METABOLIC SYNDROME IN KURNOOL DISTRICT IN ADULTS (20-60 YEARS) - A CROSS SECTIONAL STUDY USING MODIFIED NCEP ATP III CRITERIA

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&

Elizabeth Missamma

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ABBREVATIONS

AACE	American Association of Clinical Endocrinologists
ACE	Angiotensin converting enzyme
ANOVA	Analysis of Variance
AO	Abdominal Obesity
ATP III	Adult Treatment Panel III.
BMI	Body mass index.
BP	Blood pressure
CAD	Coronary artery disease
CHE	Cholesterol esterase
CHD	Coronary heart disease
CHO	Cholesterol oxidase
CVD	Cardiovascular diseases
DBP	Diastolic blood pressure
DLHS	District Level Household Survey
EGIR	European group for the study of insulin resistance
FBS	Fasting blood glucose.
FI	Fasting Insulin
GATS	Global Adult Tobacco Survey
GDDP	Gross district domestic product
GO	Generalized obesity
HDL	High density lipoprotein
HOMA-IR	Homeostasis model assessment- Insulin resistance.
HTN	Hypertension
IDF	International Diabetes Federation
IR	Insulin resistance
IRS	Insulin resistance syndrome
ISH	International Society of hypertension
JNC	Joint National Committee
LDL	Low-density lipoprotein
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease

NCDs	Non communicable diseases
NCEP	National Cholesterol Education Program
NFHS	National Family Heath Survey
NHANES	National Health and Nutritional Examination Survey
PPS	Probability proportional to size
RAAS	Renin angiotensin aldosterone system
RIA	Radio Immunoassay
SBP	Systolic blood pressure
SD	Standard deviation
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglyceride
WC	Waist circumference
WHO	World Health Organization

ABSTRACT

Background

Rapid unplanned urbanization, globalization of unhealthy lifestyle and lack of physical activity are vulnerable risk factors contributing to Non Communicable Diseases (NCDs) like type 2 diabetes mellitus and cardiovascular diseases. Over 15 million of all deaths attributed to NCDs occur between 30–60 years of age, of them 80% are estimated to occur in low and middle income countries like India. Unhealthy life style and lack of physical activity lead to increased blood pressure, elevated blood glucose, altered lipid parameters and obesity. These are called metabolic risk factors and the condition is referred as metabolic syndrome (MetS). Identification of regional prevalence of MetS and trends will enable the prioritization and implementation of interventions through existing regional collaborations.

Objective

The main objective of this study is to assess the prevalence of metabolic syndrome in urban, rural and tribal population of Kurnool district using modified NCEP ATP III criteria.

Methods

A cross sectional study has been conducted to assess the prevalence of metabolic syndrome. Total 1032 subjects were recruited in this study having 344 subjects in each group aged between 20-60 years. The subjects have been screened for metabolic syndrome using modified NCEP ATP III criteria. Fasting insulin levels are estimated and insulin resistance (defined by HOMA-IR) has been calculated in 20 subjects from each group. Correlation of HOMA-IR with each component of metabolic syndrome was done. CVD risk profile of the subjects was studied using WHO/ISH-CVD risk prediction algorithm chart-D.

Results

We found a high prevalence of metabolic syndrome (31.97%) in Kurnool district and results indicate that prevalence is highest in urban population (42.15%) as compared to rural (31.97%) and tribal (21.80%) population. While comparing the MetS between male and female it was observed that male is having higher (41.82%) as compared to female (30.82%).

The prevalence of MetS was found to be near similar in case of urban male (41.82%) and female (42.64%) as compared to rural male (33.65%) and female (29.93%), tribal male (20.93%) and female 22.67%). Decreased HDL-C (78.87%) increase of WC (57.84%) and elevation of TG (31.78%) were found to be potent risk factors for MetS in all the groups of males and females. Age dependent rise in prevalence of MetS were observed in urban and rural population, highest prevalence is noted after 50 years of age while in case of tribal population prevalence is decreased after 50 years.

In urban area post-menopausal aged females have shown higher prevalence of MetS as compared to males (58.62% vs. 44.11%); equal prevalence is noted in rural area (38.70% vs. 38.77%); while in case of tribal area males have shown higher prevalence compared to females (35.00% vs. 30.30%).

Mean fasting insulin level (µIU/ml) is 18.77(±10.61) [urban population 18.32(±9.56), rural population 23.32(±9.56) and tribal population 18.10(±5.72)]. The prevalence of hyper insulinemia in urban population is 60%, rural population 40% and tribal population 25%. Mean HOMA-IR is 4.17(±2.99) [urban: 4.14(±3.06), rural: 5.62(±3.38) and tribal population: 3.69(±1.21)]. Prevalence of Insulin resistance in urban population is 65%, rural population: 75% and tribal population: 55%.

Rural population has not shown significant correlation between Insulin resistance and MetS components [WC (p=0.6642), TG (p=0.9901) and SBP (p=0.1941)] whereas, urban and tribal population are showing correlation. HDL-C is not correlated with insulin resistance in overall (p=0.2483); urban (p=0.5209); rural (p=0.8839); tribal (p=0.4040). Moderate CVD risk is present in 11.82% subjects

[urban: 15.69%, rural: 11.33% and tribal: 11.33%] and high CVD risk is present in 4.84% subjects [urban: 6.9%, rural: 6% and tribal: 2.9%].

Only 25.38% of participants were without any habitual or physiological CVD risk factors. An alarming is 43.45% population were with combination of two or more cardiovascular risk factors.

Conclusion

The study findings reveal that prevalence of metabolic syndrome is very high in Kurnool district. The cardiovascular risk is also correspondingly high. Elevated fasting insulin and insulin resistance without correlation with metabolic syndrome components suggest the need for further improvement of awareness and promotion of lifestyle changes to reduce risk of CVD.

CHAPTER I

INTRODUCTION

1.1 Purpose of the study:

Non-Communicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of combination of genetic, physiological, environmental and behavioural factors. According to World Health Organization 40 million people are dying each year due to NCDs which is equivalent to 70% of all deaths globally. Among these almost 15 million deaths occur between the age group 30-69 years (called as "premature deaths") and almost 80% of these premature deaths occur in low and middle income countries like India [1].

Tobacco consumption, physical inactivity, alcohol consumption and unhealthy diet are found to be the primary risk factors for the rise of NCDs [2, 3]. In India, 32.5% of population is having an increased blood pressure. Both males and females were equally effected (33.2% vs. 31.7%) followed by increased blood glucose 10% (10% vs. 10%), overweight 11.0% (9.9% vs. 12.2%), raised cholesterol 27.1% (25.8% vs. 28.3%), smoking 13.9% (25.1% vs. 2.0%) and physical inactivity (10.8% vs. 17.3%) These metabolic and behavioural risk factors can lead an individual to CVD related morbidity and mortality.

WHO estimated that in India 53% of deaths were due NCDs. Most of the burden is attributed to cardiovascular diseases (24%), followed by respiratory (11%), cancer (6%), and type 2 diabetes (2%). In terms of attribute deaths, increased blood pressure accounts to 13% of global deaths, followed by tobacco use (9%), increased blood glucose (6%), physical inactivity (6%), overweight and obesity (5%) [4]. Thus all International and National guidelines have included these substantially modifiable risk factors in their CVD risk charts and guidelines.

Apart from these recently metabolic syndrome (MetS) has been added to the risk factor category of CVDs. Identifying the population under risk and timely screening of such population along with slight changes in their life style plays a key role in the prevention of these NCDs

.

Metabolic syndrome is defined as constellation of risk factors such as “abdominal obesity, increased blood pressure, elevated blood glucose, hyper triglyceridemia and decreased high density lipoprotein cholesterol” [5]. Metabolic syndrome increases risk of CVDs. Joint National Committee for Hypertension (JNC VII) recognized this syndrome as an important CVD risk factor [6].

Urbanization is a process of change in the society from a rural to an urban way of life. It leads to significant changes in lifestyle, occupational pattern and dietary habits. In most of the developing countries, urbanization occurs very quickly near rural and tribal areas [7]. Urbanization is associated with increased prevalence of CVD risk factors such as hypertension, obesity and dyslipidemia. The summation of these risk factors is more associated with CVD risk than an individual [8]. Recent evidences indicate that extensive urbanization itself is the strongest risk factor for CVDs [9]. India is a diverse country undergoing epidemiological transition due to urbanization [10, 11]. This lead to economic improvement but at the same time there is substantial health risk by increasing NCDs and communicable diseases proportionally.

The population growth rate is increasing in urban areas (30%) while it is decreasing in rural areas. The rural literacy rate is increased remarkably compared to urban literacy rate. This may due to migration of rural people to nearby urban areas [12]. Thus urban area faces a high population growth which leads to life style changes including the pattern of diet and physical activities. On the other hand rural and tribal population is getting better access to information regarding various food products, entertainment in the neighbourhood. This plays a vital role in their acceptability and affordability of lifestyle changes and food habits.

During one census year (2001-2011), the major tribal dominated areas of India like Andhra Pradesh, West Bengal, Gujarat and Madhya Pradesh have experienced more than 20-30% of urbanization [12, 13]. Even though census does not show any tribal migration, the effect of urbanization around the tribal region will show considerable influence on lifestyle and habits of tribes.

The most recent study in Nigeria showed a significant association between MetS and urbanization [8]. CHRONICALS cohort study in urban, semi urban and rural population of Peru by Antoni et al. has shown significant association between

urbanization and hypertension. He observed that semi urban population were at high risk for hypertension than highly urbanized area (IRR=1.76; 95% CI=1.39-2.33) [14]. The Cameroon study by Ntentie FR et al. revealed that population of less urbanized areas were more affected by the metabolic abnormalities and metabolic syndrome than urban areas [15].

Metabolic syndrome increased from urban area to rural area. A national representative study (United States of America) by J.D. Voss et al. reported that prevalence of obesity is significantly associated with urbanization [16]. An Indian study by Sarkar et al. examined the role of urbanization and genetic factors in MetS among two tribal populations (Toto and Bhutia). MetS was 30-50% high among the Bhutia tribes than Toto tribes. This might be due to adaptation of urban life style in Bhutia tribes while Toto tribes are still adapted to their traditional life style [17]. Tribal population shows an accelerated increase of diabetes and MetS worldwide. Nazaimoon et al. reported higher prevalence of diabetes, irregular fasting glucose and MetS from Orang Asli tribal community in Malaysia [18].

The prevalence of MetS may also be affected by ethnicity. National Health and Nutrition Examination Survey III (NHANES III) reported 30-40% higher prevalence of MetS in persons with Mexican-American origin than White and African-American origin [19].

These evidences indicate that apart from genetic predisposition, the lifestyle transition equally contributes the predisposition of Mets in Asian population. Most of the interlinked risk factors for MetS syndrome and CVDs are (obesity/overweight, smoking, sedentary life style, hypertension, low HDL-C, high LDL-C and elevated blood glucose) preventable and can be modifiable by simple life style changes. However, lack of awareness about CVD risk can lead to delay in seeking treatment and increased risk for sudden death [20].

Since MetS is a long term process that starts early in life and is involved in the pathophysiology of type 2 diabetes mellitus and atherosclerotic cardiovascular diseases (ASCVD), early management of this syndrome will have a significant impact on the prevention of both diabetes and CVD [21]. Strategies that create awareness and identify the individuals with MetS are very helpful for screening and decrease the CVD related mortality and morbidity in them.

In order to formulate the policies for the prevention and control of Mets in a population, it requires a scientific representative data that includes prevalence of MetS and related risk factors in them, collected through standardized techniques.

The population growth rate of Kurnool district in one census year (2001-2011) in rural area is 7.1% while the urban area growth rate is 40.6%. This is suggesting possibility for higher prevalence of metabolic syndrome in Kurnool district. Thus we have designed a cross sectional community based study with an aim to assess the prevalence of metabolic syndrome in urban, rural and tribal population of Kurnool district using modified NCEP ATP III criteria.

This study will help to create awareness about metabolic syndrome and its consequences in population of Kurnool district. Most of the previous studies have focused on urban, rural differences of MetS and CVD risk factors. In contrast, this study will provide the data on differences of urban, rural and tribal population in a geographical area.

1.2 Kurnool district geographic profile:

Kurnool district is located in west central part of the state of Andhra Pradesh (approximately between 14°54’ to 16°18’ North latitudes and 76°58′ to 79°34’ East longitudes). It is bounded by Mahbubnagar district in the north, Raichur district in the northwest, Bellary in west, Ananthapur district in south, YSR Cuddapah district in south east and Prakasam district in the east [Figure 1]. It occupies 10th and 2nd places in terms of area in largest districts in India and Andhra Pradesh respectively.

Population: 4,053,463 of which 28.40% were in urban area, 71.60% were in rural area and only 2% in tribal area.

Religion: Hindus: 82.11%; Muslims: 16.55%; Christians: 0.82% and others: 0.52%.

Literacy: 61.3%.

Sex ratio: 984

Gross district domestic product (GDDP): 34,359 cores.

Revenue Divisions: Three revenue divisions under these 54 mandalas, 53 panchayat (Blocks) are present.

Population growth rate (census year 2001–2011): 14.65%.

The rural growth rate is recorded as 7.1%, while the urban growth rate is 40.6% [22].

Figure 1 Geographic location Kurnool district in Andhra Pradesh (India).

CHAPTER II

AIMS AND OBJECTIVES

1.3 Aim and objectives of study:

Aim

The present study is aimed to assess the prevalence of metabolic syndrome in Kurnool district population using modified NCEP ATP III criteria.

Objectives:

1. To evaluate the metabolic syndrome and its components in Kurnool district.
2. To evaluate and compare the metabolic syndrome and its components among urban, rural and tribal population of Kurnool district.
3. To evaluate the glucose homeostasis in urban, rural and tribal population of Kurnool district.
4. To correlate the metabolic syndrome risk components with HOMA-IR (insulin resistance).
5. To determine the individual and aggregated cardiovascular risk factors and its risk by WHO/ISH - CVD risk prediction chart-D (with cholesterol).
6. To assess the direct cardiovascular risk factors (hypertension, type 2 diabetes mellitus) among the three studied population.

CHAPTER III

REVIEW OF LITERATURE

2.1 Synonym (s) of metabolic syndrome:

After the description of Syndrome X by Reaven, there were many attempts to describe and introduce the role of clustering risk factors for cardiovascular diseases and type 2 diabetes mellitus into clinical arena with different names such:

- Cardio metabolic syndrome.
- CHOAS syndrome (CAD, HTN, Obesity, Atherosclerosis, sleep apnea).
- Civilization syndrome.
- Deadly quartet.
- Gerald Reaven's syndrome.
- HONDA [Hypertension, Obesity, Non-insulin dependent diabetes, dyslipidemia and Atherosclerotic cardiovascular disease].
- International Classification of Diseases - 9
- Insulin Resistance Syndrome (IRS).
- Visceral abdominal syndrome.
- New World syndrome.

2.2 Historical aspects of metabolic syndrome

The term "Metabolic syndrome" dates back to at least the 1920s, but came into common usage in the late 1970s. In the year 1923 Kylin described the association among the various MetS components such as hypertension, hyperglycemia and elevated uric acid levels [23].

- The Marseilles physician Dr. Jean Vague presented a series of reports on sexual difference of obesity and its complications between the years 1940 to 1950. In 1956, he found an interesting observation that upper body obesity appeared to predispose to diabetes, atherosclerosis, gout, and calculi [24, 25].
- In the year 1987, Jean vague presented an updated review on his previous finding and he termed it as "Diabetogenic Obesity" in a lecture at 5th International Congress on Obesity [26].

  In the year 1960, Avogaro and Crepaldi described about a syndrome with MetS components such as hypertension, hyperglycemia and obesity [27].

- In the same year Pyorala also showed strong association between glucose intolerance hyper insulinaemia and coronary heart disease in a study among Finnish population [28].
- In the year 1966, Camus observed the association between gout, diabetes and hyperlipidemia and termed it as "Trisyndrome Metabolic" [29].
- In 1977, Haller used the term "Metabolic Syndrome" for associations of obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and steato-hepatitis when describing the additive effects of risk factors on atherosclerosis [30].
- The same year, Singer used the term for associations of obesity, gout, diabetes mellitus, and hypertension with hyperlipoproteinemia [31].
- Introduction of Radio Immuno Assay (RIA) for insulin in 1960 has been opened the door for larger explanatory in this field to describe the role of insulin resistance in pathophysiology of diabetes and cardiovascular diseases [32].
- In 1977 and 1978, Dr. Gerald B. Philips developed the concept that risk factors for myocardial infarction concur to form a constellation of abnormalities (i.e., glucose intolerance, hyperinsulinemia, hyperlipidemia hypercholesterolemia, hypertriglyceridemia and hypertension) that are associated with heart diseases, but also with aging, obesity and other clinical states [33].
- In the year 1980, Modan et al. described the link between obesity, hypertension and cardiovascular diseases [34].

In 1988, in his Banting lecture, Dr.Gerald M. Reaven proposed insulin resistance as the underlying factor and named the constellation of abnormalities as Syndrome X. Reaven did not include abdominal obesity, which has also been hypothesized as the underlying factor, as part of the condition [35].

2.3 Epidemiology of metabolic syndrome

The introduction of region specific cut off points made it possible to evaluate temporal trends and regional variations in the prevalence of metabolic syndrome. In the Middle East countries every third person above the age of 20 years satisfies the metabolic syndrome criteria. In Native Americans, nearly 60% of women ages 45-49 and 45% of men ages 45-49 meeting NCEP ATP-III criteria [36]. Looking at various studies around the world, which included population samples, aged from 20 to 25 and upwards, the prevalence varies 8% (India) to 24% (US) in males and from 7% (France) to 46% (India) in females. Two Indian studies: first used criteria suitable for Indians while the second used the standard NCEP ATP-III definitions reported prevalence of 13% in Jaipur and 41% in Chennai. A third Indian study also from Chennai reported a prevalence of 11.2% using European group for the study of insulin resistance (EGIR) criteria [37].

Type 2 diabetes mellitus epidemic in India is as a result of social influences and changing life styles. The prevalence of diabetes is higher in urban than rural areas. Type 2 diabetes mellitus affects individuals in India at a younger age as compared to their western counterparts. These data indicate that Indians as an ethnic group gave a high risk of type 2 diabetes is most likely due to genetic susceptibility According to a recent World Health Organization report, India has the highest number of people with diabetes in the world, with an estimated 32 million, which is set to increase to a staggering 80 million i.e., an increase of 160% by the year 2030. [38].

The number of people with diabetes has nearly quadrupled since 1980. The worldwide prevalence of diabetes mellitus has risen dramatically over the past two decades from an estimated 30 million cases in the year 1985 to 177 million in the year 2000. More than 360 million individuals will have diabetes by the year 203 [36]. In contrast, WHO estimated already about 422 million people worldwide have diabetes.

There is a significantly increasing trend of MetS in urban populations while among rural populations the prevalence is increasing at a slower rate. In southern India, the prevalence was found to be higher at 13.5% in Chennai, 12.4% in Bangalore and

16.6% in Hyderabad; compared with Eastern India 11.7%; Northern India 11.6% and Western India 9.3% [38].

The worldwide prevalence of obesity has increased dramatically over last several decades. In the United States alone, about one third of adult population aged between 20 and 74 years are considered obese. According to national population surveys conducted since 1960, the prevalence of obesity increases progressively from 20 to 50 years of age but it then declines after 60 to 70 years age [39]. Death rate from diabetes mellitus is approximately 4 times higher among obese than among those who control their weight. Nurses' health study estimates that 23% of all deaths in non-smoking middle aged women are attributable to being overweight [40].

2.4 Prevalence of metabolic Syndrome in South Asians:

People origin from India, Sri Lanka, Bangladesh, Nepal, Maldives and Pakistan are considered as South Asians [41]. According to WHO estimates, 70% of new incident cases of diabetes will be in the developing Asian countries [42]. It is estimated that among the 10 leading countries with diabetes, five are in Asia [43, 44]. By the year 2025, India will rank first with 57 million diabetics, followed by China with 38 million diabetics and Pakistan in 4th place with 14.5 million diabetics [45].

South Asians are particularly predisposed to develop diabetes and coronary heart disease. It is due to the fact that south Asians are more insulin resistant and with excess body fat and abdominal obesity [46]. South Asians have low BMI and they have higher body fat at a given BMI [47, 48, 49]. Overall prevalence of insulin resistance in South Asians varies between 5 to 50%. This may due to differences in methods employed to assess the insulin resistance by various scientists. Reaven emphasized that the MetS was one of the all-encompassing tools in assessment of insulin resistance. Moreover, the heterogeneity of South Asians in terms of their geographical location and partial adaptation of lifestyle of the country of residence, in addition to variations due to age, gender and socio-economic status may also contribute to this variation in prevalence of metabolic syndrome [50].

The main purpose of assessment of MetS is to initiate and implement of lifestyle changes to decrease the risk of CVD in population. Overall 15% to 16% of global

mortality due to CVD is contributed by India. This approach shows the significance of MetS in South Asians to reduce the risk of CVD [51]. In South Asia, males have higher waist/hip ratio, elevated systolic blood pressure (BP), higher insulin levels after glucose load, increased triglyceride levels and decreased high density lipoprotein (HDL-C) levels. All these confirm a high prevalence of MetS in South Asia. In addition, type 2 diabetes and CVD risk is high in South Asia: 20% compared with Caucasians: 5% [52].

2.5 Components of metabolic syndrome:

2.5.1 Major components

- Central obesity.
- Dyslipidemia.
- General obesity.
- Hyperglycemia.
- Hypertension.
- Resistance to the action of insulin
- Chronic low grade inflammation.

2.5.2 Minor components

- Endothelial dysfunction.
- Inflammatory markers.
- Procoagulant state.
- Micro albuminuria.
- Hyperuricemia.
- Cutaneous markers.
- Non-alcoholic fatty liver disease (NAFLD) and / or non-alcoholic steatohepatitis (NASH).
- Low birth weight.
- Increased sympathetic activity.
- Polycystic ovarian syndrome.
- Low cardio respiratory fitness.

2.6 Obesity and metabolic syndrome:

Obesity is a chronic disease that is causally related to serious medical illnesses. Obesity is an excess storage of triglycerides in adipose tissue. Obesity is an excess of body weight as compared to overweight which is a body weight in excess of some standard or ideal weight. Ideal weight (in pounds) can be calculated as follows [40].

Women : 100 + 4 x (height in inches - 60)

Men : 120 + 4 x (height in inches - 60)

A lean adult has about 35 billion adipocytes, each containing about 0.4 - 0.6 mg of triglyceride, an extremely obese adult can have 4 times as many adipocytes (125 billion), each containing twice as much lipid (0.8 - 1.2 mg of triglyceride) [53]. ATP-III recommended that obesity be the primary target for intervention for metabolic syndrome. Upper body rather than lower body obesity (the apple rather than pear shape) is highly correlated with insulin resistance and type 2 diabetes. A leading hypothesis is that intra-abdominal adipocytes are more lipolytically active due to their complement of adrenergic receptors (ARs) [53]. In addition; the abdominal adipose store is resistant to the antilipolytic effects of insulin. Chronic elevations in circulating free fatty acids are a classic feature of insulin resistance and type 2-diabetes.

2.6.1 Role of adipocyte secretion in insulin resistance

Adipocyte plays a role in insulin resistance not only by storing fat but also as a secretory cell producing several cytokines and hormones, as well as releasing free fatty acids.

2.6.2 Free fatty acids (FFAs)

Inadequate suppression of fatty acid oxidation by insulin is a common feature of various forms of insulin resistance [54]. Randle et al. first recognized this relationship and hypothesized glucose fatty acid cycle [55]. Recent observations have proposed that increased FFAs levels lead intramuscular accumulation of long chain fatty acids. They metabolized to lipotoxic precursors such as diacylglycerol (DAG) and ceramide. Both long chain fatty acids and lipotoxic activate the protein kinase C

and enhance Phosphorylation of serine/threonine sites on insulin receptor substrates (IRS-1 & IRS-2) in turn reducing the ability to activate phosphatidyl inositol-3' kinase (PI3K) and glucose transport [Figure 2] Increased circulating FFAs levels also impair the suppressive effects of insulin on hepatic glucose production. Conversely hyperinsulinemia promotes conditions favouring FFAs biosynthesis further aggravating the metabolic conditions [54].

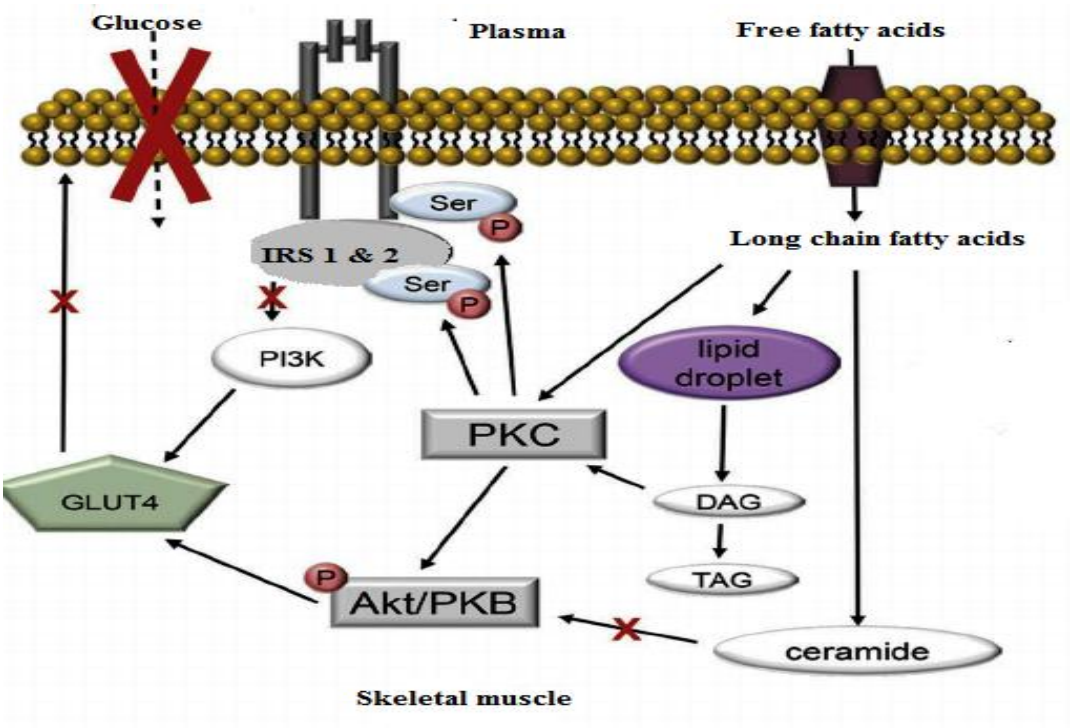


Figure 2 Intracellular pathway of insulin resistance in skeletal muscle.

2.6.3 Tumor Necrosis factor-α (TNFα)

Tumor necrosis factor-α is a 26kd trans-membrane protein [53]. It causes adipocyte insulin resistance by inducing adipocyte apoptosis and inhibition of the insulin receptor substrate signalling pathway which results in diminished activation of PI3K [56]. TNFα is the only known inhibitor of adipose tissue lipoprotein lipase [38].

2.6.4 Leptin

Leptin is a 16kd adipokine [38]. It acts on central nervous system neurons that regulate satiety and energy intake. Leptin decreases the appetite and food

consumption and increases heat production and metabolic activity. Serum leptin concentration rise in proportion to body adiposity. Beside this, leptin acts on the hypothalamus and increase the blood pressure by acting on synaptic nervous system.

Therefore obese individuals with metabolic syndrome have higher circulating leptin concentration. Obese individuals seem to be resistant to the hypothalamic effects of leptin [56]. In women, as weight increases, leptin increases 3 times more rapidly than men indicating greater resistance to its action [40]. In obese individuals majority of leptin is unbound and is active consistent with resistance hypothesis. In lean individuals the major part of circulating leptin is in bound form [40]. Therefore the catabolic pathways designed to reduce appetite and increase energy expenditure are not activated [56].

2.6.5 Interleukin-6 (IL-6)

IL-6 is a 27kd true endocrine cytokine [53]. It is released by both adipose tissue and skeletal muscle in humans. IL-6 concentrations are positively correlated with insulin resistance, and the development of type 2 diabetes [56]. IL-6 is the major determinant for the hepatic production of acute phase reactants, such as C-reactive protein (CRP), fibrinogen, complement proteins, protease inhibitors etc. Endothelial cells and vascular smooth muscle cells are targets of IL-6 resulting in increased expression of both adhesion molecules and activation of local rennin - angiotensin pathways [56].

2.6.6 Adiponectin

It is also called ACRP 30, adipo Q, GBP 28 is a 30kd protein that might couple regulation of insulin sensitivity and serve to link obesity with insulin resistance [53]. Adiponectin stimulates production of Nitric Oxide (NO), decreased expression of adhesion molecules in endothelial cells and decreased cytokine production from macrophages. Adiponectin is an antagonist to TNF-α [57] Plasma adiponectin levels are negatively correlated with adiposity and low plasma adiponectin levels are observed in patients with obesity and insulin resistance. Decreased adiponectin is inversely associated with blood pressure, low density lipoprotein and triglyceride levels [53].

2.6.7 Resistin

Resistin (12kd protein) is a member of the FIZZ (Found in Inflammatory Zone) family of proteins, which are C-terminal cysteine rich proteins. It is mainly derived from pre adipocytes and macrophages. Increased resistin levels are a biomarker and mediator for metabolic and inflammatory diseases [53].

2.6.8 Indices of obesity

The following are the various methods to measure obesity.

a. Accurate method of determining body fat is by Hydro densitometry [40]
b. Skin fold thickness measurements using calipers [40].
c. Abdominal fat can be accurately quantified by dual energy X - ray absorptiometry (DEXA) scanning or computed tomography [54].
d. Body Mass Index (BMI) - **The Quetelet index** BMI has evolved as a more standard measurement to correlate weight with morbidity and mortality [Table 1]. BMI is the ratio of weight in kilogram divided by height in meter square [40].

Table 1 Classification of overweight and obesity by BMI, waist circumference (WC) and associated disease risk [53].

Classification	BMI (body mass index)	Obesity class	Disease risk * relative to normal weight and WC
Under weight	≤ 18.5		--
Normal **	18.5 – 24.9		--
Over weight	25.0 – 29.9		Increased
Obese	30.0 – 34.9	I	High
	35.0 – 39.9	II	Very high
Extremely obese	≥ 40	III	Extremely high

*disease risk for type 2 DM, hypertension and cardiovascular disease ** increased waist circumference can also be a marker for increased risk even in person of normal weight

e. Waist circumference (WC) - Because central obesity or abdominal fat mass is a better predictor of metabolic syndrome, waist circumference and / or waist to hip circumference ratio are often used as surrogate markers for upper body obesity. Based on the epidemiologic data a waist circumference > 102 cm in men and > 88 cm for women have been proposed as cut off values for increased risk of metabolic syndrome for Whites, African Americans, and Latin Americans [53]. The categorical cut off points for Asians include WC ≥ 90 cm for men and ≥ 80 cm for women [53]**.** This suggests that Asians are at increased risk or highly susceptible to metabolic syndrome owing to genetic causes.

f. Waist to hip circumference ratio (WHR) - Another visceral fat index is Waist to hip circumference ratio (WHR). A ratio of > 0.72 is considered abnormal [54]. A WHR > 0.9 in men and 0.85 in women is a clinical criterion for metabolic syndrome as suggested by World Health Organization.

2.7 Dyslipidemia and metabolic syndrome:

Dyslipidemia is characterized by a spectrum of lipid abnormalities include alterations in the structure, metabolism and biological activity of both atherogenic and anti - atherogenic lipoproteins which include decreased HDL-C and increased triglycerides, small LDL-C particles. The triad of these abnormalities has been called as “Atherogenic dyslipidemia” or “Atherogenic lipoprotein phenotype” [54].

The physiologic basis for this abnormal lipid profile appears to be insulin resistance and impaired insulin signalling. It leads to the over production of apo lipoprotein B containing very low density lipoprotein (VLDL) particles. The apo lipoprotein B production is primarily post translational and augmented by insulin and by increased availability of FFAs in portal circulation. The over production of VLDL triglyceride results in increased transfer of VLDL triglyceride to high density lipoprotein (HDL-C) particles in exchange for HDL cholesterol ester mediated by cholesterol ester transfer protein (CETP) [53].

The triglyceride rich HDL-C is hydrolysed by hepatic lipase which results in small HDL that is degraded more readily by kidney resulting in low HDL-C levels in

serum. CETP mediated exchange of VLDL triglyceride for low density lipoprotein cholesterol ester and subsequent triglyceride hydrolysis by hepatic lipase, probably result in generation of small dense LDL-C particles found in metabolic syndrome.

Plasma lipids consist of cholesterol ester (36%), phospholipids (30%), triacylglycerol (16%), cholesterol (14%) and a very small fraction of unesterified long chain fatty acids FFAs (4%) [58]. The FFAs are metabolically the most active of plasma lipids.

Lipoproteins are spherical macromolecular complexes of lipids and specific proteins like apo-lipoproteins (or) apo proteins. Apo lipoproteins are structural protein components of lipoprotein. The distribution of apo-proteins characterizes the lipoprotein.

Apo lipoproteins play following important roles:

a. Maintain the structural integrity of lipoprotein by solubilizing the hydrophobic lipids.
b. Contain cell targeting signals and cell surface receptor to facilitate the uptake of lipoprotein into the cell.
c. Serves as an enzyme cofactor [58, 59].

2.7.1 Metabolism of triglycerides

Triglycerides are by far the most abundant subclass of neutral glycerides in nature. Mammalian tissues also contain some triglycerides and monoglycerides in traces, but mixed diglycerides are predominant [53]. Plasma triglycerides are derived from two sources [Figure 3].

1. Intestinal (exogenous pathway).
2. Liver (endogenous pathway)

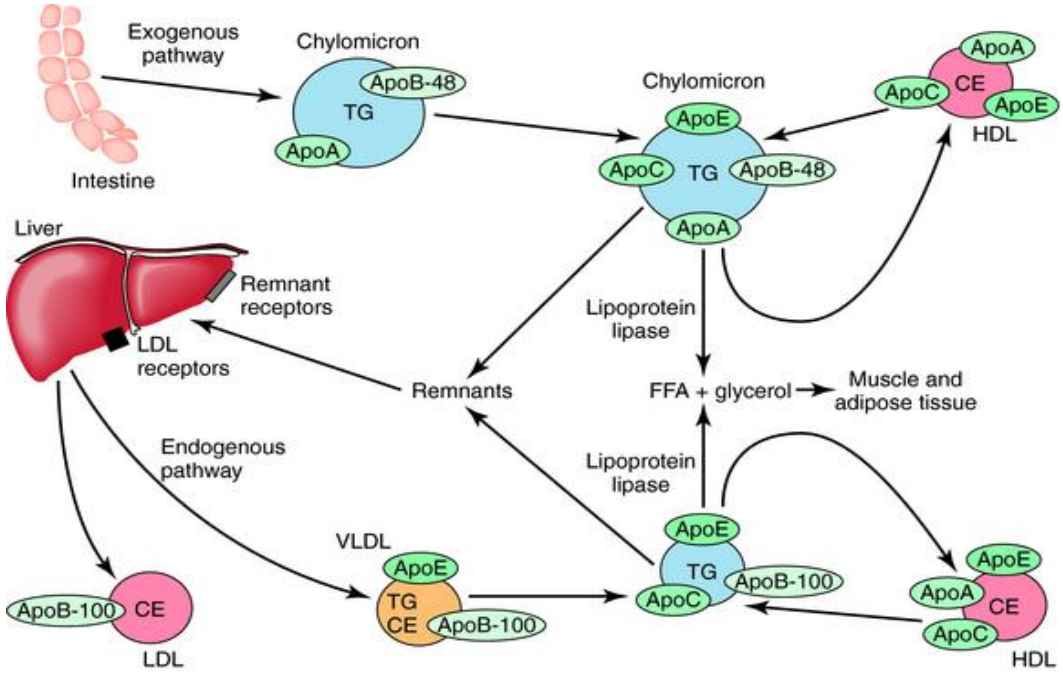


Figure 3 Sources of plasma triglycerides and lipoprotein metabolism.

2.7.2 Metabolism of Chylomicrons

Chylomicrons are responsible for the transport of all the dietary lipids into the circulation. Nascent chylomicrons are assembled from dietary triglycerides and cholesterol in the enterocyte. The lipid content of nascent chylomicrons consists of triglycerides (90% by mass), the protein component include apo B48 and the apo-proteins.

Chylomicrons are packed in the secretory vesicles of Golgi apparatus and are transported into extracellular space by exocytosis (reverse pinocytosis). They eventually make their way into the lymphatic system draining the intestine. Shortly, after entering into circulation these particles acquire the C and E apo lipoproteins from HDL-C. Apo C-II on surface of chylomicrons activates lipoprotein lipase present on endothelial cells that rapidly hydrolyses the triglycerides into free fatty acids.

The free fatty acids are associated with albumin and are delivered to adipose tissue, heart and muscle (80%) and the rest (20%) goes to liver. Reaction with LDL-C results in loss of approximately 90% of triglyceride and loss of apoC **[**58, 59].

Resulting chylomicron remnants relatively rich in cholesterol esters are taken up by the liver by receptor mediated endocytosis via two apo E dependent receptors:

a. The LDL-C (apoB100 and apoE) receptor.
b. LRP (LDL receptor related protein).

Hepatic lipase has dual role:

1. It acts like a ligand to facilitate remnant uptake.
2. It hydrolyses remnant triglyceride and phospholipids **[**58].

2.7.3 Metabolism of very low density lipoprotein (VLDL)

VLDL is responsible for the transport of endogenous triglyceride. Hepatic VLDL secretion is related to dietary and hormonal status. The endogenously made triglycerides are packed in the Golgi apparatus, transported by exocytosis into the extracellular space and introduced into circulation in form of nascent VLDL.

This VLDL contains 55% by mass of triglyceride and apoB 100. ApoE and apoC apo-proteins are added from HDL in circulation [61]. ApoC II on VLDL activates lipoprotein lipase which brings about the hydrolysis of triglyceride and release of free fatty acids. The apoC apolipoprotein is transferred back to HDL. Some of the VLDL remnants are taken up by the liver and the rest are converted into smaller denser particles called IDL, plasma half-life is about 1-3 hrs. [59].

2.7.4 Metabolism of intermediate density lipoproteins (IDL)

IDL is a transient particle usually present in very low concentration in plasma in fasting state. IDL is derived from VLDL catabolism. Cholesterol ester (CE) is transferred from HDL-C to IDL through the action of cholesterol ester exchange protein which is the major lipid of IDL. Large IDL particles bind the hepatic remnant receptors and are removed from circulation; some are further converted to LDL-C **[**59].

2.7.5 Non-HDL cholesterol

NCEP ATP III considered non HDL-C as a second goal after LDL-C in the treatment of patients with hyper triglyceridemia. Non HDL-C can be calculated by subtracting HDL-C from the total cholesterol.

Non HDL-C = Total cholesterol – HDL

As per NCEP guidelines the optimal cut off point is < 130 mg/dl [61]. In patients with metabolic syndrome who have high triglycerides (> 200 mg/dl), a sizable portion of apoB can be in very low density lipoproteins. An increase in LDL-C and VLDL is most readily identified by an elevation of non HDL-C. Total apo-B is an alternate secondary target, but non HDL-C is strongly correlated with total apoB [59].

2.7.6 Metabolism of high density lipoprotein (HDL)

According to NCEP ATP III, low HDL-C is considered as a major risk factor. The half-life of HDL in normal subjects ranges from 3.3 to 5.8 days. HDL is secreted from liver and intestine as disk shaped nascent particles. They consist primarily of phospholipids, apoA1 and a very little free cholesterol. ApoC and apoE are synthesized in liver and transferred from liver HDL-C to intestinal HDL-C. Free cholesterol is esterified in presence of apoA1 by Lecithin Cholesterol Acyl Transferase (LCAT). The resulting HDL_3 accepts cholesterol from tissues via scavenger receptor class-B (SR-B) to form less dense HDL_2. The class B, scavenger receptor is identified as HDL receptor with a dual role. In liver and steroidogenic tissues (such as testis, ovary and adrenal cortex which convert cholesterol into pregnenolone), it binds HDL via apoA1 and cholesterol ester is delivered into the cells.

In other tissues, it mediates the accumulation of cholesterol from cells (reverse cholesterol transport). A second mechanism for reverse cholesterol transport involves ATP-binding cassette transporter A1 (ABCA1) that transfers cholesterol ester to lapidated pre β HDL or apoA1. HDL_3 is reformed either by delivery of cholesterol ester to liver by scavenging receptor B-1 (SRB-1) or hydrolysis of HDL_2

phospholipids and triglyceride by hepatic lipase or by transfer of cholesterol ester from HDL to apo-B100, a process mediated by cholesterol ester transfer protein [60].

2.7.7 Metabolism of low density lipoprotein (LDL-C)

Even though the elevated blood LDL is not an integral component of the metabolic syndrome, it is an independent risk factor of metabolic syndrome. It comes into play as atherogenic risk factor. The reason is that LDL-C is the primary pathogenic agent for atherosclerosis whereas the other risk factors associated with metabolic syndrome are aggravating agents.

LDL-C is the major carrier of cholesterol. ApoB 100 is the major apo-protein of normal LDL-C and represents 90% - 95% of total plasma B100. LDL-C is frequently separated into two classes on the basis of floatation density [59].

1. LDL_1
2. LDL_2

LDL-C is formed primarily from the catabolism of VLDL. LDL-C delivers cholesterol to extra hepatic tissues and to the liver, where it is used, deposited or excreted.

Specific receptors present in the coated pits on plasma membranes bind apoB100. The LDL-C particles are internalized in coated vesicles, which then fuse to form an endosome. The acidic milieu of endosome releases LDL-C from the receptor, the latter returns to the cell surface. In the lysosome, apoB 100 is degraded to smaller peptides and amino acids. Cholesterol esters are hydrolysed. Over supply of cholesterol leads to the following:

a. Decreased rate of endogenous cholesterol synthesis by inhibiting HMG CoA reductase.
b. Increased formation of cholesterol ester by Acyl Cholesterol Acyl Transferase (ACAT).
c. Inhibition of synthesis of new LDL receptors by suppressing the transcription of receptor gene.

LDL-C is also taken up by extra hepatic tissue through scavenger receptors and non-receptor mediated pinocytosis [59]. Both are not saturable and not regulated. The

former predominate in macrophages and recognize LDL-C modified in various ways. The non-receptor mediated uptake becomes important in familial hypercholesterolemia (elevated LDL-C levels).

Modification of LDL-C: After LDL-cholesterol entrapment into the sub-endothelial space. It can undergo 2 types of modifications:

a. Derivatisation: Malondialdehyde attachment (or) glycosylation of apo-B100.
b. Oxidation: Degradation of apo B 100 by superoxide [60].

LDL-C and metabolic syndrome partners in atherogenesis: The development of atherosclerosis can be considered to occur in 2 stages: injury and response to injury. The primary injurious agents include LDL-C and other apoB containing lipoproteins. The response to injury makes up a process called inflammation. Excess LDL-C initiates atherogenesis and promotes its progression; metabolic syndrome exacerbates the inflammatory process. Each component of metabolic syndrome appears to worsen inflammation in plaques as:

- Hypertension can enhance influx of LDL-C into the arterial wall, lead to endothelial dysfunction and can cause release of proinflammatory cytokines and adhesion molecules.
- Dysglycemia, particularly diabetic hyperglycemia, may lead to formation of inflammatory advanced glycation products (AGES), glycation of extra cellular matrix, glyoxidative modification of LDL-C and activation of protein kinase C.
- A low HDL is a key component of metabolic syndrome. HDL exerts its anti-inflammatory effects at multiple levels a). It transports excess cholesterol out of macrophages and prevents conversion of LDL-C into proinflammatory modified LDL-C. b). It inhibits cytokine induced expression of cell adhesion molecules on endothelial cells.
- Increased circulating cytokines further enhance the inflammatory response to modified LDL-C.

- Abdominal adipose tissue releases the adipokines which will modulate the glucose and lipid metabolism, and participate in systemic vascular inflammation.
- Finally a prothrombotic state not only promotes inflammation within arteriosclerotic plaques but can enhance thrombus propagation following a ruptured plaque.

Table 2 Alteration of lipoprotein metabolism in type 2 diabetes mellitus **[**54]

Lipoprotein	Alterations
VLDL ↑	Increased production of triglyceride and apoB Decreased clearance of triglyceride and apoB Abnormal composition
LDL ↑	Increased production of LDL apoB Decreased receptor-mediated clearance Triglyceride enrichment Smaller (denser) particle distribution Glycation Oxidation
HDL ↑	Increased clearance of apoA Decreased proportion of large HDL Triglyceride enrichment Glycation Diminished reverse cholesterol transport
Chylomicrons	Delayed clearance; remnant accumulation

VLDL-very low density lipoprotein; LDL-C -low density lipoprotein; HDL-high density lipoprotein

2.8 State of chronic inflammation (pro-inflammatory state)

A newly emerging risk factor is a pro-inflammatory state. Chronic inflammation is a common feature of metabolic syndrome and inflammatory signals may originate within visceral adipose tissue. Both adipocytes and macrophages within fat secrete hormones and cytokines that may contribute to the characteristic pathophysiological changes seen in metabolic syndrome. Local inflammation within the adipose tissue may be the sentinel event that causes systemic insulin resistance and systemic inflammation, two of the cardinal features of metabolic syndrome.

Adipocyte derived pro-inflammatory molecules (TNF-α, IL-6, transforming growth factor β, CRP and monocyte chemotactic protein-1) are believed to induce systemic insulin resistance and contribute to the pathogenesis of many metabolic complications of obesity, type 2 diabetes and atherosclerosis [54].

Obesity is associated with increased infiltration of macrophages into adipose tissue. With onset of obesity, secretion of low levels of TNF α by adipocytes is believed to stimulate preadipocytes to produce monocyte chemotactic protein-1 (MCP-1), a chemoattractant specific for monocytes and macrophages. Adipocytes also produce colony stimulating factor-1 (CSF-1), the primary regulator of macrophage differentiation and survival. Once activated macrophages are present in sufficient numbers, it is likely that they perpetuate a vicious circle of macrophage recruitment and production of inflammatory cytokines, ultimately causing systemic insulin resistance and systemic chronic inflammatory state. [54].

The acute phase reactant, CRP, a simple downstream marker of inflammation, has now emerged as a major cardiovascular risk factor [63]. Composed with five 23 kd subunits, CRP is a circulatory member of the Pentraxin family that plays a major role in human innate immune response. More than a simple inflammatory marker, CRP may influence vascular vulnerability through:

a. Enhanced expression of local adhesion molecules.
b. Increased expression of endothelial plasminogen activator inhibitor-1
c. Decreased endothelial nitric oxide (NO) bioactivity.
d. Altered low density lipoprotein uptake by macrophages.
e. Co-localization with complement within atherosclerotic lesions.

Elevated levels of hsCRP predict not only cardiovascular events but also onset of type 2 diabetes. Perhaps because hsCRP levels correlate well with several components of metabolic syndrome, including those not easily measured in clinical practice such as insulin sensitivity, endothelial dysfunction and hypo fibrinolysis.

Thus hs CRP assessment also adds prognostic information at all levels of metabolic syndrome. Even in individuals with ATP III definition of metabolic syndrome,

knowledge of hs CRP levels < 1, 1 to 3 and > 3 mg/L further defines low, moderate, and high risk group respectively, for future vascular events.

2.9 Prothrombotic state

Several coagulation factors are commonly increased in persons having the metabolic syndrome. These include fibrinogen; factor VII, factor VIII, factor X, Von-Willebrand factor, plasminogen activator inhibitor-1 (PAI-1), and prothrombin fragments F 1+2 **[**53**,** 62].

The coagulation factor that is most consistently abnormal in metabolic syndrome is PAI-1. The synthesis of other coagulation factors is stimulated in presence of insulin resistance. The combination of coagulation factors gives rise to a prothrombotic state which predisposes to atherosclerosis.

2.10 Hypertension:

Hypertension (HTN) and overt type 2 diabetes double the risk of cardiovascular disease. Defects in vasodilatation and alterations in blood flow might provide a link to hypertension in insulin resistant subjects. The normal vasodilative response of insulin is disrupted in obese, insulin resistant and diabetic persons, perhaps through insulin inability to increase the production of the potent vasodilator Nitric Oxide by endothelial cells [53]. The defect may be magnified by plasma free fatty acids. Other proposed mechanisms for insulin resistance leading to hypertension are:

a. The activation of sympathetic nervous system by insulin.
b. The intrinsic ability of insulin to cause salt and water reabsorption in the kidney resulting in expanded plasma volume.
c. Modification of ion transport across the cell membrane and increase of cytosolic calcium.
d. Augmentation of pressor and aldosterone response to angiotensin-II [53].

The Joint National Committee on prevention detection, evaluation and treatment of high blood pressure (JNC-7) suggested a new classification of hypertension [Table 3] [63, 36].

Table 3 JNC-VII classification of hypertension

Classification	Systolic blood pressure/diastolic blood pressure
Normal	< 120 mmHg / < 80 mmHg
Prehypertension	Between 120 - 139 mmHg / 80-89 mmHg
Stage - I HTN	Between 140 - 159 mmHg / 90-99 mmHg
Stage - II HTN	> 160 mmHg / > 100 mmHg

Hypertension in patients with diabetes compared to those without diabetes has unique features such as increased salt sensitivity, volume expansion, loss of nocturnal dipping of blood pressure and pulse, increased propensity to proteinuria and orthostatic hypotension, isolated systolic hypertension [54].

2.11 Insulin

Historical aspects

- In 1869, a German medical student, Paul Langerhans noted two distinct groups of cells in pancreas: the acinar cells and the islets.
- In 1922, Frederick Banting, Macleod, Charles Best and Collip extracted insulin form pancreas and thus was the first hormone to be isolated in pure form.
- Insulin was purified and crystallized by J.J. Abel within few years of discovery (1926).
- Sanger established the amino acid sequence of insulin in 1955; the protein was synthesized in 1963, and Hodgkin and co-workers elucidated insulin three dimensional structure in 1972.
- Insulin was the hormone for which Rosalyn Yalow and Samuel Berson first developed the radioimmunoassay (1960) [64, 54].

Chemistry of Insulin - Human insulin (MW 5808) consists of 51 amino acids in two chains (A and B) joined by two disulphide bridges, with a third disulphide bridge within the A chain [59].

Synthesis of Insulin - Preproinsulin, a protein of about 100 amino acids, is formed by ribosomes in the rough endoplasmic reticulum of the pancreatic β-cells. Preproinsulin is not detectable in the circulation under normal conditions because it is rapidly converted by cleaving enzymes to proinsulin, an 86-aminoacid polypeptide. This is stored in secretory granules in the Golgi complex of the β-cells where proteolytic cleavage to insulin and connecting peptide (C peptide) occurs. At the cell membrane, insulin and C peptide are released into the portal circulation in equimolar amounts. In addition, small amounts of proinsulin and intermediate cleavage forms enter the circulation [59].

Regulation of insulin secretion - Insulin secretion is highly regulated process designed to provide stable concentrations of glucose in blood both during fasting and feeding. This is achieved by coordinated interplay of various nutrients, gastrointestinal hormones, pancreatic hormones and autonomic neurotransmitters.

Glucose, amino acids, fatty acids and ketone bodies promote the secretion of insulin. The islets of Langerhans are richly innervated by both adrenergic and cholinergic nerves. Stimulation of α_2 adrenergic receptors inhibits insulin secretion whereas β_2 adrenergic receptor agonists and vagal nerve stimulation enhance release. Glucose is the principal stimulus to insulin secretion in human beings and is an essential permissive factor for the actions of many other secretagogues. When evoked by glucose, insulin secretion is biphasic: in first phase it reaches a peak after 1 to 2 minutes and is short lived; second phase has a delayed onset but a longer duration [64].

The most potent gastrointestinal hormones that promote the secretion of insulin includes Gastro intestinal inhibitory peptide (GIP), glucagon like peptide-1 (GLP-1), gastrin, and secretin, Cholecystokinin (CCK), Vasoactive Intestinal Peptide (VIP) and Enteroglucagon. Intracellular Ca^{2+} acts as the insulin secretagogues [29].

Degradation of insulin - The basal secretory rate is about 1 IU/hr., with total daily secretion of about 40 IU. The half-life of insulin in circulation is between 4 and 5 minutes. The biological function of insulin degradation is to remove and inactivation of circulating insulin. Intracellular degradation of insulin occurs primarily in liver followed by kidney and other tissues such as adipocytes, fibroblasts, monocytes, lymphocytes, gastrointestinal cells. It is estimated that the mean residence time of endogenously secreted insulin is 71 minutes with 62 minutes spent bound to the liver receptor, 6 minutes bound to peripheral receptor and 3 minutes in blood or interstitial fluid.

1**. Liver** - It is the primary site for the degradation of portal insulin. Approximately 50% of portal insulin is removed during first pass transit through liver.

2. **Kidney** - It is the major site of insulin clearance from the systemic circulation. Approximately 50% of the circulating proinsulin and 70% of the c-peptide removed in glomerular filtration of kidney by two mechanisms:

a. Glomerular filtration.
b. Proximal tubular reabsorption and degradation.

3. **Other tissues** - Insulin not cleared by liver and kidneys is ultimately removed by other tissues. All insulin sensitive cells remove and degrade the hormone. The mechanism involves insulin binding to its receptor, internalization and degradation.

Under normal conditions insulin is degraded intra cellularly or by membrane process. The recent study suggests that significant amount of insulin may be degraded extra cellularly in wound healing activity by insulin degrading enzyme. Proteolytic degradation of insulin occurs in both at the cell surface and after receptor mediated internalization. Insulin with insulin receptors are internalized called endosome the site of initiation of degradation. Some insulin is also delivered to lysosomes or lysosome related vesicle near Golgi apparatus for degradation.

Mainly two enzyme systems are responsible for the metabolism of insulin:

- The first is Insulinase (Insulin degrading enzyme IDE) an endopeptidase, which degrades insulin with a high degree of specificity acts at several sites

preferentially A_{13} - A_{14} and B_9 - $B_{10.}$ Insulinase is inhibited by sulphydryl inhibitors and chelators such as EDTA and phenanthrolene [Figure 4].

- A second insulin degrading enzyme is hepatic glutathione - insulin transhydrogenase (protein disulfide isomerase PDI) this enzyme reduces the disulfide bonds and the individual A and B chains are rapidly degraded. In addition to insulin degradation, the signal created by insulin at the cellular level is reversed by phosphor tyrosine.

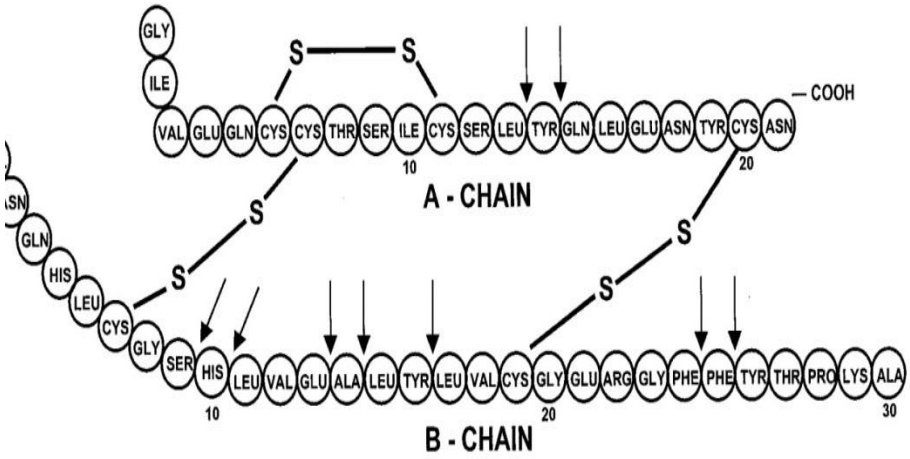


Figure 4 Cleavage sites of insulin by insulin degrading enzyme.

In kidney lysosomes play a greater and earlier role in insulin degradation, with most of the endosomal insulin and partially degraded insulin fragments delivered directly to lysosomes where degradation is completed.

Reduced hepatic clearance or degradation is associated with metabolic syndrome. Hypertension is also independently associated with insulin resistance.

Insulin secretion in type 2 diabetes - Because of the presence of concomitant insulin resistance, patients with type 2 diabetes mellitus are often hyperinsulinemic, but the degree of hyperinsulinemia is inappropriately low for the prevailing glucose concentration. The beta cell defect in patients with type 2 diabetes mellitus is characterized by an absent first phase insulin and c-peptide response to an intravenous glucose load and a decrease second phase response. Type 2 diabetes mellitus also affects proinsulin levels in serum. Elevated levels of proinsulin are

consistently seen in association with increase in proinsulin insulin molar ratio. Abnormalities in the temporal pattern of insulin secretion have also been demonstrated in patients with type 2 diabetes with a greater proportion of insulin secretion under basal conditions [53].

Insulin secretion in obesity and insulin resistance - The nature of pancreatic beta cell compensation for insulin resistance involves hyper secretion of insulin even in presence of normal glucose concentration. This can occur only if beta cell sensitivity to glucose is increased. The increase in beta cell sensitivity to glucose seen in obesity appears to be mediated by two factors: a) Increased beta cell mass and b) Insulin resistant states. Insulin resistance appears to be associated with increased expression of hexokinase in beta cell relative to the expression of glucokinase [53].

Hyperinsulinemia per se has been proposed to cause insulin resistance. Elevated concentrations of insulin can cause insulin resistance by down regulating insulin receptors and desensitizing the post receptor pathways. Suppression of insulin secretion in obese insulin resistant persons results in increased insulin sensitivity**.**

2.11.1 Mechanism of insulin action

The insulin receptor - The human insulin receptor is a dimer of two units. Each unit consists of one α chain and identical one β chain linked to one another by a single disulphide bond. The α subunit lies completely outside the cell whereas each β subunit lies primarily inside the cell, spanning the membrane with a single trans-membrane segment. The two α subunits move together to form a binding site for a single insulin molecule. β-subunit contains an intrinsic tyrosine kinase activity [66].

Signal transduction - Binding of insulin to the α-subunit induces a conformational change in the receptor resulting in the activation of the tyrosine kinase that catalyzes the phosphorylation of tyrosine residues on several proteins. One of the major substrates is the receptor itself. The intracellular substrates include the four members of the family of insulin receptor substrates (IRS-1, IRS-2, IRS-3 and IRS-4), Shc, Gab-1. The phosphorylated tyrosines, on these target proteins act as docking sites for selected intracellular signal transducer proteins. Most of these contain one or more Src homology 2 (SH2) domains. The SH2 containing proteins include

phosphatidylinositol 3' kinase (PI3K) and growth factor receptor bound protein 2 (Grb2). Insulin stimulates the mitogen activated protein (MAP) kinase via ras [59].

In addition, PI3K activates atypical protein kinase C via Akt (protein kinase B). Akt is not membrane anchored and moves through the cell to phosphorylate targets that include components that control the trafficking of the glucose transporter (GLUT 4) to the cell surface as well as enzymes that stimulate glycogen synthesis.

Termination of insulin signaling - Insulin signal is terminated by the action of phosphatases. Of particular importance are 3 classes of enzymes:

- Protein tyrosine phosphatases that remove phosphoryl groups from tyrosine residues on insulin receptor.
- Lipid phosphatases that hydrolyze phosphatidyl inositol 3,4,5-triphosphate to phosphatidyl inositol 3, 4 bisphosphate.
- Protein serine phosphatases that remove phosphoryl groups from activated protein kinases such as Akt [66].

2.11.2 Metabolic effects of insulin

1. Effects on carbohydrate metabolism - The effects of insulin on glucose metabolism are most prominent in three tissues: liver, muscle and adipose tissue. In the liver, insulin decreases the production of glucose by inhibiting gluconeogenesis and the breakdown of glycogen [67]. Insulin inhibits the transcription of the gene that codes for the m-RNA for phosphoenol pyruvate carboxykinase (PEPCK) in gluconeogenesis [65].

Insulin increases hepatic glycolysis by increasing the activity and amount of several enzymes namely glucokinase, phosphofructokinase and pyruvate kinase. It also decreases the activity of glucose-6-phosphatase [65].

In the muscle and liver, insulin increases glycogen synthesis. Insulin stimulates the synthesis of glycogen by inactivating glycogen synthase kinase. In the muscle and adipose tissue, insulin increases glucose uptake by increasing the number of glucose transporters in the cell membrane.

2. Effects on lipid metabolism - Insulin stimulates lipogenesis in adipose tissue by

- Providing acetyl CoA and NADPH required for fatty acid synthesis.
- Maintaining a normal level of acetyl CoA carboxylase.
- Providing the glycerol for triglycerides synthesis.

Insulin is also a potent inhibitor of hormone sensitive lipase. Insulin probably acts by promoting the dephosphorylation and hence inactivation of the enzyme. Thus insulin reduces the release of not only the free fatty acids but of glycerol as well [65].

Insulin increases the transport and metabolism of glucose into adipocytes providing the substrate glycerol 3 phosphate for triglyceride synthesis. Insulin also increases the lipoprotein lipase activity of adipose tissue by increasing the enzyme synthesis, thus providing fatty acids for esterification [67].

3. Effect on protein metabolism - Insulin generally has an anabolic effect on protein metabolism in that it stimulates protein synthesis and retards protein degradation. In most tissues insulin stimulates the entry of amino acids into cells. The effects of insulin on general protein synthesis are thought to be exerted at the level of mRNA translation [65].

2.11.3 Insulin resistance

Insulin resistance is the central pathology linking the various components of metabolic syndrome. The term insulin resistance indicates the presence of impaired biologic response to either exogenously administered or endogenously secreted insulin. Insulin resistance is manifested by decreased insulin stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output. The onset of insulin resistance is heralded by post-prandial hyperinsulinemia, followed by fasting hyperinsulinemia and hyperglycaemia [36].

Contribution of tissue specific insulin resistance:

Skeletal muscle: Skeletal muscle is quantitatively the most important tissue involved in systemic glucose homeostasis. Studies using hyperinsulinemic-euglycemic clamp

techniques have demonstrated that in insulin resistant people with and without type 2 diabetes, there is defect in the non-oxidative disposal of glucose related primarily to a defect in glycogen synthesis. A uniform finding in both obesity and type 2 diabetes is decreased insulin receptor substrate-1 associated tyrosine phosphorylation and decreased phosphatidyl inositol 3 kinase activity in skeletal muscle. In addition to this down regulation of proximal insulin signaling, negative regulators like plasma cell differentiation factor-1 etc. are up regulated. Total membrane bound tyrosine phosphatase activity is increased turning off the insulin signal [54].

Free fatty acids and insulin resistance in skeletal muscle: Chronic elevations in circulating free fatty acid levels are a classic feature of insulin resistance and type 2 diabetes. The Randle hypothesis or the glucose fatty acid cycle was originally proposed to account for the ability of free fatty acids to inhibit muscle glucose utilization. Recent observations proposed that increased free fatty acids leads to down regulation of insulin signaling by enhancing phosphorylation of serine / threonine sites on IRS-1 and IRS-2 reducing their ability to activate PI3K and glucose transport. Increased fatty acids may also promote inflammation [54.]

Intra muscular triglyceride accumulation: Intramuscular triglyceride accumulation is associated with muscle insulin resistance in lean and obese, non-diabetic and type 2 diabetics. The mechanism for such accumulation is probably related to the mismatching of free fatty acids uptake and oxidation. The equilibrium between oxidation and re-esterification within the muscle is paramount in determining fatty acid storage within the tissue [54].

Mitochondrial abnormalities and insulin resistance: A decrease in the oxidative capacity is seen in humans with insulin resistance/obesity and type 2 diabetes mellitus. Studies have suggested that increase in the intra myocellular content of fat may lead to alterations in the mitochondrial mass. The activity of electron transport chain and size of mitochondria are reduced in type 2 diabetes mellitus and correlated with severity of insulin resistance [53].

Adipose tissue: **-** Insulin resistance in adipose tissue is characterized by decreased suppression of adipose tissue lipolysis by insulin, resulting in elevated circulating levels of free fatty acids **[**54**]**.

Liver: - The defect in type 2 diabetes is primarily in defective regulation of glucose production from liver (the hepatic glucose output HGO). Hepatic insulin resistance plays an important role in the hyperglycaemia of type 2 diabetes. Insulin mediated suppression of hepatic glucose output is impaired at both low and high plasma insulin levels in type 2 diabetes and hepatic glucose production is elevated early in the course of disease, but it may be normal in lean, relatively insulin sensitive type 2 diabetics. Increased circulating free fatty acids levels also impair the suppressive effects of insulin on hepatic glucose production [53].

Genetic causes of insulin resistance: Syndromes of extreme insulin resistance due to several rare mutations in genes associated with insulin action are associated with typical clinical manifestations, hyperinsulinemia, dyslipidemia, hypertension, impaired glucose tolerance or type 2 diabetes mellitus. These include:

a. Insulin receptor mutations: Leprechaunism, Rabson – Mendenhall syndrome, Type A insulin resistance.
b. Insulin mediated pseudo acromegaly
c. Mutations in the peroxisome proliferator activated receptor [54].

2.11.4 Assessment of insulin resistance

1. The euglycemic hyper insulinemic clamp first described by De Fronzo and coworkers is accepted as the gold standard for assessment of insulin action in inducing glucose disposal [38].
2. Hyperinsulinemia, especially in a fasting sample taken together with normal blood sugar is considered to be an indicator of insulin resistance. Normal fasting insulin level is 3-10µIU/ml (20 - 69 pmol/L), never exceeding 14 µIU/ml [38].
3. Homeostasis model Assessment (HOMA) developed by Matthew et al. (1985) as a method for estimating insulin sensitivity from fasting serum

insulin and glucose. HOMA yields the following formula for insulin resistance [68].

$$\text{HOMA-IR} = \frac{\text{Insulin (}\mu\text{IU/ml) X glucose (mmol/L)}}{22.5}$$

(Or)

$$\text{HOMA-IR} = \frac{\text{Insulin (}\mu\text{IU/ml) X glucose (mg/dl)}}{405}$$

Low values indicate high insulin sensitivity whereas high values indicate low insulin sensitivity. Values > 2.5 were taken as insulin resistant.

4. Quantitative insulin sensitivity check index (QUICKI)

$$\text{QUICKI} = \frac{1}{\text{Log (fasting insulin) (}\mu\text{IU/ml)} + \text{log (fasting glucose) (mg/dl)}}$$

QUICKI is a non-linear transformation of the reciprocal of HOMA-IR calculated with a constant 1. Thus

$$\text{QUICKI} = \frac{1}{\text{Log HOMA-IR}}$$

5. In 2001, Mc Auley proposed an index by adding triglyceride levels [69].
   Example: [2.63-0.28 (Insulin μIU/L) - 0.31 in (triglyceride mmol/l)]

6. A simple predictor of insulin resistance in persons affected by the metabolic syndrome is to divide the fasting triglyceride concentration by the HDL-C level. A value by TG/HDL-C = 3.5 predicts insulin resistance as reliably as

fasting serum insulin levels. In addition, this ratio provides an independent estimate of coronary heart disease (CHD) risk.

2.12 Criteria for diagnosis of metabolic syndrome:

The World Health Organization (WHO) diabetes group made the first attempt to define metabolic syndrome in the year 1999 primarily cantered on the presence of insulin resistance. The same year European Group for the study of Insulin Resistance (EGIR) recommended minor modifications to the WHO definition. EGIR also required presence of insulin resistance for diagnosis.

The third report of National Cholesterol Education Program (NCEP) expert on Detection, Evaluation and Treatment of high blood cholesterol in adults (Adult Treatment Panel III) proposed its criteria in 2001 with emphasis on abdominal obesity recognized by increased waist circumference and did not require the presence of insulin resistance. The 2001 definition was later modified in the year 2004 to include the fasting plasma glucose to be ≥ 100 mg/dL and also lowering of waist circumference for Asians.

In 2005, the International Diabetes Federation (IDF) made an attempt to unify various definitions. IDF did not require the presence of insulin resistance, indeed an elevated waist girth is a mandatory criteria. The cut off value for the normal fasting plasma glucose was lowered to < 100 mg/dL in agreement to that of American Diabetes Association (ADA). The same year American Heart Association and the National Heart Lung and Blood Institute Statement on diagnosis and management of metabolic syndrome proposed definition with similarities to IDF.

2.12.1 World Health Organization (WHO), 1999, criteria [70]

Insulin resistance as identified by 1 of the following.

- Type 2 diabetes mellitus
- IFG (Impaired fasting glucose)
- IGT (Impaired glucose tolerance)

For those with normal fasting levels (< 110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyper insulinemic, euglycemic conditions plus any two of the following.

- Antihypertensive medication and / or high blood pressure.
  (≥ 140 mm of Hg systolic or ≥ 90 mm of Hg diastolic.)
- Plasma triglycerides
  ≥ 150 mg/dL (≥ 1.7 mmol/L)
- HDL cholesterol
  < 35 mg/dl in males and < 39 mg/dl in females.
- Body mass index
  (> 30 Kg/m^2 and / or Waist: Hip ratio > 0.9 in males, > 0.85 in females).
- Urinary albumin excretion rate ≥ 20 μg/min or Albumin : Creatinine ratio ≥ 30 mg/g.

2.12.2 Modified WHO criteria [71]

Presence of diabetes mellitus and ≥ 2 of the following:

- Body mass index > 30 Kg/m^2 or WHR > 0.9 in men and > 0.85 in women.
- Triglycerides ≥ 150mg/dL or HDL-C < 35 mg/dL (in male) and < 39 mg/dL (in female).
- Blood pressure ≥ 140/90 mmHg or on medication.

2.12.3 National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP-III) criteria [71]

Presence of ≥ 3 of the following:

- Central obesity: waist circumference (WC) ≥ 102 cm (male), ≥ 88 cm (female).
- Dyslipidemia: TG ≥ 150 mg/dL or specific medication.
- Dyslipidemia: HDL-C < 40 mg/dL (male), < 50 mg/dL (female) or specific medication.

- Blood Pressure: SBP ≥ 130 mmHg and / or DBP ≥ 85 mmHg or medical treatment of previously diagnosed HTN.
- Fasting plasma glucose: ≥ 110 mg/dL.

2.12.4 Modified NCEP ATP-III criteria [53]

Presence of ≥ 3 of the following

- Waist circumference: > 90 cm (male), > 80 cm (female).
- SBP ≥ 130 mmHg and / or DBP ≥ 85 mmHg or medical treatment for previously diagnosed hypertension.
- TG ≥ 150 mg/dL.
- HDL-C < 40 mg/dL (male), < 50 mg/dL (female).
- Fasting glucose ≥ 100 mg/dL.

2.12.5 International diabetes federation (IDF) criteria [36]

Presence of central obesity with Waist Circumference ≥ 90 cm (male) and ≥ 80 cm (female) plus any two of the following:

- TG ≥ 150 mg/dL or specific treatment for this lipid abnormality.
- HDL-C < 40 mg/dL (male), < 50 mg/dL (female) or specific treatment for this lipid abnormality.
- SBP ≥ 130 mmHg and / or DBP ≥ 85 mm Hg (or) medical treatment for previously diagnosed hypertension.
- Fasting plasma glucose (≥ 100 mg/dL) or previously diagnosed type 2 diabetes.

2.12.6 European group for the study of insulin resistance (EGIR) criteria [70]

Presence of insulin resistance defined as the top 25 % of the fasting insulin values among non-diabetic individuals and ≥ 2 of the following.

- Central obesity**:** WC ≥ 94 cm (male), ≥ 80 cm (female)

- Dyslipidemia**:** TG ≥ 2.0 mmol/L and / or
- HDL-C < 1.0 mg/dL or treated for dyslipidemia.
- Hypertension**:** BP ≥ 140/90 mmHg or antihypertensive medication.
- Fasting / 2 hour plasma glucose ≥ 6.1 / 7.8 mmol/L but < 7.0 /11.1 mmol/L

2.12.7 American association of clinical endocrinologists (AACE) [72]

Fasting glucose between 110 and 126 mg/dL, 2 hour post glucose challenge > 140 mg/dL plus any of the following based on clinical judgment.

- BMI ≥ 25 kg/m^2.
- TG ≥ 150 mg/dL.
- HDL-C < 40 mg/dL in men or < 50 mg/dL in women.
- BP ≥ 130/85 mmHg.

Other features of insulin resistance such as family history of type 2 diabetes mellitus; polycystic ovarian syndrome (PCOS); sedentary life style; advancing age and ethnic groups susceptible to type 2 diabetes mellitus are considered.

2.13 Metabolic syndrome and risk for atherosclerotic cardiovascular disease

- **Long term (Lifetime risk) -** In populations at risk, metabolic syndrome is accompanied by an increase in relative risk for ASCVD. In prospective epidemiologic studies, the relative risk for ASCVD events is essentially doubled [62].
- **Short term (10 years risk) -** At present more intense clinical intervention is driven by metabolic syndrome for ASCVD. Most persons with metabolic syndrome can be considered to be at least a moderate risk according to ATP-III guidelines, but many will have risk more than 10 percent [62].

2.14 Prevention of metabolic syndrome:

Various strategies have been proposed to prevent the development of metabolic syndrome. These include increased physical activity and a healthy, reduced calorie diet. Regular physical activity and attaining physical fitness will improve most of metabolic risk factors. Increased physical fitness has been reported to reduce several chronic diseases including cardiovascular disease. Emphasis should be given to reduce consumption of saturated and trans-fatty acids and cholesterol, reduced intake of simple sugars and ample intake of fruits, vegetables and whole grains.

CHAPTER IV

MATERIALS AND METHODS

3.1 Study design:

3.1.1 Scope of the study: The study has been designed as a prevalence survey for metabolic syndrome among 1032 randomly selected individuals of urban rural and tribal population in Kurnool District.

3.1.2 Study setting: Urban, Rural and Tribal population of Kurnool district, Andhra Pradesh

3.1.3 Study period: From March 2013 to December 2015.

3.1.4 Sample size: Assuming prevalence of metabolic syndrome 41% considering 95% confidence limit and ± 5.2% margin of error, the worked out sample size is 344 per group using statistical formula [73]. Total it is 1032.

$$n = \frac{(1.96)^2 \times P\,(1-P)}{d^2}$$

n= Sample size

1.96= Statistical value for 95% confidence level (Z).

In this study the results are presented with 95% confidence level

d= Precision (confidence interval)

3.1.5 Study type: It is a cross sectional community based study by adopting simple random sampling.

3.1.6 Study subjects: 20 - 60 years age Adult Population in Kurnool district

3.1.7 Study groups: The subjects were classified

- Based on type of population 3 groups i.e., Urban, Rural and Tribal
- Based on age 4 groups i.e., 20-30; 31-40; 41-50 and 51-60.

3.1.8 Inclusion and exclusion criteria:

- Healthy adults with the age of 20-60 years residing in Kurnool district.
- Severely ill patients, pregnant ladies were excluded from this study.

Subjects with any type of cancer, tuberculosis, psychiatric complications were excluded from this study

3.2 Ethical aspects:

3.2.1 Informed consent: All the subjects were explained very clearly about the purpose and outcomes of the study in their own language and a written informed consent was obtained from them.

3.2.2 Institutional approval: An Institutional Ethical committee clearance was obtained from Santhiram Medical College and General Hospital, Nandyal, Andhra Pradesh & Shri B.M. Patil Medical College, hospital and research centre, BLDE (Deemed to be University), Vijayapura, Karnataka.

3.2.3 Helsinki Declaration: During the entire study the utmost care was taken according to Helsinki Declaration about patient confidentiality.

3.3 Study protocol:

From 54 mandalas of Kurnool district; Nandyal mandal was chosen by simple random sampling. The Nandyal mandal constitutes 34 wards (urban), 20 villages and 24 tanda areas [74]. From 34 wards 6 wards were chosen by probability proportional to size sampling (PPS) method to collect data from 344 sampling units. Likewise 4 villages and 7 tandas were selected. 57 samples were collected from each ward selected by systemic random sampling technique, in the same way 86 and 49 samples were collected from each village and tandas respectively.

All the selected participants have under gone screening for metabolic syndrome by

3.3.1 Oral questionnaire (ANNEXURE-1)

3.3.2 Anthropometric analysis

3.3.3 Biochemical analysis

3.3.1 Oral questionnaire - All the participants were interviewed using prefixed questionnaire. Based on the epidemiological studies, the behavioural and physiological CVD risk factors such as gender, age, education, type of work, physical activity, personal history of disease/medication, family history of diabetes/ medication, habit of smoking, habit of alcohol consumption, habit of chewing tobacco were included in oral questionnaire. Cigarette smoking was defined as a lifetime history of smoking at least 100 cigarettes. Alcohol drinking was defined as consuming alcohol at least once per week. Physical activity was defined as participating in moderate or vigorous activity for 30 minutes or more per day at least 3 days a week. Family history of disease was defined as at least one of parents diagnosed a disease in a lifetime by self-reporting [75].

Then all the participants were analyzed for anthropometric and biochemical parameters to screen the individuals with metabolic syndrome. Modified NCEP ATP III criterion (2005) was applied [Table 4] to screen the subjects with MetS risk [76]. Presence of any three among the five metabolic syndrome risk factors in an individual was considered as existence metabolic syndrome risk in that person. It was shown that estimation of CVD risk was better using ATP III criteria [77].

Table 4 Modified NCEP ATP III criteria

RISK FACTOR	CUT OFF VALUES
Waist Circumference (WC)	Males > 90 cm
	Females > 80 cm
Blood pressure (BP) [SBP/DBP]	≥ 130 / ≥ 85 mmHg or medical treatment for previously diagnosed hypertension
Triglycerides (TG)	≥150 mg/dl
HDL cholesterol (HDL-c)	Males < 40 mg/dl
	Females < 50 mg/dl
Fasting blood glucose (FBS)	≥100 mg/dl or medical treatment for previously diagnosed diabetes mellitus

3.3.2 Anthropometric analysis

- **Waist Circumference (WC):** The measuring tape was placed in a horizontal plane around the abdomen at the level of uppermost lateral border of the iliac crest. The plane of the tape is held parallel to the floor and the tape was snug without compressing the skin. Waist circumference was measured in centimeters (cm) at a normal minimal respiration, at the end of gentle exhaling.
- **Body Mass Index (BMI):** BMI was calculated using the Quetelet's index. Body weight and height were measured without shoes and in light clothing. BMI was calculated as weight in kilograms divided by the square of height in meters.

$$\text{BMI} = \text{Weight (kg)} / (\text{Height in meters})^2$$

- **Blood Pressure:** Blood pressure was recorded to the nearest 2 mmHg using mercury sphygmomanometer in the sitting position after at least 5 minutes of rest. Two consecutive readings of blood pressure (SBP/DBP) were taken on the same arm. Mean of the two measures was taken for analysis.

3.3.3 Biochemical analysis - Blood samples (about 5ml) were collected after a 12 hour overnight fast under aseptic conditions. 2 ml of blood sample was collected in the test tube containing mixture of potassium oxalate and sodium fluoride in 3:1 ratio. Rest of 3 ml of blood was dispensed into a plain tube, allowed to clot at room temperature. Test tubes were centrifuged for 15 minutes at 2000RPM to collect plasma and serum. Plasma was used for the estimation of blood glucose and serum was used for the estimation lipid parameters and fasting insulin levels. Care was taken to procure serum free of haemolysis.

All investigations were done on the same day on a semi-automated analyzer (Transasia-Erba Chem 5 x) except insulin assay which was carried on automated analyzer (Roche-Cobas e 411).

The following biochemical parameters were estimated in the serum sample:

- Fasting glucose
- Fasting serum lipid profile
    - Total cholesterol (TC)
    - Triglycerides (TG)
    - High density lipoprotein cholesterol (HDL-C)
    - Low density lipoprotein cholesterol (LDL-C)

To estimate insulin resistance using Homeostatic model assessment for insulin resistance (HOMA-IR), 20 participants were randomly selected from each group. Total is 60. Fasting serum insulin levels were estimated and insulin resistance was calculated. HOMA-IR formula is

Glucose (mg/dl) X Insulin (µIU/L) /405.

The required number of sample size was calculated by assuming prevalence of insulin resistance as 60%, considering 95% confidence level and ± 0.2% of margin of error. Using statistical formula [73]:

$$n= (1.96)^2 \times (1-P)/d^2$$

Whereas: n= Sample size; 1.96= Statistical value for 95% confidence level (Z) and d= Precision (confidence interval)

All the biochemical estimations were done in the clinical biochemistry laboratory of Santhiram Medical College and General Hospital, Nandyal, Kurnool district, Andhra Pradesh, (India).

3.3.3.1 Estimation of blood glucose

The glucose levels in serum were determined using Glucose oxidase and Peroxidase (GOD-POD) [Trinder.P 1969; Erba diagnostics] [78].

Principle: Glucose was oxidized to gluconic acid and hydrogen peroxide in the presence of glucose oxidase. Hydrogen peroxide further reacts with phenol and 4-aminoantipyrine by the catalytic action of peroxidase to form a red colored quinoneimine dye complex. Optical density of the color formed was directly proportional to the amount of glucose present in the sample.

$$\text{Glucose} + O_2 \xrightarrow{\text{Glucose oxidase}} \text{gluconic acid} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + \text{4- Aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{red quinoneimine} + 4H_2O$$

Reagent Composition:

Reagents		Concentration
Glucose R1	Phosphate buffer (Ph 7.40)	100 mmol/l
	Phenol	10 mmol/l
Glucose R2	Glucose oxidase	≥ 10000 IU/l
	Peroxidase	≥ 600 IU/l
	4- Aminoantipyrine	270 mmol/l

Glucose Standard: Glucose standard concentration = 100 mg/dL.

Preparation of working reagent: Reagent 2 (R2) was dissolved with the volume of reagent 1 (R1) as indicated.

Procedure: Three clean dry test tubes were taken and marked them as T (test), S (standard) and B (blank). Then reagents were added into each test tube as shown in the following table.

Reagents	Reagent blank	Standard	Test
Working reagent	1 ml	1 ml	1 ml
Distilled water	10 µl	-	-
Glucose standard (100 mg/dl)	-	10 µl	-
Sample	-	-	10 µl

After mixing, the test tubes were incubated for 10 minutes at 37^0C. Then optical density (OD) was measured for standard and test against reagent blank at 505 nm.

Calculation: By the following formula concentration of glucose in the sample was calculated.

$$\text{Glucose conc. (mg / dl)} = \frac{\text{OD Test} - \text{OD Blank}}{\text{OD Standard} - \text{OD Blank}} \times \frac{\text{Concentration of standard}}{\text{Volume of sample}} \times 100$$

$$= \frac{\text{OD Test}}{\text{OD Standard}} \times \frac{10}{10} \times 100$$

$$= \text{OD Test / OD Standard} \times 100$$

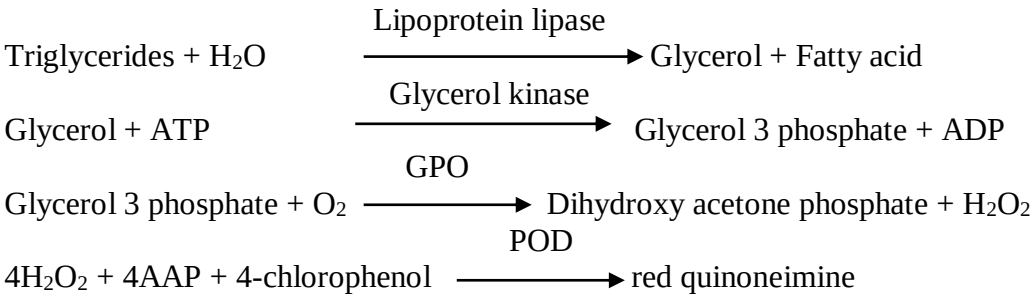
Reference intervals: serum blood glucose: 74 - 100 mg/dl **[**53].

3.3.3.2 Estimation of triglycerides

The triglyceride levels in serum were determined using Glycerophosphate oxidase - peroxidase method (GPO-POD) [Schettler.G 1960; Erba diagnostics] **[**79].

Principle: Triglycerides were enzymatically hydrolyzed by lipase to free acids and glycerol. The glycerol was phosphorylated by adenosine triphosphate (ATP) with glycerol kinase (GK) to produce glycerol 3 phosphate and adenosine diphosphate (ADP). Glycerol 3 phosphate was oxidized to dihydroxyacetone phosphate by the enzyme glycerol phosphate oxidase producing hydrogen peroxide (H_2O_2). Peroxidase catalyzes reaction of H_2O_2 with 4-aminoantipyrine (4AAP) and 4-chlorophenol to

produce a red colored compound quinoneimine. The optical density of the color formed was proportional to triglycerides concentration in the sample.



Reagent composition:

Reagent	Concentration
Pipes buffer (pH 7.0)	50 mmol/l
P-Chlorophenol	5.3 mmol/l
Potassium ferrocyanate	10 µmol/l
Magnesium salt	17 mmol/l
4-Aminoantipyrine	0.9 mmol/l
ATP	3.5 mmol/l
Lipoprotein lipase	≥ 1800 IU/l
Glycerol kinase	≥ 450 IU/l
Glycerol-3-phosphate oxidase	≥ 3500 IU/l
Peroxidase	≥ 450 IU/l

4AAP = 4 Aminoantipyrine; GPO = Glycerol 3 phosphate oxidase; POD = Peroxidase

Triglyceride standard: Triglycerides standard (TG) concentration = 200 mg/dl

Procedure: Three clean dry test tubes were taken and marked them as T (test), S (standard) and B (blank). Then reagents were added into each test tube as shown in the following table.

	Blank	Standard	Sample
Reagent	1 ml	1 ml	1 ml
Distilled water	10 µl		
TG standard (200 mg/dl)	-	10 µl	-
Sample	-	-	10 µl

After mixing, the test tubes were incubated for 10 minutes at 37^0C. Then optical density (OD) was measured for standard and test against reagent blank at 505 nm.

Calculation: By the following formula concentration of triglycerides in the sample was calculated.

$$\text{TG conc. (mg / dl)} = \frac{\text{OD Test} - \text{OD Blank}}{\text{OD Standard} - \text{OD Blank}} \times \frac{\text{Concentration of standard}}{\text{Volume of sample}} \times 100$$

$$= \frac{\text{OD Test}}{\text{OD Standard}} \times \frac{20}{10} \times 100$$

$$= \text{OD Test / OD Standard x } 200$$

Reference intervals: males: 40 - 160 mg/dl, females: 35 - 135 mg/dl

Classification of triglyceride levels (mg/dl) based on ATP III criteria [80].

- < 150 : Optimal
- 151 – 199 : Border line high
- 200– 499 : High
- > 500 : Very high

3.3.3.3 Estimation of HDL cholesterol

The HDL cholesterol levels in serum were determined using Phosphotungstate precipitation method [Burstein 1970; Erba diagnostics]

Principle: Chylomicrons, LDL (low density lipoprotein) and VLDL (Very low density lipoprotein) fractions in serum were separated from HDL by precipitating with Phosphotungstic acid and magnesium chloride. After centrifugation, the HDL cholesterol in the supernatant was estimated with enzymatic cholesterol method.

$$\text{Serum} \xrightarrow[Mg^{2+}]{\text{Phosphotungstic acid}} \underset{\text{(Supernatant)}}{\text{HDL}} + \underset{\text{(Precipitate)}}{\text{(LDL + VLDL + chylomicrons)}}$$

Reagent composition:

Reagent		Concentration
Reagent 1	Cholesterol esterase	≥ 200 IU/l
	Cholesterol oxidase	≥ 250 IU/l
	Peroxidase	≥ 1000 IU/l
	4-Aminoantipyrine	0.5 mmol/l
Reagent 1A	Pipes buffer, pH 6.90 / phenol	50 / 24 mmol/l
	Sodium cholate	0.5 mmol/l
Reagent 2	Phosphotungstic acid / $MgCl_2$	2.4 / 39 mmol/l

Standard concentration: 50 mg/dl

Reagent reconstitution: The contents of one bottle of reagent 1are mixed into one bottle of reagent 1A and mixed by gentle swirling till completely dissolved.

Procedure:

1. Precipitation:

In a clean dry test tube 0.20ml serum and precipitating reagent-2 were added respectively.

Pipette	Test
Serum	0.20 ml
Precipitating reagent-2	0.20 ml

After mixing, the test tubes were allowed to stand for 10 minutes at room temperature then centrifuged at 4000 r.p.m. for 20 minutes to obtain the supernatant.

The supernatant was used to determine the concentration of HDL cholesterol in the sample.

2. Cholesterol Assay:

Three clean dry test tubes were taken and marked them as T (test), S (standard) and B (blank). Then reagents were added into each test tube as shown in the following table.

	Blank	**Standard**	**Test**
Reconstituted reagent	1 ml	1 ml	1 mL
Distilled water	20 µl		
HDL standard (50 mg/dl)	-	20 µl	-
Supernatant		-	20µl

Calculation: By the following formula concentration of HDL-C in the sample was calculated.

$$\text{HDL conc. (mg / dl)} = \frac{\text{OD Test} - \text{OD Blank}}{\text{OD Standard} - \text{OD Blank}} \times \frac{\text{Concentration of standard}}{\text{Volume of sample}} \times 100$$

$$= \frac{\text{OD Test}}{\text{OD Standard}} \times \frac{10}{20} \times 100$$

$$= \text{OD Test / OD Standard} \times 50$$

Classification of HDL-C levels (mg/dl) based on ATP III criteria [80].

- < 40 mg/dl : Low
- ≥ 60 mg/dl : High

3.3.3.4 Estimation of serum total cholesterol

The total cholesterol levels in serum were determined using Cholesterol oxidase and peroxidase method (CHOD-POD) [Allain CC et al., Erba diagnostics] [82].

Principle: Cholesterol esters were enzymatically hydrolyzed by cholesterol esterase to cholesterol and free fatty acids. Free cholesterol then oxidized by cholesterol

oxidase to cholest-4-en-3-one and hydrogen peroxide. The hydrogen peroxide combines with 4-aminoantipyrine to form a chromophore which was quantitated at 505 nm. The optical density of the color formed was proportional to cholesterol concentration in the sample.

$$\text{Cholesterol Ester} + H_2O \xrightarrow{\text{Cholesterol esterase}} \text{Cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + (O) \xrightarrow{\text{Cholesterol oxidase}} \text{Cholestenone} + H_2O_2$$

$$2H_2O_2 + \text{Phenol} + \text{4-Aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Red quinoneimine} + 4\ H_2O$$

Reagent composition:

Reagent		**Concentration**
Reagent 1 (enzymes / chromogen)	Cholesterol esterase	≥ 200 IU/l
	Cholesterol oxidase	≥ 250 IU/l
	Peroxidase	≥ 1000 IU/l
	4- Aminoantipyrine	0.5 mmol/l
Reagent 1A (Buffer):	Pipes buffer, pH 6.90	50 mmol/l
	Phenol	4 mmol/l
	Sodium cholate	0.5 mmol/l

Standard concentration: 200 mg/dl

Reagent constitution: The reagents were allowed to attain room temperature. The contents of bottle of reagent 1 are mixed gently with one bottle of reagent 1A.

Procedure: Three clean dry test tubes were taken and marked them as T (test), S (standard) and B (blank). Then reagents were added into each test tube as shown in the following table.

Table of assay procedure:

Pipette into tubes marked	**Blank**	**Standard**	**Test**
Working reagent	1 ml	1 ml	1 ml

Cholesterol standard (200mg/dl)	-	10µl	-
Sample	-	-	10 µl

Calculation: By the following formula concentration of cholesterol in the sample was calculated.

$$\text{Cholesterol conc. (mg / dl)} = \frac{\text{OD Test} - \text{OD Blank}}{\text{OD Standard} - \text{OD Blank}} \times \frac{\text{Concentration of standard}}{\text{Volume of sample}} \times 100$$

$$= \frac{\text{OD Test}}{\text{OD Standard}} \times \frac{20}{10} \times 100$$

$$= \text{OD Test / OD Standard} \times 200$$

Classification of serum cholesterol levels (mg/dl) based on ATP III criteria [80].

- < 200 : Desirable
- 200 – 239 : Border line high
- ≥ 240 : High

3.3.3.5 Estimation of LDL cholesterol

LDL cholesterol was calculated by FRIEDEWALDS formula [83].

LDL cholesterol = Total cholesterol - (HDL + VLDL).

$$\text{VLDL} = \frac{\text{Triglycerides}}{5}$$

The factor, TG/5 was an estimate of VLDL cholesterol concentration and was based on the average ratio of triglyceride to cholesterol in VLDL.

Limitations:

Calculation using Friedewald equation is precluded.

- In samples that have triglyceride concentrations above 400 mg/dL
- In those that contain great amounts of chylomicrons [80].

Classification of LDL (mg/dl) based on ATP-III [36**,** 80].

- < 70 : Therapeutic option for high risk patients

- < 100 : Optimal
- 100 – 129 : Above optimal
- 130 – 159 : Borderline high
- 160 – 189 : High
- > 190 : Very high

3.3.3.6 Estimation of insulin

Method: Elecrochemiluminescence immunoassay (ECLIA) [Macrovina 1972; Roche diagnostics, Mannheim, Germany] [84].

Instrument: Roche Cobas e 411

Principle: ECLIA assay using Cobas-e-411 solid phase was a non-competitive sandwich immunometric assay. It uses electro chemilumiscent technique for detection and measurement of serum insulin levels. The assay employs two (biotinylated and chemiluminescent substrate Ruthenium labelled antigen) monoclonal antibodies directed against insulin. It was sandwiched between biotinylated anti insulin antibody and Ruthenium labelled anti insulin antibody to form Ab-Ag-Ab complex. Application of a voltage to the electrode induces a chemiluminescent emission which was measured by a photo multiplier. The development of ECL was based on the use of ruthenium (II) - tris (bipyridine) [Ru (bpy) 3^{2+} complex and tripropylamine (TPA).

Total duration of assay was 18 minutes.

Reagents-working solutions:

M Streptavidin-coated micro particles, 1 bottle, 605 mL:
Streptavidin-coated micro particles, 0.72 mg/mL, binding capacity:
470 ng biotin/mg micro particles; preservative.

R1 Anti-Insulin-Ab-biotin, 1 bottle, 10 mL
Biotinylated monoclonal anti-insulin antibody (mouse) 1 mg/mL;
MES buffer 50 mmol/L, pH 6.0; preservative.

R2 Anti-Insulin-Ab~Ru (bpy), 1 bottle, 10 mL:
Monoclonal anti-insulin antibody (mouse) labelled with ruthenium complex.

1.75 mg/L; MES buffer 50 mmol/L, pH 6.0; preservative.

Materials required (not provided in the kit)

- Elecsys Insulin Cal Set, 4 x 1 mL
- Elecsys Preci Control Multi Analyte 1 and
- General laboratory equipment

Storage and stability: Stable when stored at 2-8^{o}C for 12 weeks.

Specimen required: Serum, Li-heparin, K_3-EDTA, and sodium citrate plasma

Procedure:

1st incubation: Serum sample was combined in an assay cup with reagent containing biotinylated monoclonal insulin-specific antibodies, and a ruthenium labelled insulin specific antibody to form a sandwich complex.

2nd incubation

1. After addition of Streptavidin coated micro particles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
2. The reaction mixture was aspirated into the measuring cell where the micro particles were magnetically captured onto the surface of the electrode.
3. Unbound substances were then removed with procell. Application of a voltage to the electrode then induces chemiluminescent emission which was measured by a photomultiplier.
4. Results were determined via a calibration curve which was instrument-specifically generated by 2- point calibration and a master curve provided via the reagent barcode.

Measuring range: 0.2000-1000 µ IU/ml

Reference intervals: Serum: 2 - 25 µ IU/ml.

3.4 Statistical analysis:

The data were analyzed using graph pad instat software version-3. All characteristics were summarized descriptively. For continuous variables, the summary statistics of number, arithmetic mean (referred to as mean) and standard deviation about the arithmetic mean (SD) were used. For categorical data, the number and percentages were used in the data summaries. A P-value < 0.05 was considered significant and p-values < 0.001 was considered highly significant.

- One way ANOVA was used for comparison of anthropometric and biochemical parameters among urban, rural and tribal population.
- Bivariate correlation analysis using Pearson's correlation coefficient (r) was used evaluate the relationships between the variables.
- Chi-square test (χ^2 test) was to determine the significant association between two variables.
- Odds ratio was used for the comparison of magnitude of various risk factors for CVD outcome.

CHAPTER V

RESULTS AND DISCUSSION

This chapter outlines the results of demographic, clinical, anthropometric and biochemical analysis of participants. Data analyses of all the participated subjects (urban, rural and tribal groups) have also been recorded in this chapter.

4.1 Prevalence of metabolic syndrome

Metabolic syndrome is a cluster of metabolic abnormalities. It is the principle underlying cause for cardiovascular diseases all over the world [85, 86]. Since 1980 several criteria and methodologies are being followed to assess the prevalence of metabolic syndrome. Despite their differences, studies have proven that Asia pacific region is facing significant epidemic of metabolic syndrome (MetS). Irrespective of criteria applied to assess the prevalence of metabolic syndrome, it was increased by 50 - 70% over 10 year period [87].

Geographical area is one of the key factors to determine the prevalence of metabolic syndrome [88]. Prevalence of MetS is high in Africa (12.5% to 62.5%) [88], followed by South America (18.8% to 43.3%) [90]; Middle East (18.8 to 36.3%) [91]; Central America (23.0% to 35.1%) [92]; Asia-pacific (11.9% to 37.1%) [87]; Europe (11.6% to 26.3%) [93] and South Asia (26.1%) [94]. Scientific data shows that nearly one fifth adults of Asia Pacific region are affected by MetS [88].

Almost one fourth of world population reside in South Asia [95]. It has the highest CVD burden than East and West Asian countries [96]. India is an important country of South Asia having different types of populations with different cultures and lifestyles. According to Harvard School of Public Health, by 2020 India will be the country with highest number of individuals with CVD than in any other region [96]. The crucial role of metabolic syndrome to develop cardiovascular disease is well established. It is also known that each component of metabolic syndrome will play its unique role to develop CVD [98, 99].

These metabolic syndrome components were not same for all the populations; they vary with geographical area, age, gender and ethnicity. Assessment of metabolic syndrome of a population may help the clinician to formulate preventive measures to eradicate or decrease the CVD related mortality and morbidity among them.

However, there is paucity of scientific data on prevalence of metabolic syndrome till now [88].With this background our study has been designed.

Table 5 is showing demographic and clinical characteristics of overall participants. Among 1032 participants, males were: 56.68% and females were: 43.31%. Literate were 60.94% and literate were 39.05 %.

Table 5 Demographic and clinical characteristics of the study participants.

VARIABLE		Number of subjects	Percentage (%)
Gender	Male	585	56.68
	Female	447	43.31
Education level	Illiterate	403	39.05
	Up to secondary	416	40.31
	Above secondary	213	20.63
Cigarette Smoking		233	22.57
Alcohol Consumption		225	21.80
Chewing		76	7.36
Family history (FH) of DM		97	9.39
Family history of hypertension		62	6.00
Personal history of T2DM		121	11.72
Personal history of HTN		134	12.98

Table 6 is showing anthropometric and biochemical parameters of participants. Mean BMI is above the upper normal reference level: 25.72 (± 4.42) while mean HDL-C is below the lower normal reference level: 37.52 (± 6.19). Remaining parameters were in permissible limits.

Table 6 Anthropometric and biochemical variables of participants.

Variable	Mean ±SD (Range)
Waist circumference (cm)	87.92 ± 9.11 (52cm - 117cm)
Body mass index (kg/m^2)	25.72 ± 4.42 (16.44 - 45.02)
Systolic blood Pressure (mmHg)	122.17 ± 7.44 (92 mmHg - 150mmHg)
Diastolic blood pressure (mmHg	81.49 ± 4.23 (72mmHg - 96mmHg)
Fasting blood glucose (mg/dl)	89.77 ± 20.91 (65mg/dl - 440 mg/dl)
Serum triglycerides (mg/dl)	137.27 ± 27.67 (32mg/dl - 281 mg/dl)
Serum HDL-C (mg/dl)	37.52 ± 6.19 (23mg/dl - 80 mg/dl)

Table 7 is showing crude standardized prevalence of metabolic syndrome by age and gender. We have identified prevalence of MetS was increased in both genders with aging.

Table 7 Crude standardized prevalence of metabolic syndrome by age and gender.

Age group (year)	Total n/N	%	Total n/N	%	Total n/N	%
	Overall		Male		Female	
20-30	91/413	22.03	52/231	22.51	39/182	21.42
31-40	69/235	29.36	44/132	33.33	25/103	24.27
41-50	80/196	40.81	41/103	39.80	39/93	41.93
51-60	90/188	47.87	55/119	46.21	35/69	50.72
Crude Standardized	330/1032	31.97	192/585	32.82	138/447	30.87

N= total number of subjects, n= number of subjects with metabolic syndrome, % =percentage

Overall prevalence of metabolic syndrome was 31.97%. It was highly prevalent in males: 32.82% compared to females: 30.87%. This was in accordance to mean South Asian prevalence of MetS: 32.5% [88]. Prevalence of MetS in India ranges from 22.1% to 41.0% [100, 101,102]. Philippine National Health Survey has reported

11.9% of lowest MetS prevalence among them [103]. Highest prevalence was noted by Hydrie et al. in Pakistan: 49.0% [104]. South Korea National Health Survey has reported 31.3% of MetS which is concurring with this study [105].

Our findings were in contrast Aryal N et al. who have found that except with WHO criteria, MetS is highly prevalent in females than males. [WHO criteria: 12.8% vs. 15.6%; ATP III criteria: 29.5% vs. 22.1%; IDF criteria: 34.3% vs. 18.8% and modified NCEP ATP III criteria: 35.8% vs. 28.8%] [88,106].

However in accordance to our findings, Vaughan et al. Chow CK et al. and Hydrie et al. have reported higher prevalence of MetS in males compared to females [107,108, 109]. A recent study from Mumbai in India has also noted nearly two fold higher prevalence of MetS in males than females [110].

This marked gender heterogeneity in prevalence of MetS may attribute to gender specific prevalence of MetS components in this population [111-116]. Further, it can be explained by confounding factors like physical activity [117] diet [118,119] and genetic susceptibility [120]. However, distribution pattern of MetS components is not consistent in any gender across the world [121]. These gender differences are further modified with age and influence the degree of metabolic syndrome prevalence [122, 123].

Several researchers have reported age associated increase in prevalence of MetS at different geographical locations; Gupta R et al. - urban population of India [124]; Rahim MA et al. - rural Bangladesh [125]; Ravi Kiran et al. - Asian Indians [126]; Sharma SK - Nepal [127]; Prasad DS et al. - Eastern India [128]; Gupta R et al. - Urban middle class Indians [129] and Chakrawarthy S et al. - Urban Sri Lanka [130]. They have reported highest prevalence of MetS at 50 years of age, which is in accordance to our findings. We have observed higher prevalence of MetS between the age of 51 - 60 years in both males and females. This can be attributed to higher prevalence of metabolic syndrome components in older age participants than younger age participants.

This can also be explained as presence of metabolic risk factors in the younger age will increase the production of reactive oxygen species (ROS) thereby oxidative

stress. Increased oxidative stress during the process of ageing will further aggravate the metabolic dysfunction and prevalence of metabolic syndrome. Age is a measure of exposure time not a risk factor [131].

Metabolic syndrome represents a clustering of cardiovascular risk factors that are amalgamated into a single multiplex risk factor for atherosclerotic cardiovascular disease (ASCVD). The syndrome develops as a result of the interaction between exogenous and endogenous factors. Obesity is one of the major exogenous factors for MetS. Endogenous factors include dysfunctional adipose tissue, genetic forms of insulin resistance, various endocrine disorders and genetic susceptibility.

Figure 5 is showing relative number of metabolic syndrome risk factors obeyed by participants, based on modified NCEP ATP III criteria. We have identified total 31.96% of participants were with any three of the five MetS components, 59.29% were with any one or two risk factors and only 8.72% were devoid of any MetS components. This gives an impression that total 91.28% of participants were with any one metabolic syndrome risk component which is very undesirable.

Figure 5 Relative number of metabolic syndrome risk factors obeyed by participants.

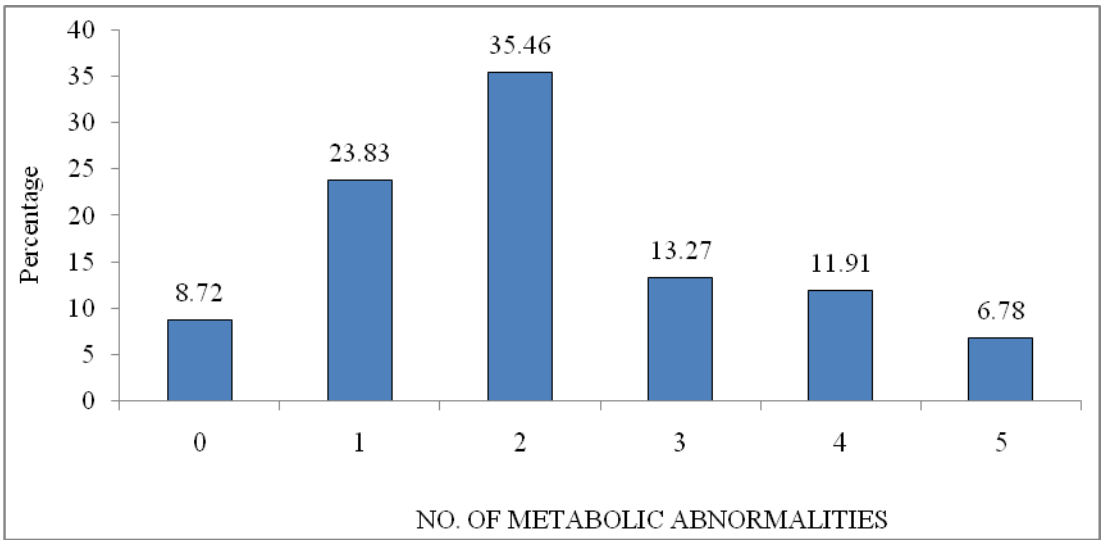


Table 8 is showing crude prevalence of individual risk factors of metabolic syndrome, decreased HDL-C, increase of waist circumference and elevation of serum triglycerides were found to be constant MetS risk factors in both males and females of this population. We have identified high prevalence of MetS in males even though MetS components were higher in females i.e. Lower HDL-C (males: 71.87% vs. females: 88.36%) and increased waist circumference (52.13% vs. 65.32%) except serum triglycerides which is high in males than females (38.29% vs. 23.26%).

Table 8 Crude prevalence of individual risk factor of the MetS by gender

Variable	**Total n/N**	**%**	**Total n/N**	**%**	**Total n/N**	**%**
	Overall		**Male**		**Female**	
Increased fasting glucose	157/1032	15.21	99/585	16.92	58/447	12.97
Elevated SBP	233/1032	22.57	152/585	25.98	81/447	18.12
Elevated DBP	193/1032	18.70	118/585	20.17	75/447	16.77
Increased. TGL	328/1032	31.78	224/585	38.29	104/447	23.26
Decreased HDL-C	814/1032	78.87	419/585	71.62	395/447	88.36
Larger waist circumference	597/1032	57.84	305/585	52.13	292/447	65.32

N= total number of subjects, n= number subjects with related variable, %= percentage

From the table 7 and 8, we have observed higher prevalence of metabolic syndrome in males before 40 years of age and after the age of 40 years it was high in females. And, higher WC and BMI among women at postmenopausal age compared to premenopausal aged women.

This can be explained by considering physiological and metabolic changes in postmenopausal women such as age related weight gain (average 0.5 Kg/year), less physical activity, loss of estrogen protective function, change in lipid concentration (increase in TG and decrease in HDL-C) [130,132,133,134].

This increased visceral adipose tissue leads to insulin resistance, increased FFA concentration, secretion of apo lipoprotein B, decreased adiponectin levels and

increased hepatic lipase activity, leading to increased triglycerides and decreased HDL cholesterol levels. These lipid changes might contribute to the number of women meeting MetS criteria in postmenopausal age [135, 136].

4.2 Prevalence of individual components of metabolic syndrome

Pathophysiology of MetS is very complex. The MetS components are inter-related and can be influenced or modulated by some common underlying mechanisms. Focus on individual risk component may provide scientific information for the future studies related to MetS. It helps to study the synergetic or potential effect of each component of MetS in development of its associated diseases such as type 2 diabetes mellitus and cardiovascular diseases.

4.2.1 Increased fasting blood glucose levels

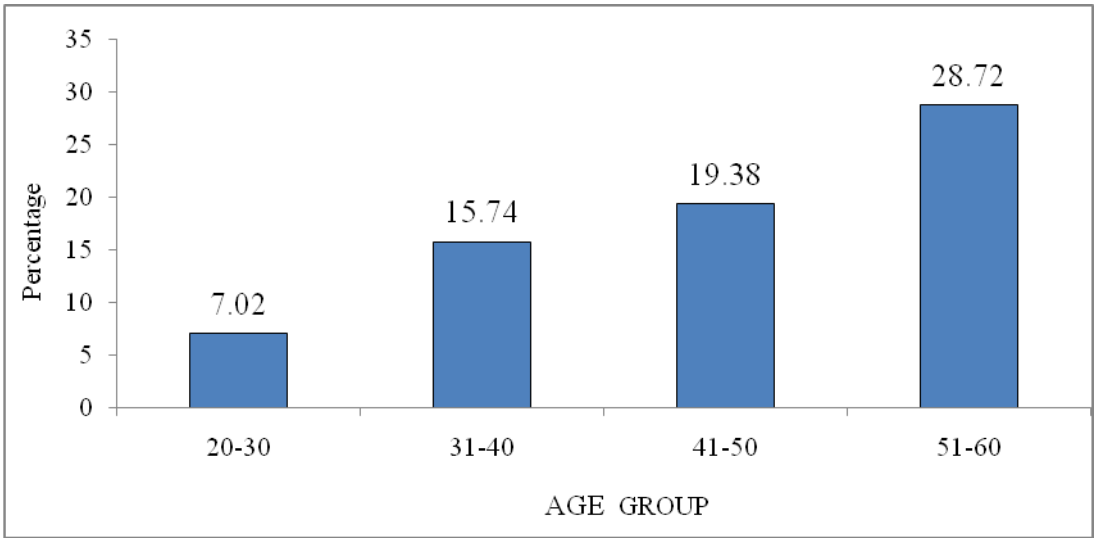
In this study total 15.21% of participants were with elevated fasting blood glucose levels (≥ 100 mg/dl). It is with in the South Asian prevalence range of elevated blood glucose (9.2% to 65.0%). The elevation was high in males: 16.92% compared to females: 12.92%. In contrast to our study, Zahid N et al. [137] Ravikiran M et al. [132] and Prasad Ds et al. [128] reported highest prevalence of elevated blood glucose in females than males.

The NFHS-IV (2015-2016) has reported that dysglycemia (Random blood glucose > 140 mg/dl) is higher in males: 15.70% compared to females: 13.10% of Andhra Pradesh [138]. This is in accordance to our results. The survey has also noted highest prevalence of dysglycemia in males of Andaman Nicobar (26% vs. 14.15%) followed by Goa (19.60% vs. 14.10%), West Bengal (17.30%) and Tamil Nadu -TN (15.30% vs. 11.70%). Interestingly, the females of Telangana (previously a part of AP) have least prevalence of dysglycemia compared with females of Andhra Pradesh (10.00% vs. 13.10%).

In this study total 11.72% of participants were with personnel history of diabetes mellitus and 9.39% were with family history of diabetes mellitus. Mean fasting blood glucose was 89.77 (± 20.19). It was increased with increase in age, it was 84.33 (± 12.61) in 20 - 30 years of age then it increased from 89.12(± 13.45) to 94.79 (± 31.48) between 31 - 40 and 41 - 50 years of age and reached to peak level 96.57 (±

24.49) by the age of 51 - 60 years. The proportion of participants with elevated blood glucose levels increased from 7.02% to 28.72% between 20 - 30 years to 51 - 60 years of age respectively. Age is significantly associated (p = < 0.0001; chi-square - 35.492) with elevated blood glucose [Figure 6].

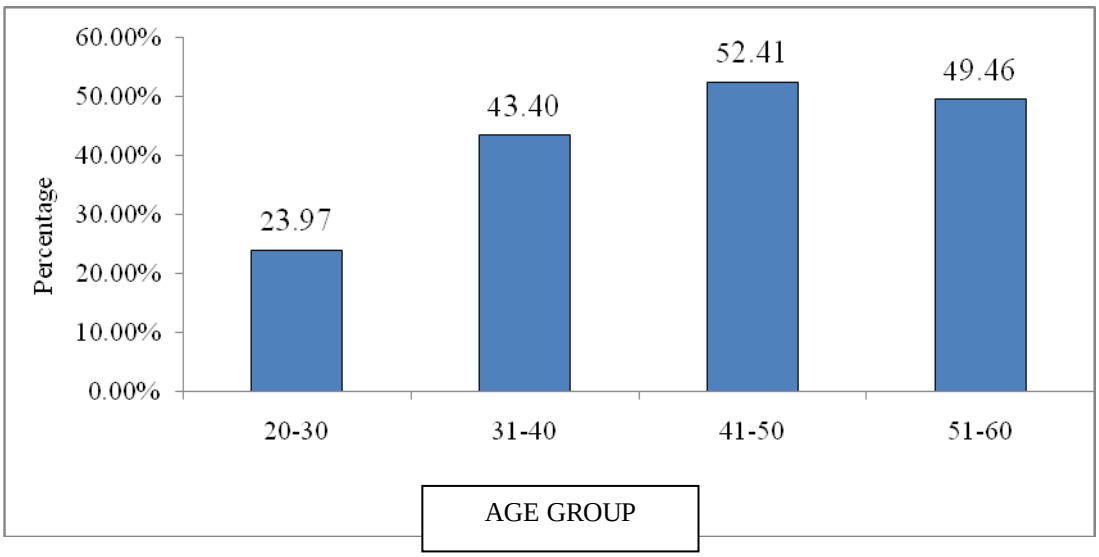
Figure 6 Percentage of participants with elevated blood glucose by age.



According to ATP III guidelines, diabetes mellitus is considered as Coronary Heart Disease (CHD) risk equivalent [139]. Luis et al. found that risk for development of diabetes mellitus is 49 % higher if fasting blood glucose is > 90 mg/dl while it is only 4.0% if fasting blood glucose is > 85 mg/dl [140]. Higher fasting blood glucose in normoglycaemic state will increase the risk of MetS and related co-morbidities [141]. Our observation from this study shows nearly half (44.18%) of the participants were with fasting blood glucose levels between > 90 mg/dl to < 100 mg/dl. Among them 52.70% of participants were with MetS, and this number is increased up to 50 years of age later it was decreased [Figure 7].

The decrease in the number of participants with higher fasting blood glucose after the age of 50 years can be explained as most of them may enter into hyperglycaemic state (≥ 100 mg/dl). The previous studies have proved that the progression of diabetes mellitus is positively correlated with baseline fasting blood glucose levels [142,143,144].

Figure 7 Percentage of participants with MetS at normal glycemic state.



Presence of one MetS component in normoglycaemic individual may precede him to type 2 diabetes mellitus and CVD in coming 10 years [145]. Some studies have also reported that it takes 5 - 7 years [142,143].

In our study total 47.57% of participants were normoglycaemic and without MetS. Among them 92.94% were with abdominal obesity, 93.58% were with decreased HDL-C and 77.56% were with increased triglycerides. This is very undesirable because presence of metabolic syndrome components at normoglycaemic state can also lead to diabetes related complications like retinopathy [145,146], cardiovascular diseases [147,148,149], cancer [150,151], and renal diseases [152].

This gives an impression that population of Kurnool district were at greater risk, they may have CVD even their glycemic status is maintained at normal level. It needs further attention to find the causes behind this scenario.

It can be explained by hyperinsulinemia, in which insulin secretion by beta cells attempts to offset the glucose load and varying degree of insulin resistance, keeping blood glucose level in the normoglycaemic range [153].

4.2.2 Changes in lipid levels

Individuals suffering with MetS, obesity, insulin resistance and type 2 diabetes mellitus are most commonly with Dyslipidemia. It is referred as an elevation of either or both plasma cholesterol and triglycerides, or decreased HDL-C levels [154,155]. Hence, it is also referred as either dyslipidemia of MetS or diabetic dyslipidemia, which is a CVD risk factor [156,157].

In our study we identified decreased HDL-C (78.87%) and increased triglycerides (31.78%) as major contributors for dyslipidemia in Kurnool district population. The reverse is noted by Onkar et al., elevated triglycerides (73.6%) and decreased HDL-C (19.4%) in Jammu. In contrast, Pandya et al. has identified elevated triglycerides and low density lipoprotein cholesterol (LDL-C) as major contributing lipids for dyslipidemia in Gujarat, India [159].

Table 9 is showing stratification of participants according to ATP III lipid reference guidelines. The data has shown an interesting finding, total 94.47% of participants were with desirable serum cholesterol levels. Decreased HDL-C was present in 56.06% of participants followed by equal prevalence of elevated TG and LDL-C (31.97% and 31.68%).

It was very unfavourable lipid profile pattern. This abnormal lipoprotein trait in Kurnool district population deserves close clinical attention and management. Since multivariate analysis revealed that presence of this type lipid pattern is a greatest independent risk factor for coronary heart disease [35].

Table 9 Classification of participants based on their lipid levels according to modified NCEP ATP III guidelines.

Lipid variable	Classification	Number	Percentage (%)
Total cholesterol	< 200-desirable	975	94.47
	≥ 200	57	5.52
HDL-Cholesterol	< 40	704	56.06
Triglycerides	< 150-normal	702	68.02
	≥ 150 high	330	31.97
LDL-cholesterol	< 100 optimal	701	67.92
	100-129	241	23.35
	≥ 130 very high	86	8.33

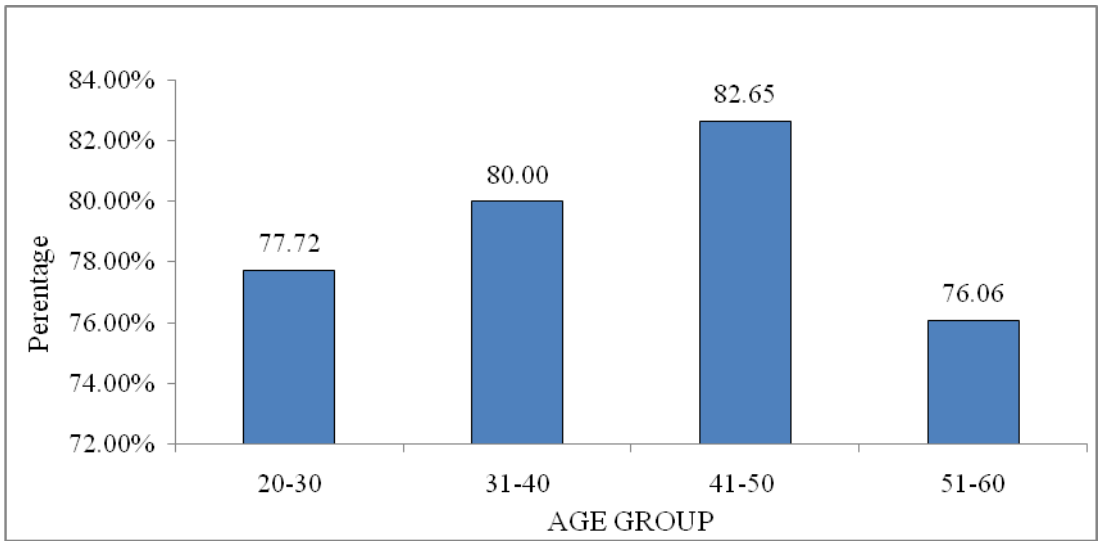
ATP= Adult Treatment Panel

In this population mean HDL-C levels were below normal reference range (37.52 ± 6.19). Males were having slightly lower mean 37.18 (± 5.94) compared to females 38.16 (± 6.41). Similar is noted by Zahid et al. [137]. In contrast, Chakrawarthy et al. [160], Gupta R et al. [161], and Prabhakaran et al. [162] have noted higher mean of HDL-C in males than females.

This can be explained by the fact that several factors those can influence HDL-C levels and CVD risk were more common in males compared to females. These include gender [163] smoking [164] and MetS [165]. Decreased HDL-C levels were highly (82.65%) prevalent in 41 - 50 years of age later it was decreased to 76.06% [Figure 8].

There is no statistically significant age wise difference in prevalence of decreased HDL-C. This might be due to most of the participants were from low to middle socio economic background. Lower socioeconomic back ground is an independent risk factor for decreased HDL-C. In Pakistan, Zahid N et al. reported decreased HDL-C levels in younger age group i.e. 20-40 years [137]. Sawant A et al. [110] Gupta R et al. [124] have also reported high prevalence of decreased HDL-C in younger age (> 40 years). In 2012, Gupta R et al. again reported highest prevalence decreased HDL - C in females at age of 30-39 years and it was 40-49 years in males [161].

Figure 8 Percentage of participants with decreased HDL-C levels by age

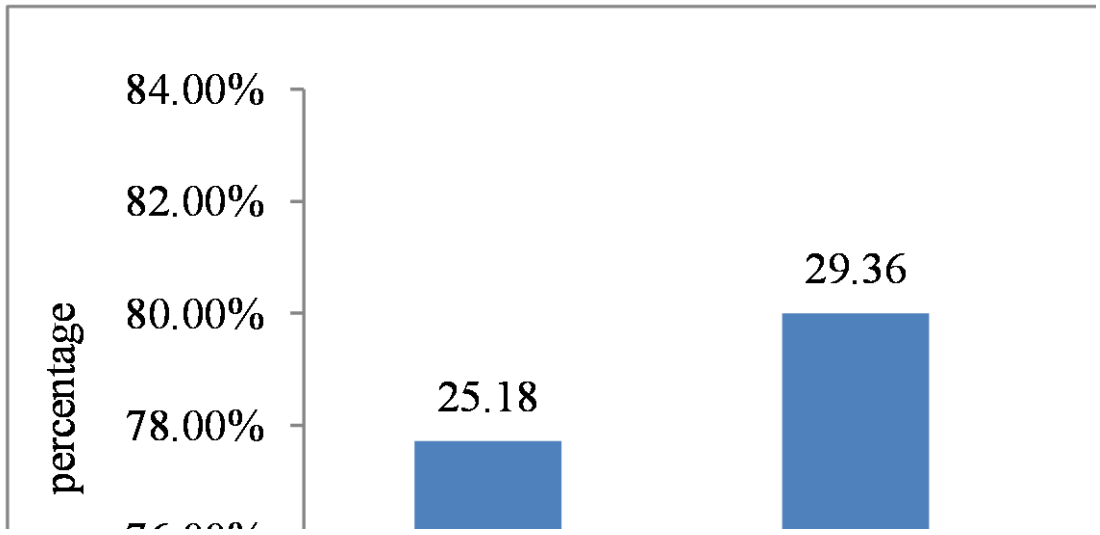


HDL-C = high density lipoprotein

It is well established that decreased HDL-C itself is a marker for CVD [166]. We have observed that overall 78.87% of subjects were with decreased HDL-C. It was high in females (88.36%) than males (71.62%). In contrast Lee S et al. have noted higher prevalence of decreased HDL-C in males: 59.0% compared to females: 31.3% [121]. Our results were in accordance to Asian pacific range of decreased HDL-C (31.60% to 79.60%) [159,137]. But it is above the mean south Asian prevalence of decreased HDL-C i.e. overall: 57.90%, male: 37.20%, and female: 68.80% [106].

Mean fasting triglyceride levels were within normal reference range (137.27± 27.67). Slightly higher mean was noted in males (141.05 ± 27.09) than females (131.05 ± 27.82). With a slight marginal difference, participants between 20-30 and 31 - 40 years of age were shown similar mean (130.75 ± 24.88 and 136.67 ± 26.22). Participants between 41 - 50 and 51 - 60 years of age were also shown same mean (143.65 ± 29.65 and 143.00 ± 31.05). Statistically significant difference in fasting triglycerides was noted between the participants with the age of < 40 and ≥40 years. We found high prevalence of hyper triglyceridemia between 51-60 year aged participants [Figure 9].

Figure 9 Percentage of participants with elevated triglycerides by age



Hyper triglyceridemia is an independent predictor of coronary heart disease (CHD). Individual with elevated triglycerides (> 200 mg/dl) had six times higher CHD risk [167]. In South Asia, prevalence of hyper triglyceridemia is only 25.20% and there is no significant gender difference (males: 37.20%; females: 36.10%). Contrast to this, in our study total 31.78% of participants were with elevated fasting triglyceride levels (> 150 mg/dl) and significant gender difference was noted between males 38.29% and females 23.26%.

Lee S et al. reported 80.83% prevalence of hyper triglyceridemia in Korean population and there is no significant gender difference (males: 83.50 % and females: 79.30%) [121]. Higher prevalence of hyper triglyceridemia in Korean population may attribute to higher carbohydrate diet. High prevalence of hyper triglyceridemia in males of our study can be explained by presence of behavioural (habitual) and physiological risk factors such as smoking, alcohol, less physical activity and elevated fasting blood glucose in them compared to females [168]. In contrast, Ravi K et al., Jahid et al. and Sankar S et al. have noted higher prevalence of hyper triglyceridemia in females than males [126,137,169].

Another explanation for this is higher prevalence of insulin resistance in South Asian adults [170,171], particularly in males due to high visceral adiposity and lack of effect of estrogen like females [172]. Insulin resistance is associated with elevated

triglyceride levels [173]. Most of the South Indian studies have reported elevated triglyceride levels as a common cluster risk factor for MetS. The other possible reasons for higher lipid abnormalities may be:

1. Higher fasting blood glucose levels. Onkar et al. found that the presence lipid abnormalities will depend on their glycemic status [174].
2. Cutoff points to HDL-C in males and females (< 40 mg/dl vs. < 50 mg/dl). The reason could be that, the values are average for above 50 years of age group. NCEP criteria might consider this type of dyslipidemia as life time risk factor in all ranges of population. Because even a mild abnormality either in triglycerides or HDL-C level is present, when it form cluster with any other MetS, it will become an important indicator of high risk [175].

Surprisingly the prevalence of low HDL-C levels was decreased after the age of 50 years while elevated triglycerides has not shown any significant change. This could be due to by this age the individuals with these metabolic defects might have been aware of their condition and followed preventive measures. The study has also observed most of the subjects at this age group informed well about their condition and the medication they are following.

4.2.3 Increased blood pressure

The mean systolic (SBP) and diastolic (DBP) blood pressures were in allowable limit (122.17±7.44 and 81.49±4.23). Surprisingly both males and females reported to have similar mean of SBP and DBP (122.97 ± 7.08 vs. 120.94±7.57 / 81.72±4.07 vs. 81.15±4.33). Total 28% of participants were having elevated blood pressure. Among them 22.57% participants were with elevated SBP and 18.70% were with elevated DBP [106]. Elevated blood pressure was highly prevalent in males (32.47%) than females (24.16%).

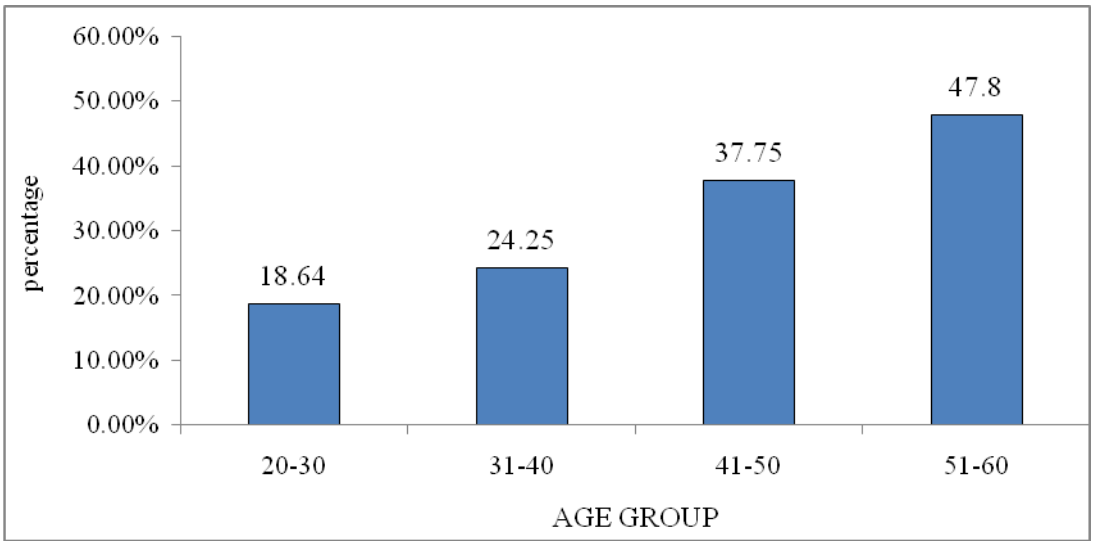
Prevalence of elevated blood pressure in South Asia ranges from 21.20% to 81.10% [162,176] and mean prevalence was 48.50%, it was high in males 42.30% compared with females 38.10%. In contrast, Manoj KS et al. reported 36.50% of elevated blood pressure in population of Nellore district in Andhra Pradesh and it was high in females 47.00% than males 29.76% [177]. PS Singh et al. has also reported 17% of

elevated blood pressure in central India, it was high in females; 18.30% than males: 15.80% [178].

Joshi et al. Chockalingam S et al., Vasan RS et al., and Player MS et al., have reported highest prevalence of elevated blood pressure in older age [179, 180,181,182]. Our study was also noted highest prevalence (47.87%) of elevated blood pressure between 51 - 60 years age [Figure 10]. This age associated increase in blood pressure may attribute to vascular changes taking place in an individual as the age advances.

This can also be explained by age related alterations in trends of MetS components such as blood glucose, decreased HDL-C and increased TG among this population. As per Joint National Committee for Hypertension (JNC) 2004 guidelines, systolic blood pressure between 120 - 139 mmHg and diastolic blood pressure between 80 - 89 mmHg is considered as cardiovascular risk factor [183].

Figure 10 Percentage of participants with elevated blood pressure.



The most recent National Family Health Survey (NFHS - 4 in 2015 - 2016) reported that 13.60 % males and 8.80 % females of India were with elevated blood pressure (SBP ≥ 140 mm / Hg; DBP ≥ 90 mm/Hg). The survey also reported that 16.30% males and 9.50% females of Andhra Pradesh were with elevated blood pressure. This is in concordance to our study. The survey reported total 27.90% of males residing in Andaman Nicobar are having elevated blood pressure which is comparable to the

prevalence among females of this study. The highest prevalence in females is noted in Sikkim (16.50%) which is very low when compared to our study results. The people of Bihar have shown lowest prevalence of elevated blood pressure both in male (9.40%) and females (5.90%). An interesting finding is that Telangana (previously a part of AP) has more prevalence of HTN i.e., 18.20% in males compared to AP and marginally similar prevalence was noted in females (Telangana: 10.10 % vs. AP: 10.00 %) [138].

The highest prevalence of elevated systolic blood pressure and its association with age can be explained by central arterial stiffening and decreased cardiac function with age. In contrast, DBP declines after sixth decade of life in normotensives [184].

Gender difference in the prevalence of elevated blood pressure can be explained by the protective role of some biological factors such as sex hormones and chromosomal differences protecting against elevated blood pressure in females. These factors become very prominent in adolescence and persist throughout adulthood until females reach menopause [185,186]. Presence of behavioural risk factors for elevated blood pressure such as higher smoking and low physical activity, elevated fasting blood glucose may also responsible for elevated blood pressure in males [187].

4.2.4 Obesity

In past 10 years obesity has been doubled in India. Even though India is facing malnutrition, the country has developed another nutritional problem called over-nutrition or obesity. Obesity is generally classified as generalized obesity (GO) and abdominal obesity (AO) [188]. In India, total 135 million are suffering from generalized obesity (AO); 153 million are from abdominal obesity (AO) and 107 million people are suffering from combined obesity (CO) [188].

Obesity is strongly associated with metabolic disorders such as insulin resistance and metabolic syndrome. These metabolic disorders are the main culprits for development of diabetes, cardiovascular diseases and even cancer. The risk for these disorders appears to start at very low BMI (21 kg/m^2).

However, presence of abdominal obesity defined by increased waist circumference is highly correlated with these metabolic disorders than an elevated generalized obesity defined by increased body mass index (BMI) [188, 189].

Based on waist circumference (WC), total 57.84% participants were with abdominal obesity (mean: 87.92 ± 9.11). An interesting finding is that abdominal obesity was highly prevalent in females: 65.32% than males: 52.13% whereas mean WC is very high in males (89.78 ± 8.16) compared to females (85.18 ± 9.59). Most of the studies have reported higher mean WC in females. Sahoo et al. reported higher WC in females of North India, it may attribute to the presence of more overweight and obese females with higher BMI in their study [190]. Ahranjani et al. also noted the same in females of Iran country this could be the consequence of their less active role in society by comparison with men [191]. In contrast, Zahid et al. reported higher mean WC in males compared to females [137].

Based on BMI, total 56.49% of participants were with generalized obesity (mean: 25.72 ± 4.42). Several Indian studies have reported higher prevalence of generalized obesity in females [192-196]. NFHS-4 has reported higher prevalence of generalized obesity in females of Kurnool district than males (33.5% vs. 14.8%). Our study has also noted higher prevalence of generalized obesity in females: 73.60% than males: 58.55%. Both males and females have shown exactly same mean of BMI (25.94 ± 4.22 and 25.28 ± 4.59). These findings demonstrate a significantly higher prevalence of generalized and abdominal obesity in females than males among the population of Kurnool district.

We have identified disparities in the prevalence of generalized and abdominal obesity by age and gender.

As the age increases, abdominal obesity was increased in females. But in males it reached peak at 30 - 40 years of age and then declined with age [Figure 11].

Whereas, generalized obesity in both males and females reached peak at the age of 41 - 50 years and then it was equally prevalent in later age [Figure 12].

The study has also identified that abdominal obesity was slightly higher than generalized obesity (57.54% vs. 55.51%). Deepa et al. has reported higher abdominal

obesity than generalized obesity in Chennai (46.6% vs. 45.9%) [197]. Bharadwaj et al. also reported the same from urban New Delhi (68.90% vs. 50.10%) [198].

Figure 11 Percentage of participants with elevated WC by age and gender

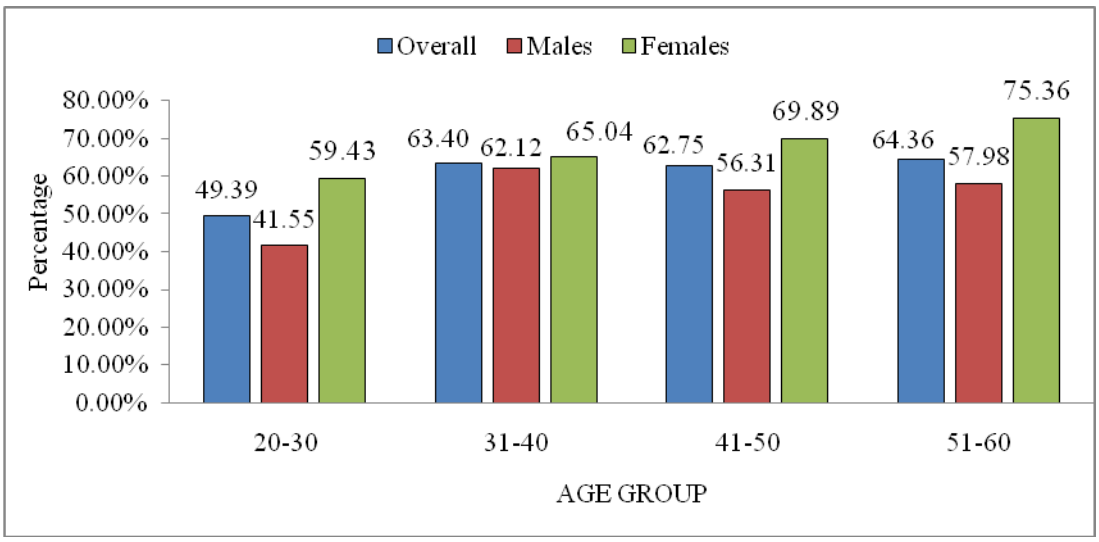
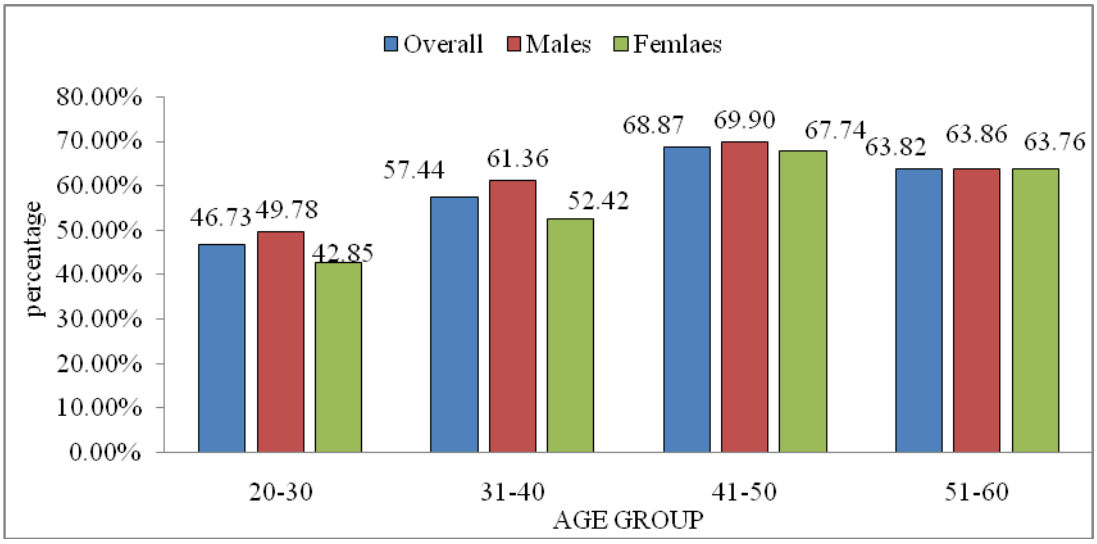


Figure 12 Percentage of participants with elevated BMI by age and gender



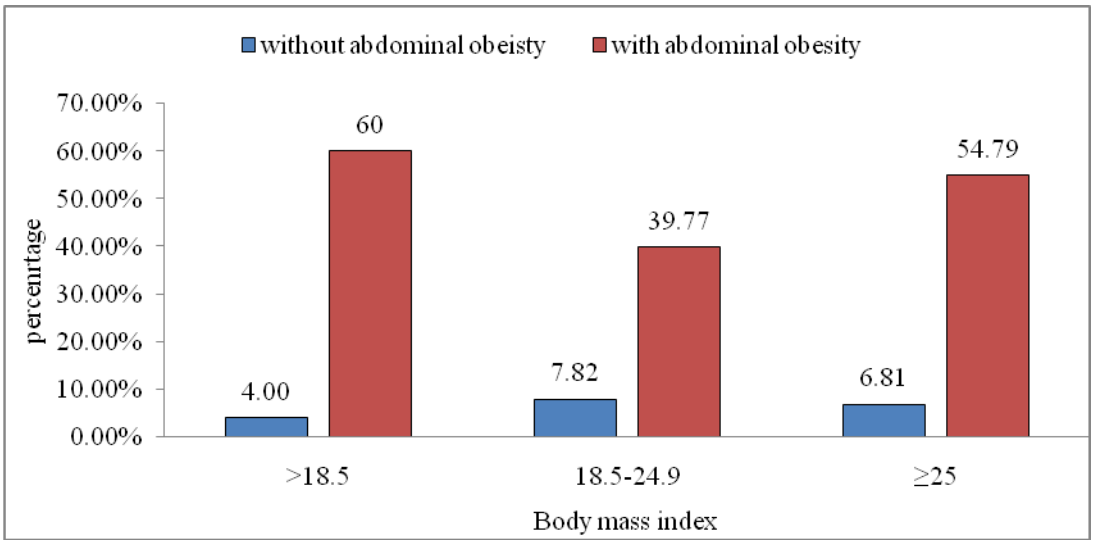
At the age < 40 years 45.67% males were with higher abdominal obesity compared to females 22.44%. It was reversed by > 40 years of age; females have shown higher abdominal obesity 43.24% than males 22.45%. The chance for the development of abdominal obesity in females is more compared to males at same BMI [199]. This gives an impression that males in Kurnool district may develop abdominal obesity in younger age (< 40years). In contrast, females will develop abdominal obesity after

40 years of age. This could be one of the reasons for higher prevalence in females after the age of 40 years than males.

This can be explained by higher visceral adipose tissue (VAT). In males at any degree of body fat free fatty acid (FFA) turnover is high in VAT compared to females. Instead, females have higher rates of FFA uptake in peripheral tissue rather than visceral adipose tissue. As the age increases in females particularly in menopause transition, preferential increase of abdominal fat will shift them to visceral adiposity [200,201]. These results are in accordance with findings of Kautzky W et al. [202].

We tried to establish the relationship between abdominal obesity (WC), generalized obesity (BMI) and the prevalence of MetS [Figure 13]. For this the subjects were divided into two groups' 1.With abdominal obesity 2.Without abdominal obesity. The prevalence of MetS compared in these two groups based on their BMI. It has shown that there is no significant effect of BMI on prevalence of MetS among the individuals without abdominal obesity.

Figure 13 MetS among the participants with and without abdominal obesity



In contrast, several studies [203-207] have shown a significant effect of BMI on MetS among the individuals without abdominal obesity. However, when compared based on the existence of abdominal obesity, it has shown that the subjects with

abdominal obesity had higher prevalence of MetS with same BMI. The result is in accordance to Grundy et al. [208] and Huang KC et al. [209].

The subjects with less BMI (< 18.5) and abdominal obesity have shown 60% prevalence of MetS. This is very high compared to the individuals with elevated BMI (≥ 25) and abdominal obesity (54.79%). Our finding is in accordance with Smith et al. [210]. These individuals may have visceral adiposity and high insulin resistance. It may cause high prevalence of MetS among them. This gives an impression that presence of abdominal obesity alone can precede the individual to develop MetS in population of Kurnool district. Therefore, the population of Kurnool district who are centrally obese must be screened for MetS even the body weight is normal.

4.3 Comparison of metabolic syndrome in urban, rural and tribal population

Most of the Indian studies have focused on prevalence of MetS either in urban or rural population [211, 212,213]. Only few studies have focused on both urban and rural population [125, 214,215,216]. However, there are no studies on disparities in the prevalence of MetS among urban, rural and tribal population of a geographical area. One of the objectives of this study is to evaluate the prevalence of MetS among urban, rural and tribal population. For this 344 subjects were screened for MetS in each group.

Table 10 is showing clinical characteristic of urban, rural and tribal participants. Behavioural and physiological cardiovascular risk factors were highly prevalent in rural than urban and tribal participants.

Behavioural risk factor such as smoking was highly prevalent in urban participants (30.81%), while alcohol consumption (27.03%) and habit of chewing (12.79%) were highly prevalent in rural participants. Habit of chewing was very in tribal (7.55%) than urban (1.74%) participants.

Physiological risk factor such as family history of type 2 diabetes mellitus was highly prevalent in rural (11.91%) than urban and tribal (8.13% vs. 8.13%) participants while personal history was almost equally prevalent between urban and rural: 13.95% vs. 13.37% ($p=0.8248$; $\chi^2=0.049$). Family history of hypertension was equally prevalent between urban and rural participants: 7.84% vs.7.55% ($p=0.8866$; $\chi^2=0.020$) while personal history was high in urban (23.83%) than rural and tribal participants.

The data give an impression that rural population were with urban population in respect of cardiovascular risk factors, while tribal population were with rural population.

Table 10 Clinical characteristics of urban, rural and tribal participants

VARIABLE		URBAN	RURAL	TRIBAL
Number of participants		344	344	344
Gender	Male	208 (60.46%)	205 (59.59%)	172 (50.00%)
	Female	136 (39.53%)	139 (40.40%)	172 (50.00%)
Education level	Illiterate	115(33.43%)	126 (36.62)	162(47.09%)
	Up to secondary	127 (36.91%)	158 (45.93)	131 (38.08%)
	Above secondary	102 (29.65%)	60 (17.44)	51 (14.82%)
Cigarette smoking		106 (30.81%)	82 (23.83)	45 (13.08%)
Alcohol consumption		87 (25.29%)	93 (27.03%)	45 (13.08%)
Habit of tobacco chewing		6 (1.74%)	44 (12.79%)	26 (7.55%)
Family history (FH) of DM		28 (8.13%)	41 (11.91%)	28 (8.13%)
Family history of hypertension		27 (7.84%)	26 (7.55%)	9 (2.61%)
Personal history of DM		48 (13.95%)	46 (13.37%)	27 (7.84%)
Personal history of HTN		82 (23.83%)	41 (11.91%)	11 (3.19%)

DM= type 2 diabetes mellitus; HTN=hypertension; n= number of subjects with related variable; %= percentage

Table 11 is showing comparison (ANOVA) of anthropometric and biochemical parameters by in urban, rural and tribal participants. Statistically significant (p= 0.001) difference is observed in all the variables among urban, rural and tribal population, except body mass index (BMI). Comparison between urban and rural populations has shown no significant difference in all the variables except waist circumference and HDL-C (p=<0.0001). When compared between rural and tribal population except waist circumference (p=0.4511), remaining all the variables were shown significant difference. The mean systolic and diastolic blood pressures and fasting blood glucose were in permissible limits. The mean BMI was towards overweight range in urban, rural and tribal participants. The mean HDL-C was below the normal reference range in urban, rural and tribal populations.

Table 11 Mean (±SD) biochemical and anthropometric parameters of urban, rural and tribal participants.

VARIABLE	URBAN n=344	RURAL n=344	TRIBAL n=344
Waist circumference (cm)	91.04 ± 5.39 (68 - 117)	85.87 ± 11.96 (52 - 117)	86.45 ± 7.78* (60 - 110)
Body mass index (kg/m^2)	26.05 ± 3.61 (17.71- 42.01)	25.88 ± 5.05 (17.72- 45.02)	25.03 ± 4.35 (16.44 - 38.10)
Systolic blood Pressure (mmHg)	122.31 ± 9.21 (92 - 150)	122.97 ± 6.97 (96 - 146)	121 ± 5.25* (110 - 140)
Diastolic blood pressure (mmHg)	81.58 ± 4.30 (72 - 94)	82.22 ± 4.46 (74 - 96)	80.64 ± 3.63* (74 - 90)
Fasting blood glucose (mg/dl)	93.06 ± 16.86 (65 - 186)	90.65 ± 27.76 (68 - 440)	85.20 ± 13.88* (70 - 154)
Serum triglycerides (mg/dl)	142.68 ± 29.13 (73 - 281)	142.49 ±26.08 (32 - 272)	125.16±24.41* (32 - 196)
Serum HDL-C (mg/dl)	34.37 ± 4.34 (23 - 52)	38.56 ± 6.64 (23 - 80)	39.87 ± 6.08* (28 - 54)

*P value calculated by ANOVA, * indicates p= <0.05 statistically significant.

Some interesting findings observed are:

1. Tribal participants have shown slightly higher mean of WC compared to rural participants (f=1.193; p=0.10342).
2. The mean systolic blood pressure (f=2.200 p=<0.001) and triglycerides (f=1.248; p=0.0409) were equally noted in urban and rural participants while diastolic blood pressure was observed to be high in rural participants.

Table 12 is showing prevalence of metabolic syndrome by age, and gender among the three groups. We have identified higher prevalence of metabolic syndrome in urban population (42.15%) than in rural population (31.97%) and tribal population (21.80%). However, previous studies have noted prevalence of metabolic syndrome in India ranges between 28-36% in urban population and 18-30% in rural population [128,217,218,219].

Overall, metabolic syndrome was almost equally prevalent (using two sample t-test between percents) in males and females of urban participants: 41.82% vs. 42.64% (p=0.6964; χ^2=1.152; 95% CI -6.9908 to 10.4415); rural: 33.65% vs 29.93% (p=0.3908; χ^2 = 0.736; 95% CI -5.7003 to 14.6455) and tribal population: 20.93% vs 22.67% (p=0.8805; χ^2=0.023; 95% CI -9.76723 to 11.4397).

Table 12 Crude standardized prevalence of metabolic syndrome in urban, rural and tribal participants by age and gender

Age group (year)	URBAN n/N	%	RURAL n/N	%	TRIBAL n/N	%
Overall						
20 – 30	37/133	27.81	28/124	22.58	26/156	16.66
31 – 40	30/80	37.50	25/87	28.73	14/68	28.58
41 – 50	32/63	50.79	31/80	38.75	17/53	32.07
51 – 60	46/68	67.64	26/53	49.05	18/67	26.86
Crude Standardized	145/344	42.15	110/344	31.97	75/344	21.80
Male						
20 – 30	23/83	27.77	17/71	23.94	12/77	15.58
31 – 40	22/51	43.13	16/48	33.33	6/33	18.18
41 – 50	15/34	44.11	19/49	38.77	7/20	35.00
51 – 60	27/40	67.50	17/37	45.94	11/42	26.19
Crude Standardized	87/208	41.82	69/205	33.65	36/172	20.93
Female						
20-30	14/50	28.00	11/53	20.75	14/79	17.72
31-40	8/29	27.58	9/39	23.07	8/35	22.85
41-50	17/29	58.62	12/31	38.70	10/33	30.30
51-60	19/28	67.85	9/16	56.25	7/25	28.00
Crude Standardized	58/136	42.64	41/139	29.49	39/172	22.67

N= total number of subjects; n= number of subjects with metabolic syndrome; %=percentage

The South Asian mean prevalence of MetS in urban and rural areas is 38.8% and 11.6% respectively. In urban South Asia, MetS is highly present in males compared to females (42.9% vs. 34.6%), while it is equally prevalent in rural South Asian males and females (11.7% vs. 11.6%). Ahonen et al. [220] and Y He et al. [221] have reported higher prevalence of MetS in females than males; the reverse is noted by Njelekela et al and Fezeu et al. [222, 223].

The National Cardiovascular disease data [224], Misra et al. [225] and Ramachandran et al. [226] have reported higher prevalence of MetS in urban residents than rural. They also reported MetS is highly prevalent in females than males. In contrast, Sarkar et al. reported no rural-urban difference in prevalence of metabolic syndrome in Bhutia tribes [227]. Xu S et al. reported no significant difference in prevalence of MetS in urban and semi urban residents of China [75].

The epidemiological studies reported higher prevalence of MetS in rural residents than urban residents [205,214,215,216].

These differences can be attributed to the differences in geographical area, participant's age and criteria used to screen the metabolic syndrome.

On comparison of our study results with other studies, it has been observed that, the tribal population of our study has lesser prevalence (21.80%) of MetS compared to Bhutia: 39.20% [228] and Kennavam tribes: 28.30 % [229]. Ashari et al. reported 17% of MetS in Malaysian tribes (males: 21.80% vs. females: 5.80%) [230]. Disparities in prevalence of MetS may be attributed to the criteria used for diagnosis MetS. He also reported 63.60% higher prevalence of MetS in Oran Kanaq sub tribes. The other sub tribes Che-Wong: 8.50%, Kensiu: 16.40%, Lenou: 12.50% have lesser prevalence of MetS than tribal population of our study.

The previous studies by Thomas F et al. and Vishram JK et al. have reported significant influence of age and gender on prevalence of MetS respectively [231, 232]. The prevalence of MetS increases with age [233, 234]. We have compared the disparities in the prevalence of MetS by age and gender among the urban, rural and tribal population of Kurnool district.

The data of table 12 has been depicted in figures from 14 to 16.

Disparities in the prevalence of MetS by age

1. Irrespective of gender, highest prevalence of MetS in urban and rural participants is noted at 50 - 60 years of age.
2. Contrast to this, tribal population have shown highest prevalence of MetS at 40 - 50 years of age later slightly declined in both the genders.

Disparities in the prevalence of MetS by age, gender and geographical area

1) Between the 20 - 30 years, urban participants have shown equal prevalence of MetS both in males and females.
2) Contrast to this slight gender disparity is noted among rural and tribal population at the same age group. In rural area males have shown higher prevalence of MetS

than females while in tribal females are slightly dominating males in the prevalence of MetS.

3) Between 31 - 40 years of age, all the three groups have shown gender disparity in the prevalence of MetS. In urban and rural participant, males have dominated females while in tribal population females have dominated males.

4) Between 41 - 50 years of age, females have shown a sudden raise the prevalence of MetS and dominated males in urban population. The rural population in this age group shows equal dominance whereas males have dominated females in the tribal population.

5) Females have shown further increase of MetS between 51- 60 years of age. By this age prevalence of MetS is equally reported in male and female participants of urban area while females have dominated males in rural and tribal population.

Figure 14 Disparities in the prevalence of MetS in urban participants by age

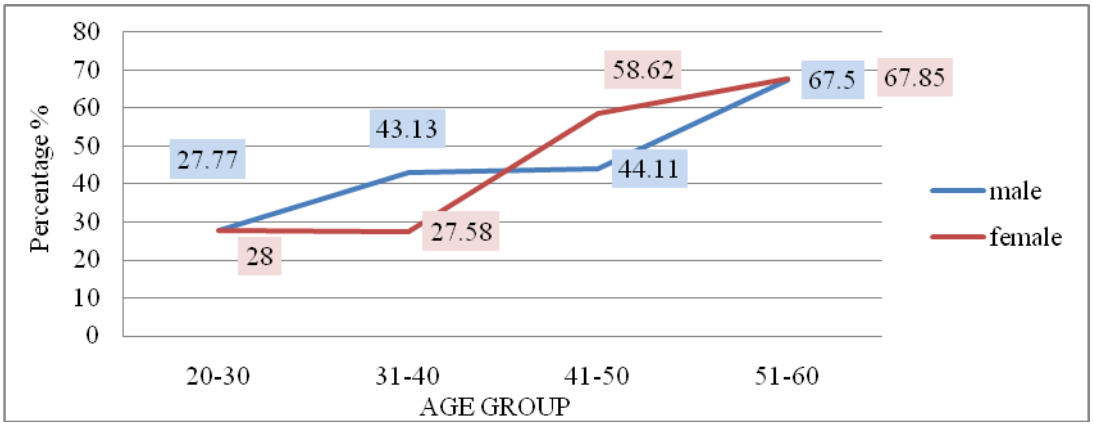


Figure 15 Disparities in the prevalence of MetS in rural participants by age

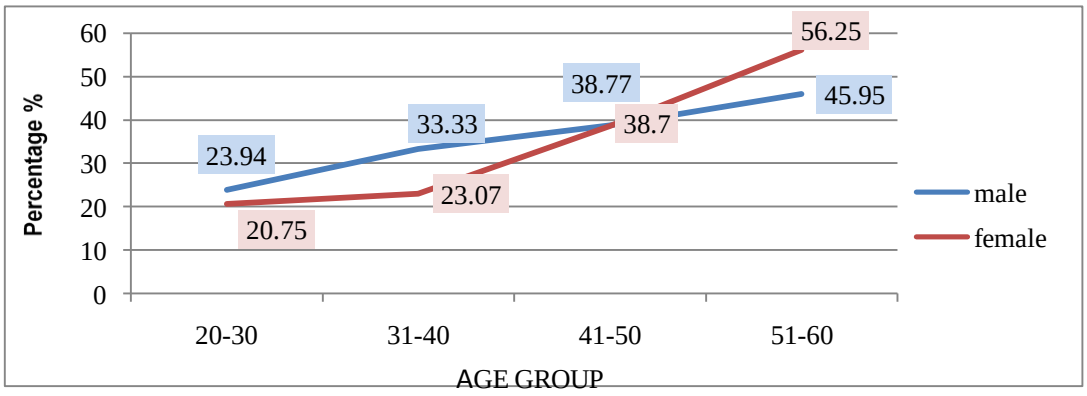
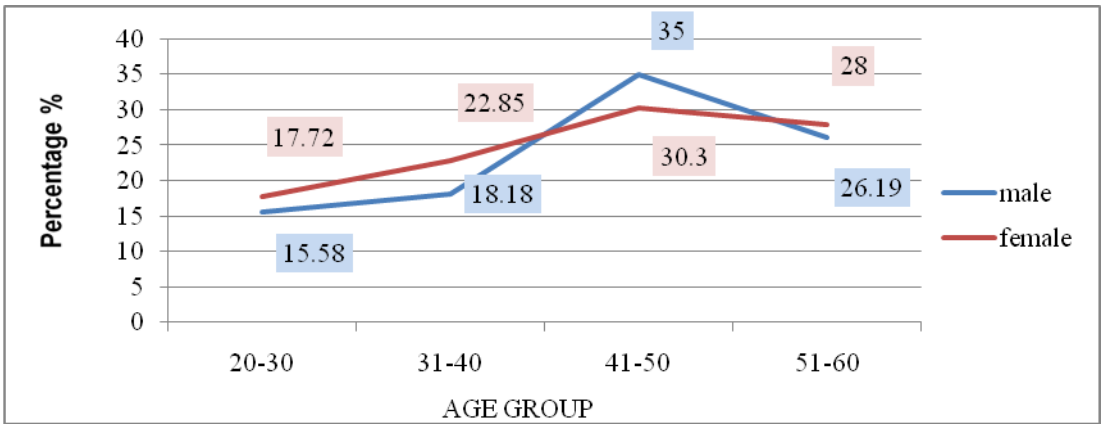
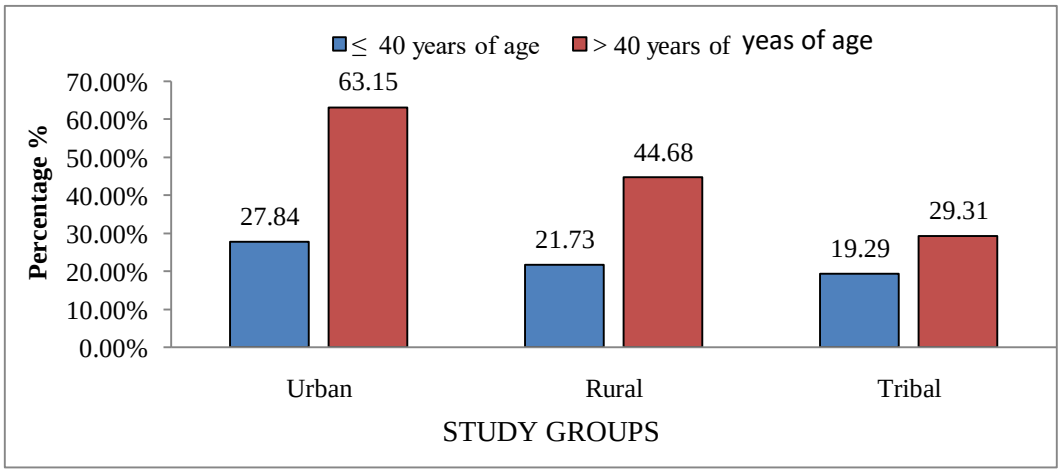


Figure 16 Disparities in the prevalence of MetS in tribal participants by age



The increase in prevalence of MetS after 40 years of age in females can be explained by postmenopausal state. Post-menopausal age is considered as an important period for development of MetS. According to Indian menopause society, in Indian women menopause starts after the age of 40 years (45.59 ± 5.59) [235]. In view of above findings the female participants were classified based on their age into ≤ 40 years and > 40 years, can be considered as premenopausal and menopausal age[Figure 17].

Figure 17 Disparities in prevalence of MetS in females at the age ≤ 40 and > 40 years.



The important observations include:

1. Irrespective of geographical area, after 40 years of age, females have shown an elevation in the prevalence of MetS. Almost two fold elevation has been observed in urban and rural population.

2. At below 40 years of age, the females of rural: 21.75% and tribal: 29.31% population has shown almost equal prevalence of MetS.
3. After 40 years of age, the prevalence of MetS was observed to be highest in urban participants followed by rural and tribal population.

Previous studies have reported that prevalence of MetS in post-menopausal age ranges between 19.2% - 32.4% [236]. Our results are in accordance to Pandey S et al. [237] who reported prevalence of MetS as 45 % in premenopausal age and 55% in post-menopausal age in Mumbai. Figueiredo et al. reported higher prevalence of MetS in post-menopausal age compared to premenopausal age using NCEP criteria (24% vs. 44.4%) and IDF criteria (37% vs. 61.5%) in Brazil [238]. Sandeep S et al. reported 62.6% vs. 65.7% of MetS among the females of North India between 45 - 55 years of age [193].

Table 13 is showing prevalence of individual component of MetS by gender. Decreased HDL-C followed by increased WC and elevated triglycerides were identified as common preceding risk factors for Mets in urban, rural and tribal participants.

Gender disparities were noted in the prevalence of the above metabolic risk factors.

The most important disparities include:

1. Decreased HDL-C and increased WC are highly prevalent in females than males in all the three groups while increased triglycerides are more prevalent in male than in females in all the three groups.
2. The overall prevalence of lower HDL-C in rural and tribal population is 73.83% vs. 67.73% respectively.
3. But it has shown higher gender variation both in rural (males: 63.90% vs. females: 88.48%) and tribal population (males: 53.98% vs. females: 81.97%).
4. More than three fourth females are with decreased HDL-C levels in urban, rural and tribal population.

Table 13 Crude standardized prevalence of individual component of MetS by gender

Variable	URBAN n/N	%	RURAL n/N	%	TRIBAL n/N	%
Overall						
Increased fasting glucose	69/344	20.05	62/344	18.02	26/344	7.55
Elevated SBP	104/344	30.23	81/344	23.54	48/344	13.95
Elevated DBP	84/344	24.41	67/344	19.47	42/344	12.20
Increased TG	142/344	41.27	129/344	37.50	57/344	16.56
Decreased HDL-C	327/344	95.34	254/344	73.83	233/344	67.73
Larger waist circumference	255/344	74.12	179/344	52.03	163/344	47.38
Male						
Increased fasting glucose	43/208	20.67	42/205	20.48	14/172	8.13
Elevated SBP	66/208	31.73	56/205	27.31	30/172	17.44
Elevated DBP	52/208	25.00	41/205	20.00	25/172	14.53
Increased TG	95/208	45.67	88/205	42.92	41/172	23.83
Decreased HDL-C	196/208	94.23	131/205	63.90	92/172	53.48
Larger waist circumference	135/208	64.90	104/205	50.73	66/172	38.37
Female						
Increased fasting glucose	26/136	19.11	20/139	14.38	12/172	6.97
Elevated SBP	38/136	27.94	25/139	17.98	18/172	10.46
Elevated DBP	32/136	23.52	26/139	18.70	17/172	9.88
Increased TG	47/136	34.55	41/139	29.49	16/172	9.30
Decreased HDL-C	131/136	96.32	123/139	88.48	141/172	81.97
Increased WC	120/136	88.23	75/139	53.95	97/172	56.39

SBP= systolic blood pressure; DBP= diastolic blood pressure; TG=triglycerides; HDL= high density lipoprotein; WC= waist circumference; N=total number of subjects; n=number of subjects with related risk factor; %=percentage

5. Increased WC is more prevalent in tribal female than rural females (56.39 % vs. 53.59 %).
6. Elevated fasting blood glucose in rural population is in concur with urban population (20.05 % vs. 18.02 %)
7. Male participants of urban and rural area have shown equal prevalence (20.67 % and 20.48 %) of elevated fasting blood glucose

The recent studies have shown higher prevalence of metabolic abnormalities in rural and tribal population. Joshi R has found that decreased HDL-C is highly prevalent in rural population: 61.7% than urban population: 39.0% among the population of Jharkhand [239]. Ismail et al. found higher prevalence: 69.0% of decreased HDL in Kennavam tribal population [229]. The findings of Ismail et al. were in comparable with our study results but he has reported only 29.2% of increased WC. In contrast, we noted 38.37 % males and 56.39% of females are with increased WC, overall it is 47.38%. Kshatriya et al. demonstrated high prevalence of CVD and related risk factors in tribal communities of Orissa, West Bengal and Gujarat [240].

The metabolic abnormalities in rural and tribal population were in concurrence with urban population. It gives an impression that these populations were in transition state to urban lifestyle pattern.

Table 14 is showing classification of participants based on their age, gender and geographical area. The data has shown differences in the prevalence of MetS components by age, gender and area. An interesting finding is tribal population have shown decreased prevalence of all the MetS components after age of 50 years. This may be the reason for decreased of MetS in tribal population between 51 - 60 years of age.

This can also be explained by competing mortality or gradual loss (death) of the individuals with MetS or any other ethiology; still it is unclear and needs further prospective studies [241]. In contrast, Hildrum et al. has noted linear increase of MetS in both genders up to 90 years of age in Norwegian population [242].

Table 14 Overall disparities in the prevalence of MetS components by age, gender (males vs. females) and geographical area.

	Gr.	20 - 30 years	31 - 40 years	41 - 50 years	51 - 60 years
↑WC	Urban	71.42 (57.83 vs 94.0)	76.25 (70.58 vs 86.20)	74.25 (73.52 vs 75.80)	77.94 (65.0 vs 96.42)
	Rural	41.93 (35.21vs 39.62)	51.83 (62.5 vs 48.71)	60 (51.02 vs 74.19)	67.92 (64.86 vs 75.0)
	Tribal	40.38 (29.87 vs 50.56)	51.29 (48.48 vs 71.42)	45.73 (40.0 vs 60.60)	28.04 (21.42 vs 52.0)
↑SBP	Urban	15.03 (8.07 vs 10.0)	26.25 (27.45 vs 24.13)	39.63 (41.1 vs 37.93)	55.88 (57.5 vs 53.57)
	Rural	15.03 (5.49 vs 9.43)	22.98 (29.16 vs 15.38	28.75 (32.65 vs 22.58)	41.50 (40.54 vs 43.75)
	Tribal	3.97 (9.09 vs 8.86)	7.41 (9.09 vs 8.57)	14.54 (35.0 vs 12.12)	14.46 (16.66 vs 20.0)
↑DBP	Urban	15.03 (31.32 vs 22.0)	21.25 (21.56 vs 24.13)	34.92 (32.35 vs 37.93)	36.76 (42.5 vs 28.57)
	Rural	9.45 (4.22 vs 15.09)	28.75 (30.61 vs 25.80)	17.24 (22.91 vs 10.25)	33.96 (32.43 vs 37.50)
	Tribal	10.25 (11.68 vs 8.86)	6.41 (6.06 vs 8.57)	16.32 (25.0 vs 18.18)	6.49 (11.90 vs 4.0)
↑TG	Urban	27.81 (31.32 vs 22.0)	35.0 (43.13 vs 24.13)	49.20 (50.0 vs 48.27)	66.17 (75.0 vs 53.57)
	Rural	11.06 (46.47 vs 18.86)	35.63 (41.66 vs 28.20)	41.25 (44.89 vs 35.48)	41.50 (35.13 vs 56.25)
	Tribal	3.97 (11.68 vs 8.86)	9.94 (21.21 vs 5.71)	19.20 (30.0 vs 21.21)	5.98 (7.14 vs 8.0)
↓HDL	Urban	93.23 (100 vs 94.0)	93.75 (94.11 vs 93.10)	79.03 (87.05 vs100)	79.17 (95.0 vs 100)
	Rural	84.51 (63.38 vs 92.45)	70.11 (62.5 vs 79.48)	77.5 (65.30 vs 96.77)	59.81 (64.86 vs 81.25)
	Tribal	56.02 (48.05 vs 83.54)	62.82 (69.69 vs 82.85)	64.60 (40.0 vs 90.90)	25.88 (57.14 vs 64.0)
↑FBS	Urban	7.51 (5.02 vs 10.0)	21.25 (27.45 vs 10.34)	23.80 (14.70 vs 39.48)	42.64 (50.0 vs 32.14)
	Rural	9.61 (11.26 vs 3.77)	8.00 (16.66 vs 17.94)	25.0 (24.48 vs 25.80)	35.84 (37.83 vs 31.25)
	Tribal	5.76 (7.79 vs 3.79)	7.88 (6.06 vs 11.42)	7.66 (10.0 vs 9.09)	6.98 (9.52 vs 2.98)

↑=increased; ↓=decreased; Gr.=group; results were depicted in percentages.

4.4 Study of insulin resistance of the participants:

Table 15 is showing comparison of fasting insulin and HOMA-IR levels (glucose homeostasis) in urban, rural and tribal population. There is no statistically significant difference between mean values of fasting insulin (p= 0.852) and HOMA-IR (p= 0.1548) among urban and rural population. When compared between rural and tribal population both have shown significant difference (p= 0.0039 and 0.0040 respectively). However, overall comparison of fasting insulin (p= 0.0111) and HOMA-IR (p= 0.0163) among urban, rural and tribal population the difference is statistically significant

Table 15 Fasting insulin and HOMA-IR levels in urban, rural and tribal participants.

Variable	Overall (n=60)	Urban (n=20)	Rural (n=20)	Tribal (n=20)
Fasting Insulin (µU/ml)	18.77±10.61	18.32±9.56	23.83±10.15	14.18±9.68**
HOMA-IR	4.17±2.99	4.14±3.06	5.62±3.38	2.90±2.08**

HOMA-IR=Homeostasis model assessment of insulin resistance, ANOVA**statistically significant

Fasting insulin (FI) and insulin resistance (HOMA-IR) has been estimated in 60 subjects, who are randomly selected from urban, rural and tribal population of Kurnool district. The mean fasting insulin level was within the reference range but towards the upper normal limits of insulin in overall (18.77 ± 10.61), urban (18.32 ± 9.56); rural (23.83 ± 9.56) and tribal (14.18 ± 9.68) populations.

Like our findings, Varun et al. noted mean fasting insulin level as 18.10 (± 5.72) among the normal adults of Warangal in Andhra Pradesh [243]. In contrast, Gurinder Mohan et al. have reported similar mean among (17.09 ± 8.17) hypertensive subjects of Amritsar in Punjab [244]. He also noted that mean fasting insulin was normal (9.33 ± 2.67) in normal adults.

In this study hyperinsulinemia (fasting insulin ≥18µIU/ml) is high in rural population: 60% than urban population: 40%. Similar results were noted by R Jayatissa et al. in Sri Lankan population rural: 33.1% and urban population: 21.0%

[245]. Tribal population of our study has shown 25% of hyperinsulinemia, interestingly it is higher than urban population of Sri Lanka.

The insulin resistance was estimated by HOMA-IR model. The results have shown a notable prevalence of insulin resistance. Overall prevalence of insulin resistance is 63.33 % and it was highly prevalent in rural population: 70% followed by urban: 65 % and tribal population: 55%. Neelam et al. has noted 25 % of insulin resistance in urban population of Ranchi which is equal to tribal population of seen in this study [246]. Ganesh Bhat et al. noted 80 % prevalence of insulin resistance among NAFLD subjects with normal BMI and WC [247]. It is almost equal to urban population of our study.

HOMA-IR is a surrogate marker for insulin resistance [248]. In this study overall mean of HOMA-IR is 4.17 (± 2.99). It is very high in rural population 5.62 (± 3.38) as compared to urban 4.14 (± 3.06) and tribal population 2.90 (± 2.08). Varun et al. has reported 3.69 (± 1.21) mean HOMA-IR in normal urban population of Warangal in Andhra Pradesh [243]. It is almost equal to tribal population in this study. Peterson et al. showed higher prevalence of insulin resistance in lean Asian Indians compared to other ethnic groups [249].

There is no significant correlation between fasting blood glucose and fasting insulin in urban, rural and tribal population [Table 16]. This is an indication for possible high prevalence of insulin resistance in urban, rural and tribal population of Kurnool district. The overall significant association between fasting glucose and HOMA-IR gives an impression that assessment of overall insulin resistance rather than population wise has no insulin resistance which is not true. This is making most of the individuals to develop metabolic dysfunction there by contributing towards the development of disorders like CVD, type 2 diabetes mellitus and hypertension.

The study has shown higher fasting insulin and HOMA-IR levels in urban, rural and tribal population. This may lead to the development of atherosclerotic cardiovascular diseases [250].

Table 16 Correlation between FBS (mg/dl) and FI (µU/ml) levels

FBG vs. FI	r-value	95% confidence interval	P-value
Urban	0.3194	– 0.1578 - 0.6757	0.1826
Rural	0.1302	– 0.5416 - 0.01696	0.5842
Tribal	0.4095	– 0.07109 - 0.7358	0.0915
Total	0.2909	0.03275 - 0.054127	0.0281*

FBS=fasting blood sugar; FI =fasting Insulin; * =significantly correlated

A study of J Lopez C et al. has showed significant association between degree of insulin resistance and higher prevalence of metabolic syndrome components [251]. Jaber LA reported WC is a simple tool to exclude insulin resistance [252]. The biological link between abdominal obesity and IR suggest an important biochemical mechanism at fat cell level [253].

HOMA was developed by Mathews et al. in 1985 [254]. It is a method for estimation of insulin resistance from fasting insulin and blood glucose. Low HOMA indicates insulin sensitivity and high HOMA indicates insulin resistance [254]. We have correlated the insulin resistance (HOMA-IR) with each MetS component in urban, rural and tribal population.

The results have shown that in rural population insulin resistance is not correlated with any of the MetS component except diastolic blood pressure. The HDL-C has not shown any correlation with insulin resistance any group whereas DBP has shown significant correlation with insulin resistance in all the three groups. The association between the parameters is more significant in tribal population in all the parameter except DBP which is highly correlated in urban population [Table 17-21].

Table 17 Correlation between WC and HOMA-IR

WC vs. HOMA IR	r-value	95% confidence interval	P-value
Urban	0.4586	0.005388 - 0.7555	0.0483*
Rural	0.1035	– 0.3554 - 0.5222	0.6642
Tribal	0.8333	0.5996 - 0.9360	< 0.0001*
Total	0.5258	0.3072 –0.2764	< 0.0001*

WC=waist circumference; HOMA-IR = homeostatic model assessment of insulin resistance; *=significantly correlated

Table 18 Correlation of TG and HOMA-IR

TG vs. HOMA IR	r-value	95% confidence interval	P-value
Urban	0.5848	0.1486 - 0.8110	0.0118*
Rural	0.002958	– 0.4402 - 0.4450	0.9901
Tribal	0.7381	0.4137 - 0.8962	0.0005*
Total	0.5714	0.3652 - 0.7242	< 0.0001*

TG= triglycerides; HOMA-IR = homeostatic model assessment of insulin resistance.

Table 19 Correlation of SBP and HOMA-IR

SBP vs. HOMA IR	r-value	95% confidence interval	P-value
Urban	0.4406	– 0.01719 - 0.7456	0.0590 *
Rural	0.3030	– 0.1612 - 0.6575	0.1941
Tribal	0.5359	– 0.09190 - 0.8021	0.0219 *
Total	0.4241	0.1838 - 0.6166	0.0010 *

SBP= systolic blood pressure; HOMA-IR = homeostatic model assessment of insulin resistance; *=significantly correlated

Table 20 Correlation of DBP and HOMA-IR

DBP vs. HOMA IR	r-value	95% confidence interval	P-value
Urban	0.8093	0.5613 - 0.9239	< 0.0001 *
Rural	0.6372	0.2710 - 0.8423	0.0025 *
Tribal	0.5052	0.05007 - 0.7866	0.0325 *
Total	0.5906	0.3901 - 0.7377	< 0.0001 *

DBP= diastolic blood pressure; HOMA-IR = homeostatic model assessment of insulin resistance; *=significantly correlated

Table 21 Correlation of HDL and HOMA-IR

HDL vs. HOMA IR	r-value	95% confidence interval	P-value
Urban	– 0.1570	– 0.5706 - 0.3201	0.5209 NS
Rural	– 0.03458	0.5209 - 0.4141	0.8839 NS
Tribal	0.2095	– 0.2853 - 0.6162	0.4040 NS
Total	– 0.1554	– 0.3998 - 0.1097	0.2483 NS

HDL= high density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; NS= not significantly correlated.

The findings of our study are in accordance with Asher Fawwad et al. who showed no correlation between MetS parameters with any of the insulin resistance parameters (HOMA-IR, QUICKI, and Mc Auley) among the subjects with type 2 diabetic subjects [255]. Several studies like Naglaa et al. [256] Sameer et.al [257] and X Ying et al. [258] have shown significant positive correlation between HOMA-IR and metabolic syndrome components except HDL, which has shown negative correlation. In contrast, Aurea Maria et al. have shown positive correlation between HOMA-IR and metabolic syndrome components including HDL-C [259].

Considering the pathological relationship between insulin resistance and dyslipidemia and lack of correlation between these parameters in rural population of Kurnool district needs to conduct further studies based on genetic susceptibility. Because the existed scenario gives an impression that susceptibility to insulin

resistance and related consequences such as MetS and CVD risk were high in rural population. They are unique population to carry out genetic studies to find out the role of genetic predisposition in higher prevalence of insulin resistance without having any correlation with metabolic syndrome.

4.5 Study of cardiovascular (CVD) risk profile of the participants:

Several studies have reported that presence of metabolic syndrome increases the risk for development of CVD by 3 - 10 times and probability of developing type 2 diabetes mellitus by 3 to 4 folds [260]. The prevalence of CVD and type 2 diabetes mellitus is high in Asian Indians [261,262]. The reported CVD burden in urban population is 7-10 % and 3 - 10 % in rural population [263]. According to Riha et al. urbanization is a strong risk factor the development of CVD [264].

The latest census (Census of India 2011) have shown 20 - 30% increase of CVD risk in tribal dominated states like Andhra Pradesh, Maharashtra, West Bengal, Gujarat and Madhya Pradesh during the year 2001 to 2011 [240]. Even though MetS criteria are formulated to predict the risk of CVD, most of the important CVD risk factors like age, smoking, family history of diabetes and hypertension and physical activity were not included in the MetS criteria. While the data from several studies confirm type 2 diabetes mellitus, hypertension, smoking, alcohol consumption, dyslipidemia and obesity were highly prevent in India.

The above cardiovascular risk factors were very high in this population. However, there are no studies on multivariable risk prediction for cardiovascular disease in Kurnool district. Screening for these risk factors, providing information about the importance of life style modifications (LSM) and management of treatable conditions are very important to decrease the future burden of CVD risk factor, morbidity and mortality in this population. In this view we have included an objective to estimate individual and aggregated CVD risk factors and predict the CVD risk event in this population using World Health Organization/ International society for hypertension (WHO/ISH) risk prediction algorithm chart-D.

There are several CVD risk estimation models are in existence [265–271].

1. Framingham model: It is the best known and probably widely used risk score globally. It was made for the population of United States of America. The main drawback is overestimation of CVD risk than the existing risk. It may be due to large secular fall in population risk of coronary heart disease (CHD), since the cohort was established [272].

Several risk factors were noted like family history, BMI, MetS, socio-economic status and lacking of physical activity. So the modified Framingham risk model was prepared by adding new variable like C-reactive protein. It was further recalibrated to reflect the higher incidence of CVD in ethnic population, even there was a difference in the conventional risk factors. In 1976 the first publication of the risk score was done. Later many alternatives for Framingham score have been developed to estimate the CVD risk, mainly in developed countries.

2. Systematic Coronary Risk Evaluation - SCORE: It is mainly developed for the population of Europe for the clinical management of CVD risk. It has several advantages over Framingham score recent, more diverse and similar to the British population ethnically and genetically [273]. Separate equations are formulated for coronary and non-coronary heart diseases and high risk and low risk regions of Europe. The equations are mainly based on five variables like sex, age, smoking, systolic BP and either cholesterol or ratio between total cholesterol and HDL-C.

3. Assessing cardiovascular risk using SIGN (Scottish Intercollegiate Guidelines Network) guidelines: It was developed for Scotland population. It has incorporated socioeconomic status and family history as the previous studies highlighted importance of these factors. The main drawback is it has not included the obesity and lack of physical activity in CVD risk assessment [273].

4. QRISK score: It was developed based on the medical records of 10 billion British people over 17 years. The first model QRISK-1 included age, sex, smoking, systolic BP, T.CHO/HDL-C ratio, BMI, family history of CHD (in first degree relatives at less than 60 years of age) and treatment for hypertension. It was subsequently modified as QRISK-2 by further inclusion of - ethnicity, type 2 diabetes mellitus,

treated hypertension, rheumatoid arthritis, renal disease and arterial fibrillation [266]. QRISK-2 is better than QRISK-1 and modified Framingham score in predicting CVD risk event.

As stated above all these CVD risk predictors were formulated in view of high income countries. Thus, the World Health Organization / International Society of Hypertension (WHO/ISH) have developed 10-years risk prediction charts for 14 WHO sub-regions. The National Programme for Prevention and Control of Diabetes, Cardiovascular diseases and Stroke - NPDCS has also recommended the use of this CVD risk predication chart for routine screening [274,275].

We used WHO/ISH CVD risk predication chart-D (with serum cholesterol) to predict approximate estimation of the cardiovascular risk events in the population of Kurnool district using existing risk factors. The chart included age, sex, blood pressure, smoking status and type 2 diabetes mellitus.

For studying cardiovascular risk profile

4.5.1 Individual and aggregated CVD risk factors were studied

4.5.2 WHO/ISH risk prediction chart-D (with cholesterol) was studied

4.5. 3 Direct CVD risk factors (HTN, T2DM) were assessed.

4.5.1 Study of Individual and aggregated cardiovascular risk factors

Table 22 is showing the prevalence of physiological and behavioural or habitual cardiovascular risk factors in males and females. In accordance to 7th report of Joint National committee (JNC-7 criteria), prevalence of hypertension was found to be 18.31% [276]. It is highly prevalent in males (20.68%) compared to females (15.21%). Based on the previous Indian studies, prevalence of hypertension ranges from 26% to 33% [277].

The District Level Households facility Survey (DLHS) 2012-2013 has reported that 23.4% of Kurnool district population has an elevated blood pressure [278]. Among them total 9.0% (males: 8.6% vs. females: 9.9%) were having moderately elevated blood pressure and 3.5 % (3.4% vs. 3.9%) were having highly elevated blood pressure. Slightly lower prevalence of elevated blood pressure in our study may

attribute to inclusion of tribal along with urban and rural population while DLHS included urban and rural population only.

Interestingly, 75.48% participants were affected by pre-hypertension according to JNC VII criteria [Table 3]. It is very high in females: 79.19% than in males: 75.75%. Srinivas et al. reported 30.0% prevalence of prehypertension in Andhra Pradesh [278]. M R Ravi et al. noted 28.8% of prehypertension in South Indian population [280]. The other studies have noted 40-60% prehypertension in India [281]. Previously, > 40% prevalence of prehypertension was noted by Yadav V et al. [282] and Prabhakaran et al. [283] in North India; and Deepa et al. [284] Chennai Urban population.

Our study has noted higher prevalence of pre hypertension in females than males. In contrast, Premkumar R et al. reported 21.6% of hypertension and 32.2% of prehypertension in Central India [285]. Males were highly affected by both hypertension (23.2% vs. 19.3%) and prehypertension (34.2% vs. 30.7%) [285]. Similar was noted by Prasanna et al. [286]. They have noted 30% of hypertension and 55% of prehypertension in South India; it was highly prevalent among males compared with females.

The higher prevalence of hypertension in males than females may be attributed to the gender difference in the rennin angiotensin aldosterone system (RAAS). Females are protected to some extent from hypertension and other cardiovascular risk factors. This is due to sex hormones like estrogen which regulate the angiotensin levels, decrease the rennin levels and angiotensin converting enzyme (ACE) activity, angiotensin 1 receptor density and aldosterone production. Estrogen also activates counterparts of the RAAS such as natriuretic peptides, angiotensin 2 receptor densities and angiotensinogen.

In contrast androgens like testosterone will increase the RAAS activity by increasing renin levels and ACE activity [287,288]. Prehypertension can increase the risk of CVD event irrespective of presence of other CVD risk factors if appropriate intervention is not done [282, 289,290,291].

Table 22 Percentage of cardiovascular risk factors among the participants by gender

Variable	Male (n=585) N (%)	Female (n=447) N (%)	Total (n=1032) N (%)
Physiological risk factors			
Prehypertension SBP: ≥ 120 - ≤ 139 / DBP: ≥ 80 - ≤ 89	479 (75.72)	376 (79.19)	797 (75.48)
Hypertension SBP/DBP: ≥ 140 / 90	85 (20.68)	46 (15.21)	131 (18.31)
Prediabetes FBS: 100 - 125 mg/dl	56 (9.57)	39 (11.01)	95 (9.20)
Diabetes FBS: ≥126 mg/dl	79 (13.50)	31 (8.75)	110 (10.65)
HTN and DM	40 (6.93)	9 (2.01)	49 (4.74)
Behavioral risk factors			
Overweight/Obesity BMI ≥ 25.0	344 (58.88)	239 (73.60)	583 (56.49)
Physical activity	58 (9.91)	58 (12.97)	116 (21.80)
Alcohol consumption	202 (34.52)	23 (5.14)	225 (21.80)
Smoking	210 (20.34)	23(2.22)	233(22.57)

N= Total number of subjects; n=number of subjects with related risk factor; %=percentage; HTN=hypertension; DM=diabetes mellitus; BMI =body mass index

According to Anjana R et al., in India 62.4 million people are diabetic and 77.2% are prediabetes [292]. The present study shows prevalence of diabetes (FBS ≥ 126 mg/dl) is 10.56% and it is highly prevalent in males 13.50% than females 8.75%. Indian studies reported considerable variation in the prevalence of type 2 diabetes mellitus ranging from 1% to 33%.

The District Level Household facility Survey (DLHS-4) of the year 2012 - 2013 in Kurnool has reported 13.2% overall prevalence of diabetes (FBS > 140 mg/dl), it is 17.9% in urban population and 11.2% in rural population [278]. In this study pre-diabetes (FBS 100 - 125 mg/dl) was reported in 9.20% of participants. In contrast to diabetes, prediabetes is more prevalent in females 11.01% than males: 9.57%. Slightly similar results were noted by Hemavathi D et al. in urban slums of Bangalore (12.33 % of type 2 diabetes and 11.57 % prediabetes) [292]. The major

contribution (62.23 %) for prediabetes was by females. In contrast, our study has noted major contribution from males: 58.94% than females: 41.05%.

According to National Urban Diabetes Survey, prevalence of diabetes is 12.1% and prediabetes is 14% in India [294]. Our study has also reflected same results. Higher prevalence of prediabetes in females of our study may attribute to higher prevalence of prehypertension among them. The higher prevalence of diabetes in males may attribute to higher prevalence of smoking, alcohol consumption, low physical activity and hypertension among them.

The co-prevalence of hypertension and diabetes will increase the risk of coronary artery disease (CAD) and nephropathy related mortality [295]. Hemavathi D et al. noted 7.7 % co-prevalence in urban slum of Bangalore [290]. Ahsana S noted 13.8% in Manipur [296], Marre et al. reported almost one third of diabetics are hypertensive [297]. In Afro-American adults, increased blood pressure is highly present in the individuals with glucose intolerance and diabetes than non-diabetics [296].

Our study has noted 4.74% of participants were with pre diagnosed co-prevalence of hypertension and diabetes. It was highly prevalent in males: 6.93% than females: 2.01%. This can be attributed to high alcohol consumption in males; Shah et al. [214] reported a significant association between consumption alcohol and co-occurrence of type 2 diabetes mellitus and hypertension.

We have observed total 22.57% participants were smoking (males: 20.34% vs. females: 2.22%) and 21.80% were consuming alcohol (34.52% vs. 5.14%). Global Adult Tobacco Survey-1 in the year 2009-2010 (GATS -1) reported that 15% males and 1.90% females were smoking [298]. The recent GATS-2 (2016-2017) reported fivefold increased smoking in females, total 6.5% (urban: 1.4%; rural: 5.1%) of females and 20.2% males (urban: 5.4% vs. rural: 14.8%) were smoking [299]. Overall smoking is decreased from 34.6% in GATS-1 to 28.6% in GATS-1. However, smoking has shown fivefold increase in females while it is decrease in males. Our results are coinciding with GATS-2 report. We observed that smoking is very high in urban: 30.81%; rural: 23.83% and tribal population: 13.08%. As well as

alcohol consumption is also high in urban: 25.29%; rural: 27.03% and tribal: 13.08% population of Kurnool district.

The National Family Health Survey-4 (NFHS-4) of the year 2015-2016 reported 19.7% males (urban: 30.5% vs. rural: 26.8%) and 2.3% females (urban: 1.05% vs. rural: 2.9%) were using tobacco [138]. The survey also reported 34.9% males (urban: 29.6% vs. rural: 37.7%) and 0.4% females (urban: 0.1% vs. rural: 0.6%) consume alcohol in Andhra Pradesh. The NFHS-3 reported that consumption of alcohol in India ranges between 11 - 20% [300]. Our results are in agreement with NFHS-4. The difference in prevalence of among females may attribute inclusion of rural and tribal population in our study. In contrast NFHS-4 enrolled participants mainly from urban area. The data give an impression that consumption of smoking and alcohol increasing in females while it is decreasing in males.

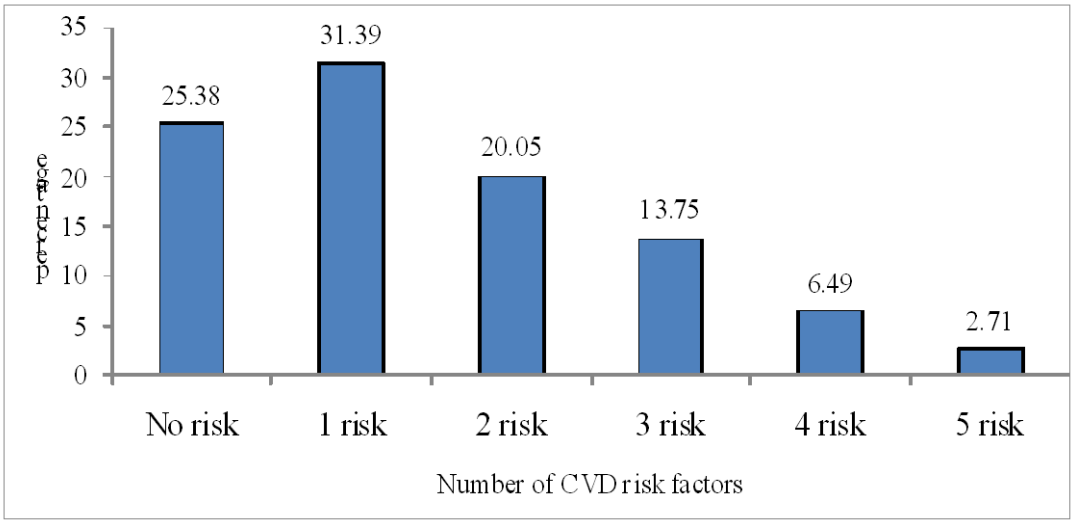
Total 56.49% population in Kurnool district were found to be overweight or obese (BMI $\geq$ 25.0 kg/m^2). It was highly prevalent in females: 73.60% than males: 58.88%. Other studies have reported that prevalence of overweight/obesity ranges from 16% to 45% in India. NFHS-4 (2015-2016) in Andhra Pradesh reported equal prevalence of overweight or obesity in males: 33.5% and females: 33.5%. In our study also male and female participants of urban (44.4% vs. 45.6%) and rural (28.0% vs. 27.6%) area were shown equal prevalence of MetS. This gives an impression that overweight and obesity is not confined to any single gender or geographical area in Kurnool district. This may be attributed to the higher prevalence of sedentary life style in Kurnool district population.

Lifestyle changes like decreased physical activity and increased obesity leads to increase of diabetes and Insulin resistance [301]. Studies have reported that sedentary life style in India ranges from 80% to 89% [302,303]. We observed 88.75% population were with physical inactivity in Kurnool district.

Presences of multiple risk factors possess a greater risk of getting a myocardial infarction or stroke because of their complex interactions and synergistic effect [302]. We observed only 25.38 % of participants were without any behavioural and physiological risk factors for CVD. Total 43.45 % participants were with any one or

two cardiovascular risk factors. All of them were economically productive age (20 - 60 yrs.) most of them are males [Figure 18].

Figure 18 Percentage of aggregated cardiovascular risk factors



Aggregated risk factors included in this study include: HTN, DM, increased BMI, Smoking, alcohol were taken as risk factors (Total number of subjects =1032)

4.5.2 Study of WHO/ISH risk prediction-D chart (with cholesterol):

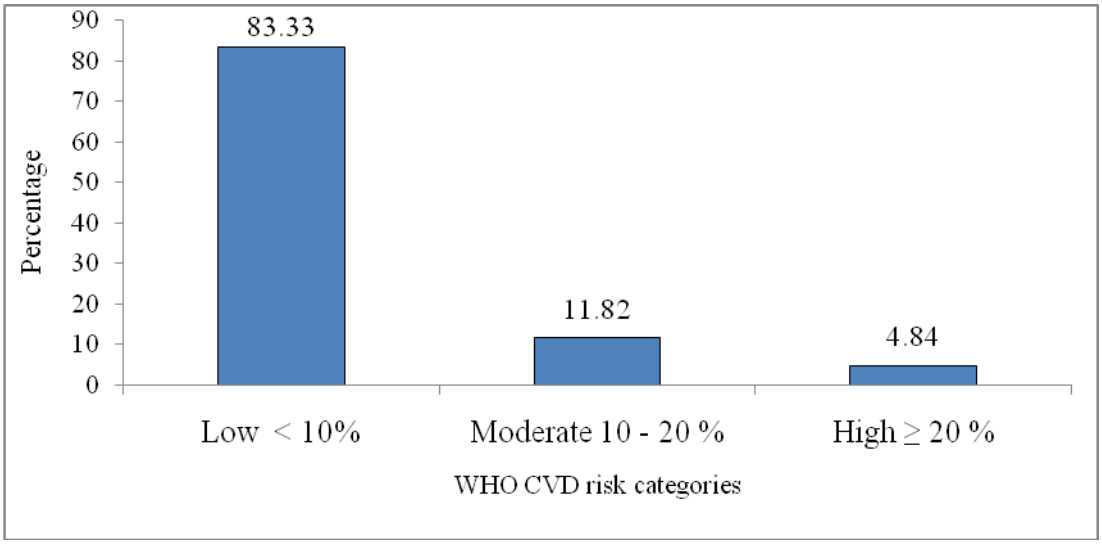
The CVD risk prediction of the participants was done in this study, using WHO/ISH CVD risk prediction chart-D (with cholesterol). The CVD risk was classified into 3 categories such as low risk (< 10%); moderate risk 10% to 20% and high risk ≥ 20%. It was found that 16.66% (moderate: 11.82%; high: 4.82%) of participants between 20 - 60 years of age had more than 10% of CVD risk and 83.33% of participants were having low CVD risk [Figure 19].

We observed that total 4.8% of participants were with >20% of CVD risk. Compared with other Asian countries like Cambodia (1.3%) and Mongolia (3.3%) it is high and with Pakistan 10% and Malaysia 6% it is lower [304]. Norman G et al. have reported a very high: 28.04% CVD risk (>20%) in the population of Devanahalli taluk in Bangalore rural district, Karnataka. A recent study by M K Khanal et al. reported 86.4%, 9.3% and 4.3% of low, moderate and high CVD risk in rural area of Nepal [305]. Ghorpade A. G et al. reported 86%, 6.8% and 10.2% low, moderate and high CVD risk in rural South Indian population [203]. A study from an urban population

of Dhaka in Bangladesh has reported 81.3%, 15.3% and 3.4% low, moderate and high CVD risk respectively [306].

The differences in CVD risk may be due other studies have enrolled participants were mainly from 40 - 80 years age; most of them were from urban and rural area but we considered tribal population also and most of them were younger age (20 – 60 years).

Figure 19 Overall percentages of WHO/ISH cardiovascular risk categories



WHO= World Health Organization; ISH=International society of hypertension

The study has stratified the participants based on the age and gender and assessed the CVD risk in each group [Table 23]. The results have shown that moderate and higher CVD risk was found to be high in males compared to females. Whereas low CVD risk is equally present in male and female participants (50.93 % vs. 49.06%) [Figure 20]. In contrast, a study in rural population of Bangladesh [306] has reported higher CVD risk in females (moderate 17.2% and high 4.0%) compared to males (1.8% vs. 2.0%). Total 11.82% of subjects were with moderate CVD risk and 4.84% were with high CVD risk. The majority of participants with moderate and high CVD risk are males (80.32% and 98%) whereas females are only 19.67% and 2.0% respectively [Figure 20].

Based on metabolic syndrome the participants were classified. The results have shown that CVD risk is very high in subjects with metabolic syndrome compared to

subjects without metabolic syndrome. Total 33.93% of subjects with MetS were with moderate to high CVD risk while it was 8.54% in subjects without MetS [Figure 21].

The most recent study in Nigerian population by Ogumoma VM et al. reported poor agreement between MetS and CVD risk score (kappa= 0.209; p= 0.001) [307]. This gives an impression that there is a possibility for establishment of CVD risk among the subjects without MetS also.

Table 23 Stratification of participants according to WHO/ISH cardiovascular risk categories by age and gender.

Age (years) (N) M/F	**Low risk < 10 %**		**Moderate risk 10 – 20 %**		**High risk ≥ 20 %**	
	Total	M/F	Total	M/F	Total	M/F
20 – 30 (N= 413) 232/181	99.75 (412)	99.56 (231)	0.242 (1)	0.43 (1)	Nil	Nil
		100 (181)		Nil		Nil
31 – 40 (N= 235) 132/103	98.72 (232)	96.96 (128)	1.27 (3)	2.27 (3)	Nil	Nil
		100 (103)		Nil		Nil
41 – 50 (N= 196) 103/93	74.48 (146)	54.36 (56)	20.91 (41)	36.89 (38)	Nil	8.73 (9)
		96.77 (90)		3.22 (3)		0
51 – 60 (N= 188) 119/69	37.23 (70)	19.32 (23)	40.95 (77)	47.05 (56)	21.80 (41)	33.61 (40)
		68.11 (47)		30.43 (21)		1.44 (1)

N=total number of subjects by age group; M/F= male/female; results are displayed as percentage (number of subjects); Nil=indicates no subjects were with CVD risk in related age group or gender.

Figure 20 Proportion of WHO/ISH cardiovascular risk by gender

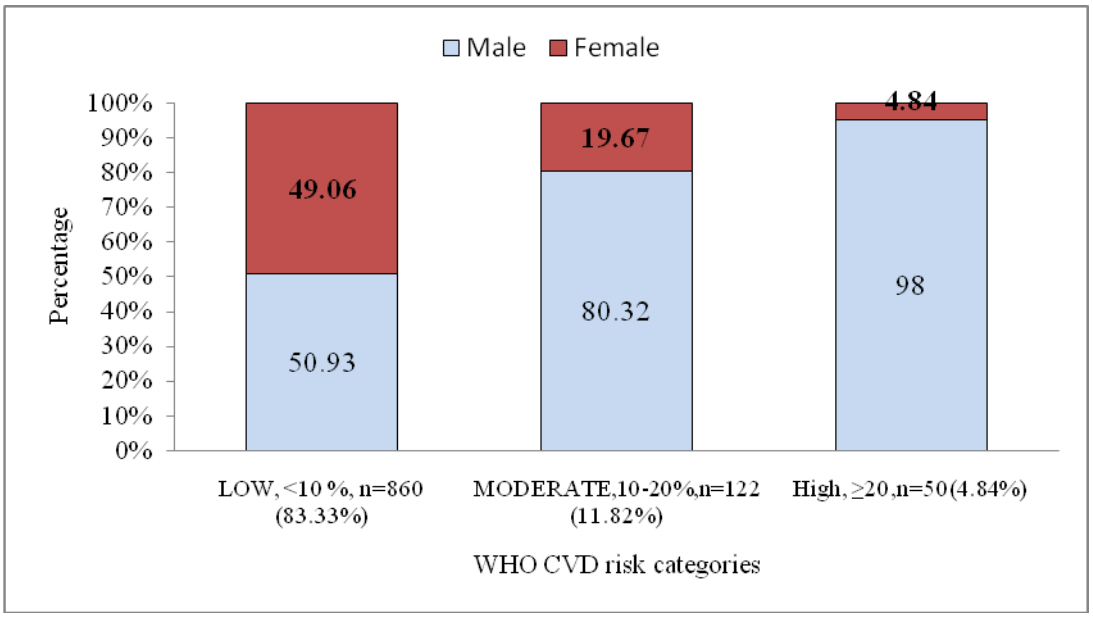
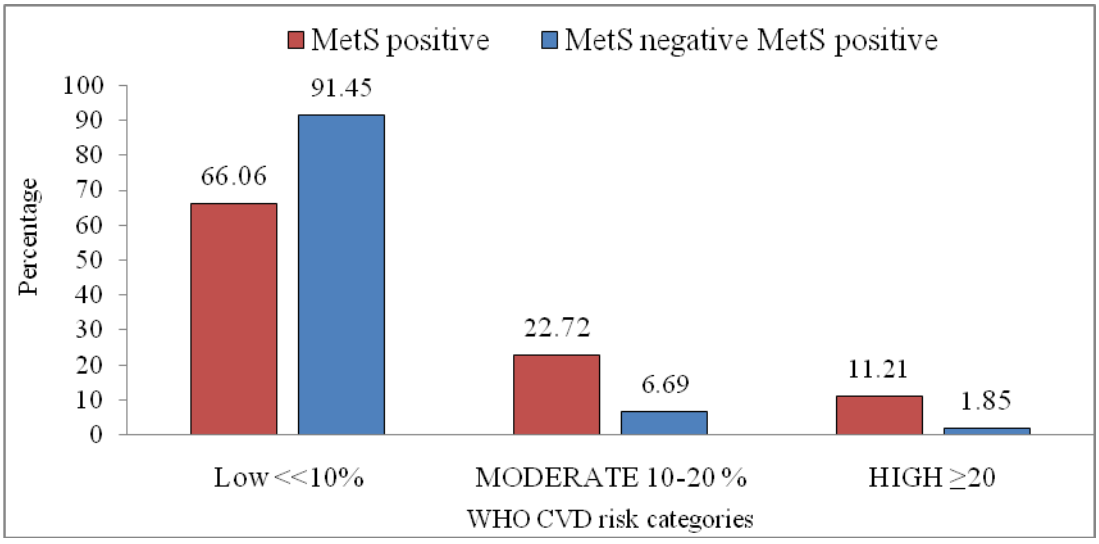


Figure 21 Overall percentage of WHO/ISH - CVD risk by presence or absence of MetS



WHO= World Health Organization, ISH =International society for hypertension

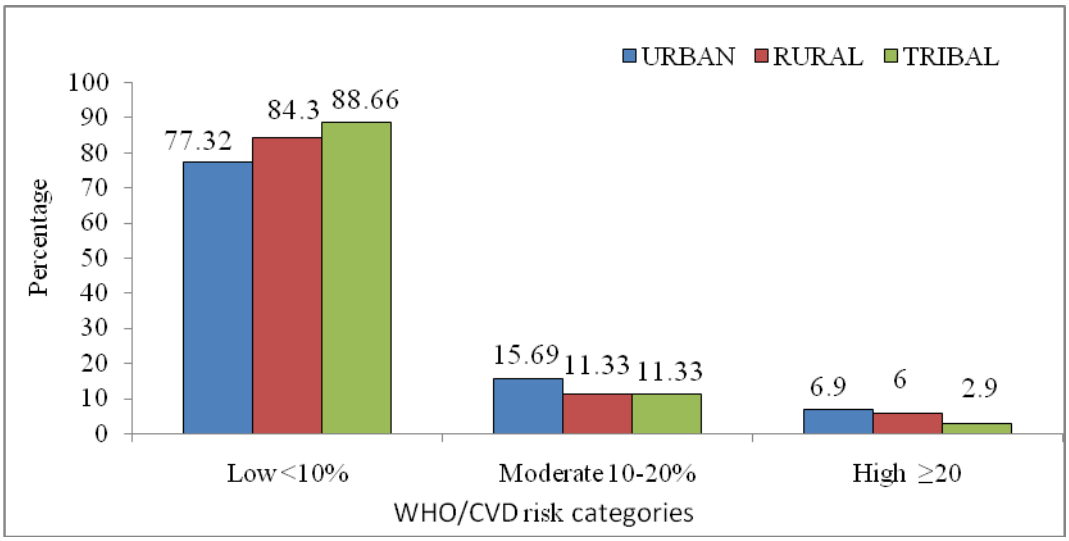
We have observed that increased abdominal obesity as one of the cluster risk factor for MetS in Kurnool district population for both males and females. [Table 8] Theodora et al. has observed abdominal obesity as a strongest correlate among all the MetS risk factors for establishment of cardiovascular diseases [308]. This gives an impression that presence abdominal obesity can itself precede an individual to have CVD risk.

As the age increases females have shown increased CVD risk compared to males. In pre-menopausal age the moderate to higher CVD risk is 3.22% and 0.1% but in post-menopausal age it has shown strong elevation in moderate 8.73% and higher 33.61% CVD risk. This gives an impression that females of Kurnool district were at increased CVD risk at postmenopausal age. This can be explained by increased prevalence of CVD risk factors like MetS, abdominal and general obesity at postmenopausal age.

The District Level Household Survey (DLHS) - 2012-2013 in Kurnool district reported 8.5% of CVD risk events during the year 2011-2012 [278]. With slight marginal difference it was equally prevalent in rural: 8.0% and urban: 9.8%. Our study observed 22.9% of cardiovascular risk (moderate to higher) in urban population, 17.33% in rural population and 14.3% in tribal population. .

The most important observation is moderate CVD risk is equally prevalent in rural: 11.33% and tribal: 11.33% population and higher CVD risk is almost equally prevalent in urban: 6.9% and rural: 6.0% population [Figure 22].

Figure 22 Proportion of WHO/ISH cardiovascular risk in urban, rural and tribal population of Kurnool district.



This can be explained by similarities and variations in the prevalence of some key CVD risk factors (smoking, alcohol consumption, hypertension, diabetes, obesity and dyslipidemia) in urban, rural and tribal population of the this study. Most of these

CVD risk factors and insulin resistance are aggregated in rural population of Kurnool district.

Cooney MT et al., Mathers CD et al., and WHO observed regional variation in the prevalence of these CVD risk factors [309,310,311]. The interplay between genetic, socio-economic, environmental, individual and health care delivery systems is the main cause for the differences in the prevalence of CVD risk in different populations. A recent study by N H Ismail et al. estimated CVD risk by INTERHEART Risk Score in urban and rural population of Malaysia and reported that CVD risk and risk factors were very high in rural population than urban population [312]. Lindroth et al. has also noted higher CVD risk factors in rural than in the urban population of North Sweden in 2014 [313].

The association of demographic and behavioural parameters associated with various WHO risk groups were analyzed by χ^2 (Chi^2) and univariate analysis [Table 24]. The results have shown that age, gender, BMI, education, alcohol consumption, smoking and physical activity were significantly associated with WHO/ISH-CVD risk categories in univariate analysis and family history of hypertension, type 2 diabetes mellitus or combination were not associated with CVD risk.

Table 24 Association of variables with WHO/ISH cardiovascular risk categories

Variable		Low risk (< 10%) N (%)	Moderate risk (10–20%) N (%)	High risk (> 20%) N (%)	χ^2	P-value
Age	20-40	644 (64.34)	4(0.38)	0 (0)	323.14	0.0001*
	41-60	216 (20.93)	118 (11.43)	150 (14.53)		
Gender	Male	438 (42.44)	98 (9.49)	49 (4.74)	74.134	<0.0001*
	Female	422 (40.89)	24 (2.32)	1 (0.09)		
BMI	Yes	465(45.05)	86 (8.33)	32 (1.10)	12.928	<0.0001*
	No	395(38.27)	36 (3.48)	18 (1.74)		
Education	None	324 (31.39)	59 (5.71)	22 (2.13)	14.965	0.0048*
	School	341 (33.04)	47 (4.55)	25 (2.42)		
	College	195 (18.89)	16 (15.50)	3 (0.29)		
Alcohol	Yes	143 (13.85)	53 (5.13)	29 (2.28)	85.44	<0.0001*
	No	717(69.47)	69 (52.27)	21 (2.03)		
Smoking	Yes	130 (12.59)	58 (5.62)	45 (4.36)	200.91	<0.0001*
	No	730 (70.73)	64 (6.20)	5(0.48)		
Family history	Yes	129(12.5)	10 (0.96)	8(0.77)	4.181	0.1236
	No	731 (70.83)	112(10.85)	42 (4.06)		
Physical Activity	Yes	7(0.67)	13(1.25)	6(0.58)	54.073	<0.0001*
	No	763(73.93)	109(10.56)	44(4.26)		

N=Total number of subjects; %= percentage, * statistically significant; BMI=body mass index

All the above variables were included in the multi nominal logistic regression analysis [Table 25]. Advanced age, gender, alcohol consumption, smoking and physical activity were significantly associated with high CVD risk as compared to low CVD risk in multi-nominal logistic model. Whereas BMI and education were better associated with moderate CVD risk and family history was not associated with either moderate or high risk.

Table 25 Multi nominal logistic regression analysis of various parameters and WHO/ISH cardiovascular risk categories

Variable		<10 %	10-20 %			>20 %		
			OR	CI	P-value	OR	CI	P-value
Age	20-40 R	R	878.954	32.081-241.14	0.001*	300.67	18.45-4897.3	<0.001*
	41-60	R						
Gender	Female	R	0.254	0.1595-0.4051	<0.001*	0.02118	0.002-0.1542	<0.001*
	Male	R						
BMI	Yes R	R	0.4928	0.3265-0.7438	0.0009*	0.6622	0.366-1.198	0.2206
	No	R						
Educ-cation.	Educated R		1.549	1.058-2.268	0.0304*	1.348	0.754-2.407	0.388.9
	None							
Alcohol	No R	R	3.851	2.580-5.749	0.0001*	3.631	2.013-6.548	<0.001*
	Yes	R						
Smo-King	No R	R	5.089	3.406-7.603	0.0001*	50.538	19.68-129.74	<0.001*
	Yes	R						
Physical activity	Yes R	R	12.540	4.894-32.129	0.0001*	14.338	4.621-44.88	<0.001*
	No	R						
Family history	No R		0.5060	0.2580-0.9923	1.079	1.434	0.4952-2.352	0.8476
	Yes							

< 10%= low CVD risk, 10–20%=moderate CVD risk; > 20%= high CVD risk; R=reference category dependent variable; OR=adjusted odds ratio.

4.5. 3 Assessment of direct cardiovascular risk factors

The study has described the profile of people with direct CVD risk factors like hypertension and type 2 diabetes mellitus either alone or in combination. The results have shown Alcohol consumption (OR= 2.754) BMI ((OR= 1.886) and smoking (OR= 2.783) found to be independently associated with hypertension and diabetes with in multivariate logistic regression analysis [Table 26].

Table 26 Direct risk factors and its correlates: A multivariate logistic regression - analysis

Variable		Adjusted OR	CI	P-value
Age	$< 40^R$	0.6328	0.4542 - 0.8815	0.0070
	≥ 40			
Gender	Female ^{R}	0.6263	0.4497 - 0.8722	0.0055
	Male			
Alcohol	No ^{R}	2.754	1.953 - 3.884	< 0.0001*
	Yes			
Family History	No ^{R}	1.249	0.8008 - 1.947	0.3414
	Yes			
BMI risk	No ^{R}	1.886	1.346 - 2.644	0.0002*
	Yes			
Smoking	No ^{R}	2.783	1.979 - 3.915	< 0.0001*
	Yes			

*=significant, R=reference category dependent variable, Presence of direct risk factors type 2 diabetes, hypertension have been considered as direct risk factors

Garg NC et al. and Norman G et al. have observed that CVD risk stratification of a population is better in low and middle income countries like India than assessing individual CVD risk factors [197,277]. It is very useful for prioritizing resource allocation; planning of health interventions and measuring effectiveness of intervention programmes. WHO risk algorithm has excluded the individual and adjusted the effects of some important CVD risk factors like BMI, family history, alcohol consumption and physical activity. We included these physiological and behavioural risk factors to assess the CVD risk of Kurnool district.

CHAPTER VI

SUMMARY AND CONCLUSION

The purpose of the study is to assess the prevalence of metabolic syndrome in Kurnool district including three different populations (urban, rural and tribal) with different ethnic backgrounds.

All the objectives were evaluated with a cross sectional study among urban, rural and tribal population of Kurnool district aged between 20-60 years. 1032 subjects were recruited in this study having 344 subjects in each group.

The following parameters were assessed to screen the subjects for MetS include were fasting blood glucose, serum triglycerides, high density lipoprotein, waist circumference, systolic blood pressure and diastolic blood pressure. Other parameters include were total cholesterol, LDL-C cholesterol, body mass index, fasting insulin and HOMA-IR and CVD risk profile. Subjects were assessed by WHO/ISH – CVD risk prediction algorithm.

- Results showed a high metabolic syndrome (31.97%) in Kurnool district.
- Further results indicate the prevalence is highest in urban population (42.15%) as compared to rural (31.97%) and tribal (21.80%) population.
- While comparing the MetS between male and female it was observed that male is having higher (41.82%) as compared to female (30.82%).
- The prevalence of MetS was found to be near similar in case of urban male (41.82%) and female (42.64%) as compared to rural male (33.65%) and female (29.93%), tribal male (20.93%) and female 22.67%).
- Decreased HDL-C (78.87%) increase of WC (57.84%) and elevation of TG (31.78%) were found to be potent risk factors for MetS in all the groups of males and females.
- Age dependent rise in prevalence of MetS were found urban and rural population in both male and females. While in case of tribal population it showed a fall of prevalence after the age of 50 year

- Higher mean values were noted for fasting insulin (18.77 ± 10.61) and HOMA-IR (4.17 ± 2.99). Fasting insulin levels were not correlated with HOMA-IR in urban (r= 0.3194, p= 0.1826), rural (r= 0.1302, p= 0.5842) and tribal(r=0.4095, p=0.0915) population, which indicate a possible insulin resistance among them.
- In case of rural population HOMA-IR did not correlate with any of MetS risk factor except DBP.
- Hypertension was present in 18.31% of urban, rural and tribal population; pre-hypertension was present in 78.48%, diabetes was present in 10.65% and pre-diabetes was present in 9.29%.
- The present study also reveals only 25.38% among all the populations were devoid of habitual risk factors like, smoking, alcohol etc., for CVD.
- 43.45% among all the population were found to have at least two of the CVD risk factors.
- Among the CVD risk factors smoking (22.57%) and alcohol consumption (21.80%) were found to highly prevalent among all the study subjects.
- Of all the subjects studied higher CVD risk is present in 4.84% subjects, moderate CVD risk in 11.82% of subjects. Moderate CVD risk is equally present in rural and tribal population (11.33% and 11.33%). High CVD is almost equally present in urban and rural population (6.9% vs. 6%).
- In chi^2, univariate analysis age, gender, BMI, education, alcohol consumption, smoking and physical activity were significantly associated (p=0.0001) with WHO/ISH – CVD risk categories whereas family history of hypertension, type 2 diabetes mellitus or in combination were not associated (($\chi 2$=4.181, p=0.1236).
- Based on gender moderate and higher CVD risk is found to be high in males as compared to females.

- MetS influences CVD risk with a degree of severity.
- As per NCEP ATP III risk stratification atherogenic dyslipidemia due to MetS found in our study was reflected by observed data from urban, rural and tribal population of Kurnool district.
- In multi-nominal logistic model age, gender, alcohol consumption smoking, physical activity found to the significant risk factors associated with high risk as compared to low risk. Whereas BMI and education were better associated with moderate risk and family history was not associated with either moderate (odds ratio: 0.5060, p=1.079) or high risk (odds ratio: 1.434, p=0.8476).
- The direct risk factors for hypertension and diabetes are identified as alcohol consumption (odds ratio: 2.754, p=<0.0001), elevated BMI (odds ratio: 1.886, p=0.0002) and smoking (odds ratio: 2.783, p=<0.0001).
- In this study, the individual and adjusted effects of the risk factors that are excluded in WHO/ISH - CVD risk algorithm (BMI, education, family history, alcohol consumption and physical activity) were analyzed for people with low and high risk for getting CVD event. Among these BMI, education were associated to moderate CVD risk whereas alcohol consumption, physical activity were associated with high CVD risk.

The study findings reveal that prevalence of metabolic syndrome is very high in Kurnool district. The CVD risk is also correspondingly high (16.66%). Increased fasting insulin and HOMA-IR without having any correlation with metabolic syndrome suggest for the need of further improvement of awareness and promotion of the lifestyle changes to reduce risk of CVD.

5.2 Limitations of the study:

- The study is an observational study.
- Longitudinal studies are with big data are needed to make causal inferences and to identify unmeasured or unknown risk factors for metabolic syndrome in this population

5.3 Future directions

1. To evaluate the dietary role of influence whether it differentially act on MetS among urban, rural and tribal population.
2. To evaluate MetS among young children in urban, rural and tribal population with a possible differential outcome.
3. To focus on higher fasting insulin and HOMA-IR levels in this population.

CHAPTER VII

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CHAPTER VIII

ANNEXURES

ANNEXURE-1

CASE REPORT FORM [CRF] Date:

TOPIC: "Metabolic syndrome in Kurnool district in adults (20-60 years) -A cross sectional study using modified NCEP ATP III criteria" Registered at BLDE University, Shri B.M.patil medical college and research canter, Bijapur -586103, Karnataka, India.

Regd No: 11PHDB12 **Guide: DR.J.G.AMBEKAR**
Investigator: Pandit Vinodh Bandela

Patient Regd Number:

CONSENT FORM: I _____exercising my free power of choice, hereby give my consent to be included as a subject in the clinical study "Metabolic syndrome in Kurnool district in adults (20-60 years) -A cross sectional study using Modified NECP ATP III criteria ".

1. CONTACT DETAILS

1.1 First Name/middle name/surname:

1.2 Current house address:

1.3 Type of place: Urban/Rural/Tribal

1.4 Mobile Number:

2. PERSONAL DETAILS:

2.1 Age (years completed):

2.2 Sex: Male/Female

2.3 Marital status: Never married/ Married/widow-widower/separated-divorced

2.4 Primary occupation:

a) At home doing house work b) unemployed, retired/disabled c) Unemployed, seeking work d) student/ training e) unskilled manual f) semi-skilled manual g) skilled manual h) semi-professional h) professional

2.5 Highest Educational level:

a) Illiterate b) Literate, no formal education c) up to primary school (class IV) d) secondary school (ITI ,X/XII , Intermediate) e) Graduate (BA, B.Com, Diploma) f) Professional degree/ Post Graduate (MA, M.Sc, MBBS, MSW, B.Th, PhD)

3. BLOOD SAMPLING:

3.1 Any illness within the last week? [ ] 1= Yes; 2=No

3.2 If yes, specify what illness: ----------

3.3 Do you have diabetes: [ ] 1=Yes; 2=No(if yes don't give glucose load)

3.4 Day of last meal: [ ] 1= Today; 2= yesterday (don't accept sample if today)

3.5 Time of last meal: ------/------- (hours/min)

3.6 Time of blood taken (5 ml):-------/------ {1ml for plasma; 4 ml for serum)

4. HEALTH AND LIFE STYLE:

4.1 Smoking: never/former (stopped 6 months)/current (in last 6 months)

4.2 Chewing: never/former (stopped 6 months)/current (in last 6 months)

4.3 Alcohol: daily/weekends only//1-2 times in month/special occasions/never

4.4 Type of work: Normal/moderate/heavy/sedentary

4.5. Sports/Games/Exercise: Yes/ No

4.6 Food habits: vegetarian /Non-vegetarian

5. MEDICAL HISTORY:

5.1 Are you suffering from any of the following diseases?

Diabetes/Hypertension/Heart Diseases/thyroid

5.2 Does your father or mother suffering from any of the following?

Diabetes/Hypertension/Heart Diseases/Overweight-obesity/ Lung

5.3 Drugs: Anti-Hypertensive / Anti diabetic

6. ANTHROPOMETRIC MEASUREMENTS (Enter average of two readings)

6.1 Weight: ----------Kg

6.2 Standing Height: ----------cm

6.3 Waist circumference: ----------cm

6.5 Blood Pressure (Systolic / Diastolic): ----------mmHg (average of two readings)

7. BIOCHEICAL PARAMETERS:

7.1 Fasting Serum Triglycerides (TGL) ---------- mg/dl

7.2 Fasting Serum High density lipoprotein (HDL) ---------- mg/dl

7.3 Total cholesterol (T.CHO) ----------mg/dl

7.4 Low density lipoprotein (LDL) ----------mg/dl

7.5 Fasting Blood Sugar (FBS) ----------mg/dl

7.6 Fasting Insulin (FI) ---------- µU/ml

7.7 HOMA IR ----------

Signature of subject: ---------- Name of enumerator: : ----------

Date of data entry: ----------

ANNEXURE-2

PUBLICATIONS:

1. Pandit vinodh Bandela et al. Assessment of cardiovascluar risk of rural population in Kurnool district using WHO/ISH multivariable risk prediction algorithm. Int.J.Pharm. Sci. & Res.2016, 8:338-42.

2. Pandit Vinodh Bandela et al. Study of risk factors for metabolic syndrome in subjects from rural area of Kurnool district. J. Chem. Pharm. Res., 2016, 8:963-968.

3. Pandit Vinodh Bandela et al. Study of metabolic syndrome and its components among Kurnool district population of Andhra Pradesh with different ethnic backgrounds. J. Cardiovasc. Dis. Res., 2017, 8:83–88.

PUBLICATIONS

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Assessment of Cardiovascluar Risk of Rural Populaiton in Kurnool District Using WHO/ISH Multivariable Risk Prediction Algorithm.

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Abstract:

Background: The Indian subcontinent is undergoing epidemiological transition as non communicable diseases like type 2 diabetes mellitus and cardiovascular diseases are becoming the leading cause of morbidity and mortality. This increased prevalence has been ascribed to the rapid changes in the demographic, nutritional as well as the socio economic factors i.e., transition phase. World Health Organization (WHO) estimates that with 19.4 million people with diabetes in India in 1995, the number is projected to increase to 80 million by the year 2030. Establishment of scientific data on predominance of CVD risk factors that will reflect a population can be helpful to implement or formulating prevention strategies in order to decrease or prevent the mortality. There is no published data on multivariable risk prediction for cardiovascular disease from rural population of Kurnool district, Andhra Pradesh.

Aims and objective: To determine the cardiovascular risk profile and fatal and non fatal cardiovascular in rural population of Kurnool district

Materials and Methods: This is a cross sectional study done among total 344 [male n=205; female n=139] adults aged between 20-60 years. The assessment of CVD risk profile of participants was done using WHO/ International Society of Hypertension (ISH) CVD risk prediction algorithm.

Results: The study has revealed that among this population; 69.76% were pre-hypertension, 27.61% had hypertension; 14.24% found to be pre-diabetes 4.36% were having diabetes; 57.84% showed overweight/obesity; 83.33% has no physical inactivity; 27.03% alcoholism; and 23.83% smoking. 36.62% subjects were with 2 or more risk factors; 26.74% participants are without any physiological or behavioral CVD risk factors. 93.84% subjects were at <10%; 5.48% were at 10-30% and only 0.69% more than 30% CVD risk. Modifiable risk factors were high among this population. Older age, physical inactivity, smoking, alcohol consumption were associated with high risk of CVD.

Conclusion: The prevalence of cardiovascular risk factors and fatal and non fatal CVD risk is high in this rural population. This scenario alarming the need to strict implementation of prevention strategies that could create awareness on life style modifications to reduce CVD risk of this population.

Keywords: Cardiovascular risk (CVD); prevalence; risk factors; rural population; World Health Organization /International Society of Hypertension WHO/ISH;

INTRODUCTION:

According to World Health Report 2002, cardiovascular diseases (CVDs) will be the largest cause of death and disability by 2020 in India. In 2020 AD, 2.6 million Indians are predicted to die due to coronary heart disease which constitutes 54.1 % of all CVD deaths. Nearly half of these deaths are likely to occur in young and middle aged individuals (30-69 years). Several cross-sectional studies have confirmed that hypertension, dyslipidemia, diabetes, overweight, obesity, physical inactivity and tobacco use are highly prevalent CVD risk factors in Indians.[1] The exact etiology for predisposition to CVD in Indians still a debate. Increased health care costs make it difficult to identify or diagnose the individuals with CVD risk at an early stage eventually most of them were left un-diagnosed. It is very essential to implement primary health care interventions and public health measure targeting diet, lifestyles and environment, in order to minimize or prevent the risk of CVD. It requires a nationally representative data collected through standardized techniques.

The current study designed with an aim to estimate the individual and aggregated risk factors and predict the risk of fatal and non-fatal cardiovascular event among the rural population of Kurnool district using WHO/ISH CVD risk prediction chart. [2].The study is very useful to identify the persons at high CVD risk and to motivate patients to change lifestyle behavior and to take antihypertensive and lipid-lowering drugs when appropriate.

MATERIALS AND METHODS:

This cross-sectional study carried out in rural area of Nandyal, Kurnool district, Andhra Pradesh, during 4-01-2014 to 19-06-2014. Total 344 eligible male and female adults between 20-60 years were screened for CVD risk factors randomly. The study includes a face to face interview using semi structured questionnaire such as demographic details, history of hypertension, diabetes and heart disease, physical activity, smoking and alcohol intake. The subsequent health examination includes anthropometric parameters like body mass index (BMI). BMI was calculated by dividing weight by height squared (kg/m^2); Systolic and Diastolic blood pressure (BP) was measured by using Sphygmomanometer in supine position. Average of two brachial systolic and diastolic blood pressure readings was taken. 5ml fasting blood samples after 12 hours overnight fasting were collected to estimate serum cholesterol (cholesterol oxidase and peroxidase method) and fasting blood glucose level (glucose oxidase and peroxidase method)]

Diagnostic criteria:

Hypertension was diagnosed as per Seventh Report of the Joint National Committee (JNC 7) on Prevention Detection, Evaluation, and Treatment of High Blood Pressure criteria (JNC 7). Normal <120/80; Prehypertension 120-130/80-90; Stage 1 hypertension 140-159/90-99; stage 2 hypertension ≥160 /≥100; Hypertension >140/90 mmHg or past medical history of hypertension

Diabetes Mellitus was diagnosed as per World Health Organization criteria (WHO criteria). The patients were labeled as diabetics who had fasting blood glucose level ≥126 mg/dl or past diabetic history and prediabetes were those having fasting blood glucose level 100-125 mg/dl.

The assessment of CVD risk profile of participants was done by using three different Guidelines 1) Study of individual and aggregated risk cardiovascular risk (Hypertension, diabetes, BMI, inadequate physical activity, smoking and alcohol consumption) 2) Risk profiling using WHO/ International Society of Hypertension (ISH) CVD risk prediction algorithm-D (with serum cholesterol) and 3) Direct risk cardiovascular risk factor (hypertension, diabetes and pre-existing heart disease) assessment.

WHO/ISH risk prediction D chart (with serum cholesterol) can be used for countries of the WHO region of South-East Asia. It can predict the combined myocardial infarction and stroke (fatal and non-fatal) risk in people who do not have established coronary heart disease, stroke or other atherosclerotic disease by gender, age, systolic blood pressure, total cholesterol, smoking status and presence or absence of diabetes mellitus. The risk level is classified as <10%; 10%-20%: 20%-30%; 30%-40%; and >40%. [3]

During the entire study the utmost care was taken according to Helsinki Declaration about patient confidentiality. [4]The study was approved by Institutional Ethical Committee (IEC). Written Informed consent of participants was taken prior to study.

Statistical Analysis:

Prevalence rates were calculated for the risk factors and presented as percentages.

RESULTS:

The screened population baseline characteristic were as follows – all were belongs to below poverty line status, 36.33% of them were illiterate. The mean age of the screened subjects was 37.67±11.5 [males 38.67±11.60; females 36.20±11.41].

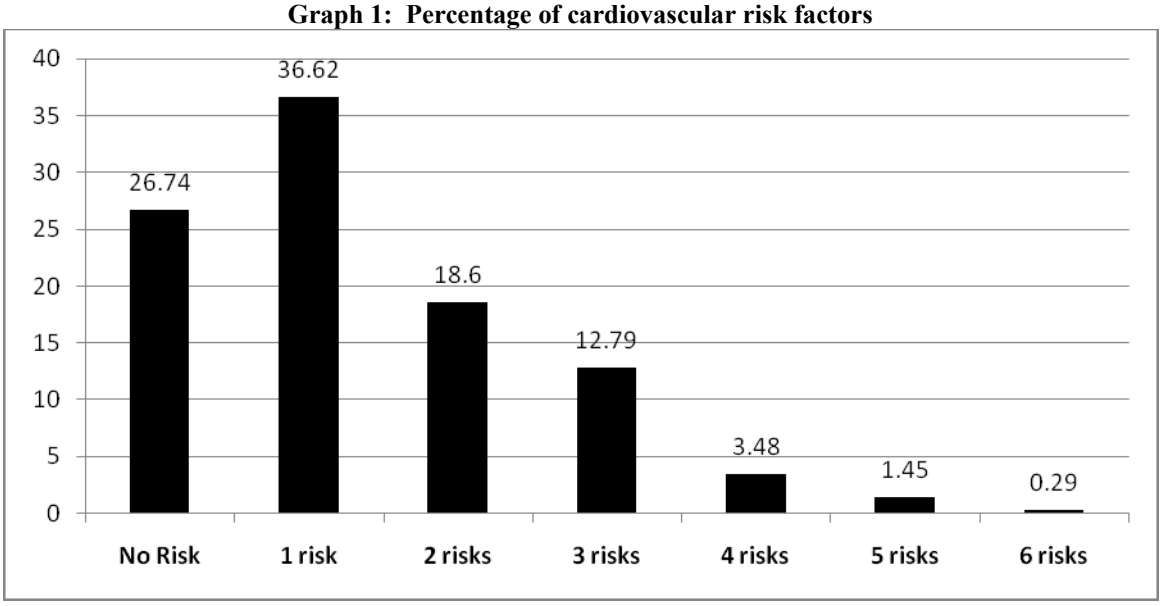
The mean blood pressure is 123.50±6.83/82.51±4.92; fasting blood sugar 90.80±27.81; body mass index (BMI) 25.88±5.05 Table 1 shows the prevalence of CVD risk factors among the study population. Hypertension is the most prevalent risk factor, a total of 27.61% subjects were hypertensive and 69.76% were pre-hypertensive. Majority 297 (83.33%) of the population did not reported (should be report) adequate physical activity.

Graph 1: Delineate the presence of the aggregated CVD risk factors. Classified based on the number of risk factors present either single or in combination. The presence multiple risk factors in an individual lead to greater risk for getting myocardial infarction (MI) or Stroke. 26.74% participants are without any physiological or behavioral CVD risk factors. 36.62% subjects were with 2 or more risk factors. Hypertension, diabetes, risk of BMI, lack of physical activity, smoking, alcohol consumption were taken as CVD risk factors

Table:1 Prevalence of Cardiovascular (CV) risk factors

Variable	Male (N=205) Number (%)	Female (N=139) Number (%)	Total (N=344) Number (%)
Physiological Risk Factors			
Pre hypertension	144 (70.24)	96 (69.06)	240 (69.76)
Hypertension	57 (27.80)	38 (27.33)	95 (27.61)
Stage-I Hypertension	57 (27.80)	38 (27.33)	95 (27.61)
Stage-II Hypertension	Nil	Nil	Nil
Pre diabetes	34 (16.58)	15 (10.79)	49 (14.24)
Diabetes	9 (4.39)	6 (4.31)	15 (4.36)
Behavioural Risk Factors			
Overweight &obese	125 (60.97)	64 (46.04)	199 (57.84)
Alcohol consumption	87 (42.43)	6 (4.31)	93 (27.03)
Smoking	77 (37.56)	5 (3.59)	82 (23.83)

Graph 1: Percentage of cardiovascular risk factors



Graph 2: Depicts risk prediction of screened participants based on WHO/ISH risk prediction chart of fatal or nonfatal (MI or stroke) CVD events. This algorithm was applied only on 146 participants of the total. The risk of CVD events were grouped as low risk (<10%); moderate risk (<10 %-< 30%) and high risk (≥ 30%). It was found that only a negligible portion (0.69%) is with more than 30% risk for MI or stroke. And 5.48% of participants were with moderate risk for CVD events.

Graph: 2 Stratification of subjects according to WHO/ISH CVD risk categories

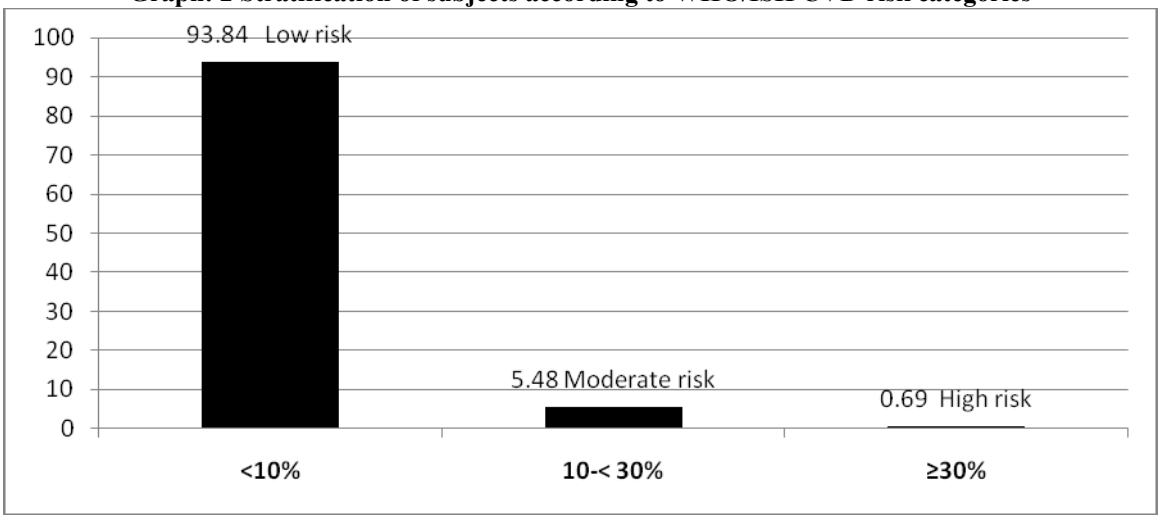


Table 2: Shows the association of variables (age, education and smoking) with WHO risk groups. In univariate analysis of variables advanced age was significantly associated with WHO risk categories.

Table -2 Association of variables with WHO/ISH risk categories

Variables		Low (<10%) No (%)	Moderate (10-30%) No (%)	High (≥30%) No (%)	X^2	P value
Age	40-49	76	0	0	10.41	0.005**
	50-59	61	8	1		
Education	None	72	4	1	1.321	0.8578
	School	56	3	0		
	College	9	1	0		
Smoking	yes	44	5	1	5.032	0.08
	No	93	3	0		

Table 3: explains that in multi-nominal logistic regression analysis, advanced age was significantly associated with moderate risk as compared to high risk.
*significant; R reference category dependent variable

Table:3 Multi-nominal regression analysis of parameters and WHO/ISH risk categories								
Parameter		Low Risk	Moderate Risk			High Risk		
			Odds Ratio	CI	P Value	Odds Ratio	CI	P Value
Age	40-49 R	R	21.146	1.196-373.92	0.0021**	3.732	0.1493-93.300	0.4493
	50-60	R						
Education	Educated	R	0.9028	0.2169-3.7518	1.000	2.710	0.1084-67.753	1.000
	None R	R						
Smoking	No R	R	1.268	0.2899-5.549	0.7142	6.303	0.2155-157.296	0.3261
	Yes	R						

Table 4: Shows the association of variables with direct risk factors (hypertension, diabetes) alone or in combination by multivariate logistic regression analysis. Age >40 years (OR=15.526); gender (OR=12.788); increased BMI (OR=4.467) alcohol consumption (OR=15.375); and family history (OR=17.911) were independently associated direct risk factors.

Table:4 Multivariate regression analysis of direct CVD risk factors and its correlates				
Parameter		Odd Ratio	CI	P value
Age	<40R	15.526	8.543-21.287	0.0001**
	>40			
Gender	Female R	12.788	7.527-21.725	0.0001**
	Male			
Alcohol	No R	15.375	8.962-26.377	0.0001**
	Yes			
Family History	No R	17.911	9.585-33.469	0.0001**
	Yes			
BMI risk	No R	4.467	2.915-6.844	0.0001**
	Yes			

DISCUSSION:

India approximately 25% are cardiovascular-related deaths and would serve as a home to more than 50% of the patients with heart ailments worldwide within next 15 years.[5] Framingham risk score is a widely recognized tool used by clinicians worldwide to calculate cardiovascular risk in an individual and classify them for risk of coronary death or myocardial infarction (MI).[6] The study has estimated CVD risk factors prevalence and myocardial and stroke risk based on WHO/ISH risk prediction chart.[2]

Most of the Indian studies have shown that prevalence of hypertension ranged from 26% - 33%. In accordance the study has identified the prevalence of hypertension was 27.61% with mean blood pressure ranged from 123.50±6.83/82.51±4.92. Anchala R [7] etal has also noted 27.6% prevalence of hypertension among rural population of India. It was also found that Prehypertension was 69.76% highly prevalent among this population; this is very high when compared to other studies of India (20%, 40%; [8, 9] 27.14%. [3]

The first phase of ICMR-INDIAB study has reported 62.4 million diabetes; 77.2 million prediabetes in India, diabetes was reported ranging from 5.3%-13.6%. [10] In our study we noted 4.36% of diabetes and 14.24% prediabetes which is consistent with overall diabetic and pre-diabetic rate of India. Zaman etal [11] noted higher prevalence of diabetes 19.78% among the rural population of Arunachal Pradesh. The mean fasting blood glucose level was noted as 90.80±27.81 which is in normal range.

Our study has shown 57.84% population overweight/obese based on their BMI. Males were highly susceptible 60.97% than females 46.04%. The mean BMI was noted as 25.88±5.0 (Males 26.19±4.94; Females 25.32±5.13 two tail p value 0.1182). Whereas all the other Indian studies have shown high overweight/obesity among females. Koukoulis GN[12] etal noted overweight being more prominent in males (27.8%) than in females (25.6%), the mean BMI was also significantly higher in males (28.2±4.4) than in females (26.9±6.2) among the adults of Central Greece.

This study has also reported higher prevalence of behavioral CVD risk factors among this population. Alcohol consumption is high in both the sex (males 42.43%/females4.31%)compared to smoking (males 37.56%/females 3.59%). Overall 27.03% alcoholism; and 23.83% smoking was reported. According to Global Adults Tobacco Survey (GATS) – 2010, smoking is about 15% in males and 1.90% in females.[13] Ganesh Kumar et al[14] has reported 16.8% alcohol consumption in males and 1.3% in females among the rural population of Tamilnadu. The National health profile survey reported 11%-20% alcohol consumption. [15] In our study alcohol consumption and smoking is high in females compared to other studies.

The current study has recorded 6.17% were at >10% of CVD risk among the age group 40-60 years. The other studies using WHO/ISH prediction chart has recorded 6%; 2.3% and 1.3% >20% chance of developing a cardiovascular event in Mongolia, Malaysia and Cambodia at 40-64 years age group.[16] Nordet P [17] has reported 2.9% with cholesterol; 4.6% without cholesterol ≥20% CVD risks in Cuba at 40-80 years age group. Aswin K [18] reported 3.7% subjects had >10 % risk of developing cardiovascular disease. Gift Norman [3] reported >20% CVD risk among 28.04% the rural population of India at 40-80 years age. The difference may attribute to the age group and sample size taken.

CONCLUSION:

The cardiovascular risk factors such as high central obesity, smoking, alcohol consumption are quite alarming in this rural population. The cardiovascular risk is also correspondingly high. This warrants strategies that would improve awareness and promote healthy life-styles to reduce the risk of CVD in this population.

Study limitations: The screened population was very less in number to generalize the population as a whole. Large multi-centric studies are required to establish more accurate findings. However Sharmini Selvarajah [19] has recommended FRS (Framingham Risk Score) and SCORE (Systemic Coronary Risk Evaluation) models in Asian population, this arises a need to establish a suitable CVD risk model that is applicable to local people setting.

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Research Article

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Study of risk factors for metabolic syndrome in subjects from rural area of Kurnool district

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ABSTRACT

The ongoing rapid urbanization of India offers rural population the opportunity not only of economic improvement but also substantial health risk. The non-communicable disease (NCD) risk in India is increasing proportionally with increased risk for metabolic syndrome (MetS). There is no published data on metabolic syndrome risk factors from rural population of Kurnool district. To assess the MetS risk factors among rural population of Kurnool district using modified NCEP ATP III criteria. We studied 344 individuals with the age range 20-60 years. The risk factors for MetS were considered on the basis of modified NCEP ATP III criteria was defined by modified NCEP ATP III criteria, determined in terms of age and sex. Other variables were evaluated by using simple logistic regression methods. A total 33.65% men and 29.49% women were at high risk for MetS. Increased WC (52.03%) and decreased HDL-C (73.83%) followed by hypertriglyceridemia (37.50%); hypertension (36.04%); and hyperglycemia (18.02%) are found to be the main culprits for MetS in this population. The other physiological and behavioural CVD risk factors are as follows smoking 23.83%, alcohol intake 27.03%, history of type 2 DM 13.27%, history of HTN 11.91%, family history of type 2 DM 11.91% and family history of hypertension 7.55%.. Based on BMI percentage of underweight subjects is 6.10%; overweight/obesity (BMI ≥25.0)-57.26% and only 34.88% subjects are with normal BMI. MetS is present in 21.27% of subjects with normal BMI. Cardiovascular risk index calculated by Castelli index I, II and non HDL/HDL-c have shown significant correlation (r=0.0625; 0.0575; 0.0578 respectively) with number of MetS risk factors. MetS is present in 36.11% sedentary life style subjects whereas it was 30.88% among the subjects doing normal to hard work life style. MetS risk factors were high among this population. Central obesity and decreased HDL-c are found to be major risk factors. This scenario needs a better appraisal in order to create awareness to prevent or reduce these modifiable MetS risk factors among this population.

Key words: Kurnool, Prevalence, Metabolic Syndrome (MetS)

INTRODUCTION

Metabolic syndrome is a multi-dimensional risk factor of atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes mellitus (T2DM).[1, 2] According to World Health Report 2002, CVDs are going to be the largest cause of death and disability by 2020 [3] and by 2030 diabetes mellitus (DM) afflict up to 79.4 million individuals in India, while china (42.3 million) and the US (30.3 million).[4] The National Cholesterol Education Program (NCEP) The Adult Treatment Panel (ATP III) defines MetS as 3 or more of the following abnormalities:

hypertriglyceridemia, low HDL, high fasting glucose, excessive waist circumference, and hypertension.[5] These risk factors may oscillate with ethnic population, region and country.[6]

Our previous hospital based cross sectional studies reported 19.80%[7]; 29.6% [8] prevalence MetS in adults of Nandyal an urban area of Kurnool district, Andhra Pradesh, India using WHO, modified NCEP ATP III criteria in the year 2012, 2013 respectively. This scenario deserves better appraisal to assess prevalence of metabolic syndrome among rural population at ground level.

Therefore we have under taken this study designed with an objective to assess the metabolic syndrome and related risk factors among apparently healthy rural adults (20-60 years) of this population. This research provides a substratum to explore the pathophysiology and treatment modalities of associated cluster risk factors with the entity of metabolic syndrome.

EXPERIMENTAL SECTION

This transversal study is conducted in Neravada, located in Kurnool district of Andhra Pradesh, India. Total 344 subjects aged 20 to 60 years analyzed for MetS in the year 2014. Simple random technique applied for selection of participants.

Inclusion criteria: - Apparently healthy adults (aged 20-60 years) are included.

Exclusion criteria: - Pregnant women, lactating mothers and those who are severely ill excluded from this study.

The required data information is collected from the subject by a face to face interview, anthropometric, clinical and biochemical examination. The data variables are shown in table-1.

Table 1: The variables used in the present Study

STUDY VARIABLES	
Demographic	Age, Gender
Behavioural	Smoking, tobacco Chewing and alcohol consumption
Clinical Examination	Weight (kg), Height (cm), Waist circumference (WC)cm Blood Pressure (BP)
Oral Questionnaire	Family history (FH)/History of diabetes, Hypertension (HTN), type of work and History corresponding medication
Biochemical tests	Fasting blood sugar (FBS), Total cholesterol(T.CHO), Triglycerides (TG), HDL-cholesterol (HDL-C)

The WC is measured at the level of uppermost lateral border of the iliac crest, made at a normal minimal respiration, at the end of gentle exhaling. BP is recorded, the average of two brachial systolic and diastolic blood pressure readings were taken.

5 ml of fasting blood samples after 12 hours overnight fasting were collected for analysis of biochemical parameters like FBS, T.CHO, TG and HDL-c etc. All the investigations are done on the same day on a semi automated analyzer (Transasia–Erba Chem. V5 X) using standard protocol. VLDL-C is calculated using the formula TG/5; LDL-C by subtracting VLDL-C and HDL-C from total cholesterol (Freidwald formula) and body mass index (BMI) was calculated by dividing weight by height squared (kg/m^2).

Cigarette smoking is defined by history of smoking at least 100 cigarettes in one's lifetime, alcohol drinking is defined as at least once in a week alcohol consumption, physical activity is defined as participating in moderate or vigorous activity for 30 minutes or more per day at least 3 days per week and family history is defined as at least one of the parent, brother or sister diagnosed as diabetic in a life time by self reporting.

The participants were divided based on their age into 4 groups i.e., 21-30, 31-40, 41-50 and 51-60 years. The MetS defined by Asian specific modified NCEP ATP III criteria. Presence of any three following risk factors is considered as positive for risk of MetS. Central obesity - WC > 90 cm (men), > 80 cm (women); BP - SBP ≥ 130 mmHg and / or DBP ≥ 85 mmHg or medical treatment for previously diagnosed hypertension; hypertriglyceridemia - TG ≥ 150 mg/dL; low HDL-C < 40 mg/dL (men), < 50 mg/dL (women); impaired FBS ≥ 100 mg/dl. The Atherogenic ratios (AR) were calculated as follows: Atherogenic Index of Plasma (AIP) = log (TG/HDL); Castelli Risk Index (CRI-1) = TC/HDL; Castelli Risk Index (CRI-2) = LDL/HDL; Atherogenic Coefficient (AC) = non HDL/HDL.

During the entire study the utmost care was taken according to Helsinki Declaration about patient confidentiality. The study was approved by Institutional Ethical Committee (IEC). Written Informed consent of participants was taken prior to study

STATISTICAL ANALYSIS

Data analysis was done by graph pad instat 3 version. Mean and standard deviation (S.D.) of the numerical variables were calculated. Un-paired student's "t" test is used for statistical significance. A p value <0.05 was considered significant. Correlation was seen by applying correlation coefficient.

RESULTS

The study includes 344 subjects comprising Males (n=205) & Females (139). The data in **Table 2** shows gender difference in MetS risk factors in percentage. Among 344 subjects, 110 (31.97%) are at risk of MetS, impact is more in men than women 33.65% (n=69); 29.49% (n=49) respectively.

Table 2 Showing gender difference in Percentage of risk factors for MetS

Variable	**Men** % (n)	**Women** % (n)
Central obesity	50.73(104)	53.95 (75)
Elevated SBP	27.31(56)	37.41 (25)
Elevated DBP	20.00(41)	18.70 (26)
Hyper triglyceridemia	42.92(88)	29.49 (41)
Low HDL-C	63.90(131)	88.48(123)
Impaired fasting plasma glucose	20.48(42)	14.38 (20)

Graph: 1 showing relative number of modified NCEP ATP III criteria obeyed by the subjects. Any one or two risk factors present in 60.46% subjects. Only 7.5% are without any risk factors.

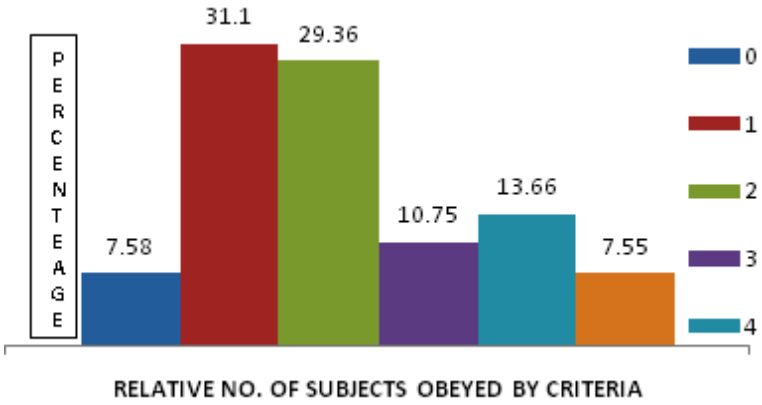


Table 3 is showing predominance (%) of MetS in study age groups. Women at the age of 51-60 years are more prone as compared to men.

Table 3 Predominance (%) of metabolic syndrome by age and gender

Age Group	Total	Men % (n)	Women % (n)
21-30	22.58	23.94 (17)	20.75 (11)
31-40	28.73	33.33 (16)	23.07 (9)
41-50	38.75	38.77 (19)	38.70 (12)
51-60	49.05	45.94 (17)	56.25 (9)

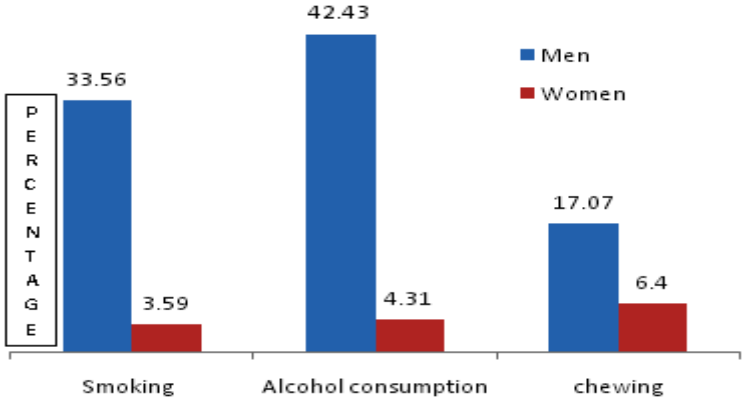
The analysis of BMI shows underweight is 6.10%; overweight/obesity-57.26% and only 34.88% subjects are with normal BMI. Total 60.97% men and 53.23% women are overweight / obese. MetS present in 21.27% of subjects with normal BMI.

Table 4 is showing Mean±SD of atherogenic risk index lipid ratios of MetS positive and negative subjects, and correlation with number of risk factors of an individual

Atherogenic risk index lipid ratio	MetS **positive**	MetS **negative**	R	R^2
Atherogenic index of plasma (AIP)	0.65±0.13	0.52±0.10*	0.2697	0.0727
Castelli Risk Index -1 (CRI-1)	5.64±5.75	3.99±0.84*	0.2500	0.0625
Castelli Risk Index -2 (LDL/HDL)	3.62±4.73	2.31±0.80*	0.2398	0.0575
Atherogenic Co-efficient (Non HDL/HDL)	4.59±5.77	2.99±0.84*	0.2404	0.0578

*r = coefficient variation; R^2= coefficient determination * = significant*

Graph: 2 showing percentage of smoking, alcohol consumption, chewing in men and women. Relative risk ratio (RR) for the development of MetS in alcohol consumption is 1.517 (p=0.0266; CI 1.517 to 1.076); smoking-1.837 (p=0.0018; CI 1.269 to 2.661); chewing- 2.127 (p=1.232 to 3.672).



History of type 2 diabetes is present in 13.27%; hypertension -11.91%; family history of-diabetes-11.91%; family history of hypertension-7.55% subjects. However impaired fasting blood glucose levels are present in 58.69 % subjects, who are already under treatment for DM. Furthermore, it was 68.29% in case of hypertension. MetS is present in 36.11% sedentary life style subjects whereas 30.88% among the subjects doing normal to hard work life style.

DISCUSSION

The importance of MetS lies in the cardiometabolic risk factors of the criteria applied in screening. This syndrome will elevate the risk for development of ASCVD by 2 fold and T2DM by 3-fold. [9] The current study implemented a modified NCEP ATP III criterion that is specific for Asian. A total 31.97 % (men-33.65%; women-31.97%) were at high risk for MetS. Chow CK et.al. [10], MA Njelekela et al [11], L Fezeu et.al. [12] also noted high prevalence of MetS in men compared to women. The reverse is reported by T Ahonen et al [13], Y He et al [14]. This may attribute to high prevalence of waist girth (obesity) in men than women among this population.

The contribution of MetS components may oscillate with ethnic population, gender and country. [15] We identified elevated WC and decreased HDL-C is the consistent cluster components for MetS among this population. **[Table-2]** The results were in accordance with PC Deedwaina et al [16], Seerat Hussain et.al. [17] This occurs commonly irrespective of MetS definition applied. The obesity plays a role in the development of MetS and appears to precede the appearance of the other MetS component.[15] The approximate cut off level of WC [calculated using mean±2SD method] for appearing two other MetS factors in men is 83.86; it is 75.62 in case of women seems to be very low. However, in support to this we observed 21.27% MetS among the subjects with normal BMI. This condition gives us a scope to study other risk factors for MetS among this population. In multiple logistic regression model education (OR=1.358) and sedentary life style (OR=1.265) has no effect on MetS, while smoking (OR=0.4388) and alcohol (OR=0.5650) are showing significant effect.

The risk of MetS is increased with increasing age. Significant difference is noted in men and women at the age group 51-60 years that is prevalence decreased in men than women. **[Table 3]** In Finnish study [18] the prevalence of MetS was found to increase with increasing age in women. This gives an impression that the CVD risk will be increased in women by post menopausal, and in accordance with Regitz-ZV [15] et al who reported that women develop cardiovascular disease (CVD) at an older age compared men. In supporting to this, the age based fragmented analysis of current data revealed that MetS is 44.68% in women with ≥ 41 years of age while it was only 21.73% in men.

On evaluation of lipid ratios **[Table 4]** of the current study, we observed that AIP is statistically higher in MetS positive subjects compared to negative subjects (p=<0.0001). Consequently it has shown significant positive

correlation with number of MetS risk factors of an individual. It is suggested that AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high Cardiovascular risk.[19] We observed that mean AIP of MetS positive and negative subjects is >0.24. This may attribute to high abdominal obesity in this population, that causes deranged (high TG and low HDL-C) lipid pattern. An inverse relationship between TG and HDL-C is noted by several studies and that the ratio of TG to HDLc is a strong predictor of infarction. [20]

The Castelli Risk Ratio (CRI) is based on three important lipids i.e. TC, LDL and HDL-C. CRI-1 calculated as the ratio of [TC/HDL] and CRI-2 as [LDL/HDL]. [21] A Significant difference is observed between MetS positive and negative subjects in respect individual lipid parameters. However the mean values of TC is 166.77 and TG 146.02 found to be under normal range i.e. <200 mg/dl; < 150mg/dl respectively in MetS positive subjects. Whereas the ratio of these parameters has shown a clear cut statistically significant variation between MetS positive and negative subjects. Even though CRI-1 mean is slightly above the upper limit for the normal range i.e. >3.0 in MetS negative subjects, CRI-2 is under allowed range i.e. <3.0. In PROCAM study [22], it was observed that subjects with >5 of Castelli index-2 had six times higher rate of coronary events. The Quebec Cardiovascular study shown variations in Castelli index 1 and 2 ratios may be associated with more substantial alterations in metabolic indices predictive of ischemic heart disease risk and related to MetS. [23]

Studies have shown that non-HDL is similar to Apo-B in assessing atherogenic cholesterol and lipoprotein burden. [24] Atherogenic Coefficient (AC), calculated as non-HDL/HDL is a measure of cholesterol in LDL, VLDL, IDL lipoprotein fractions with respect to HDL. It reflects atherogenic potential of the entire spectrum of lipoprotein fractions. As per ATP III guidelines non HDL is the second target of therapy after LDL especially in individuals with increased triglycerides.[25] In the current study AC ratio is high in MetS positive subjects compared to negative one and significantly correlated with number of MetS risk factors. It gives an impression that atherogenic index will increase correspondingly with increasing MetS risk factors.

Alcohol consumption is high in both the gender (men 42.43% / women 4.31%) compared to smoking (men 35.56% / women 3.59 %). Overall 27.03% alcoholism; and 23.83% smoking was reported.**[Graph 2]** According to Global Adults Tobacco Survey (GATS) – 2010, smoking is about 15% in men and 1.90% in women.[26] Ganesh Kumar et.al.[27] has reported 16.8% alcohol consumption men and 1.3% in women among the rural population of Tamilnadu. The National health profile survey reported 11%-20% alcohol consumption. [28] In this current study alcohol and smoking is high in women compared to other studies. The Relative Risk Ratio (RR) showed that chewing of non smoke tobacco was a strong risk factor for MetS; this may due to 75% of them are having habit of alcohol consumption and smoking. The risk for MetS with alcohol consumption is low (r=1.517 CI 1.076 to 2.139) whereas along with smoking it is high (r=1.738 1.258 to 2.401). This gives an impression that clustering of modifiable risk factors may increase the cardio metabolic risk.

CONCLUSION

Metabolic syndrome related risk factors are high among this population. Males were at high risk may be due to high prevalence of central obesity. Females with postmenopausal age group are at high risk than males this may attributed to hormonal changes at this age. Most of the subjects receiving regular medication for diabetes and hypertension, having elevated blood pressure and fasting blood glucose levels. This warrants strategies that would improve awareness and promote healthy life-styles to reduce the risk for metabolic syndrome there by cardiovascular risk in this population.

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Original Article

Study of Metabolic Syndrome and Its Components Among Kurnool District Population of Andhra Pradesh with Different Ethnic Backgrounds

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ABSTRACT

Background: There is a constant increase in the preponderance of cardiovascular diseases in India. The recent scientific evidences have shown that if you do not detect and treat the metabolic syndrome patients at an early stage, it may proceed to cardiovascular disease. A scientific data on pattern of metabolic syndrome components of a population is very essential to formulate the preventive and treatment modalities among them. **Aim:** To explore the prevalence of metabolic syndrome and its components among Kurnool district population of Andhra Pradesh with different ethnic background. **Method:** A total of 1032 (344 subjects in each group) participants of 20-60 years of age group were analyzed for MetS. A modified NCEP ATP III criterion was applied for this. From each group 20 subjects were analyzed for fasting serum insulin and HOMA-IR randomly. **Results:** Overall prevalence of metabolic syndrome was found to 31.97%. It was almost equally prevalent among men (32.82%) and women (30.87%). Urban population (42.15%) were found to be highly inflicted by metabolic syndrome than rural (31.97%) and tribal (21.80%). Decreased HDL (78.87%) followed by increased waist circumference (57.84%) and hypertriglyceridemia (31.78%) were found to be the preceding risk factors of Mets in all the groups. The lipid estimates were not in correlation with insulin resistance (by HOMA IR) in rural population. Tribal women were found to be having a slightly higher mean waist circumference (86.45cm) compared to rural women (85.87cm). The behavioural cardiovascular risk factors like smoking alcohol consumption decreased circadian physical activity were high in rural and tribal population compared to urban population. Whereas other physiological cardiovascular risk factors like family history of hypertension and diabetes of rural population were in concordance to urban population. **Conclusion:** Metabolic syndrome prevalence is very high in Kurnool district population. Mets components are highly prevalent among the individuals with low WC (Waist Circumference) and BMI (Body Mass Index). This warrants the need to implement preventive strategies for Mets among the population of Kurnool district. The future projects has to be formulated with an aim to find out the genetic factors behind this scenario.

Key words: Adults, Insulin Resistance, Kurnool District, Prevalence of Metabolic Syndrome, Rural, Tribal, Urban, Population.

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INTRODUCTION

Metabolic syndrome (Mets) is a cluster of metabolic abnormalities that predispose an individual to develop cardiovascular disease (CVD).[1] The treatment modalities of CVD are very costly. It represents a major health care economic burden of poor people. However, early detection of Mets can help us to prevent or delay the CVD risk among them. Simple non-expensive diagnostic modalities are enough to identify the individuals with Mets. Moreover, the treatment for Mets is very cost effective.

According to the modified NCEP APT III (National Cholesterol Education Programme Adult Treatment Panel III) Mets is present if three or more of the following criteria are satisfied:[2] increased waist circumference, fasting blood glucose, serum triacylglycerol, blood pressure and decreased high density lipoprotein. Scientific studies have proved that insulin resistance is playing a crucial role in pathological transformation of metabolic syndrome to cardiovascular disease. Insulin resistance in lean persons can increase the risk of CVD two fold than in obese individual. Most of the lean persons with insulin resistance having metabolic syndrome are left undiagnosed. This causes increase in CVD related deaths in India.

The pattern of the metabolic syndrome components may vary with geographic elements, age, gender and type of population.[3] However, genetic susceptibility, behavioural and physiological factors also should be considered. This scenario implies that preventive strategies have to be formulated intended to that population. So, a scientific data representing the prevalence of metabolic syndrome risk factors of an area is very important to achieve the above.

Kurnool district is located in west-central part of Andhra Pradesh in India. It is having 28.40% of urban population and 71.60% rural population whereas schedule tribe are 2.00% of the total population in Kurnool district. Most of them are with poor and middle class economic background. Thereby this study is designed with an aim to determine the prevalence of metabolic syndrome in Kurnool district among urban, rural and tribal population.

MATERIALS AND METHOD

This is a cross sectional study done among the urban, rural and tribal population of Kurnool district in Andhra Pradesh, India. Assuming prevalence of Mets 41%, considering 95% confidence limit and ±5.2% margin of error the worked out sample size is 344 in each group together it is 1032.

From 54 mandal of Kurnool district, Nandyal was chosen by simple random sampling. In Nandyal 34 wards (in urban) 20 villages (rural) and 24 thandas areas are present. From 34 wards 6 wards were chosen by probability proportional to size sampling (PPS) method to collect 344 sampling units. Likewise 4 villages and 7 thandas were selected. 57 samples were collected from each ward by systemic random sampling technique, like wise 86 and 49 samples were collected from each village and thandas respectively. Pregnant women, lactating mothers and those who refused to participate were excluded from this study.

The subjects were analyzed by oral, anthropometric and biochemical parameters. WC (Waist Circumference) is measured at the level of uppermost lateral border of the iliac crest. Blood pressure was measured in supine position using sphygmomanometer; average of two brachial readings was taken. Cigarette smoking is defined by lifetime history of smoking at least 100 cigarettes, alcohol drinking is defined as at least once in a week alcohol consumption, physical activity is defined as participating in moderate activity for 30 min every day and family history is defined as at least one of the parent diagnosed as diabetic or hypertension in a life time by self-reporting.

5 ml of fasting (12 h overnight) venous blood was collected from the subjects and analyzed for FBS (Fasting Blood Glucose) by glucose oxidase and peroxidase method,[4] T.CHO (Total Cholesterol) by cholesterol oxidase-peroxidase method,[5] TGL (Triacylglycerol) by GPO peroxidase method,[6] HDL (High Density Lipoprotein) by Phosphotungstate method,[7] Fasting insulin levels by elecrochemiluminescence immunoassay "ECLIA" method.[8] The sensitivity of the assay was 0.2-1000 µU/ml. Insulin resistance (IR) was derived using the Homeostasis Model Assessment (HOMA) non-computerised calculation.[9]

The MetS defined by Asian specific modified NCEP ATP III criteria. Presence of any three following risk factors is considered as positive for risk of MetS. Central obesity - WC > 90 cm (men), > 80 cm (women); BP – SBP (Systolic Blood Pressure) ≥ 130 mmHg and / or DBP (Diastolic Blood Pressure) ≥ 85 mmHg or medical treatment for previously diagnosed hypertension; hypertriglyceridemia - TGL ≥ 150 mg/dl; low HDL-C < 40 mg/dl (men), < 50 mg/dl (women); impaired FBS ≥ 100 mg/dl. During the entire study the utmost care was taken according to Helsinki Declaration about patient confidentiality.[10] The study was approved by Institutional Ethical Committee (IEC). Written Informed consent of the participants was taken prior to study

Data analysis was done by graph pad instat 3 version. Mean and standard deviation (S.D.) of the numerical variables were calculated. Unpaired student's "t" test was used for statistical significance. A p value <0.05 was considered significant. Correlation was seen by applying correlation coefficient (r).

RESULTS

The clinical, behavioural and physiological characteristics of the participants are shown in Table 1. Compared to urban and tribal residents alcohol consumption, smoking, fasting serum insulin and insulin resistance were very high in rural. The MetS components have shown a statistically significant difference (p=<0.05) among the groups. Family history of DM and HTN of rural population both were in concordance with urban population.

N= number of participants; n=number of participant with that Mets component

Table 2 & 3 are showing that overall prevalence of Mets in Kurnool district is 31.97%. It is almost equally prevalent among men (32.82%) and women (30.87%). Urban (42.15%) population is highly effected than rural (31.97%) and tribal (21.80%) population. Mets risk factors are found to be increase with increasing age in all, male and female subgroups. Low HDL, high WC followed by raised TGL is found to be potent risk factors for Mets. Increased waist circumference is highly prevalent in tribal women compared to rural women. Blood pressure is highly prevalent in men than women. There is a sudden increase in Mets among the women at postmenopausal age group. *= p value is less than 0.05

Table 4 shows that fasting plasma insulin and HOMA IR are not correlated. HOMA IR in rural residents does not show correlation with any Mets risk factors except DBP. HOMA IR does not show any correlation with HDL in any of the three study groups.

DISCUSSION

The underlying systemic inflammation is the main cause of cardiovascular diseases among the patients with Mets. It increases the CVD risk by 2 fold and type 2 diabetes mellitus by 3 fold.[11] The importance of Mets lies in the cardiovascular risk factors of the Mets criteria applied. The current study has implemented a modified NCEP ATP III criterion that is specific for Asian population. Total 31.97 % participants are estimated to be afflicted by Mets. The previous studies have noted 19.80%[12] (WHO criteria); and 29.60%[13] (ATP III criteria) of MetS prevalence in this population. Mets is almost equally present in males (32.82%) and females (30.87%) of this population. The slight difference may be attribute to the low physical activity, high smoking and alcohol consumption among the male of this population (Table 1). Chow CK *et al*[14] MA Njelekela *et al*,[15] L Fezeu *et al*[16] have noted high prevalence of Mets in men compared to women. The reverse was reported by T Ahonen *et al*,[17] Y He *et al*.[18]

The current study has focused on distribution pattern of metabolic syndrome and its components among urban, rural and tribal population of Kurnool district. The results imply that urban population are highly afflicted by Mets than rural and tribal population. Like our findings, previous studies also reported a higher prevalence of MetS in urban when compared with semi-urban and rural population, Gu D *et al*[1] survey among Chinese adults aged 35-74 years showed 18.60% prevalence of MetS in urban population than in rural 12.70%. The reverse was noted by Shanoyong *et al*[20] among north-western population of china, age-standardized prevalence of MetS was significantly higher in rural (29.00%) residents than urban (25.90%) counterparts.

The contribution of Mets components may oscillate with ethnic population, gender and country.[21] We have identified that elevated WC followed by decreased HDL-C and increased triglycerides are common cluster components of MetS in this population (Table 2-3). The results were in accordance with Deedwaina *et al* [22] and Hussain *et al*.[23] The proportion of MetS risk factors was found to increase with increasing age in all, male and female subgroups. This may be attributed to the increased BMI (Body Mass Index) with increasing age in this population. The cardio metabolic abnormalities which may develop at lower BMI in Indians compared to other ethnic groups is also to be considered. The current study has identified total 95.16% of participants as having any one or two Mets with normal WC or BMI. This givens an impression that all the above participants are may proceed to Mets.

Obesity plays a role in the development of MetS and appears to precede the appearance of the other MetS components.[21] The other important outcome of the study is tribal women have high mean waist circumference (86.45 cm) compared to rural women (85.87 cm). It represents recent scientific data showing that increasing burden of central obesity all over the world irrespective of ethnicity. This scenario alarms the need to study the role of Mets component in development of CVD on ethnic bases. In supporting to this Bharathi *et al*[18] have recorded 95 cm of larger WC in Bhagatha tribal women of Eastern Ghats in Vijayanagaram district of Andhra Pradesh. The study has also identified preponderance of Mets among the females of Kurnool district at post-menopausal age. This can be explained by metabolic changes in menopause and the fac-

Table 1: Clinical characteristic of study participants in Kurnool district.

VARIABLE		URBAN	RURAL	TRIBAL	TOTAL
Number (n)		344	344	344	1032
Gender	Male n (%)	208 (60.46)	205 (59.59)	172 (50.00)	585(56.68)
	Female n (%)	136 (39.53)	139 (40.40)	172 (50.00)	447(43.31)
Literacy	Illiterate	115(33.43)	126 (36.62)	162(47.09)	403(39.05)
	up to secondary	127 (36.91)	158 (45.93)	131 (38.08)	416(40.31)
	Above secondary	102 (29.65)	60 (17.44)	51 (14.82)	213(20.63)
Cigarette Smoking n (%)		106 (30.81)	82 (23.83)	45 (13.08)	233(22.57)
Alcohol Consumption n (%)		87 (25.29)	93 (27.03)	45 (13.08)	225(21.80)
Chewing n (%)		6 (1.74)	44 (12.79)	26 (7.55)	76(7.36)
Family History (FH) of diabetes mellitus (DM) n (%)		28 (8.13)	41 (11.91)	28 (8.13)	97(9.39)
FH of hypertension n (%)		27 (7.84)	26 (7.55)	9 (2.61)	62(6.00)
Personnel history of DM n (%)		48 (13.95)	46 (13.37)	27 (7.84)	121(11.72)
Personnel history of HTN n (%)		82 (23.83)	41 (11.91)	11 (3.19)	134(12.98)
Waist circumference (cm)		91.04±5.39	85.87±11.96	86.45±7.78*	87.92±9.11
Systolic blood Pressure (mmHg)		122.31±9.21	122.97±6.97	121±5.25*	122.17±7.44
Diastolic blood pressure (mmHg)		81.58±4.30	82.22±4.46	80.64±3.63*	81.49±4.23
Fasting blood glucose (mg/dl)		93.06±16.86	90.65±27.76	85.20±13.88*	89.77±20.91
Serum triglycerides (mg/dl)		142.68±29.13	142.49±26.08	125.16±24.41*	89.77±20.91
Serum HDL-C (mg/dl)		34.37±4.34	38.56±6.64	39.87±6.08*	37.27±27.67
Fasting Insulin µU/ml		18.32±9.56	23.83±10.15	14.18±9.68*	18.77±10.61
HOMA-IR		4.14±3.06	5.62±3.38	2.90±2.08*	4.17±2.99

Table 2: Crude and age standardized prevalence of metabolic syndrome in the study groups by gender.

Age group (year)	URBAN n/N-%		RURAL n/N-%		TRIBAL n/N-%		Total n/N-%	
			All					
20-30	37/133	27.81	28/124	22.58	26/156	16.66	91/413	22.03
31-40	30/80	37.50	25/87	28.73	14/68	28.58	69/235	29.36
41-50	32/63	50.79	31/80	38.75	17/53	32.07	80/196	40.81
51-60	46/68	67.64	26/53	49.05	18/67	26.86	90/188	47.87
Crude Standardized	145/344	42.15	110/344	31.97	75/344	21.80	330/1032	31.97
			Male					
20-30	23/83	27.77	17/71	23.94	12/77	15.58	52/231	22.51
31-40	22/51	43.13	16/48	33.33	6/33	18.18	44/132	33.33
41-50	15/34	44.11	19/49	38.77	7/20	35.00	41/103	39.80
51-60	27/40	67.50	17/37	45.94	11/42	26.19	55/119	46.21
Crude Standardized	87/208	41.82	69/205	33.65	36/172	20.93	192/585	32.82
			Female					
20-30	14/50	28.00	11/53	20.75	14/79	17.72	39/182	21.42
31-40	8/29	27.58	9/39	23.07	8/35	22.85	25/103	24.27
41-50	17/29	58.62	12/31	38.70	10/33	30.30	39/93	41.93
51-60	19/28	67.85	9/16	56.25	7/25	28.00	35/69	50.72
Crude Standardized	58/136	42.64	41/139	29.49	39/172	22.67	138/447	30.87

Table 3: Crude prevalence of individual component of metabolic syndrome in the study groups by gender

Variable	URBAN n/N-%		RURAL n/N-%		TRIBAL n/N-%		TOTAL n/N-%	
Overall								
Raised fasting glucose	69/344	20.05	62/344	18.02	26/344	7.55	157/1032	15.21
Raised SBP	104/344	30.23	81/344	23.54	48/344	13.95	233/1032	22.57
Raised DBP	84/344	24.41	67/344	19.47	42/344	12.20	193/1032	18.70
Raised sr. TGL	142/344	41.27	129/344	37.50	57/344	16.56	328/1032	31.78
Lowered sr. HDL	327/344	95.34	254/344	73.83	233/344	67.73	814/1032	78.87
Larger waist circumference	255/344	74.12	179/344	52.03	163/344	47.38	597/1032	57.84
Male								
Raised fasting glucose	43/208	20.67	42/205	20.48	14/172	8.13	99/585	9.59
Raised SBP	66/208	31.73	56/205	27.31	30/172	17.44	152/585	14.72
Raised DBP	52/208	25.00	41/205	20.00	25/172	14.53	118/585	11.43
Raised sr. TGL	95/208	45.67	88/205	42.92	41/172	23.83	224/585	21.70
Lowered sr. HDL	196/208	94.23	131/205	63.90	92/172	53.48	419/585	40.60
Larger waist circumference	135/208	64.90	104/205	50.73	66/172	38.37	305/585	29.55
Female								
Raised fasting glucose	26/136	19.11	20/139	14.38	12/172	6.97	58/447	5.62
Raised SBP	38/136	27.94	25/139	17.98	18/172	10.46	81/447	7.84
Raised DBP	32/136	23.52	26/139	18.70	17/172	9.88	75/447	7.26
Raised sr. TGL	47/136	34.55	41/139	29.49	16/172	9.30	104/447	10.07
Lowered sr. HDL	131/136	96.32	123/139	88.48	141/172	81.97	395/447	38.27
Larger waist circumference	120/136	88.23	75/139	53.95	97/172	56.39	292/447	28.29

N= number of participants; n=number of participant with that Mets component

Table: 4 Correlation between components of Mets and insulin resistance.

Correlation between	Urban	Rural	Tribal	Overall	
FBS	r-value	0.3194	0.1302	0.4095	0.2909
s.	95% CI	-0.1578-0.6757	-0.5416-0.01696	-0.07109-0.7358	0.03275-0.054127
Fasting Insulin	P-value	0.1826	0.5842	0.0915	0.0281
WC	r-value	0.4586	0.1035	0.8333	0.5258
vs.	95% CI	0.005388-0.7555	-0.3554-0.5222	0.5996-0.9360	0.3072-0.2764
HOMA IR	P-value	0.0483*	0.6642	<0.0001*	<0.0001*
TGL	r-value	0.5848	0.002958	0.7381	0.5714
vs.	95% CI	0.1486-0.8110	-0.4402-0.4450	0.4137-0.8962	0.3652-0.7242
HOMA IR	P-value	0.0118*	0.9901	0.0005*	<0.0001*
SBP	r-value	0.4406	0.3030	0.5359	0.4241
vs.	95% CI	-0.01719–0.7456	-0.1612-0.6575	-0.09190-0.8021	0.1838-0.6166
HOMA IR	P-value	0.0590*	0.1941	0.0219*	0.0010*
DBP	r-value	0.8093	0.6372	0.5052	0.5906
vs.	95% CI	0.5613-0.9239	0.2710-0.8423	0.05007-0.7866	0.3901-0.7377
HOMA IR	P-value	<0.0001*	0.0025*	0.0325*	<0.0001*
HDL	r-value	-0.1570	-0.03458	0.2095	-0.1554
vs.	95% CI	-0.5706-0.3201	0.5209-0.4141	0.2853-0.6162	-0.3998-0.1097
HOMA IR	P-value	0.5209	0.8839	0.4040	0.2483

*= p value is less than 0.05

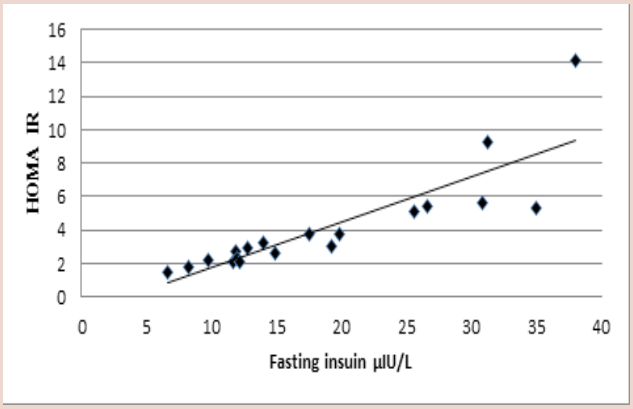

Figure1: Correltion of Fasting Insulin and HOMA IR in urban population.

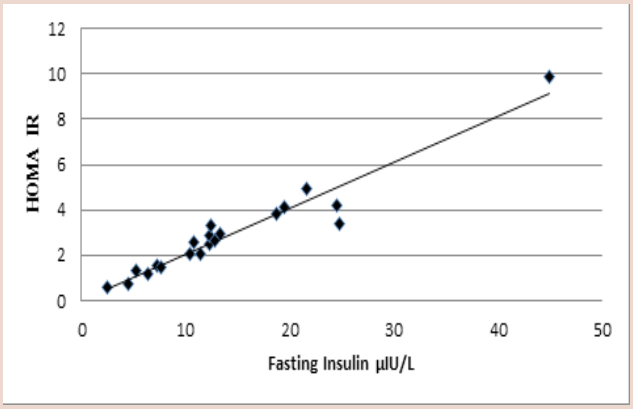

Figure 2: Correlation of fasting insulin and HOMA IR in rural population.

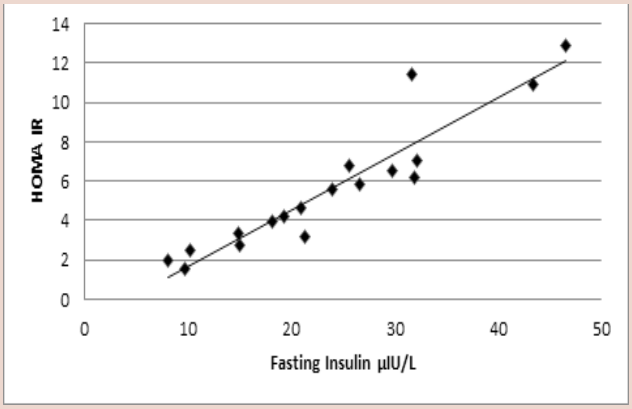

Figure:3 Correlation of Fasting Insulin and HOMA IR in tribal poplation.

tors protecting women like endogenous estrogens against atherosclerosis in premenopausal females. The results have shown postmenopausal female have higher BMI. Higher prevalence of blood pressure (BP) in males compared with females can be explained by gender and sex hormones effect on components of the rennin-angiotensin system.

Insulin resistance is the preceding cause for CVD in patients with Mets. We have correlated the Mets components with HOMA IR. The estimates have shown that fasting plasma insulin and HOMA-IR were not correlated (Table 4). It proves presence of insulin resistance in all the three groups (Figure 1-3).

HOMA IR in rural residents has not shown correlation with any MetS risk factors except DBP. The results are coincides with the findings of M.K. Garg *et al* and Snehalatha *et al.*[20, 21] On the contrary, others found significant positive correlation between HOMA-IR and lipid parameters, and fasting plasma glucose. HDL was not correlated with HOMA IR in all three groups. Inverse correlation between HOMA-IR and HDL cholesterol was noted by Kressel G *et al.*[22] The results are showing that lipids do not directly interfering with MetS in this population. May be genetic predisposition is playing the major role for insulin resistance and MetS among this population. This scenario needs an attention to study the role genetic factors in Kurnool district population for Mets.

The behavioural CVD risk factors like alcohol consumption is high in both the gender (men 34.52%; women 5.14%) compared to smoking (men 20.34; women 2.22 %). Overall 21.80% alcoholism; and 21.80% smoking was reported (Table-1). According to Global Adults Tobacco Survey (GATS) – 2010, smoking is about 15% in men and 1.90% in women.[24] Ganesh Kumar *et al.*[25] have reported 16.80% alcohol consumption in men and 1.30% in women among the rural population of Tamilnadu. The National health profile survey reported 11%-20% alcohol consumption.[26] In this current study alcohol and smoking is high in women compared to other studies. Our previous study[27] have shown that risk for MetS with alcohol consumption is low (r=1.517 CI 1.076 to 2.139) whereas along with smoking it is high (r=1.738 1.258 to 2.401). This gives an impression that clustering of modifiable risk factors may increase the cardio metabolic risk.

The outcome of the study includes

1. High prevalence of metabolic syndrome in Kurnool district
2. Higher levels of HOMA IR in rural population than urban residents
3. There is no correlation of insulin resistance (HOMA IR) with any Mets components in rural population

4. Higher prevalence of physiological and behavioural risk factors among rural and tribal population in concordance to urban population.
5. Higher prevalence of Mets components in low waist circumference and normal BMI.
6. High mean of BMI in tribal women compared to rual women.

CONCLUSION

Metabolic syndrome prevalence is very high in Kurnool district population. Almost all the lean participants showed the presence of 1 or 2 of the Mets components. This warrants a regular screening for Mets irrespective of obesity. It may help in preventing the consequent CVD related mortality and morbidity by taking preventive measures like simple life style modifications.

LIMITATIONS OF THE STUDY

The study is an observational study. Longitudinal studies are important to make causal inferences and to identify unmeasured or unknown risk factors for cardiometabolic risk in this population. The subjects are almost from middle class to poor socioeconomic background.

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CONFLICT OF INTEREST

None

ABBREVIATION USED

CVD: Cardiovascular disease; ECLIA: elecrochemiluminescence Immunoassay; FBS: Fasting blood glucose; HDL: High density lipoprotein; Mets: Metabolic syndrome; NCEP ATP III: National Cholesterol Education Programme Adult Treatment Panel III; T.CHO= total cholesterol; TGL=Triacylglycerol; WC: Waist circumference.

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Annexure -I

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3. **Department:** BIOCHEMISTRY
4. **Name of the Guide & Designation:** DR. J.G. AMBEKAR, PROFESSOR
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Name of the faculty member: **Mr. Pandit Vinodh Bandela,** department of Biochemistry.

Name of Guide/Co-guide: **Dr. J.G.AMBEKAR,** Professor, Department of Biochemistry, Shri B.M. Patil Medical College, Bijapur-586 103.

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