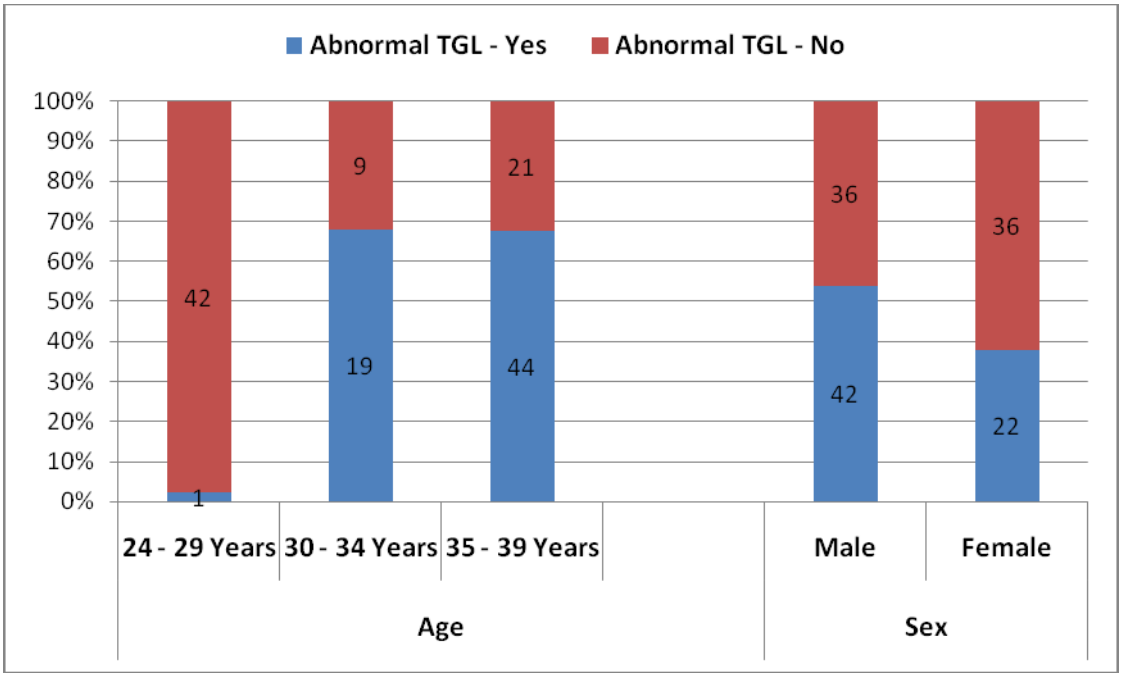
In our study, maximum number of persons 44 (67.7%) have affected by abnormal triglycerides comes under the age group of 35-39 years, followed by 19 (67.9%) persons of 30-34 years and 1 (2.3%) persons of 24-29 years. So, prevalence of abnormal triglycerides with the age category has significant correlation according to the p-value 0.000 (<0.01).

5.3.4.2 Abnormal TGL and Sex

Sex Category	ABNORMAL TGL		Total
	Yes	No	
Male	42(53.8%)	36(46.2%)	78 (100%)
Female	22(37.9%)	36(62.1%)	58 (100%)
Total	64(47.1%)	72(52.9%)	136 (100%)

Chi^2 Value –3.382 df – 1 p-Value – 0.066 (Not Significant)

According to abnormal triglycerides and sex category, maximum number of males 42 (53.8%) were affected by abnormal triglycerides levels than the females 22 (37.9%). Prevalence of abnormal triglycerides with the age category has no significant correlation according to the p-value 0.066 (>0.05).



5.3.5 ABNORMAL HDL

5.3.5.1 Abnormal HDL and Age

Age Category	ABNORMAL HDL		Total
	Yes	No	
24 - 29 Years	2(4.7%)	41(95.3%)	43 (100%)
30 - 34 Years	9(32.1%)	19(67.9%)	28 (100%)
35 - 39 Years	39(60%)	26(40.0%)	65 (100%)
Total	50(36.8%)	86(63.2%)	136 (100%)

Chi^2 Value – 34.426 df – 2 p-Value – 0.000 (Significant)

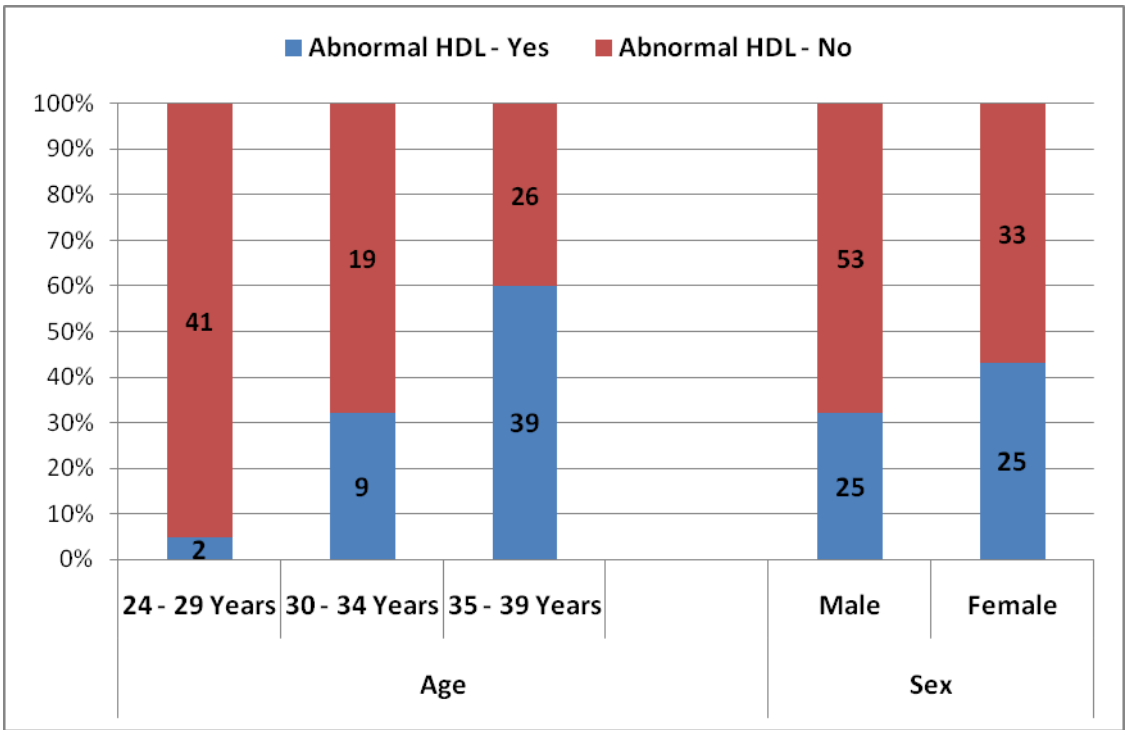
In our study, maximum number of persons 39 (60%) have affected by abnormal HDL levels comes under the age group of 35-39 years, followed by 9 (32.1%) persons of 30-34 years and 2 (4.7%) persons of 24-29 years. So, prevalence of abnormal HDL levels with the age category has significant correlation according to the p-value 0.000 (<0.01).

5.3.5.2 Abnormal HDL and Sex

Sex Category	ABNORMAL HDL		Total
	Yes	No	
Male	25(32.1%)	53(67.9%)	78 (100%)
Female	25(43.1%)	33(56.9%)	58 (100%)
Total	50(36.8%)	86(63.2%)	136 (100%)

Chi^2 Value – 1.748 df – 1 p-Value – 0.186 (Significant)

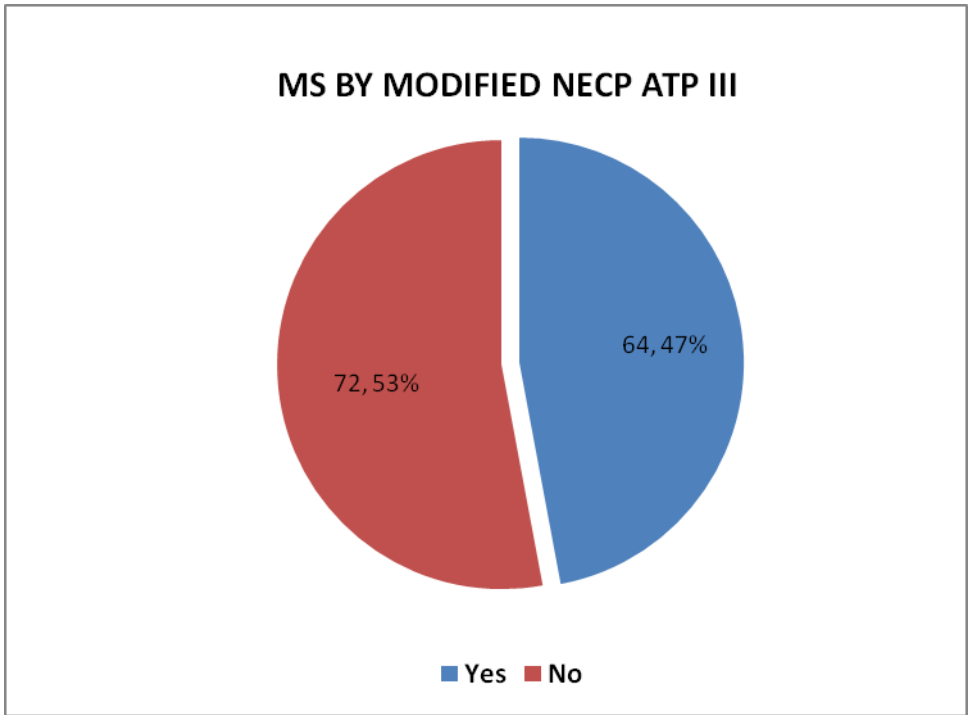
According to abnormal HDL levels and sex category, maximum number of males 25 (32.1%) were affected by abnormal HDL levels than the females 25 (43.1%). Prevalence of abnormal HDL levels with the age category has significant correlation according to the p-value 0.186 (<0.05).

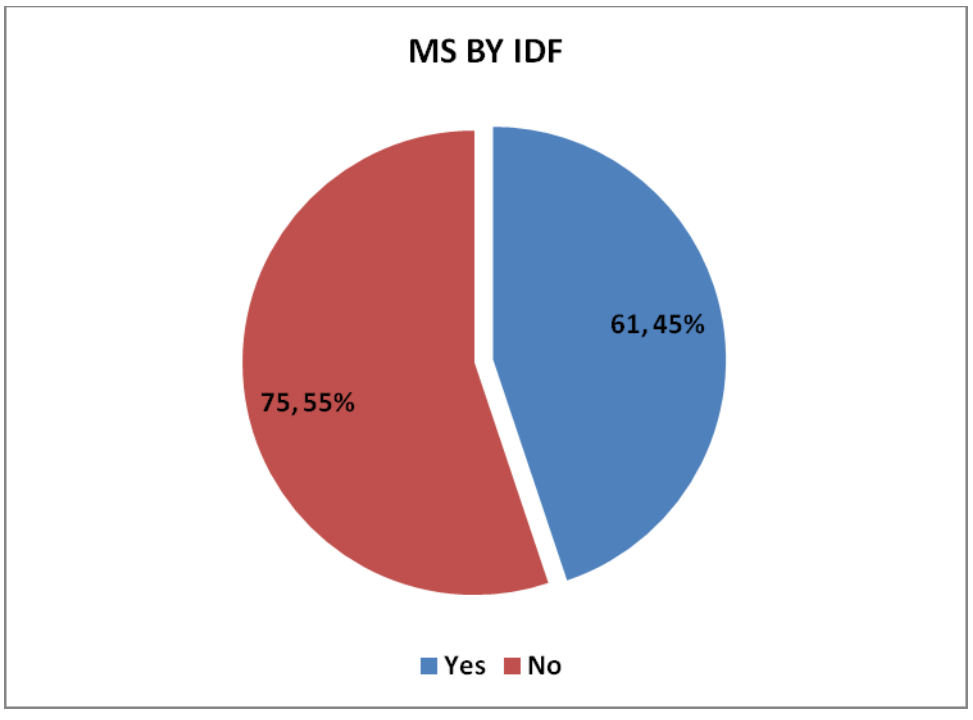


5.4 PREVALENCE OF METABOLIC SYNDROME

MS CRITERIA	Category	Number	Percentage
Modified NECP ATP III	Yes	64	47.1
	No	72	52.9
IDF	YES	61	44.9
	No	75	55.1

In our study population, prevalence of metabolic syndrome is 47.1% (64 persons) according to the Modified NCEP ATP III Criteria and according to the IDF Criteria; prevalence is 44.9% (61 persons). It is little lower than the NCEP ATP III Criteria prevalence.


MS BY MODIFIED NECP ATP III
64, 47%
72, 53%
Yes
No


MS BY IDF
61, 45%
75, 55%
Yes
No

5.4.1 METABOLIC SYNDROME AMONG AGE CATEGORY

5.4.1.1 Metabolic Syndrome by Modified NECP ATP III and Age

Age Category	MS BY MODIFIED NECP ATP III		Total
	Yes	No	
24 - 29 Years	0 (0%)	43(100%)	43 (100%)
30 - 34 Years	14(50%)	14(50%)	28 (100%)
35 - 39 Years	50(76.9%)	15(23.1%)	65 (100%)
Total	64(47.1%)	72(52.9%)	136 (100%)

Chi^2 Value – 61.589 df – 2 p-Value – 0.000 (Significant)

According to the Modified NCEP ATP III Criteria, prevalence of metabolic syndrome is maximum 50 (76.9%) persons at the age group of 35-39 years, followed by 14 (50%) persons in the age group of 30-34 years and no persons in the age group of 24-29 years in our study population. Prevalence of metabolic syndrome (By Modified NCEP ATP III Criteria) with the age category has significant correlation according to the p-value 0.000 (<0.01).

5.4.1.2 Metabolic Syndrome by IDF and Age

Age Category	MS BY IDF		Total
	Yes	No	
24 - 29 Years	0(0%)	43 (100.0%)	43 (100%)
30 - 34 Years	13(46.4%)	15(53.6%)	28 (100%)
35 - 39 Years	48(73.8%)	17(26.2%)	65 (100%)
Total	61(44.9%)	75(55.1%)	136 (100%)

Chi^2 Value – 57.091 df – 2 p-Value – 0.000 (Significant)

According to the IDF Criteria, prevalence of metabolic syndrome is maximum 48 (73.8%) persons at the age group of 35-39 years, followed by 13 (46.4%) persons in the age group of 30-34 years and no persons in the age group of 24-29 years in our study population. Prevalence of metabolic syndrome (By IDF Criteria) with the age category has significant correlation according to the p-value 0.000 (<0.01).

5.4.2 METABOLIC SYNDROME AMONG SEX CATEGORY

5.4.2.1 Metabolic Syndrome by Modified NECP ATP III and Sex

Sex Category	MS BY MODIFIED NECP ATP III		Total
	Yes	No	
Male	37(47.4%)	41(52.6%)	78 (100%)
Female	27(46.6%)	31(53.4%)	58 (100%)
Total	64(47.1%)	72(52.9%)	136 (100%)

Chi^2 Value – 0.10 df – 1 p-Value – 0.919 (Not Significant)

According to Modified NCEP ATP III Criteria, maximum numbers of males 37 (47.4%) were affected by metabolic syndrome than the females 27 (46.6%). Prevalence of metabolic syndrome with the sex category has no significant correlation according to the p-value 0.919 (>0.05).

5.4.2.2 Metabolic Syndrome by IDF and Sex

Sex Category	MS BY IDF		Total
	Yes	No	
Male	36(46.2%)	42(53.8%)	78 (100%)
Female	25(43.1%)	33(56.9%)	58 (100%)
Total	61(44.9%)	75(55.1%)	136 (100%)

Chi^2 Value – 0.125 df – 1 p-Value – 0.724 (Not Significant)

According to IDF Criteria, maximum numbers of males 36 (46.2%) were affected by metabolic syndrome than the females 25 (43.1%). Prevalence of metabolic syndrome with the sex category has no significant correlation according to the p-value 0.724 (>0.05).

5.4.3 METABOLIC SYNDROME AMONG RELIGION CATEGORY

5.4.3.1 Metabolic Syndrome by Modified NECP ATP III and Religion

Religion Category	MS BY MODIFIED NECP ATP III		Total
	Yes	No	
Hindu	39(47.6%)	43(52.4%)	82 (100%)
Christian	19(45.2%)	23(54.8%)	42 (100%)
Muslim	6(50%)	6(50%)	12 (100%)
Total	64(47.1%)	72(52.9%)	136 (100%)

Chi^2 Value – 0.106 df – 2 p-Value – 0.948 (Not Significant)

According to the Modified NCEP ATP III Criteria, religion wise, maximum 50% (6 persons) prevalence of metabolic syndrome is seen in Muslims, followed by Hindus 47.6% (39 persons) and then Christians 45.2% (19 persons). Prevalence of metabolic syndrome (By Modified NCEP ATP III Criteria) with the religion category has no significant correlation according to the p-value 0.948 (>0.05).

5.4.3.2 Metabolic Syndrome by IDF and Religion

Religion Category	MS BY IDF		Total
	Yes	No	
Hindu	38(46.3%)	44(53.7%)	82 (100%)
Christian	17(40.5%)	25(59.5%)	42 (100%)
Muslim	6(50%)	6(50%)	12 (100%)
Total	61(44.9%)	75(55.1%)	136 (100%)

Chi^2 Value – 0.527 df – 2 p-Value – 0.768 (Not Significant)

According to the IDF Criteria, religion wise, maximum 50% (6 persons) prevalence of metabolic syndrome is seen in Muslims, followed by Christians 40.5% (17 persons) and then Hindus 46.3% (38 persons). Prevalence of metabolic syndrome (By IDF Criteria) with the religion category has no significant correlation according to the p-value 0.768 (>0.05).

5.5. DISTRIBUTION OF METABOLIC SYNDROME PARAMETERS

5.5.1 Distribution of Metabolic Syndrome Parameters among Age Category

AGE.CAT		WC	SBP	DBP	FBS	TGL	HDL
24 - 29 Years	N	43	43	43	43	43	43
	Mean	88.00	119.67	77.81	96.33	133.44	44.51
	SD	4.018	7.596	4.447	6.951	10.664	4.930
30 - 34 Years	N	28	28	28	28	28	28
	Mean	91.57	132.14	84.86	106.36	163.89	40.57
	SD	5.666	7.075	7.271	8.274	17.635	5.909
35 - 39 Years	N	65	65	65	65	65	65
	Mean	94.66	139.17	87.88	113.97	166.92	37.82
	SD	4.560	8.916	5.476	13.691	18.487	7.137
Total	N	136	136	136	136	136	136
	Mean	91.92	131.56	84.07	106.82	155.71	40.50
	SD	5.462	11.772	7.107	13.316	22.180	6.877
F - Value		26.659	73.895	42.067	33.782	59.525	14.776
p- Value		0.000*	0.000*	0.000*	0.000*	0.000*	0.000*

* Significant at 0.01 level

Table 5.5.1 shows the distribution of individual metabolic syndrome parameters among the various age categories with their mean and standard deviation. All the metabolic syndrome parameters waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood sugar, abnormal triglycerides and abnormal HDL levels, individually has significant correlation with the age category, according to their p-value <0.01 level.

5.5.2 Distribution of Metabolic Syndrome Parameters among Sex Category

SEX		WC	SBP	DBP	FBS	TGL	HDL
Male	N	78	78	78	78	78	78
	Mean	93.63	135.18	85.97	109.95	159.40	37.35
	SD	5.604	10.999	6.610	14.710	22.872	5.564
Female	N	58	58	58	58	58	58
	Mean	89.62	126.69	81.52	102.62	150.76	44.74
	SD	4.344	11.079	7.002	9.814	20.371	6.186
Total	N	136	136	136	136	136	136
	Mean	91.92	131.56	84.07	106.82	155.71	40.50
	SD	5.462	11.772	7.107	13.316	22.180	6.877
F – Value		20.490	19.696	14.379	10.806	5.203	53.404
p- Value		0.000*	0.000*	0.000*	0.001*	0.024**	0.000*

* Significant at 0.01 level

** Significant at 0.05 level

Table 5.5.2 shows the distribution of individual metabolic syndrome parameters among the sex categories with their mean and standard deviation. All the metabolic syndrome parameters waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood sugar, abnormal HDL levels, individually has significant correlation with the age category, according to their p-value <0.01 level and abnormal triglycerides have significant correlation with the age category, according to their p-value <0.05 level.

5.5.3 Distribution of Parameters among MS Category by Modified NECP ATP III

MS.BY. NECP. ATPIII		AGE	WC	SBP	DBP	FBS	TGL	HDL
Yes	N	64	64	64	64	64	64	64
	Mean	35.58	95.50	139.91	89.25	114.69	172.70	36.97
	SD	2.984	4.704	7.932	5.595	13.509	16.898	6.907
No	N	72	72	72	72	72	72	72
	Mean	27.92	88.74	124.14	79.47	99.83	140.61	43.64
	SD	3.931	3.907	9.437	4.759	8.362	13.805	5.133
Total	N	136	136	136	136	136	136	136
	Mean	32.60	91.92	131.56	84.07	106.82	155.71	40.50
	SD	5.040	5.462	11.772	7.107	13.316	22.180	6.877
F - Value		165.525	83.825	109.736	121.250	60.855	148.347	41.422
p- Value		0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*

* Significant at 0.01 level

Table 5.5.3 shows the distribution of parameters among metabolic syndrome category by NCEP ATP III Criteria with their mean and standard deviation. All the parameters waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood sugar, abnormal triglycerides and abnormal HDL levels, individually has significant correlation with the metabolic syndrome category, according to their p-value <0.01 level.

5.5.4 Distribution of Parameters among MS Category by IDF

MS.BY.IDF		AGE	WC	SBP	DBP	FBS	TGL	HDL
Yes	N	61	61	61	61	61	61	61
	Mean	35.76	95.7	140.33	89.31	115.11	171.59	37.11
	SD	2.967	4.663	7.951	5.315	13.680	17.553	6.785
No	N	75	75	75	75	75	75	75
	Mean	28.21	88.84	124.43	79.81	100.08	142.80	43.25
	SD	3.908	3.922	9.307	5.314	8.306	16.459	5.640
Total	N	136	136	136	136	136	136	136
	Mean	32.60	91.92	131.56	84.07	106.82	155.71	40.50
	SD	5.040	5.462	11.772	7.107	13.316	22.180	6.877
F - Value		163.978	86.965	111.701	107.456	62.383	96.965	33.199
p - Value		0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*

* Significant at 0.01 level

Table 5.5.4 shows the distribution of parameters among metabolic syndrome category by IDF Criteria with their mean and standard deviation. All the parameters waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood sugar, abnormal triglycerides and abnormal HDL levels, individually has significant correlation with the metabolic syndrome category, according to their p-value <0.01 level.

5.6 Lp(a) AND OTHER PARAMETERS

5.6.1 Lp(a) and Age, Sex, Religion Categories

Factors	Category	Number	Mean	SD	F- Value	p- Value
Age	24 - 29 Years	43	21.3681	5.66707	70.471	0.000*
	30 - 34 Years	28	45.6282	14.11606		
	35 - 39 Years	65	56.9342	19.49907		
Sex	Male	78	46.2577	24.53144	3.292	0.072
	Female	58	39.4662	16.81050		
Religion	Hindu	82	43.8849	22.73297	1.080	0.343
	Christian	42	40.3057	18.83605		
	Muslim	12	50.4783	24.40403		

* Significant at 0.01 level

In our study population, maximum amount of lipoprotein (a) is present in the age group of 35-39 years with the mean and standard deviation of 56.93 ± 19.49, followed by 30-34 years with the mean and standard deviation of 45.62 ± 14.11 and then 24-29 years with the mean and standard deviation of 21.36 ± 5.66. Amount of lipoprotein (a) among various age categories has significant correlation according to their p-value 0.000 (<0.01). In sex category, maximum amount of lipoprotein (a) is present in the males with the mean and standard deviation of 46.25 ± 24.53 compared to the females with the mean and standard deviation of 39.46 ± 16.81. Amount of lipoprotein (a) among sex category has no significant correlation according to their p-value 0.072 (>0.05).In religion category, maximum amount of lipoprotein (a) is present in Muslims with the mean and standard deviation of 50.47 ± 24.40 followed by Hindus with the mean and standard deviation of 43.88 ± 23.73 and then Christians with the mean and standard deviation of 39.46 ± 16.81. Amount of lipoprotein (a) among religion category has no significant correlation according to their p-value 0.343 (>0.05).

5.6.2 Lp(a) and Metabolic Syndrome

MS Category		Number	Mean	SD	F –Value	p- Value
Modified NECP ATP III	Yes	64	58.5331	18.54920	103.137	0.000*
	No	72	29.8753	14.27932		
IDF	Yes	61	58.6128	18.60316	90.136	0.000*
	No	75	30.9568	15.37194		

* Significant at 0.01 level

Amount of lipoprotein (a) is present in the metabolic syndrome category, by Modified NECP ATP III Criteria with the mean and standard deviation of 55.65 ± 18.30 and IDF Criteria with the mean and standard deviation of 56.07 ± 18.10. Metabolic syndrome category by either Modified NECP ATP III Criteria or IDF Criteria has significant correlation with lipoprotein (a) according to their p-value 0.000 (<0.01).

5.7 CORRELATION OF PARAMETERS

5.7.1 Correlation of Lp(a) with Other Parameters

	Number	Correlation Coefficient	Significance
AGE	136	0.751	0.000*
WC	136	0.681	0.000*
SBP	136	0.691	0.000*
DBP	136	0.644	0.000*
FBS	136	0.668	0.000*
TGL	136	0.668	0.000*
HDL	136	-0.636	0.000*

* Correlation is significant at 0.01 level.

In our study, lipoprotein (a) with the age category has significant correlation according to the correlation coefficient 0.751 and p-value 0.000 (<0.01) and the lipoprotein (a) with the waist circumference has significant correlation according to the correlation coefficient 0.681 and p-value 0.000 (<0.01). Lipoprotein (a) with the systolic blood pressure has significant correlation according to the correlation coefficient 0.691 and p-value 0.000 (<0.01) and diastolic blood pressure has significant correlation according to the correlation coefficient 0.644 and p-value 0.000 (<0.01).Lipoprotein (a) with the fasting blood sugar has significant correlation according to the correlation coefficient 0.668 and p-value 0.000 (<0.01) and also with the triglyceride level has significant correlation according to the correlation coefficient 0.668 and p-value 0.000 (<0.01). Finally, lipoprotein (a) with HDL cholesterol has significant negative correlation according to the correlation coefficient -0.636 and p-value 0.000 (<0.01).

5.7.2 Correlation of Age with Other Parameters

	Number	Correlation Coefficient	Significance
WC	136	0.579	0.000*
SBP	136	0.723	0.000*
DBP	136	0.627	0.000*
FBS	136	0.624	0.000*
TGL	136	0.628	0.000*
HDL	136	-0.443	0.000*

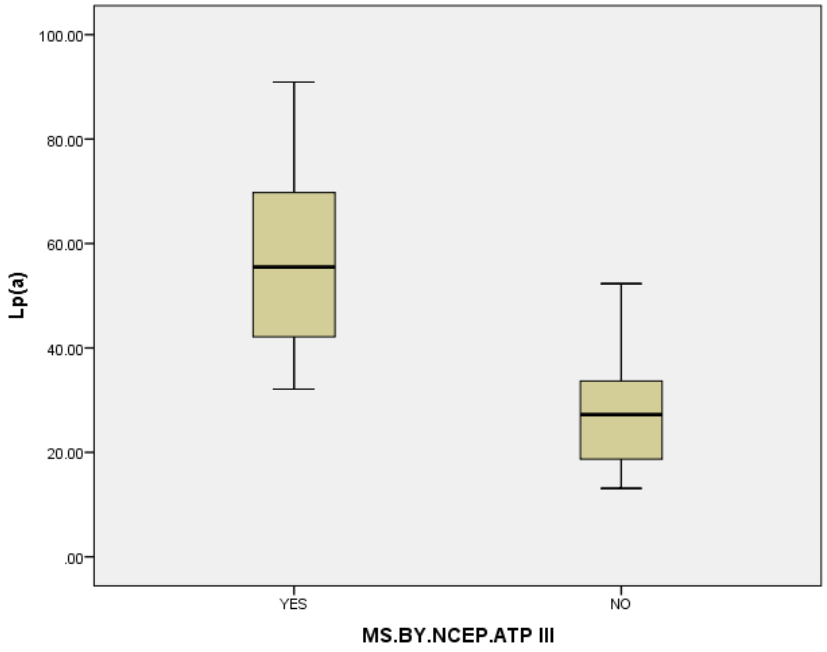
* Correlation is significant at 0.01 level.

Table 5.7.2 shows correlation of age with metabolic syndrome parameters. Waist circumference, systolic blood pressure, diastolic blood pressure, fasting blood sugar and triglycerides have significant correlation with the age category according to their correlation coefficients (and p-values) respectively 0.579 (0.000) ,0.723 (0.000), 0.627 (0.000), 0.624(0.000), 0.628 (0.000).HDL cholesterol has significant negative correlation with the age category according to their correlation coefficient -0.443 and p-value 0.000.

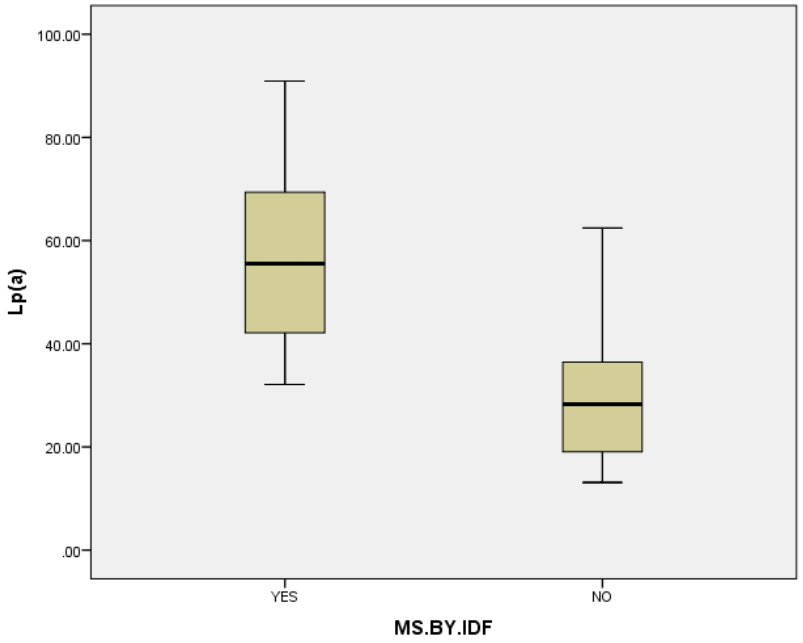
5.7.3 Correlation of Other Parameters

Control Variables	Other Variables	WC	SBP	DBP	FBS	TGL	HDL
AGE & Lp(a)	**WC**	1.000	.406**	.357**	.401**	.292**	-.392**
	SBP	.406**	1.000	.573**	.423**	.318**	-.416**
	DBP	.357**	.573**	1.000	.297**	.350**	-.216*
	FBS	.401**	.423**	.297**	1.000	.165	-.233**
	TGL	.292**	.318**	.350**	.165	1.000	-.247**
	HDL	-.392**	-.416**	-.216*	-.233**	-.247**	1.000
**. Correlation is significant at 0.01 level							
*. Correlation is significant at 0.05 level							

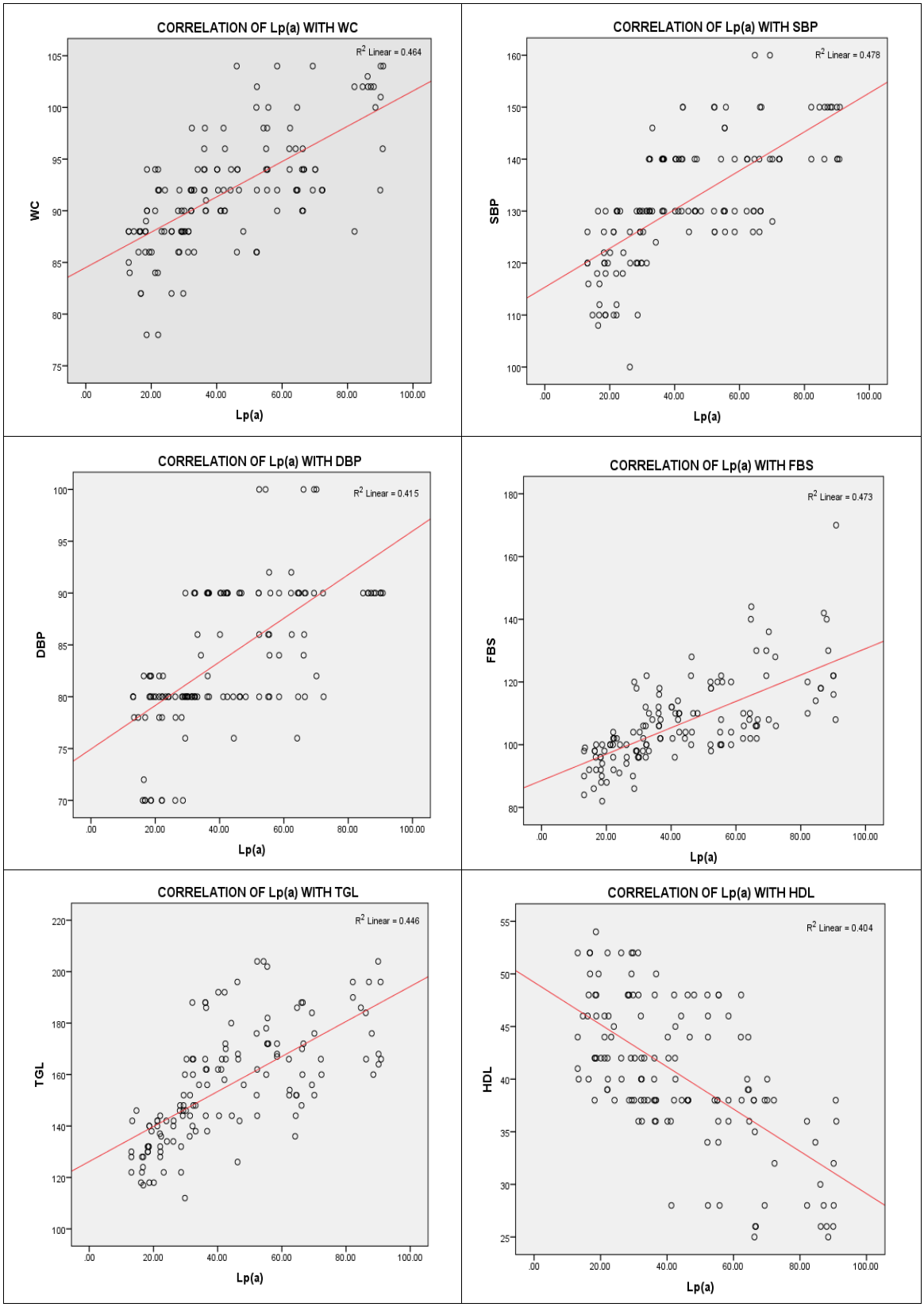
Age and lipoprotein (a) is taking as control variables, correlation of other parameters of metabolic syndrome individually shows significant correlation except systolic and diastolic blood pressure. HDL has negative correlation with all other parameters of metabolic syndrome.



Lp(a) IN MS BY MODIFIED NCEP ATP III CATEGORY



Lp(a) IN MS BY IDF CATEGORY



CORRELATION OF Lp(a) WITH MS PARAMETERS

DISCUSSION

DISCUSSION

Metabolic syndrome (MS), major components of which include central obesity, hypertriglyceridemia, low high-density lipoprotein levels, elevated BP and fasting hyperglycaemia has emerged as an important determinant of CV risk. Nowadays metabolic syndrome prevalence is increasing in the childhood and adolescent population.

. Applying the criteria of metabolic syndrome serves as a simple and inexpensive tool for identifying patients at high risk for diabetes mellitus and cardiovascular disease particularly those who do not fall into traditional risk categories. Though various diagnostic criteria for MS have been published, since Asian Indians have a tendency to develop metabolic abnormalities at a lower body mass index and waist circumference than other groups, conventional criteria may under estimate the prevalence of MS. This was also confirmed in our study; if abdominal obesity was considered an essential criterion (as recommended by the IDF guidelines) the prevalence of MS was underestimated (came down to 44.9% from 47.1%). Such a discrepancy has also been noted in previous studies and underscores the importance of using the modified South Asian guidelines to diagnose MS in the ethnic Indian population, (using obesity as an optional, and not an essential criterion, and the South Asian-specific waist circumference).

Shahbazian et al[148] reported the prevalence of metabolic syndrome based on ATP III criteria was 22.8% in an urban population in south west of Iran. Jun Hyun et al[149] reported the prevalence of metabolic syndrome based on ATP III criteria was 38.8% in rural population of Korea.

The ICMR task force collaborative study reported the prevalence of metabolic syndrome to be 30 per cent in urban areas of Delhi and 11 per cent in rural Haryana

using ATP-III criteria. Mishra et al[2] reported 30 per cent prevalence among the urban slum population in Delhi. Ramchandran et al[150] reported a prevalence of 41 per cent in urban area of Chennai using modified ATP-3 criteria among adults aged 20 to 75 yr. They also reported that prevalence was higher in women than men (46.5 vs. 36.4%) and in older people. Sarkar et al[32] reported 40-50 per cent prevalence in Bhutia tribe, with no rural-urban difference. Among the Toto tribe, the rural community prevalence was low 4-9 per cent.

Ramachandran et al[150] reported prevalence of 46.5% while using a modified waist circumference for Indian women ≥ 85 cm (modified NCEP ATP-III criteria for Asian Indian). Pandit vinodh et al[151] reported 29.6 percent of metabolic syndrome by modified ATP-III criteria among urban adults of Kurnool, Karnataka. Thakur et al[152] reported 68.6 percent of metabolic syndrome by modified ATP-III criteria (63.6% by IDF criteria) among adults in the northern hilly state of Himachal Pradesh. In our study, it was 47.1 % by modified NCEP ATP-III criteria and 44.9 % by IDF criteria.

The differences may be attributed to the difference in study areas, and the different definitions of metabolic syndrome used. Thus our study reports higher prevalence of metabolic syndrome. It is reported that prevalence of metabolic syndrome may vary with ethnic background. Thus higher prevalence observed in our study suggests that Indian Asians may be more prone to metabolic syndrome compared to other parts of the world. However, certain reports from different parts of India has observed that even within the same ethnic population group significant differences in the prevalence metabolic syndrome may prevail. Thus it appears that apart from ethnicity several other characteristic features of given population may collectively contribute to the higher prevalence of metabolic syndrome.

Many factors including: age, weight, menopause in women, race, smoking, no alcohol consumption, low income economies, high carbohydrate intake, consumption of soft drink, low physical activity, poor cardiovascular fitness, Genetic factors and antipsychotic drugs may playing a role in MS.

According to waist circumference cut off criteria, Rajeev Gupta et al stuty[153] was 108cm (M) and 80cm (F). Dongfeng Gu et al[154] and Pandit Vinodh et al[151] studies used 90cm (M) and 80 cm (F) as a cut off criteria. We also used 90cm (M) and 80 cm (F) as a cut off criteria similar to above studies. Different studies uses different criteria, in this analysis, we have used the ATP III criteria, with a modification to the value for waist circumference (WC) that is more applicable to the Asian Indian population. The waist circumference criteria followed in this study is comparable with A.Ramachandran et al[150], Dongfeng Gu et al[154] and Pandit Vinodh et al[151].

G.P.Parale et al[155] study shows 13.22% of males and 7.36% of females are affected by diabetes mellitus. Rajeev Gupta et al[153] (16.9% males, 16.1% females), Pandit Vinodh et al[151] (18.4% males, 11.2% females) also shows maximum numbers of males are affected by diabetes compared to females. However Sarkar et al[32] study shows 20.7% males and 41.3% females, which is contradictory to other three studies. In our study males are mostly affected than females.

The percentage of subjects with diabetes mellitus are high both in males and females compared to other studies and it shows a rising trend in the prevalence of diabetes. In our study, incidence of diabetes mellitus in males was higher than the females because women mainly develop peripheral adiposity with gluteal fat accumulation, whereas men are more prone to development of central or android obesity. (However, concentrations of lipoproteins as well as body fat distribution in women shift to a male pattern after menopause). According to previous studies, obesity

and insulin resistance are closely linked, and obesity may precede development of insulin resistance. Insulin resistance subsequently leads to elevation in triglyceride, glucose level and blood pressure, and reduction of HDL-cholesterol levels.

Shahbazian et al[148] study (13.7% males & 16.9% females), Kamble et al[156] study (53.5% males & 54.2% females) shows females are maximum affected by hypertension compared to males. Pandit Vinodh et al[151] (21.6% males & 18.4% females), Surana et al[157] (75.1% males & 71.01% females) shows males are affected mostly by hypertension.

The percentage of hypertension in our study (52.6% males and 34.5% females) is similar to Kamble et al[156] study in rural wartha, central India. Males are more affected by hypertension than the females because of android type obesity and smoking. Smoking leads to narrowing of blood vessels and increases the blood pressure.

Kamble et al[156] study (33.5% in males & 26% in females), Shahbazian et al[148] study (47.8% in males & 34.2% in females), Surana et al[157] study (58.32% in males & 57.25% in females) show abnormal triglyceride levels more in males compared to females. Pandit Vinodh et al[151] study shows the other way i.e abnormal triglyceride levels more in females (24.0% in females and 20.8% in males). However our study substantiates Kamble et al[156], Shahbazian et al[148] and Surana et al[157] study results. The value of our study is similar to Surana et al study (53.8% in males and 37.9% in females).

Pandit Vinodh et al[151] studies show decreased HDL levels 22.4% in males and 20.8% in females. Here decreased HDL levels are more or less similar in males and females. The other studies show decreased HDL levels more in females compared to males. Shahbazian et al[148] study shows decreased HDL 28.5% in males and 50.7% in females, Surana et al[157] study shows 43.05% in males and 64.59% in females, and Kamble et al[156] study shows 50% in males and 70.2% in females. Likewise our study

also shows HDL levels decreased more in females compared to males. The values are similar to Shahbazian et al[148] study.

Metabolic syndrome category by either Modified NECP ATP III Criteria or IDF Criteria has significant correlation with lipoprotein (a) according to their p-value 0.000 (<0.01). Lipoprotein (a) and individual parameters of metabolic syndrome has also significant correlation according to their p-value (<0.01) levels. Among them HDL has negative correlation with lipoprotein (a).

Subjects with MS have increased levels of Lp(a) compared to the normal subjects. Our result is similar to the study of Bermudez et al[159] and Bozbas et al[158]. This association differs from the study done in older Japanese adults[160] where Lp(a) and MS have no significant correlation.

There are not much of studies explaining the relationship between individual components of MS and Lp(a) [163]. Only few studies dealt about this relationship. In our study, every individual component of the MS has significant correlation with Lp(a) like Bermudez et al[159] study. Our results differ from the study done by Candido et al[164] in 400 Brazilian individuals (here, no significant correlation between MS and Lp(a)).

In our population, age and sex has significant correlation with Lp(a).so, age also the main risk factor for presenting elevated Lp(a), similar to previous studies on Swedish subjects [166] and on Taiwanese population[165]. According to sex, males have higher Lp(a) levels than females similar to Kotani et al study[160].

One limitation of our study was that, this study was cross sectional that does not allow us to draw any causal interference. Therefore in the future large prospective studies should be used to confirm the association between above mentioned factors and metabolic syndrome.

CONCLUSION

CONCLUSION

In our study, prevalence of metabolic syndrome in younger population (24-39 years) by Modified NCEP ATP III Criteria is 47.1%. Prevalence is maximum 76.9% at the age group of 35-39 years followed by 50% in the age group of 30-34 years and then 0% in 24-29 years. Prevalence of metabolic syndrome with age category has significant correlation. According to gender, 47.4% males and 46.6% females were affected by metabolic syndrome. It has no significant correlation.

Prevalence of metabolic syndrome in younger population (24-39 years) by IDF Criteria is 44.9%. Prevalence is maximum 73.8% at the age group of 35-39 years followed by 46.4% in the age group of 30-34 years and then 0% in 24-29 years. Prevalence of metabolic syndrome with age category has significant correlation. According to gender, 46.2% males and 43.1% females were affected by metabolic syndrome. It has no significant correlation. Lipoprotein (a) level is increased in the metabolic syndrome category by Modified NCEP ATP III Criteria and IDF Criteria. Lipoprotein (a) level has significant correlation with the metabolic syndrome according to their p values (<0.01). It has significantly correlated with the individual components of metabolic syndrome and age category also (p value <0.01).

The significant increase in the prevalence of metabolic syndrome is the major risk factor for mainly coronary heart disease and diabetes mellitus. Health education and awareness among individuals about nutrition, physical exercise and maintenance of waist circumference from the younger age group is required to prevent major non-communicable health disorders in the era of increasing life expectancy. Detection of one component of the metabolic syndrome should lead to the search for the other components and its management.

SUMMARY

SUMMARY

The metabolic syndrome is a multiplex risk factor for atherosclerotic cardiovascular disease. It consists of an abdominal obesity, atherogenic dyslipidemia, elevation of blood pressure and glucose, prothrombotic and proinflammatory states. The risk of ASCVD accompanying the MS is approximately doubled compared with an absence of the syndrome.

The present study aims to know the prevalence of metabolic syndrome among younger population (24-39 years) and to study the relationship between Lipoprotein (a) and metabolic syndrome.

We evaluated 136 patients and bystanders, who attended the medicine OPD of SMIMS. The following parameters were collected: age, gender, religion, waist circumference, blood pressure and fasting blood sugar, serum triglycerides and serum HDL.

In our study, prevalence of metabolic syndrome in younger population (24-39 years) by Modified NCEP ATP III Criteria is 47.1% and IDF Criteria is 44.9%. Lipoprotein (a) level is increased in the metabolic syndrome and it has significant correlation with the metabolic syndrome. It has significantly correlated even with the individual components of metabolic syndrome and age category also.

The significant increase in the prevalence of MS is the major risk factor for mainly coronary heart disease and diabetes mellitus. Elevation of Lipoprotein (a) levels also main risk factor for coronary heart disease. Health education and awareness among individuals about nutrition, physical exercise and maintenance of waist circumference from the younger age group is required to prevent MS and also the CHD in future.

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ANNEXURE

CONSENT FORM

PART – II

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled "Study of Lipoprotein(a) and biochemical parameters of metabolic syndrome among younger population". I give consent for withdrawing blood (10ml) from my body for your study.

Serial no/Reference no:

Name of the Participant: **Address of the Participant:**

Contact number of the Participant:

Signature/Thumb impression of the participant/Legal guardian:

Witness

1.

2.

Date:

Place: Kulasekharam

ANNEXURE I - CASE PROFORMA

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES, KULASEKHARAM

TITLE OF STUDY : Study of Lipoprotein(a) and biochemical parameters of metabolic syndrome among younger population

HOSPITAL NO :

SERIAL NO :

DATE :

NAME :

AGE :

SEX :

ADDRESS & PHONE NO :

BRIEF HISTORY :

GENERAL EXAMINATION:

WAIST CIRCUMFERENCE:

BLOOD PRESSURE

Systolic BP :

Diastolic BP :

INVESTIGATIONS : FBS,
SERUM TRIGLYCERIDES,
SERUM HDL,
LIPOPROTEIN(a).

SIGNATURE OF INVESTIGATOR

Sree Mookambika Institute of Medical Sciences
Kulasekharam (K.K District, TN) 629161

Phone No: 04651-280866, Fax No. 04651-280740

Institutional Human Ethics Committee

Registered under CDSCO with Reg No. ECR/446/Inst/TN/2013

Ref. No. SMIMS/IHEC/2013/C/07 **Date: 27th December 2013**

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/C/07,** entitled "Study of Lipoprotein (a) and Biochemical Parameters of Metabolic Syndrome Among Young Population" submitted by Dr. B. Poonguzhali, Postgraduate of Department of Biochemistry, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 19th of December 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES ★ KULASEKHARAM ★
IHEC
Date 27/12/2013

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam [K.K District]
Tamil Nadu -629161

CERTIFICATE

We the members of the Research committee have screened the protocol of the dissertation submitted by the P.G. Students Dr.B.Ranganathi.....in detail and found itself to be fit enough for submitting to the IHEC for approval.

Kumari Sheela MS
6.5.2013

Chairperson

Dr. Haneephabi.

6/5/13

Professor of Community Medicine

Convenor

Dr. M.S. Kumari Sheela MD.

Professor & HOD Physiology

Members

1) Mr. M.B. Kumar - Statistician
2) Dr. Rema Menon - Professor & HOD Pharmacology
3) Dr. Pethuru - Epidemiologist
4) Dr. Kaniraj Peter – Professor of Medicine
5) Dr. Balachandran - Professor of OBG
6) Dr. Sreelal - Professor dental College.

MASTER CHART														
S.NO	NAME	AGE	GENDER	RELIGON	WC	HIST.HTN	SBP	DBP	HIST.DM	FBS	HIST.ANTILIP	TGL	HDL	Lp(a)
1	RAM PRAKASH	24	1. MALE	1. HINDU	92	2. NO	120	80	2. NO	120	2. NO	122	38	28.6
2	RADHA	24	2. FEMALE	1. HINDU	82	2. NO	100	70	2. NO	94	2. NO	134	52	26.2
3	AUGUSTIN	24	1. MALE	2. CHRISTIAN	94	2. NO	126	80	2. NO	100	2. NO	140	44	21.2
4	PRADEEPKUMAR	24	1. MALE	1. HINDU	88	2. NO	118	80	2. NO	91	2. NO	142	45	24
5	KALPANA	24	2. FEMALE	1. HINDU	84	2. NO	118	70	2. NO	100	2. NO	137	39	22
6	AJAYAN	24	1. MALE	1. HINDU	86	2. NO	120	80	2. NO	98	2. NO	138	50	19.4
7	HUMAYOON	24	1. MALE	3. MUSLIM	84	2. NO	110	78	2. NO	100	2. NO	142	42	21.2
8	RAMYA	24	2. FEMALE	1. HINDU	78	2. NO	110	70	2. NO	96	2. NO	128	52	22.1
9	RAMESH	24	1. MALE	1. HINDU	88	2. NO	126	80	2. NO	98	2. NO	130	41	13.12
10	SREEKALA	24	2. FEMALE	1. HINDU	82	2. NO	116	70	2. NO	100	2. NO	117	52	16.83
11	VANITHARANI	24	2. FEMALE	2. CHRISTIAN	78	2. NO	110	70	2. NO	90	2. NO	132	54	18.6
12	SHAJI	25	1. MALE	2. CHRISTIAN	92	2. NO	130	80	2. NO	92	2. NO	130	40	22.2
13	SHAHAYARAJ	25	1. MALE	2. CHRISTIAN	88	2. NO	126	82	2. NO	96	2. NO	132	42	18.2
14	MONIKA	25	2. FEMALE	1. HINDU	82	2. NO	112	78	2. NO	92	2. NO	128	50	16.83
15	SUMAN	25	1. MALE	1. HINDU	94	2. NO	130	80	2. NO	94	2. NO	140	42	18.71
16	PADMA	25	2. FEMALE	1. HINDU	86	2. NO	118	70	2. NO	86	2. NO	118	46	16.12
17	VAISHANTH	25	1. MALE	1. HINDU	89	2. NO	120	82	2. NO	88	2. NO	132	48	18.4
18	RADHA	25	2. FEMALE	1. HINDU	88	2. NO	120	80	2. NO	90	2. NO	128	52	13.12
19	ANTONYJERSON	25	1. MALE	2. CHRISTIAN	90	2. NO	126	82	2. NO	100	2. NO	142	46	21.2
20	ADVIN	26	1. MALE	2. CHRISTIAN	85	2. NO	120	80	2. NO	84	2. NO	122	44	13.12
21	JEBA	26	2. FEMALE	2. CHRISTIAN	90	2. NO	118	82	2. NO	82	2. NO	118	48	18.71
22	MANOJ	26	1. MALE	1. HINDU	88	2. NO	126	80	2. NO	100	2. NO	140	42	26.2
23	RAMYA	26	2. FEMALE	1. HINDU	88	2. NO	110	70	2. NO	96	2. NO	124	52	16.73
24	JOSEPH	26	1. MALE	2. CHRISTIAN	92	2. NO	130	82	2. NO	102	2. NO	136	46	22.4
25	REJIN	27	1. MALE	2. CHRISTIAN	92	2. NO	122	80	2. NO	100	2. NO	134	38	24.2
26	LALITHA	27	2. FEMALE	1. HINDU	88	2. NO	108	72	2. NO	98	2. NO	128	48	16.43
27	PREETHI	27	2. FEMALE	1. HINDU	90	2. NO	110	70	2. NO	100	2. NO	140	46	18.71
28	AKSHAY	27	1. MALE	1. HINDU	88	2. NO	120	78	2. NO	96	2. NO	142	40	26.3
29	LATHA	27	2. FEMALE	1. HINDU	92	2. NO	112	78	2. NO	102	2. NO	132	39	22.1
30	BENRAJ	27	1. MALE	2. CHRISTIAN	86	2. NO	122	80	2. NO	88	2. NO	118	42	20.1
31	VIJAYAKUMAR	27	1. MALE	1. HINDU	88	2. NO	130	80	2. NO	102	2. NO	122	44	23.2
32	AHAMED	28	1. MALE	3. MUSLIM	94	2. NO	130	80	2. NO	104	2. NO	144	42	22.1
33	VINOTHJOY	28	1. MALE	2. CHRISTIAN	88	2. NO	130	82	2. NO	98	2. NO	122	40	16.4
34	ABDULRASHAK	28	1. MALE	3. MUSLIM	86	2. NO	122	80	2. NO	96	2. NO	130	38	18.2
35	RASHIKA	28	2. FEMALE	1. HINDU	90	2. NO	120	78	2. NO	90	2. NO	146	48	28.2
36	BRYSONPAUL	28	1. MALE	2. CHRISTIAN	84	2. NO	116	78	2. NO	99	2. NO	142	40	13.4
37	ANUJA	28	2. FEMALE	1. HINDU	88	2. NO	110	78	2. NO	92	2. NO	146	46	14.7
38	RAMKUMAR	29	1. MALE	1. HINDU	92	2. NO	130	80	2. NO	100	2. NO	148	40	32.4
39	ARTHY	29	2. FEMALE	1. HINDU	86	2. NO	110	70	2. NO	86	2. NO	132	48	28.6
40	RASHEER	29	1. MALE	3. MUSLIM	94	2. NO	130	82	2. NO	106	2. NO	162	36	36.3
41	MANIKANDAN	29	1. MALE	1. HINDU	94	2. NO	124	84	2. NO	108	2. NO	156	38	34.2
42	JOHN	29	1. MALE	2. CHRISTIAN	88	2. NO	120	80	2. NO	92	2. NO	130	42	18.3

43	ABINAYA	29	2. FEMALE	1. HINDU	88	2. NO	120	80	2. NO	96	2. NO	112	52	29.8
44	RAJAN	30	1. MALE	1. HINDU	88	2. NO	126	80	2. NO	104	2. NO	166	42	30.3
45	RAMYA	30	2. FEMALE	1. HINDU	82	2. NO	120	80	2. NO	96	2. NO	160	48	29.8
46	NIBINKUMAR	30	1. MALE	1. HINDU	88	2. NO	126	80	2. NO	98	2. NO	152	38	29.4
47	AMALRAJ	30	1. MALE	2. CHRISTIAN	98	1. YES	140	90	1. YES	118	2. NO	186	38	36.4
48	SATHYAMMAL	30	2. FEMALE	1. HINDU	90	2. NO	130	80	2. NO	100	2. NO	160	42	32.3
49	RIYAS	30	1. MALE	3. MUSLIM	104	2. NO	140	90	1. YES	120	2. NO	167	36	58.5
50	VINUJA	30	2. FEMALE	1. HINDU	88	2. NO	120	80	2. NO	102	2. NO	144	48	31.4
51	PAULRAJ	31	1. MALE	2. CHRISTIAN	86	2. NO	130	80	2. NO	98	2. NO	148	38	33.1
52	RAMCHANDHAR	31	1. MALE	1. HINDU	90	2. NO	140	80	1. YES	110	2. NO	172	42	42.4
53	JENIFER	31	2. FEMALE	2. CHRISTIAN	86	2. NO	130	80	1. YES	104	2. NO	148	48	28.3
54	BRITTO	31	1. MALE	2. CHRISTIAN	94	2. NO	130	80	2. NO	104	2. NO	166	38	46.4
55	KOCHURANI	31	2. FEMALE	1. HINDU	86	2. NO	126	86	2. NO	98	2. NO	162	46	52.3
56	ALEX	31	1. MALE	2. CHRISTIAN	94	1. YES	140	100	2. NO	106	2. NO	188	38	66.1
57	SREENIVAS	32	1. MALE	1. HINDU	90	2. NO	140	90	1. YES	110	2. NO	166	28	41.3
58	NAGARAJ	32	1. MALE	1. HINDU	88	2. NO	130	80	2. NO	106	2. NO	152	36	31.4
59	LISHIKA	32	2. FEMALE	2. CHRISTIAN	86	2. NO	130	80	2. NO	100	2. NO	126	48	46.2
60	RIYAZAHAMED	32	1. MALE	3. MUSLIM	98	1. YES	140	100	1. YES	120	2. NO	204	38	54.3
61	PARVATHI	34	2. FEMALE	1. HINDU	86	2. NO	130	80	2. NO	98	2. NO	136	52	31.3
62	KRISHNAN	34	1. MALE	1. HINDU	92	2. NO	130	80	2. NO	104	1. YES	168	38	58.5
63	HARISH	34	1. MALE	1. HINDU	104	1. YES	140	100	1. YES	122	2. NO	184	28	69.36
64	CHANDRAMANI	34	2. FEMALE	1. HINDU	92	2. NO	126	80	1. YES	118	2. NO	144	44	52.31
65	SARADHA	34	2. FEMALE	1. HINDU	94	2. NO	130	80	2. NO	100	2. NO	160	38	55.13
66	LAKSHMI	34	2. FEMALE	1. HINDU	90	2. NO	130	80	2. NO	96	2. NO	162	36	41.13
67	MURALI	34	1. MALE	1. HINDU	94	2. NO	140	90	1. YES	112	2. NO	166	40	36.12
68	VISHWANATH	34	1. MALE	1. HINDU	96	1. YES	130	86	2. NO	104	1. YES	178	38	55.11
69	MINATHULMUFITHA	34	2. FEMALE	3. MUSLIM	90	2. NO	126	84	2. NO	100	2. NO	172	46	58.5
70	LAIDON	34	1. MALE	2. CHRISTIAN	102	1. YES	150	100	2. NO	120	1. YES	196	36	82.1
71	MARYPAULIN	34	2. FEMALE	2. CHRISTIAN	88	2. NO	130	80	1. YES	110	2. NO	156	48	48.13
72	VISHWANATHAN	35	1. MALE	1. HINDU	88	2. NO	130	80	2. NO	98	2. NO	144	42	29.13
73	SUBRAMANIYAM	35	1. MALE	1. HINDU	91	2. NO	130	80	2. NO	102	2. NO	156	38	36.73
74	CHANDRAKUMAR	35	1. MALE	1. HINDU	96	1. YES	150	90	1. YES	110	2. NO	166	40	42.53
75	CHANDRA	35	2. FEMALE	1. HINDU	92	2. NO	146	92	2. NO	108	2. NO	172	36	55.41
76	SAHAYARANI	35	2. FEMALE	2. CHRISTIAN	94	2. NO	130	80	2. NO	106	1. YES	188	26	66.52
77	RAHAV	35	1. MALE	1. HINDU	90	2. NO	140	90	2. NO	102	2. NO	162	36	36.6
78	MINI	35	2. FEMALE	2. CHRISTIAN	90	2. NO	150	90	2. NO	104	2. NO	170	45	42.51
79	JOSEPH	35	1. MALE	2. CHRISTIAN	102	1. YES	150	100	1. YES	118	1. YES	204	28	52.3
80	MARYARULPRIYA	35	2. FEMALE	2. CHRISTIAN	94	2. NO	140	90	1. YES	112	2. NO	192	44	40.21
81	BINDHU	35	2. FEMALE	1. HINDU	92	1. YES	140	80	1. YES	112	2. NO	188	46	32.12
82	JAINSON	35	1. MALE	2. CHRISTIAN	90	2. NO	130	80	2. NO	96	1. YES	146	38	30.12
83	SHEELA	35	2. FEMALE	2. CHRISTIAN	94	2. NO	126	84	2. NO	100	2. NO	182	48	55.52
84	BRAVIANJOHN	35	1. MALE	2. CHRISTIAN	104	1. YES	140	90	1. YES	122	2. NO	196	38	46.13
85	RAJESH	36	1. MALE	1. HINDU	92	1. YES	146	86	1. YES	110	2. NO	138	42	33.13
86	LINDA	36	2. FEMALE	2. CHRISTIAN	88	2. NO	130	90	2. NO	98	2. NO	148	52	29.36
87	SHIVA	36	1. MALE	1. HINDU	92	1. YES	140	90	2. NO	106	1. YES	166	38	32.13
88	YAMUNA	36	2. FEMALE	1. HINDU	90	2. NO	140	90	2. NO	108	2. NO	138	50	36.72
89	ALENKIRUBA	36	1. MALE	2. CHRISTIAN	94	2. NO	130	86	1. YES	112	2. NO	162	36	40.12

90	PRASATH	36	1. MALE	1. HINDU	92	2. NO	140	80	2. NO	106	2. NO	160	32	72.34
91	ANDAL	36	2. FEMALE	1. HINDU	86	2. NO	130	90	2. NO	100	2. NO	152	48	52.15
92	VISHNU	36	1. MALE	1. HINDU	94	1. YES	150	90	1. YES	108	2. NO	172	26	66.72
93	SHANKAR	36	1. MALE	1. HINDU	88	2. NO	140	100	2. NO	110	2. NO	190	28	82.13
94	AMUDHA	37	2. FEMALE	1. HINDU	92	2. NO	140	90	1. YES	110	2. NO	142	44	46.81
95	KARTHIKEYAN	37	1. MALE	1. HINDU	104	1. YES	140	90	1. YES	122	1. YES	164	28	90.13
96	SOWNDHARYA	37	2. FEMALE	1. HINDU	90	2. NO	130	90	2. NO	102	2. NO	160	35	66.41
97	SUBRAMANIYAM	37	1. MALE	1. HINDU	102	1. YES	150	90	1. YES	140	1. YES	176	26	88.02
98	RADHIKA	37	2. FEMALE	2. CHRISTIAN	94	2. NO	128	82	2. NO	108	2. NO	152	38	70.12
99	SURESH	37	1. MALE	1. HINDU	98	1. YES	140	86	2. NO	106	2. NO	154	38	62.43
100	SHAKIN	37	1. MALE	3. MUSLIM	96	2. NO	126	76	2. NO	108	2. NO	136	40	64.13
101	PRAVEEN	37	1. MALE	1. HINDU	100	2. NO	150	90	1. YES	130	1. YES	160	25	88.5
102	KANMANI	37	2. FEMALE	1. HINDU	96	1. YES	130	90	2. NO	102	2. NO	166	44	62.2
103	REVANDH	37	1. MALE	1. HINDU	92	2. NO	130	90	2. NO	110	2. NO	144	39	64.31
104	NISHANDH	37	1. MALE	1. HINDU	102	1. YES	150	90	1. YES	142	1. YES	196	28	87.13
105	LEKHA	37	2. FEMALE	1. HINDU	94	2. NO	130	80	2. NO	100	2. NO	172	48	55.5
106	LINGAMMAL	37	2. FEMALE	2. CHRISTIAN	92	2. NO	130	80	1. YES	102	1. YES	180	46	44.24
107	RAJASEKAR	37	1. MALE	2. CHRISTIAN	92	2. NO	140	90	2. NO	110	2. NO	188	38	36.13
108	MYTHILI	38	2. FEMALE	1. HINDU	90	2. NO	126	84	2. NO	106	2. NO	148	38	66.14
109	MIMMYRAJ	38	2. FEMALE	2. CHRISTIAN	92	2. NO	130	80	2. NO	102	2. NO	152	44	64.43
110	ABILESH	38	1. MALE	1. HINDU	102	1. YES	150	90	1. YES	118	1. YES	166	26	86.24
111	SAJEETHA	38	2. FEMALE	2. CHRISTIAN	94	2. NO	130	90	1. YES	128	2. NO	168	38	46.31
112	SUJI	38	2. FEMALE	1. HINDU	90	2. NO	130	90	2. NO	96	2. NO	140	40	32.16
113	ROBINSON	38	1. MALE	2. CHRISTIAN	100	1. YES	150	90	1. YES	120	1. YES	172	28	55.8
114	PREMA	38	2. FEMALE	1. HINDU	92	1. YES	140	90	2. NO	102	2. NO	144	42	40.42
115	JOHNSON	38	1. MALE	2. CHRISTIAN	100	1. YES	150	90	1. YES	120	1. YES	176	34	52.15
116	ROMY	38	2. FEMALE	2. CHRISTIAN	98	2. NO	140	90	2. NO	114	2. NO	158	38	42.1
117	JEYARAM	38	1. MALE	1. HINDU	101	1. YES	140	90	2. NO	116	1. YES	168	32	90.12
118	DHINESH	38	1. MALE	1. HINDU	103	2. NO	140	90	2. NO	118	2. NO	184	30	86.13
119	SAHAYAMARI	38	2. FEMALE	2. CHRISTIAN	96	2. NO	150	86	1. YES	130	2. NO	170	25	66.3
120	SASIKUMAR	38	1. MALE	1. HINDU	98	1. YES	146	86	1. YES	122	2. NO	202	34	55.43
121	DIVYA	38	2. FEMALE	1. HINDU	92	2. NO	130	90	2. NO	108	2. NO	192	48	42.14
122	VINUJA	38	2. FEMALE	2. CHRISTIAN	96	2. NO	130	80	2. NO	106	2. NO	188	42	36.2
123	ANEER	38	1. MALE	3. MUSLIM	98	2. NO	140	90	1. YES	122	2. NO	166	36	32.42
124	DEVI	38	2. FEMALE	1. HINDU	94	2. NO	126	76	2. NO	104	2. NO	144	38	44.42
125	ANWAR	38	1. MALE	3. MUSLIM	102	1. YES	150	90	1. YES	114	1. YES	186	34	84.61
126	SATHEESH	39	1. MALE	1. HINDU	100	2. NO	140	90	1. YES	140	2. NO	152	39	64.59
127	PUSHPARAJAN	39	1. MALE	1. HINDU	104	1. YES	150	100	1. YES	170	1. YES	166	36	90.91
128	SHAJI	39	1. MALE	2. CHRISTIAN	92	1. YES	160	90	1. YES	130	2. NO	156	38	69.36
129	SREJITH	39	1. MALE	1. HINDU	94	2. NO	140	100	1. YES	136	2. NO	176	40	70.13
130	JEBA	39	2. FEMALE	2. CHRISTIAN	92	1. YES	140	90	2. NO	128	1. YES	166	38	72.15
131	KAJAMYTHEEN	39	1. MALE	3. MUSLIM	92	1. YES	160	90	1. YES	144	2. NO	186	36	64.73
132	SUJI	39	2. FEMALE	1. HINDU	90	2. NO	126	76	2. NO	118	2. NO	146	50	29.31
133	ARAVINDH	39	1. MALE	1. HINDU	92	1. YES	150	90	1. YES	122	2. NO	204	26	90
134	MARIYMMAL	39	2. FEMALE	1. HINDU	92	1. YES	140	90	2. NO	116	1. YES	144	48	36.3
135	AJEEN	39	1. MALE	3. MUSLIM	96	1. YES	140	90	2. NO	108	1. YES	196	38	90.75
136	LEKHA	39	2. FEMALE	1. HINDU	94	2. NO	140	92	2. NO	110	2. NO	152	48	62.28