"STUDY OF SUBCLINCAL THYROID DYSFUNCTION IN PATIENTS WITH METABOLIC SYNDROME"

By

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION, KOLAR, KARNATAKA

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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IN

GENERAL MEDICINE

Under the guidance of

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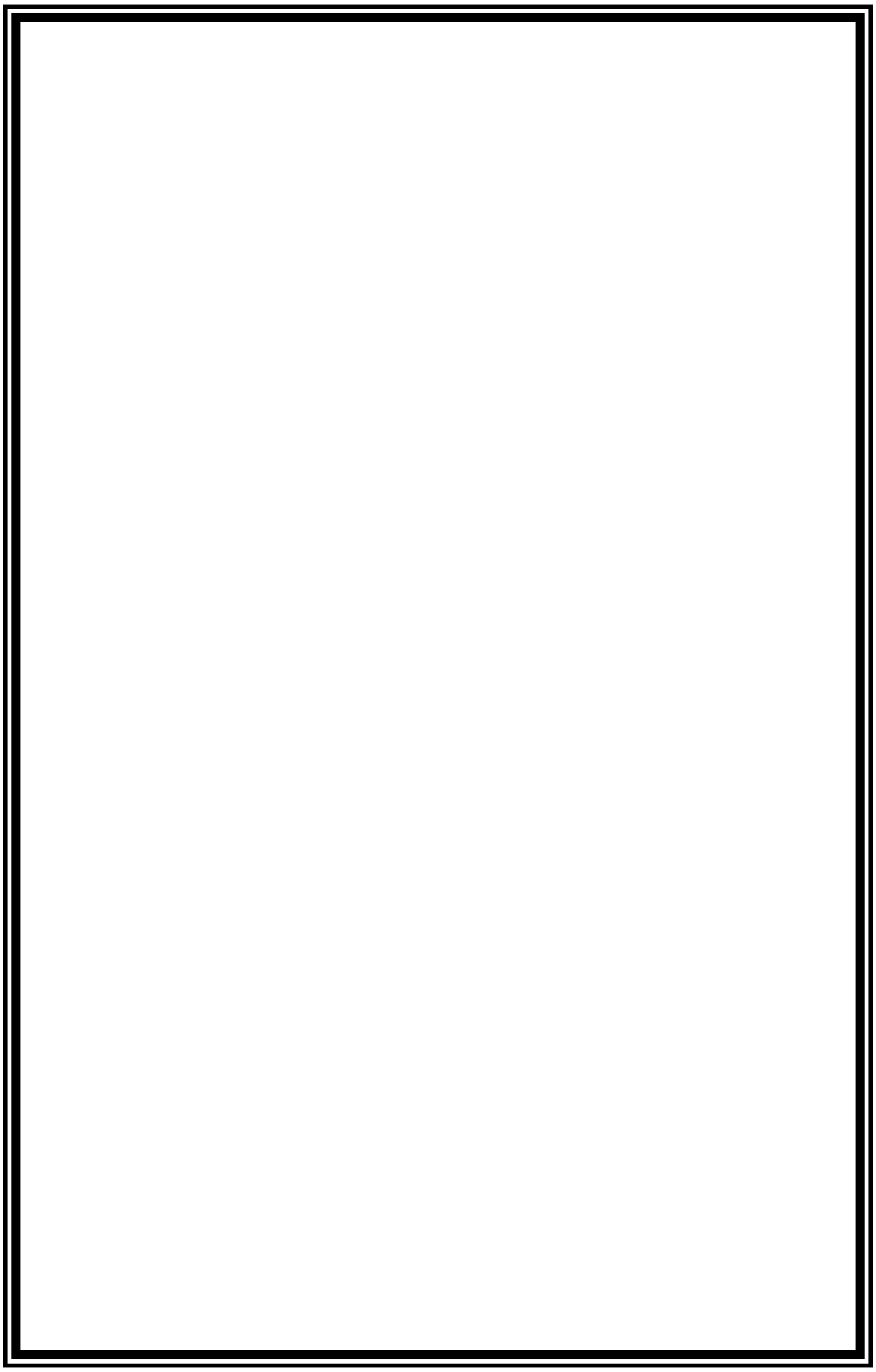

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ABSTRACT

BACKGROUND:

The metabolic syndrome is a cluster of cardiovascular risk factors like diabetes, hypertension, abdominal obesity and dyslipidemia. Thyroid disease is associated with atherosclerotic cardiovascular disease. Subclinical abnormalities in TSH levels are associated with detrimental effects on cardiovascular system. Metabolic syndrome and thyroid dysfunction are independent risk factors of atherosclerotic cardiovascular diseases and the coexistence of the two will substantially increase cardiovascular risk.

OBJECTIVES:

- To study the association between metabolic syndrome and subclinical thyroid dysfunction.

METHODS:

This study is a prospective case control study based on analysis of 100 patients (50 cases and 50 controls) during a period from January 2012 to January 2013.

The study group comprised of inpatients and outpatients of R.L.Jalappa hospital and research centre attached to the Sri Devaraj Urs Medical College, Kolar.

Every patient will be evaluated by history, clinical examination and relevant investigations.

RESULTS:

The age of the patients ranged from 31 to 90 years, with a median age of 61.18 years. Maximum number of cases was in the 51-60 years (34%). Male and Females were equal in cases, while males predominated in controls (66%).

Incidence of subclinical Hypothyroidism are more in Cases (22.0%) compared to Controls (8.0%) with P=0.091. Incidence of subclinical Hyperthyroidism are more in Cases (10.0%) compared to Controls (4.0%) . Subclinical hypothyroidism was maximum in age group between 50-70 years in males and 30-50 years in females.

CONCLUSION:

In this study we found that 32% of the subjects with metabolic syndrome had subclinical thyroid dysfunction, which is quite a significant number. 22% of metabolic syndrome patients had subclinical hypothyroidism as compared to 8% of the general population, which was statistically significant. 10% of metabolic syndrome patients had subclinical hyperthyroidism as compared to 4% of the general population studied, which is also quite a high number. Investigation for subclinical thyroid dysfunction- both hyperthyroid and hypothyroid prior to initiation of treatment for MetS patient may be a reasonable strategy.

KEY WORDS: Metabolic Syndrome, subclinical hypothyroidism, subclinical hyperthyroidism

LIST OF ABBREVIATIONS

AACE	American association of clinical endocrinologists
ATPIII	Adult treatment panel
CAD	Coronary artery disease
CHD	Coronary heart disease
CRP	C-reactive protein
CVD	Coronary vascular disease
DBP	Diastolic blood pressure
DM	Diabetes Mellitus
FBS	Fasting plasma sugar.
FFAS	Free fatty acids
FPG	Fasting plasma glucose
HbA1C	Glycated haemoglobin
HDL	High-density lipoprotein
IL-6	Interleukin 6
IRS	Insulin resistance syndrome
LDL	Low-density lipoproteins
MI	Myocardial infarction
MetS	Metabolic syndrome
NCEP	National cholesterol education program
NHNES	National health and nutrition examination survey
OGTT	Oral glucose tolerance test
OHA	Oral Hpoglycemic Agents
PAI	Plasma plasminogen activator inhibitor
PPBS	Post pranidial blood glucose
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
VLDL	Very low density lipoproteins
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-to-hip ratios

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INTRODUCTION

Sub clinical thyroid dysfunction, defined as thyroid-stimulating hormone (TSH) levels outside the normal reference range with normal thyroid hormone levels[1],

Metabolic syndrome is generally characterized as a clustering of the abnormal levels of blood lipids (low HDL and high triglycerides), impaired fasting glucose, elevated blood pressure, and excess abdominal obesity.[2]

People with metabolic syndrome are at an increased risk of atherosclerotic cardiovascular disease.[3]

A recent review of insulin resistance syndrome revealed a rapid escalation of this syndrome among Indians.[4]

Studies have revealed the pathophysiology of this syndrome, with close to a six fold increase in cardiovascular mortality in those possessing this disorder.[5]

Thyroid disease, especially overt hypothyroidism, is associated with atherosclerotic cardiovascular disease.[6]

Multifaceted etiology of cardiovascular diseases (CVD), especially coronary heart disease, has been recognized for a long time.[7]

The thyroid hormone is known to play a role in regulating the synthesis, metabolism, and the mobilization of lipids. It is associated with various adverse cardiovascular outcomes, including atherosclerotic disease, altered total and low-density-lipoprotein cholesterol (LDL-C) and atrial fibrillation.[8]

Cardiovascular manifestations are frequent in thyroid dysfunction. Overt hyperthyroidism induces a hyperdynamic cardiovascular state which is associated with an increased heart rate, enhanced left ventricular systolic and diastolic function

and an increased prevalence of atrial fibrillation, whereas the opposite changes occur in overt hypothyroidism.[9]

Overt hypothyroidism acts as a CVD risk factor through several mechanisms, as a result of which the incidence of heart attack can increase over two fold in hypothyroid subjects.[10]

A positive association between overt hypothyroidism and hypercholesterolemia is well recognized.[11]

In addition thyroid hormones influence vascular smooth muscles, consequently reducing arterial resistance, and causing a decline in diastolic blood pressure.

Insulin sensitivity can be affected by thyroid function and a positive association between overt hypothyroidism and BMI has been well documented.[12]

Metabolic syndrome has been linked to subclinical thyroid disease due to the pathophysiology of thyroid function on lipid and glucose metabolism, blood pressure, and cardiovascular dysfunction.[8]

Since metabolic syndrome and thyroid dysfunction are independent risk factors of atherosclerotic cardiovascular disease (CVD), the concurrent existence of the two will substantially increase the risk of CVD.

AIMS AND OBJECTIVES

1. To study the association between metabolic syndrome and subclinical thyroid dysfunction.

REVIEW OF LITERATURE

METABOLIC SYNDROME HISTORICAL PERSPECTIVE

The concept of metabolic syndrome (METS) has existed for at least 80 years. This constellation of metabolic disturbances, all risk factors for CVD, was first described in the 1920s by Kylin, a Swedish physician, as the clustering of hypertension, hyperglycemia, and gout.[13]

Abnormalities of glucose metabolism and diabetes were added to this risk factor conglomerate later. Insulin Resistance (IR) in diabetes was reported by Himsworth in 1939 in a series of Goulstonian lecturer to the Royal College of Physicians in London.[14]

Later in 1947, Vague drew attention to upper body adiposity (android or male-type obesity) as the obesity phenotype that was commonly associated with metabolic abnormalities associated with type 2 diabetes and CVD.[15]

The Reaven Banting lecture from the year 1988 introduced the concept of syndrome X as a fundamental factor in the pathogenesis and clinical course of what are often referred to as the diseases of western civilization – type 2 diabetes, hypertension (HT), and atherosclerotic CVD –received much attention.[16]

Reaven's syndrome X originally consisted of resistance to insulin stimulated glucose uptake, hyperinsulinemia, hyperglycemia, an increased concentration of very-low-density lipoprotein triglycerides, a decreased concentration of high-density lipoprotein cholesterol (HDL-C), and high BP.[16]

Reaven did not offer specific criteria for having syndrome X, and he did not include obesity or visceral obesity as a criterion. Later, others, including leading organizations and associations working in primary and secondary prevention of CVD,

added measures of visceral obesity and offered specific criteria to define this syndrome.[17]

Reaven proposed that IR was the most important abnormality, while Lemieux proposed that visceral obesity and hyperglyceridemic waist was important.[16, 18, 19] Despite the ongoing arguments among various groups, the ultimate importance of this condition is that it helps to identify individuals at high risk of CVD.[18]

THYROID GLAND HISTORICAL PERSPECTIVE

The thyroid gland was known at least from the time of Galen, who thought it provided a fluid for the lubrication of the larynx. Wharton gave the name thyroid (Greek thyroid-Shield) who considered that it was designed by nature to give especially in females a rotundity and beauty to the neck.

Andrecos Vesslius (1514-64) gave the first description of the thyroid gland as two glands on each side of the root of the larynx which are large fungus like, flesh colored and covered with blood vessels.

Eustachius (1520-74 Ad) discovered the isthmus of the thyroid gland. The anatomical site, size and weight were described by Wharton (1614-73 AD) in his book Adenographia. Scharge noted special blood supply of the thyroid. It was Alberchut Von hallen (1768 - 78) who classified thyroid among the ductless gland.
The Thyroid hormone, thyroxine was first isolated by Dendall of Mayo clinic in 1915.
CR. Harrington (1925) determined the chemical constitution and devised means for artificial synthesis and pointed out the principal chemical features responsible for specific physiological activity (F Cuelly 1961).

METABOLIC SYNDROME

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease (CVD) and diabetes mellitus (DM). [20]

The criteria for the metabolic syndrome have evolved since the original definition by the World Health Organization in 1998, reflecting growing clinical evidence and analysis by a variety of consensus conferences and professional organizations. The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperglycemia, and hypertension as per NCEP: ATPIII (National Cholesterol Education Program, Adult Treatment Panel III)

NCEP: ATPIII 2001 DEFINITION OF METABOLIC SYNDROME[21]

Three or more of the following:

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

INTERNATIONAL DIABETES FOUNDATION (IDF) DEFINTION OF METABOLIC SYNDROME[20]

1. Waist circumference:

MEN	WOMEN	ETHINICITY
>94 cm	>80 cm	Europid, Sub-Saharan African, Eastern and Middle Eastern
>90 cm	>80 cm	South Asian, Chinese, and ethnic South and Central American
>85 cm	>90 cm	Japanese

2. **Two or more of the following:**

- Fasting triglycerides >150 mg/dL or specific medication.
- HDL cholesterol <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication.
- Blood pressure >130 mm systolic or >85 mm diastolic or previous diagnosis or specific medication.
- Fasting plasma glucose >100 mg/dL or previously diagnosed Type 2 diabetes.

The **World Health Organization**(WHO)[22] proposal was designed as a first attempt to define the syndrome in 1999 includes Diabetes or impaired fasting glycemia or impaired glucose tolerance or IR (under hyperinsulinemic and euglycemic conditions, glucose uptake in lowest 25%) plus two or more of the following:

1. Obesity: body mass index >30 kg/m2 or waist: hip ratio > 0.9 (male) or > 0.85 (female).

2. Dyslipidemia: TGs ≥ 1.7 mmol/L or HDL-C <0.9 (male) or <1.0 (female) mmol/L.
3. Hypertension: BP ≥ 140/90 mmHg.
4. Microalbuminuria: albumin excretion ≥ 20 μg/min.

The **European group for the study** (EGIR)[23] of IR also defined the METS in 1999 includes – IR (defined as hyperinsulinemia, top 25% of fasting insulin valves among the non-diabetic population) plus two or more of the following:

1. Central obesity: waist circumference ≥ 94 cm (male) or ≥ 80 cm (female).
2. Dyslipidemia: TGs >2.0 mmol/L or HDL-C <1.0 mmol/L.
3. Hypertension: BP ≥140/90 mmHg and/or medication.
4. Fasting plasma glucose >6.1 mol/L.

In retrospect, it is apparent that the WHO definition more suited as a research tool whereas the NCEP: ATP III definition was more useful for clinical practice.[24]
The criteria for defining METS in adult Asian Indians needs revision. Inclusion of modified cutoffs of waist circumference (>90 cm for men, > 80 cm women) and BMI (>23 kg/cm2) and measures of truncal subcutaneous fat in the NCEP ATP III definition requires further validation.[25]

Yet another attempt at definition came from the American Association of Endocrinology and American Association of clinical endocrinologist.[26]

The **American Association of Clinical Endocrinologists (AACE)** proposes a third set of clinical criteria for the insulin resistance syndrome. These criteria appear

to be a hybrid of those of ATP III and WHO MS. However, no defined number of risk factors is specified; diagnosis is left to clinical judgment. When a person develops categorical diabetes, the term insulin resistance syndrome no longer applies. In patients without IFG, a 2-hour post glucose challenge is recommended when an abnormality is clinically suspected. Finding abnormal 2-hour glucose will improve prediction of type 2 diabetes.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS (AACE) CLINICAL CRITERIA FOR DIAGNOSIS OF THE INSULIN RESISTANCE SYNDROME RISK FACTOR COMPONENTS CUTPOINTS FOR ABNORMALITY

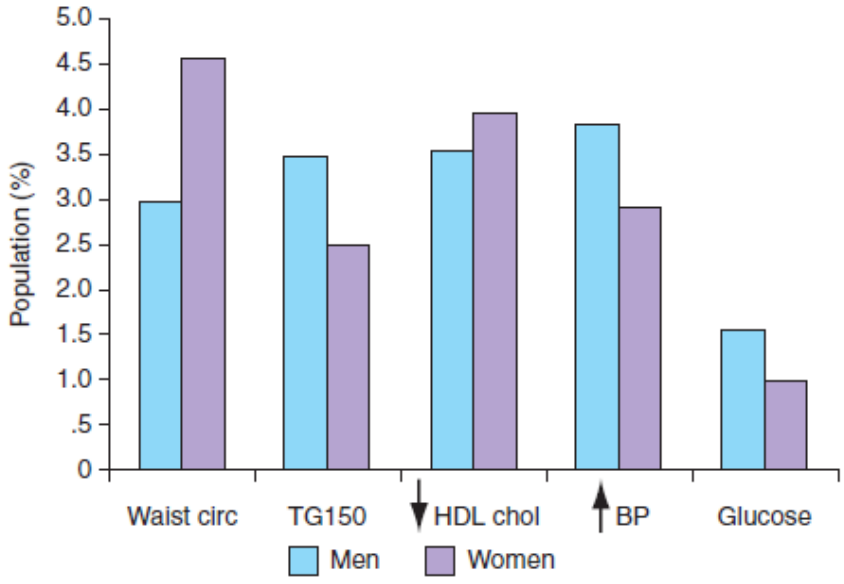
Overweight/obesity	> BMI _25 kg/m2
Elevated triglycerides	>150 mg/dL (1.69 mmol/L)
Low	HDL cholesterol
Men	40 mg/dL (1.04 mmol/L)
Women	50 mg/dL (1.29 mmol/L)
Elevated blood pressure	130/85 mm Hg
2-Hour postglucose challenge	>140 mg/dL
Fasting glucose	Between 110 and 126 mg/dL
Other risk factors	
Family history of type 2 diabetes,	
Hypertension or CVD	
Polycystic ovary syndrome	
Sedentary lifestyle	

A constellation of metabolic derangements that are often seen in patients with insulin resistance and T2DM are individually associated with an increased risk of cardiovascular disease. These metabolic derangements have been variously designated syndrome X; the dysmetabolic syndrome; hypertension, obesity, non–insulin-dependent diabetes mellitus (NIDDM), dyslipidemia, and atherosclerotic cardiovascular disease (HONDA); or the "deadly quartet."[27, 28]

The syndrome has also been associated with easily oxidized, small LDL particles; heightened blood-clotting activity (e.g., increased plasminogen activator inhibitor 1); and elevated serum uric acid concentration. The proposed central abnormality associated with syndrome X is insulin resistance. Some of the abnormalities have also been proposed to contribute to insulin resistance.[29]

EPIDEMIOLOGY

The prevalence of metabolic syndrome varies around the world, in part reflecting the age and ethnicity of the populations studied and the diagnostic criteria applied. In general, the prevalence of metabolic syndrome increases with age. The highest recorded prevalence worldwide is in Native Americans, with nearly 60% of women ages 45–49 and 45% of men ages 45–49 meeting National Cholesterol Education Program and Adult Treatment Panel III (NCEP:ATPIII) criteria. In the United States, metabolic syndrome is less common in African-American men and more common in Mexican-American women. Increases in waist circumference predominate in women, whereas fasting triglycerides >150 mg/dL and hypertension are more likely in men.



Prevalence of the metabolic syndrome components, from NHANES III.[30]

[The frequency distribution of the five components of the syndrome for the U.S. population (NHANES III)]

Two Indian studies, which differed in their definition of obesity; one study used obesity criteria that were suitable for Indians, while the others used the standard ATP III definition of obesity. Both studies used population-based samples writing the same age range but reported prevalence of 13% in Jaipur and 41% in Chennai.[31, 32]

Interestingly, a third Indian study[33] also from Chennai, reported a METS prevalence of 11.2% (using EGIR criteria), which was much closer to the prevalence reported for Jaipur than the other Chennai study.

Therefore, even within the same ethnic population group it appears that there can be significant differences in the prevalence of both the individual factors that constitute the METS and the METS itself.[34]

High prevalence of obesity and IR in urban Indian population is well known. A study from Chennai report 18.7% prevalence of IRS in upper socio-economic strata in south India, while it was 6.5% in the low socioeconomic strata.[35]

Higher prevalence of METS in women as compared with men is seen in urban south Indian population.[31]

Approximately 20-25 percent of urban south Asians has evidence of the METS. Furthermore, IR was reported, to be present in nearly 30 percent of children and adolescents in India, more so in girls.[36]

According to a recent study on south Indians, the prevalence of the METS (%) was estimated to be 23.2, 18.3 and 25.8 according to WHO, ATP III and IDF definitions respectively.[37]

High prevalence of cardiovascular risk factors and the METS (~12%) have been shown by our group in intra-country rural-to-urban migrant population belonging to low socio-economic stratum residing in urban shins. Further, certain

communities in India (eg. Punjabi, Bhatia community) have inordinately high tendency to develop obesity, type 2 diabetes mellitus, and METS.[36]

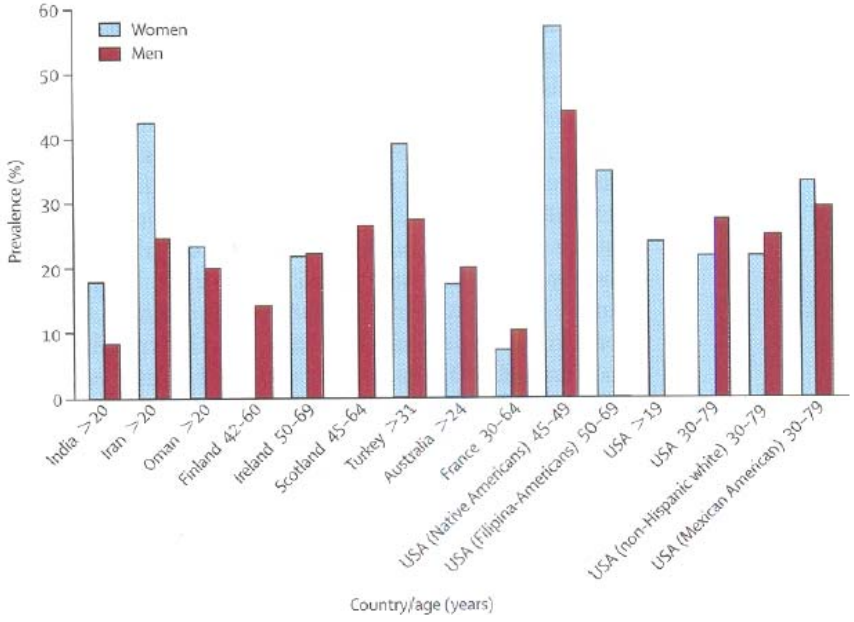
The METS was present in 31.6% of Indian urban population, prevalence was 22.9% in men and 39.9% in women, the age-adjusted prevalence was 24.9%, 18.4% in men and 30.9% in women there was a significant age-related increase in its prevalence.[38]

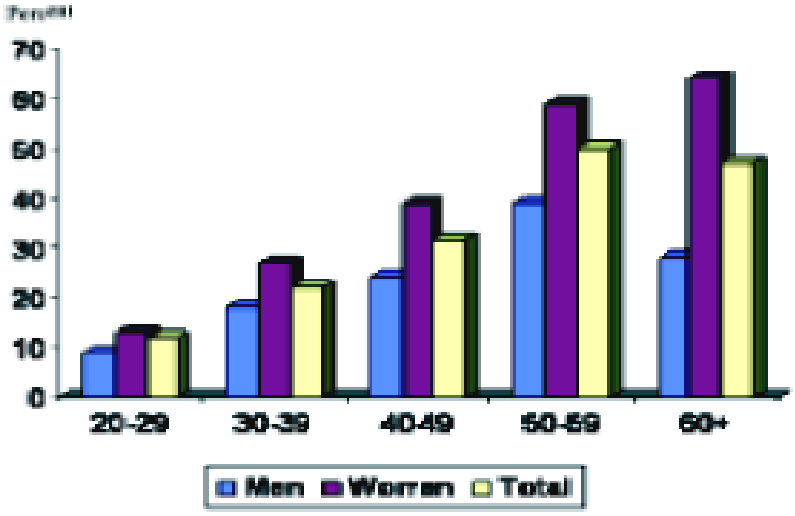
India is currently experiencing an increasing obesity epidemic. This is in contrast to the 1990's where the National Nutrition Monitoring Bureau documented the prevalence of obesity in Indian women to be 4.1%[39] and the National Family Health Survey (NFHS) reported obesity prevalence rates ranging 3.5% to 4.1%.[40]

Today, over 20% of men and 30% of women in urban areas have generalized obesity and nearly 40% of females have abdominal obesity.[35]

It is further predicted that the prevalence of obesity in India would further increase by 89% in males and 82% in females between 2002 and 2010.[41]

PREVALANCE OF METABOLIC SYNDROME ACCORDING TO NCEP-ATPIII CRITERIA [34]





AGE SPECIFIC PREVALANCE RATES OF METABOLIC SYNDROME (JAIPUR HEART WATCH – 2) [38]

COMPONENTS OF METABOLIC SYNDROME[42]

NCEP-ATP III[21] identified six components of the metabolic syndrome that relate to CVD:

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

These components of the metabolic syndrome constitute a particular combination of what ATP III[21] terms:

- underlying risk factors
- major risk factors
- Emerging risk factors.

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

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

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

RISK FACTORS[20, 43]

1. OVERWEIGHT/OBESITY

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

2. ATHEROGENIC DYSLIPIDEMIA

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

3. LIPODYSTROPHY

Lipodystrophic disorders in general are associated with the metabolic syndrome. Both genetic (e.g., Berardinelli-Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired (e.g., HIV-related lipodystrophy in patients treated with highly active antiretroviral therapy) forms of lipodystrophy may give rise to severe insulin resistance and many of the components of the metabolic syndrome.[20]

4. SEDENTARY LIFESTYLE

Physical inactivity is a predictor of CVD events and related mortality rate. Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central), reduced HDL cholesterol, and a trend toward increased triglycerides, high blood pressure, and increased glucose in the genetically susceptible. Compared with individuals who watched television or videos or used the computer <1 h daily, those who carried out those behaviors for >4 h daily had a twofold increased risk of the metabolic syndrome.

5. AGING

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

6. DIABETES MELLITUS

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

7. ELEVATED BLOOD PRESSURE

It strongly associates with obesity and commonly occurs in insulin-resistant persons. Hypertension thus commonly is listed among metabolic risk factors. However, some investigators believe that hypertension is less "metabolic" than other metabolic-syndrome components. Certainly, hypertension is multifactorial in origin.

8. CORONARY HEART DISEASE

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

9. INSULIN RESISTANCE

It is present in the majority of people with the metabolic syndrome. It strongly associates with other metabolic risk factors and correlates univariately with CVD risk. These associations, combined with belief in its priority, account for the term insulin resistance syndrome. Even so, mechanisms underlying the link to CVD risk factors are uncertain, hence the ATP III's classification of insulin resistance as an emerging risk factor. Patients with longstanding insulin resistance frequently manifest glucose intolerance, another emerging risk factor. When glucose intolerance evolves into diabetes-level hyperglycemia, elevated glucose constitutes a major, independent risk factor for CVD.

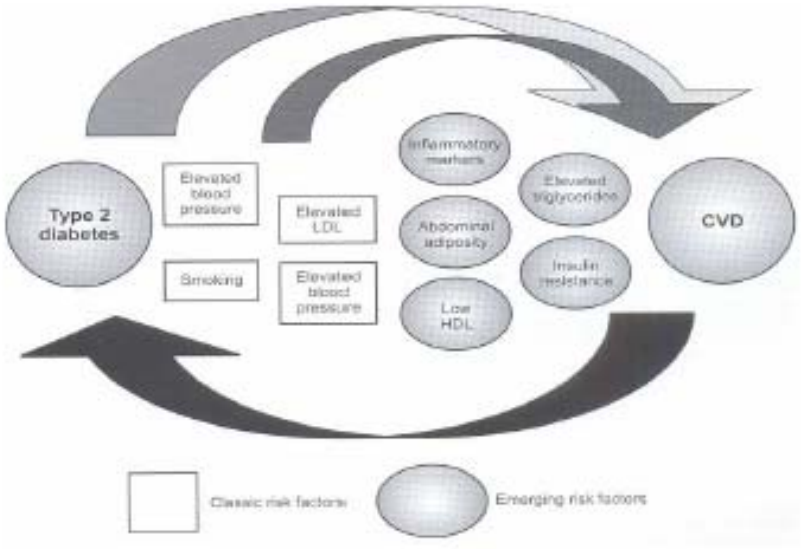
10. A PROINFLAMMATORY STATE

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

11. A PROTHROMBOTIC STATE

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

RISK FACTORS FOR METABOLIC SYNDROME[47]



ETIOPATHOGENESIS[20, 43]

The metabolic syndrome seems to have 3 potential etiological categories: obesity and disorders of adipose tissue, insulin resistance and a constellation of independent factors (eg, molecules of hepatic, vascular, and immunologic origin) that mediate specific components of the metabolic syndrome. Other factors—aging, proinflammatory state, and hormonal changes—have been implicated as contributors as well.

- **OBESITY AND ABNORMAL BODY FAT DISTRIBUTION**

ATP III considered the "obesity epidemic" as mainly responsible for the rising prevalence of metabolic syndrome. Obesity contributes to hypertension, high serum cholesterol, low HDL cholesterol, and hyperglycemia, and it otherwise associates with higher CVD risk. Abdominal obesity especially correlates with metabolic risk factors. With increases in visceral adipose tissue, adipose tissue-derived FFAs are

directed to the liver. In contrast, increases in abdominal subcutaneous fat release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism. Excess adipose tissue releases several products that apparently exacerbate these risk factors. They include nonesterified fatty acids (NEFA), cytokines, PAI-1, and adiponectin. A high plasma NEFA level overloads muscle and liver with lipid, which enhances insulin resistance. High CRP levels accompanying obesity may signify cytokine excess and a proinflammatory state. An elevated PAI-1 contributes to a prothrombotic state, whereas low adiponectin levels that accompany obesity correlate with worsening of metabolic risk factors. The strong connection between obesity (especially abdominal obesity) and risk factors led ATP III to define the metabolic syndrome essentially as a clustering of metabolic complications of obesity.

Measuring waist circumference does not reliably distinguish increases in subcutaneous adipose tissue vs. visceral fat; this distinction requires CT or MRI.

Relative increases in visceral versus subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the greater prevalence of the syndrome in those populations compared with African-American men in whom subcutaneous fat predominates. It is also possible that visceral fat is a marker for, but not the source of, excess postprandial FFAs in obesity.

- **INSULIN RESISTANCE**

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, which is caused by an incompletely understood defect in insulin action. The onset of insulin resistance is heralded by

postprandial hyperinsulinemia, followed by fasting hyperinsulinemia and, ultimately, hyperglycemia.

Many investigators place a greater priority on insulin resistance than on obesity in pathogenesis.[27, 44] They argue that insulin resistance, or its accomplice, hyperinsulinemia, directly causes other metabolic risk factors. Identifying a unique role for insulin resistance is complicated by the fact that it is linked to obesity.

Insulin resistance generally rises with increasing body fat content, yet a broad range of insulin sensitivities exists at any given level of body fat.[45] Most people with categorical obesity (body mass index [BMI] >30 kg/m^2) have postprandial hyperinsulinemia and relatively low insulin sensitivity[27], but variation in insulin sensitivities exists even within the obese population.[45]

Overweight persons (BMI 25 to 29.9 kg/m^2) likewise exhibit a spectrum of insulin sensitivities, suggesting an inherited component to insulin resistance.

In some populations (eg, South Asians), insulin resistance occurs commonly even with BMI <25 kg/m^2 and apparently contributes to a high prevalence of type 2 diabetes and premature CVD. South Asians and others who manifest insulin resistance with only mild-to-moderate overweight can be said to have primary insulin resistance. Even with primary insulin resistance, however, weight gain seems to enhance insulin resistance and metabolic syndrome. Thus, dissociation of obesity and primary insulin resistance in patients with metabolic syndrome is difficult.

An early major contributor to the development of insulin resistance is an overabundance of circulating fatty acids. Plasma albumin-bound free fatty acids (FFAs) are derived predominantly from adipose tissue triglyceride stores released by lipolytic enzymes lipase. Fatty acids are also derived from the lipolysis of triglyceride-rich lipoproteins in tissues by lipoprotein lipase (LPL). Insulin mediates

both antilipolysis and the stimulation of LPL in adipose tissue. Inhibition of lipolysis in adipose tissue is the most sensitive pathway of insulin action. Thus, when insulin resistance develops, increased lipolysis produces more fatty acids, which further decrease the antilipolytic effect of insulin. Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids impair insulin-mediated glucose uptake and accumulate as triglycerides in both skeletal and cardiac muscle, whereas increased glucose production and triglyceride accumulation are seen in liver.

When insulin-resistant muscle is already overloaded with lipid from high plasma NEFA levels, some excess NEFA presumably is diverted to the liver, promoting fatty liver and atherogenic dyslipidemia. Hyperinsulinemia may enhance output of very low- density lipoprotein triglycerides, raising triglycerides. Insulin resistance in muscle predisposes to glucose intolerance, which can be worsened by increased hepatic gluconeogenesis in insulin-resistant liver.

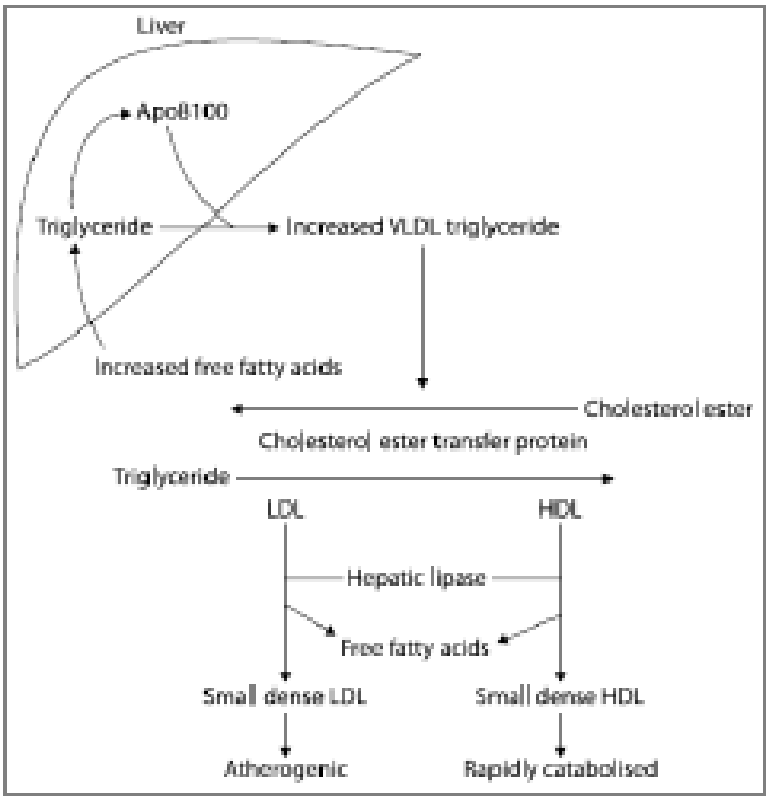
- **DYSLIPIDEMIA**

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

The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL cholesterol. This reduction is a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL is a consequence of reduced cholesteryl ester content of the lipoprotein core in combination with cholesteryl ester transfer protein–mediated

alterations in triglyceride, making the particle small and dense. This change in lipoprotein composition also results in increased clearance of HDL from the circulation. The relationships of these changes in HDL to insulin resistance are probably indirect, occurring in concert with the changes in triglyceride-rich lipoprotein metabolism.

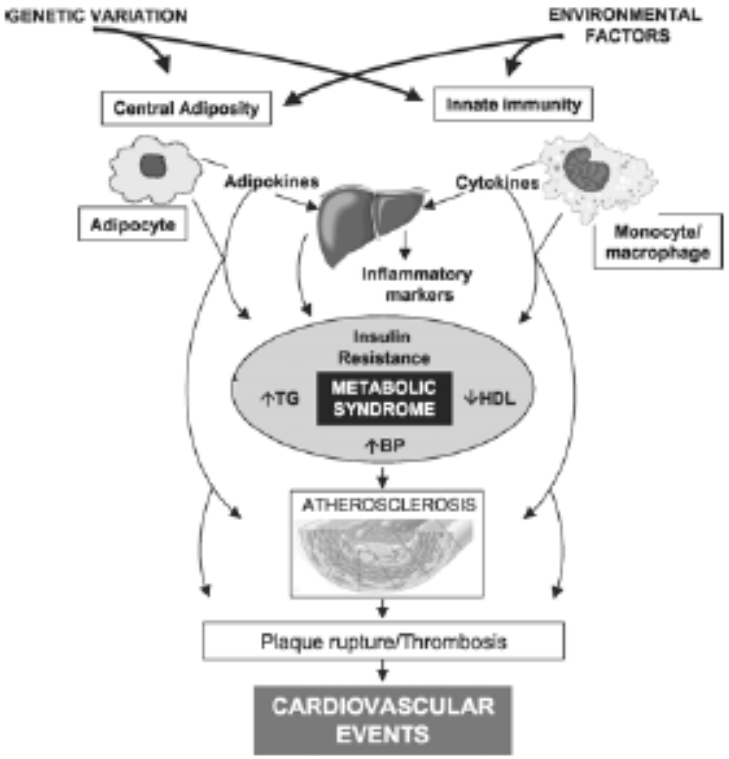
In addition to HDL, low-density lipoproteins (LDLs) are modified in composition. With fasting serum triglycerides >2.0 mM (~180 mg/dL), there is almost always a predominance of small dense LDLs. Small dense LDLs are thought to be more atherogenic. They may be toxic to the endothelium, and they are able to transit through the endothelial basement membrane and adhere to glycosaminoglycans. They also have increased susceptibility to oxidation and are selectively bound to scavenger receptors on monocyte-derived macrophages. Subjects with increased small dense LDL particles and hypertriglyceridemia also have increased cholesterol content of both VLDL1 and VLDL2 sub fractions. This relatively cholesterol-rich VLDL particle may contribute to the atherogenic risk in patients with metabolic syndrome.



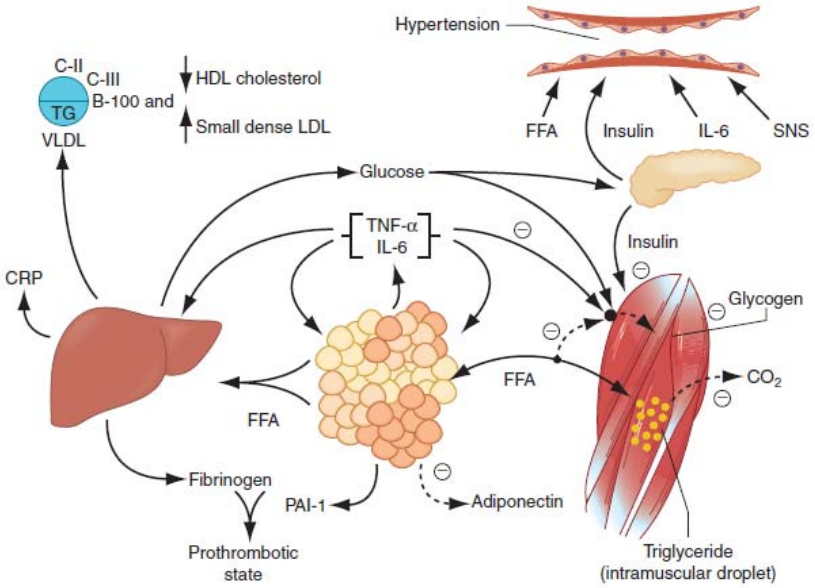
PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME[20]

Free fatty acids (FFAs) are released in abundance from an expanded adipose tissue mass. In the liver, FFAs result in an increased production of glucose and triglycerides and secretion of very low density lipoproteins (VLDLs). Associated lipid/lipoprotein abnormalities include reductions in high-density lipoprotein (HDL) cholesterol and an increased density of low-density lipoproteins (LDLs). FFAs also reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in triglyceride (TG). Increases in circulating glucose, and to some extent FFA, increase pancreatic insulin secretion, resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and

increased sympathetic nervous system (SNS) activity and contribute to the hypertension, as might increased levels of circulating FFAs. The proinflammatory state is superimposed and contributory to the insulin resistance produced by excessive FFAs. The enhanced secretion of interleukin 6 (IL-6) and tumor necrosis factor (TNF-α) produced by adipocytes and monocyte-derived macrophages results in more insulin resistance and lipolysis of adipose tissue triglyceride stores to circulating FFAs. IL-6 and other cytokines also enhance hepatic glucose production, VLDL production by the liver, and insulin resistance in muscle. Cytokines and FFAs also increase the hepatic production of fibrinogen and adipocytes production of plasminogen activator inhibitor 1 (PAI-1), resulting in a prothrombotic state. Higher levels of circulating cytokines also stimulate the hepatic production of C-reactive protein (CRP). Reduced production of the anti-inflammatory and insulin-sensitizing cytokine adiponectin is also associated with the metabolic syndrome.



PATHOPHYSIOLOGY OF METABOLIC SYNDROME



METABOLIC SYNDROME – THE INDIAN PHENOTYPE

The group of Malhotra.P et al from PGI Chandigarh, reports isolated lipid abnormalities in 47 to 51 % in rural-urban non diabetic cohort essentially highlighting the low HDL and elevated Triglycerides.[48] The classical Indian lipid triad is low HDL, elevated triglyceride and elevated LDL cholesterol; apart form abnormal ratios as the most common finding in most other Indian studies. Therefore such varied results only highlight that there is no standardized normal lipid levels in the Indian population.

The normal Indian lipid cut offs which are likely to emerge are Total Cholesterol < 180 mg%,

Triglyceride < 100 to 150 mg%, HDL > 35 mg% for men and 38 mg% women and LDL < 80-100 mg%. High prevalence of obesity and insulin resistance in urban Indian population is well known.

In a study form Chennai, Mohan et al report 18.7% prevalence of IRS in upper socioeconomic strata in South India, while it was 6.5% in the low socio-economic strata.[33] The data on rural urban differences in prevalence of Insulin resistance parallel the prevalence of type 2 diabetes in rural and urban areas.

In the first study with increasing educational status a significant increase of obesity, total cholesterol, LDL cholesterol and triglycerides and decrease in smoking was observed. In the second study increasing education was associated with decrease in smoking, leisure time, physical inactivity, total and LDL cholesterol, and triglycerides and increase in obesity, truncal obesity and hypertension. Increase in smoking, diabetes and dyslipidemia was greater in the less educated groups.

The emerging typical Asian Indian urban/migrant has phenotype of higher percentage of body fat at a lower value of body mass index (BMI), high waist hip

ratio (WHR) at a relatively low waist circumference and less lean body mass as compared to ethnic groups. Asian Indian migrants have higher values of BMI and WHR and thicker skin folds as compared to urban subjects in India, Asian Indian men had significantly thicker truncal skin folds as compared to Caucasians. High body fat, often at BMI values that are in non-obese range is another characteristic phenotypic feature of Asian Indians, reported by several groups, including Banerji et al in Asian Indians in USA (mean BMI, 24.5 kg/ m^2, body fat ~33%) and Dudeja, Misra et al in Asian Indians in India (mean BMI 23.3 kg/m^2, body fat ~35%).

In addition, studies have also revealed that Asian Indians are more insulin resistant than Caucasians, independent of their generalized or truncal adiposity.[49] Genetic predisposition could be one of the explanations for this escalation in prevalence of the components of the metabolic syndrome in Indians although it is most likely to represent rapid urbanization.

METABOLIC SYNDROME AS A PREDICTOR OF CVD

Individuals with metabolic syndrome are at increased risk for CHD.[50] In Framingham, the metabolic syndrome alone predicted 25% of all new-onset CVD. In the absence of diabetes, the metabolic syndrome generally did not raise 10-year risk for CHD to 20%; this is the threshold for ATP III's CHD risk equivalent.

Ten-year risk in men with metabolic syndrome generally ranged from 10% to 20%. Framingham women with metabolic syndrome had relatively few CHD events during the course of the 8-year follow-up; this was due in part to the high proportion of women who were under 50 years of age.

CVD is the primary clinical outcome of metabolic syndrome. Additionally, risk for type 2 diabetes is higher, and diabetes is a major risk factor for CVD. ATP III criteria provide a practical tool to identify patients at increased risk for CVD.[43]

DEVELOPMENT OF THYROID GLAND[51, 52]

The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct to reach its final location in the neck. This feature accounts for the rare ectopic location of thyroid tissue at the base of the tongue (lingual thyroid) as well as the occurrence of thyroglossal duct cysts along this developmental tract.Thyroid hormone synthesis normally begins at about 11 weeks' gestation.

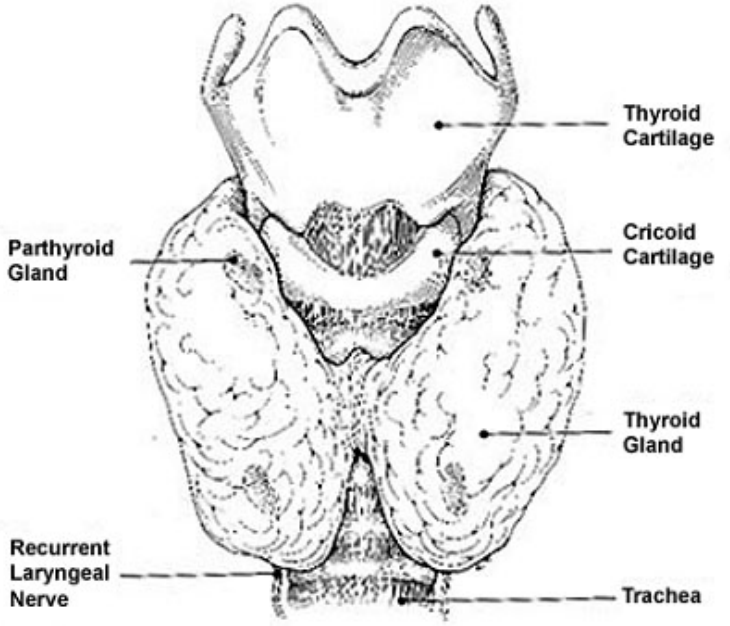
Neural crest derivatives from the ultimobranchial body give rise to thyroid medullary C cells that produce calcitonin, a calcium-lowering hormone. The C cells are interspersed throughout the thyroid gland, although their density is greatest in the juncture of the upper one-third and lower two-thirds of the gland. Calcitonin plays a minimal role in calcium homeostasis in humans but the C-cells are important because of their involvement in medullary thyroid cancer.

Thyroid gland development is orchestrated by the coordinated expression of several developmental transcription factors. Thyroid transcription factor (TTF)-1, TTF-2, and paired homeobox-8 (PAX-8) are expressed selectively, but not exclusively, in the thyroid gland. In combination, they dictate thyroid cell development and the induction of thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (Na^+/I, NIS), and the thyroid-stimulating hormone receptor (TSH-R). Mutations in these developmental transcription factors or their downstream target genes are rare causes of thyroid agenesis or dyshormonogenesis

ANATOMY OF THYROID GLAND[51, 52]

The thyroid (Greek thyreos, shield, plus eidos, form) consists of two lobes connected by an isthmus. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch.

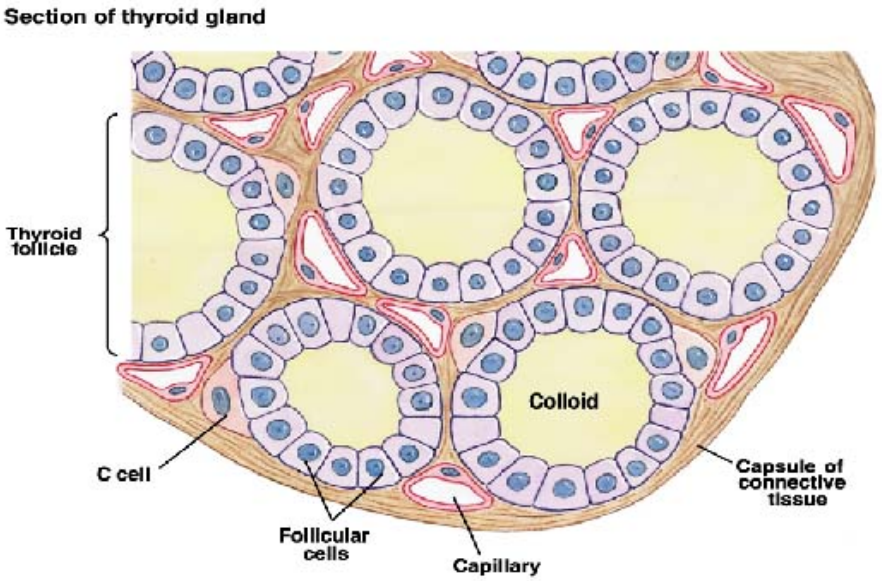
The normal thyroid is 12–20 g in size, highly vascular, and soft in consistency. Four parathyroid glands, which produce parathyroid hormone, are located posterior to each pole of the thyroid. The recurrent laryngeal nerves traverse the lateral borders of the thyroid gland and must be identified during thyroid surgery to avoid injury and vocal cord paralysis.



The thyroid gland consists of numerous spherical follicles composed of thyroid follicular cells that surround secreted colloid, a proteinaceous fluid containing large amounts of thyroglobulin, the protein precursor of thyroid hormones.

The thyroid follicular cells are polarized—the basolateral surface is apposed to the bloodstream and an apical surface faces the follicular lumen. Increased demand for thyroid hormone is regulated by thyroid-stimulating hormone (TSH), which binds

to its receptor on the basolateral surface of the follicular cells, leading to Tg reabsorption from the follicular lumen, proteolysis within the cytoplasm, yielding thyroid hormones for secretion into the bloodstream.



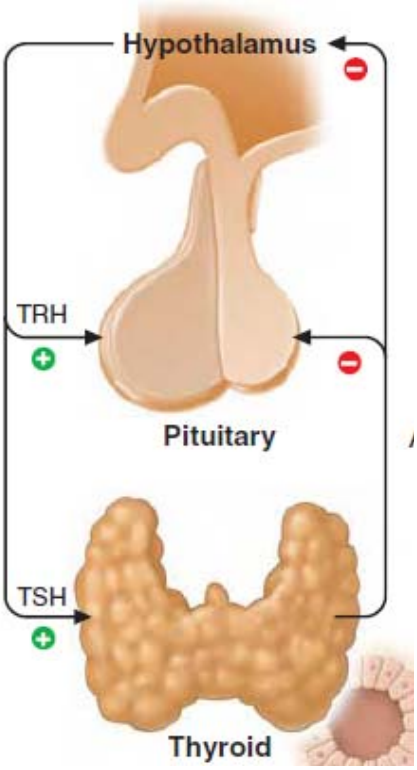
REGULATION OF THE THYROID AXIS[51, 52]

TSH, secreted by the thyrotrope cells of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. TSH is a 31-kDa hormone composed of α and β subunits; the α subunit is common to the other glycoprotein hormones [luteinizing hormone, follicle-stimulating hormone, human chorionic gonadotropin (hCG)], whereas the TSH β subunit is unique to TSH. The extent and nature of carbohydrate modification are modulated by thyrotropin-releasing hormone (TRH) stimulation and influence the biologic activity of the hormone.

The thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic TRH stimulates pituitary production of TSH, which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones, acting predominantly through thyroid hormone receptor β2 (TRβ2), feed back to inhibit TRH and TSH production. The "set-point" in this axis is established by TSH. TRH is the major positive regulator of TSH synthesis and secretion. Peak TSH secretion occurs 15 min after administration of exogenous TRH.

Dopamine, glucocorticoids, and somatostatin suppress TSH but are not of major physiologic importance except when these agents are administered in pharmacologic doses. Reduced levels of thyroid hormone increase basal TSH production and enhance TRH-mediated stimulation of TSH. High thyroid hormone levels rapidly and directly suppress TSH gene expression secretion and inhibit TRH stimulation of TSH, indicating that thyroid hormones are the dominant regulator of TSH production.

Like other pituitary hormones, TSH is released in a pulsatile manner and exhibits a diurnal rhythm; its highest levels occur at night. However, these TSH excursions are modest in comparison to those of other pituitary hormones, in part, because TSH has a relatively long plasma half-life (50 minutes). Consequently, single measurements of TSH are adequate for assessing its circulating level. TSH is measured using immunoradiometric assays that are highly sensitive and specific. These assays readily distinguish between normal and suppressed TSH values; thus, TSH can be used for the diagnosis of hyperthyroidism (low TSH) as well as hypothyroidism (high TSH).



THYROID HORMONE SYNTHESIS, METABOLISM, AND ACTION[51, 52]

A) THYROID HORMONE SYNTHESIS

Thyroid hormones are derived from Tg, a large iodinated glycoprotein. After secretion into the thyroid follicle, Tg is iodinated on tyrosine residues that are subsequently coupled via an ether linkage. Reuptake of Tg into the thyroid follicular cell allows proteolysis and the release of newly synthesized T4 and T_3.

B) IODINE METABOLISM AND TRANSPORT

Iodide uptake is a critical first step in thyroid hormone synthesis. Ingested iodine is bound to serum proteins, particularly albumin. Unbound iodine is excreted in the urine. The thyroid gland extracts iodine from the circulation in a highly efficient manner.

Iodide uptake is mediated by NIS, which is expressed at the basolateral membrane of thyroid follicular cells. NIS is most highly expressed in the thyroid gland, but low levels are present in the salivary glands, lactating breast, and placenta.

The iodide transport mechanism is highly regulated, allowing adaptation to variations in dietary supply. Low iodine levels increase the amount of NIS and stimulate uptake, whereas high iodine levels suppress NIS expression and uptake. The selective expression of NIS in the thyroid allows isotopic scanning, treatment of hyperthyroidism, and ablation of thyroid cancer with radioisotopes of iodine, without significant effects on other organs.

Another iodine transporter, pendrin, is located on the apical surface of thyroid cells and mediates iodine efflux into the lumen.

C) ORGANIFICATION, COUPLING, STORAGE, RELEASE

After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide.

The reactive iodine atom is added to selected tyrosyl residues within Tg, a large (660 kDa) dimeric protein that consists of 2769 amino acids. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T4 or T_3 can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines.

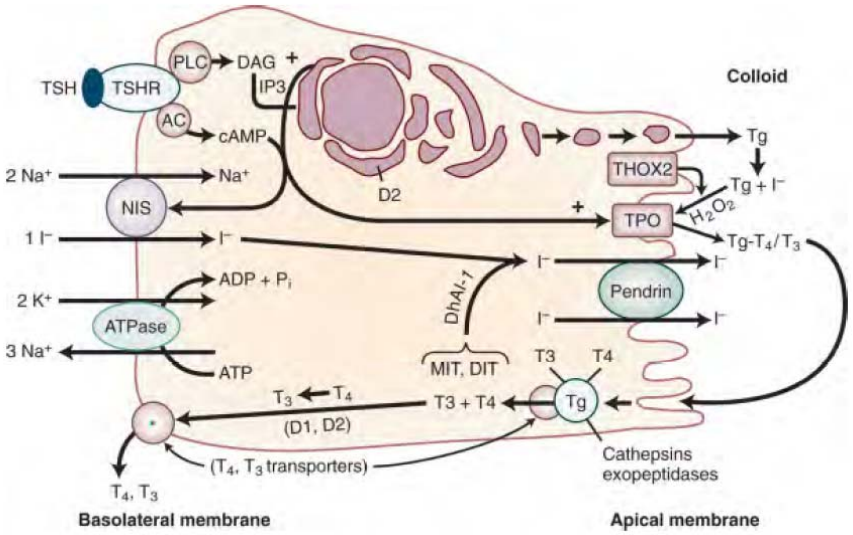
After coupling, Tg is taken back into the thyroid cell, where it is processed in lysosomes to release T_4 and T_3. Uncoupled mono- and di iodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones.

D) THYROID HORMONE TRANSPORT AND METABOLISM -SERUM BINDING PROTEINS

T4 is secreted from the thyroid gland in about twenty fold excess over T_3. Both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG), transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or TBPA), and albumin.

The plasma-binding proteins increase the pool of circulating hormone, delay hormone clearance, and may modulate hormone delivery to selected tissue sites. The concentration of TBG is relatively low (1–2 mg/dL), but because of its high affinity for thyroid hormones ($T_4 > T_3$), it carries about 80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (3.5 g/dL), and it binds up to 10% of T_4 and 30% of T_3. TTR carries about 10% of T_4 but little T_3.

When the effects of the various binding proteins are combined, approximately 99.98% of T4 and 99.7% of T_3 are protein-bound. Because T_3 is less tightly bound than T_4, the fraction of unbound T_3 is greater than unbound T_4, but there is less unbound T_3 in the circulation because it is produced in smaller amounts and cleared more rapidly than T_4. The unbound or "free" concentrations of the hormones are 2×10^{11}M for T_4 and 6×10^{12}M for T_3, which roughly correspond to the thyroid hormone receptor binding constants for these hormones. The unbound hormone is thought to be biologically available to tissues. Nonetheless, the homeostatic mechanisms that regulate the thyroid axis are directed toward maintenance of normal concentrations of unbound hormones.


PLC
DAG
IP3
TSH
TSHR
AC
cAMP
Colloid
Tg
THOX2
Tg + I⁻
2 Na⁺
Na⁺
NIS
D2
TPO
H2O2
Tg-T4/T3
1 I⁻
I⁻
2 K⁺
ADP + Pi
Pendrin
DhAL-1
ATPase
3 Na⁺
ATP
MIT, DIT
T3
T4
T3 + T4
Tg
(D1, D2)
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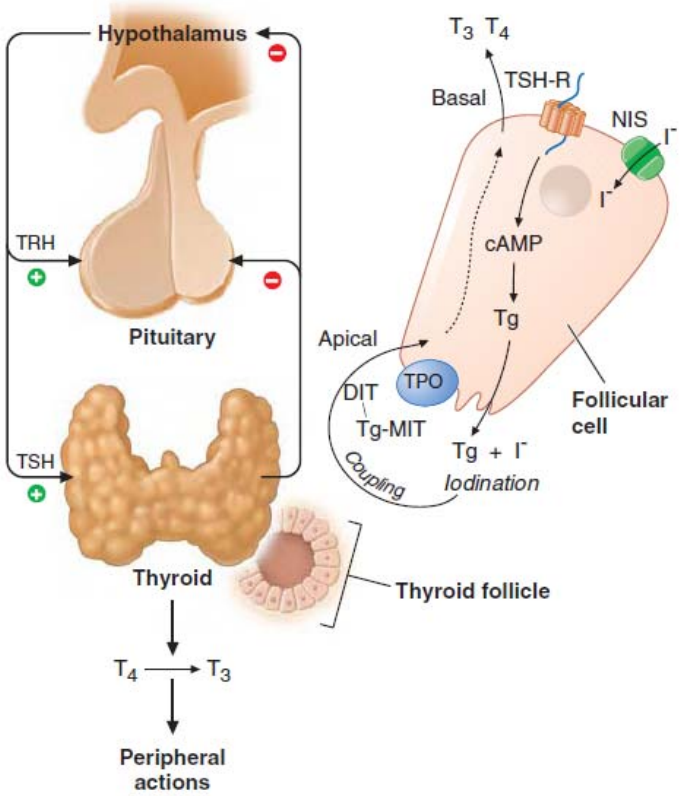
Cathepsins
exopeptidases
T4, T3
Basolateral membrane
Apical membrane


Hypothalamus
TRH
Pituitary
TSH
Thyroid
Thyroid follicle
T4
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Peripheral
actions
T3 T4
Basal
TSH-R
NIS
I⁻
cAMP
Tg
Apical
TPO
DIT
Tg-MIT
Tg + I⁻
Coupling
Iodination
Follicular
cell

PHYSIOLOGY OF THYROID HORMONES[51, 52, 53]

THYROID HORMONE ACTION

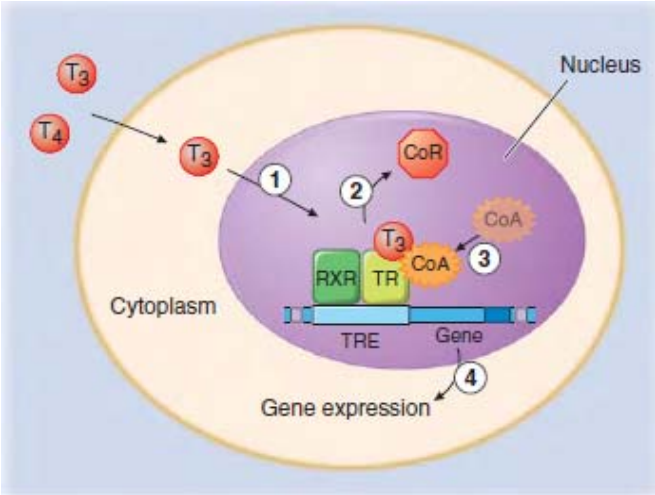
A) THYROID HORMONE TRANSPORT

Circulating thyroid hormones enter cells by passive diffusion and via specific transporters such as the monocarboxylate 8 (MCT8) transporter. After entering cells, thyroid hormones act primarily through nuclear receptors, although they also have nongenomic actions through stimulating plasma membrane and mitochondrial enzymatic responses.

B) NUCLEAR THYROID HORMONE RECEPTORS

Thyroid hormones bind with high affinity to nuclear thyroid hormone receptors (TRs) α and β. Both TRα and TRβ are expressed in most tissues, but their relative expression levels vary among organs. TRα is particularly abundant in brain, kidneys, gonads, muscle, and heart, whereas TRβ expression is relatively high in the pituitary and liver. Both receptors are variably spliced to form unique isoforms. The TRβ2 isoform, which has a unique amino terminus, is selectively expressed in the hypothalamus and pituitary, where it plays a role in feedback control of the thyroid axis. The TRα2 isoform contains a unique carboxy terminus that precludes thyroid hormone binding; it may function to block the action of other TR isoforms.

The TRs contain a central DNA-binding domain and a C-terminal ligand-binding domain. They bind to specific DNA sequences, termed thyroid response elements (TREs), in the promoter regions of target genes.. The activated receptor can either stimulate gene transcription or inhibit transcription depending on the nature of the regulatory elements in the target gene.



The thyroid hormone receptor (TR) and retinoid X receptor (RXR) form heterodimers that bind specifically to thyroid hormone response elements (TRE) in the promoter regions of target genes. In the absence of hormone, TR binds co-repressor (CoR) proteins that silence gene expression. The numbers refer to a series of ordered reactions that occur in response to thyroid hormone: (1) T4 or T_3 enters the nucleus; (2) T_3 binding dissociates CoR from TR; (3) Coactivators (CoA) are recruited to the T_3-bound receptor; (4) gene expression is altered.

EFFECTS OF THYROID HORMONES ON LIPID METABOLISM

Thyroid hormones influence all aspects of lipid metabolism including synthesis, mobilization, and degradation.

Thyroid hormones stimulate cholesterol synthesis by inducing 3-hydroxy-3-methyl-glutaryl coenzyme A reductase in the liver.[54]

Thyroid hormones affect lipoprotein lipase activity and thus, the hydrolysis of triglycerides into very-low, density lipoprotein (VLDL) and chylomicrons into fatty acids and glycerol.[55]

In hypothyroidism, lipoprotein lipase activity in the adipose tissue has been found normal or decreased, in addition to decreased hepatic lipase activity resulting in normal or high levels of triglycerides.[56]

In hyperthyroidism, although lipoprotein lipase activity is usually normal [57], an increased liver fatty acid synthesis and oxidation is observed due to enhanced acetyl-CoA carboxylase 1 and carnitine palmitoyltransferase Ia expression leading to increased VLDL biosynthesis.[58]

Thyroid hormones affect cholesteryl ester transfer protein and hepatic lipase activity, which are increased in hyperthyroidism and decreased in hypothyroidism, with consequent changes not only in total high-density lipoprotein (HDL) but also in HDL subfraction levels.[59]

Thyroid hormones, especially triiodothyronine (T3), induce low density lipoprotein (LDL) receptor gene expression in the liver, enhancing LDL clearance and explaining the decreased or increased LDL levels observed in hyperthyroidism and hypothyroidism, respectively.[55]

Changes in enzyme activities, transfer proteins, and receptors involved in lipid metabolism induced by thyroid hormones.[60]

Enzymes, transfer proteins, and liver receptors	Thyroid hormone effect
3-hydroxy-3-methyl-glutaryl coenzyme A reductase	↑
Adipose lipoprotein lipase	Usually normal (may be ↓ in hypothyroidism)
Hepatic lipase	↑
Cholesteryl ester transfer protein	↑
ATP-binding cassette transporter A1	↓
Acetyl-CoA carboxylase 1	↑
Carnitine palmitoyltransferase Ia	↑
7alpha-hydroxylase	↓
LDL receptor	↑

Subclinical hypothyroidism is associated with lipid abnormalities, including mainly increased total and LDL cholesterol in most[55], but not all[61] studies.

In contrast, HDL, triglycerides, Lp(a), apoB, and apoA1 levels did not exhibit any difference between patients with subclinical hypothyroidism and controls in the majority[62,63,64], but not all [65,66] studies.

Rondeau et al. found that TSH was negatively correlated with HDL-C in euthyroid overweight or obese postmenopausal women.[67] A quite recent study showed that transfer of triglycerides to HDL and phospholipids was lower in patients with subclinical hypothyroidism than that in controls while transfer of free and esterified cholesterol to HDL, HDL particle size, and paraoxonase 1 activity did not exhibit any difference.[68]

Most of the existing studies support lower total and LDL cholesterol levels in patients with hyperthyroidism[55,69,70], while only a few data support no change.[71]

Lower triglycerides, HDL, apoA1, apoB, and Lp(a) levels have been found in patients with hyperthyroidism compared with euthyroid controls, which is questionable by other reports.[71,72]

In hyperthyroidism, qualitative lipid changes, including increased levels of oxidized LDL, higher contents of thiobarbituric acid-reactive substances and dienes in LDL, low paraoxonase activity in HDL particles, and lower LDL content in antioxidant vitamin E and β-carotene have been found.[71,72]

Lipid abnormalities in subclinical hypothyroidism and subclinical hyperthyroidism[60]

	Clinical hypothyroidism	Subclinical hypothyroidism	Clinical hyperthyroidism	Subclinical hyperthyroidism
Total cholesterol	Increased	Increased or unaltered	Decreased (rarely unaltered)	Decreased or unaltered
LDL	Increased	Increased (rarely unaltered)	Decreased (rarely unaltered)	Decreased or unaltered
HDL	Unaltered or increased	Unaltered (rarely decreased)	Unaltered or decreased	Unaltered? (a few data exist)
Lipoprotein (a)	Unaltered or increased	Unaltered (rarely increased)	Decreased? (a few data exist)	Unaltered? (a few data exist)
Triglycerides	Unaltered or increased	Unaltered (rarely increased)	Unaltered (rarely decreased)	Unaltered? (a few data exist)
Apolipoprotein B	Unaltered or increased	Unaltered or increased	Decreased? (a few data exist)	Unaltered? (a few data exist)
Apolipoprotein A1	Unaltered or increased	Unaltered (usually)	Unaltered or decreased	Unaltered? (a few data exist)

THYROID DISEASE AND CARDIOVASCULAR RISK

In hypothyroidism, the main functional cardiovascular disturbances involve decreased heart rate, elevated peripheral vascular resistance, increased diastolic blood pressure and cardiac afterload, reduced blood volume and cardiac preload, and diminished cardiac output.

Impaired left ventricular systolic contractility at least during exercise and delayed left ventricular diastolic relaxation at rest and during exercise are common in both overt and subclinical hypothyroidism. Hypothyroidism is also associated with diastolic heart failure in the elderly.[73,74]

In hyperthyroidism, hemodynamic changes result mainly from increased β1-adrenergic activity. Increased triiodothyronine levels exert positive inotropic and chronotropic effects, leading to enhanced heart rate and systolic contractility and, consequently, increased cardiac output.

Increased triiodothyronine stimulates sarcoplasmic reticulum Ca- ATPase, leading to systolic and diastolic dysfunction. Moreover, triiodothyronine reduces peripheral vascular resistance, causing a decrease in diastolic blood pressure and cardiac afterload, which further raises cardiac output.

Biondi et al. found that even patients with subclinical hyperthyroidism had significantly higher average heart rate, enhanced systolic function, impaired diastolic function with prolonged isovolumic relaxation time, and increased left ventricular mass compared with euthyroid subjects.[75]

THYROID DISEASE AND ATHEROSCLEROSIS

Thyroid disease is related to the development of dyslipidemia which is a well-known atherogenic factor. Dyslipidemia induces insulin resistance oxidative stress, via a vicious cycle.[72] Insulin resistance, hypertension, inflammation, oxidative stress, and coagulation deficits are also promoted by thyroid disease, independently of dyslipidemia.[73,74,75] The above associations support a multifactorial origin of atherosclerosis in thyroid disease, with dyslipidemia playing an important role.[73,74,75] Sub clinical hypothyroidism has been also associated with diastolic hypertension.[76] A few studies have reported hyperhomocysteinemia[76], and possible coagulation deficits in patients with sub clinical hypothyroidism.[77]

Increased intima media thickness of the common carotid artery has been found in some studies in sub clinical hypothyroidism.[78]

In the Whickham Survey, an association was found between incident coronary heart disease and related mortality in patients with subclinical hypothyroidism over the 20 yrs of follow-up, which was attenuated after levothyroxine treatment.[79]

Meta-analysis by Razvi et al. showed that the incidence and prevalence of coronary heart disease and the risk of cardiovascular mortality were higher in subclinical hypothyroidism, in patients younger than 65 years old and more prevalent in women.[80]

Subclinical hyperthyroidism has been also associated with hypertension.[81] increased carotid intima thickness have been found in patients with subclinical hyperthyroidism. However, the association of subclinical hyperthyroidism with coronary heart disease risk and cardiovascular mortality is still unclear.[82]

MATERIALS AND METHODS

SOURCE OF DATA:

This study is a prospective case control study based on analysis of 100 patients (50 cases and 50 controls) during a period from January 2012 to January 2013.

The study group comprised of inpatients and outpatients of R.L.Jalappa hospital and research centre attached to the Sri Devaraj Urs Medical College, Kolar. The study group includes 50 patients. The study population comprised of men and women above 18 years of age.

50 controls both inpatients and outpatients of R.L.Jalappa hospital and research centre who are not having metabolic syndrome.

CRIETRIA:

- **INCLUSION CRITERIA:**

1. Participants having Metabolic syndrome, for which they should have at least 3 components of the following (NCEP ATPIII criteria)[20]:-

a. Fasting blood glucose level of 110 mg/dl or greater or on anti diabetic medications.

b. Fasting triglycerides level of 150 mg/dl or greater.

c. HDL level less than 50 mg/dl in females and less than 40 mg/dl in males.

d. Blood Pressure greater than or equal to 130/85 mm Hg or antihypertensive medications.

e. Waist circumference >88cm in females and >102 cm in males.

- **EXCLUSION CRITERIA:**

1. Persons diagnosed as having hyperthyroidism, hypothyroidism and those under any treatment for thyroid related disorders.
2. Patients on OC Pills, lipid lowering drugs, thyroid replacement drugs.
3. Liver disorders.
4. Renal disorders.
5. Congestive cardiac failure.
6. Pregnant women.

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

- History of duration of diabetes, hypertension, and dyslipidemia was taken.
- Treatment history of diabetes, hypertension, and dyslipidemia was taken.

Routine physical examination was done and waist circumferences (WC) were calculated in all patients.

Vital parameters (like pulse, BP etc) of each patient were recorded as per proforma.

Blood pressure recordings were taken 3 times at the interval of ten minutes and mean of the 3 readings will be taken as a final value.

Waist circumference was measured at the plane between anterior superior iliac spines and the lower costal margin of the waistline while the person is standing and during expiration.

INVESTIGATIONS:

- FBS
- HDL, TRIGLYCERIDES
- TSH,T3,T4

After fasting of 8 hours, a venous blood sample was taken for estimation of glucose, HDL, triglycerides, TSH, T4 and T3 levels.

STATISTICAL METHODS:

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

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

1. Significant figures

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

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

** Strongly significant (P value: $P \leq 0.01$)

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

RESULTS

A Cases-Control clinical study on 50 metabolic syndrome patients (Cases Group) and 50 non metabolic syndrome subjects (Control group) is undertaken to study the subclinical thyroid dysfunction in metabolic syndrome patients.

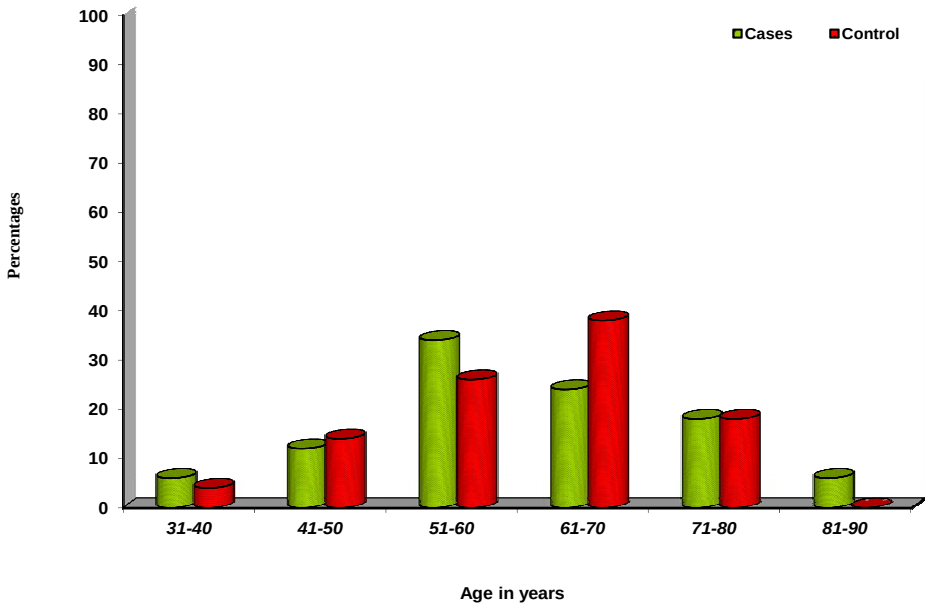
The study group (Controls & Cases) was matched with the age, gender to compare the important variables.

Table 1: Age distribution of patients studied

Age in years	Cases		Control	
	No	%	No	%
31-40	3	6.0	2	4.0
41-50	6	12.0	7	14.0
51-60	17	34.0	13	26.0
61-70	12	24.0	19	38.0
71-80	9	18.0	9	18.0
81-90	3	6.0	0	0.0
Total	50	100.0	50	100.0
Mean ± SD	**61.18±12.67**		**61.14±10.79**	

Samples are age matched with P=0.986

Age is matched in both the groups (controls & cases). Samples are age matched with P=0.986. Maximum number of subjects were in the age group of 51-70 years, and minimum were in the age group of 81-90 years. Mean age in controls was 61.18±12.67 and in cases was 61.14±10.79.

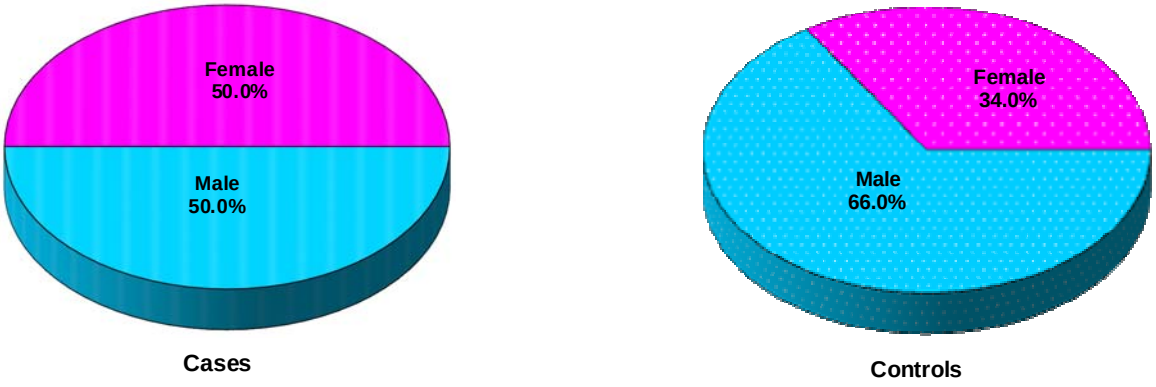


Graph 1 : Age distribution of patients studied

Table 2: Gender distribution of patients studied

Gender	Cases		Control	
	No	%	No	%
Male	25	50.0	33	66.0
Female	25	50.0	17	34.0
Total	**50**	**100.0**	**50**	**100.0**

Samples are gender matched with P=0.105



Graph 2 : Gender distribution of patients studied

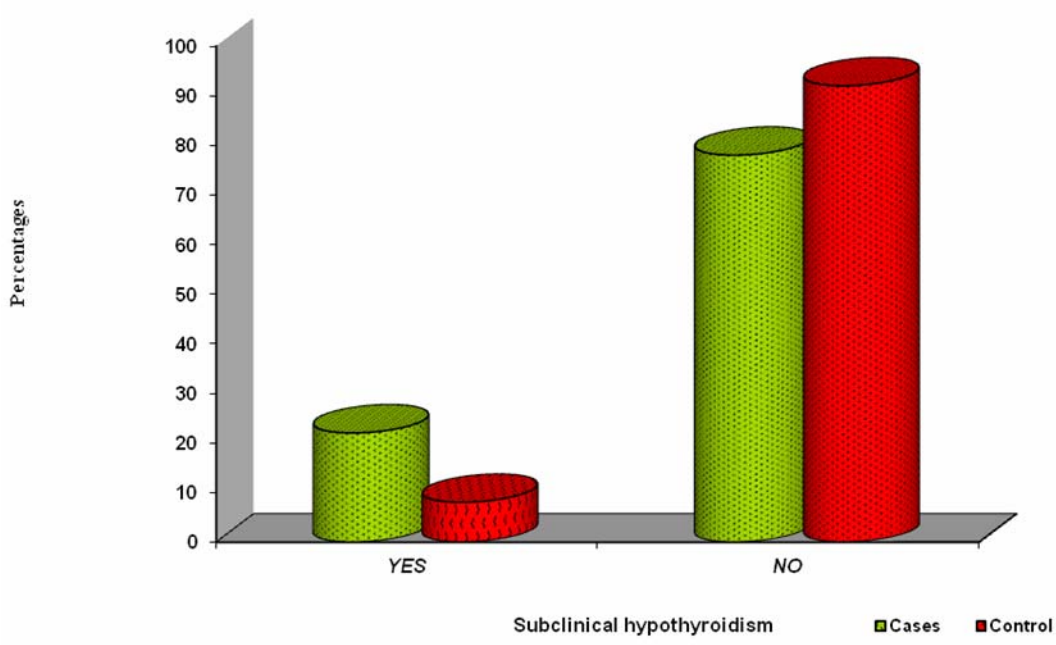
Out of 50 subjects with metabolic syndrome 11 patients had subclinical hypothyroidism.

Out of 50 controls, 4 had subclinical hypothyroidism.

Table 3: Prevalence of Sub-clinical hypo thyroidism in patients studied

Subclinical hypothyroidism	Cases (n=50)		Control (n=50)	
	No	**%**	**No**	**%**
No	39	78.0	46	92.0
Yes	**11**	**22.0**	**4**	**8.0**

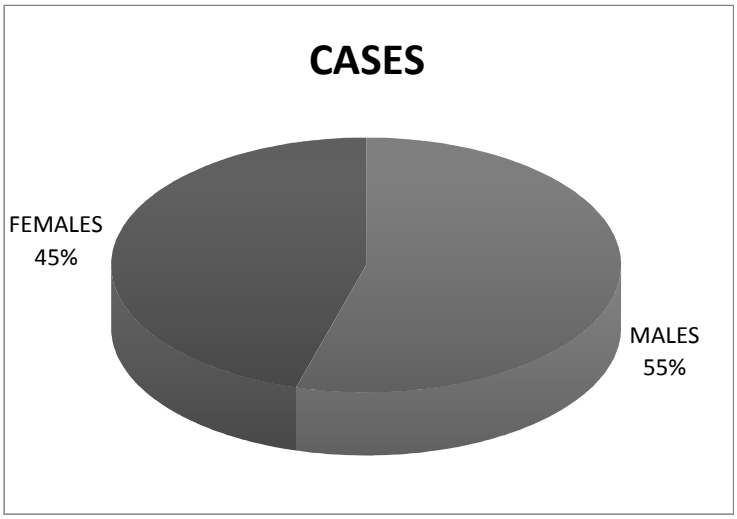
Incidence of subclinical Hypothyroidism are more in Cases (22.0%) compared to Controls (8.0%) with **p=0.091+**



Graph 3 : Prevalence of Sub-clinical hypo thyroidism in patients studied

Table 4: Incidence of subclinical hypothyroidism in various age groups

Age in years	Cases	Control
	No	No
31-40	2	0
41-50	1	0
51-60	2	2
61-70	4	1
71-80	1	1
81-90	1	0
Total	**11**	**4**



Graph 4 : Gender distribution of patients with subclinical hypothyroidism

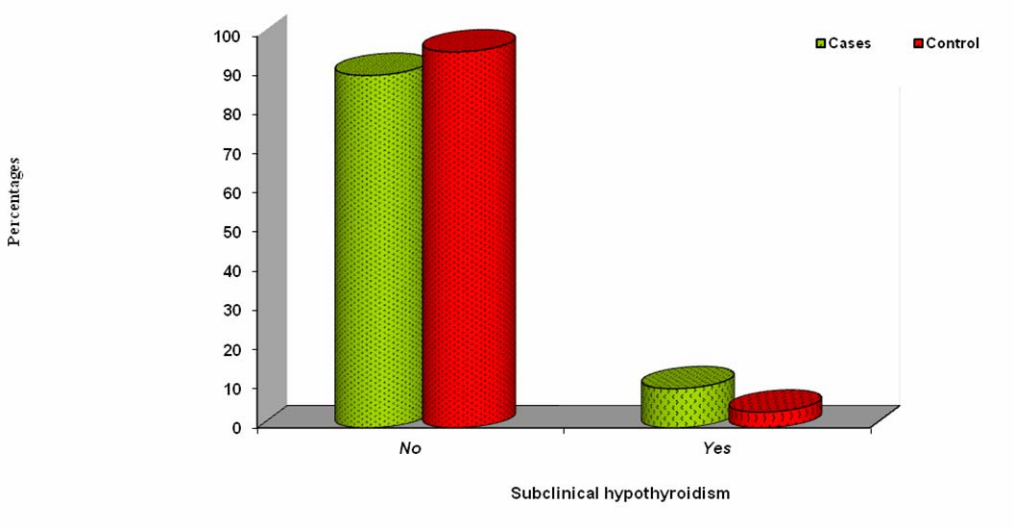
Out of 50 subjects with metabolic syndrome 5 had subclinical hyperthyroidism.

Out of 50 controls, 2 had subclinical hyperthyroidism.

Table 5: Prevalence of Subclinical hyperthyroidism in patients studied

Subclinical hyperthyroidism	Cases (n=50)		Control (n=50)	
	No	%	No	%
No	45	90.0	48	96.0
Yes	5	10.0	2	4.0

Incidence of subclinical Hyperthyroidism are more in Cases (10.0%) compared to Controls (4.0%) with P=0.436 but not statistically significant.

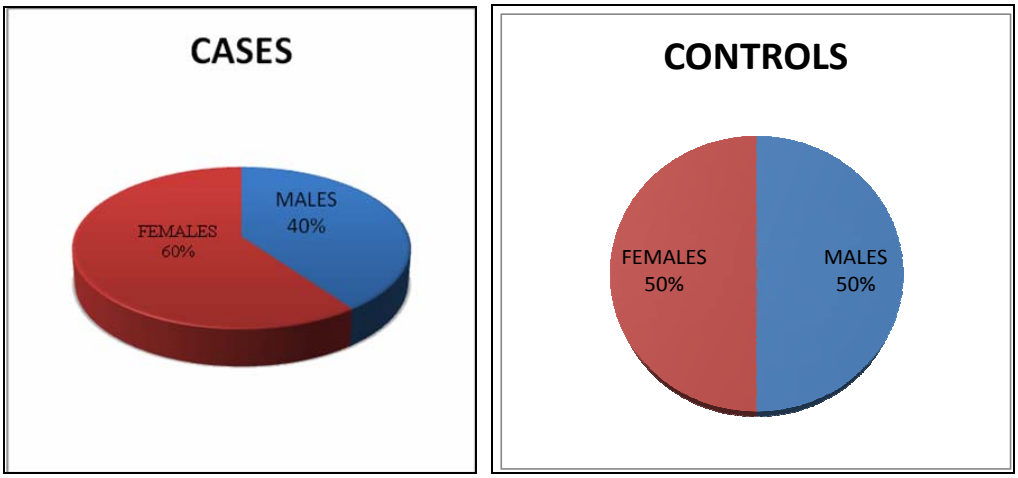


Graph 5 : Prevalence of Subclinical hyperthyroidism in patients studied

Table 6: Incidence of subclinical hyperthyroidism in various age groups

Age in years	Cases		Control	
	No	%	No	%
31-40	0	6.0	0	0
41-50	0	12.0	0	0
51-60	1	34.0	0	26.0
61-70	4	24.0	2	38.0
71-80	0	18.0	0	18.0
81-90	0	6.0	0	0.0
Total	**5**	**100.0**	**2**	**100.0**

Gender distribution of patients with subclinical hyperthyroidism

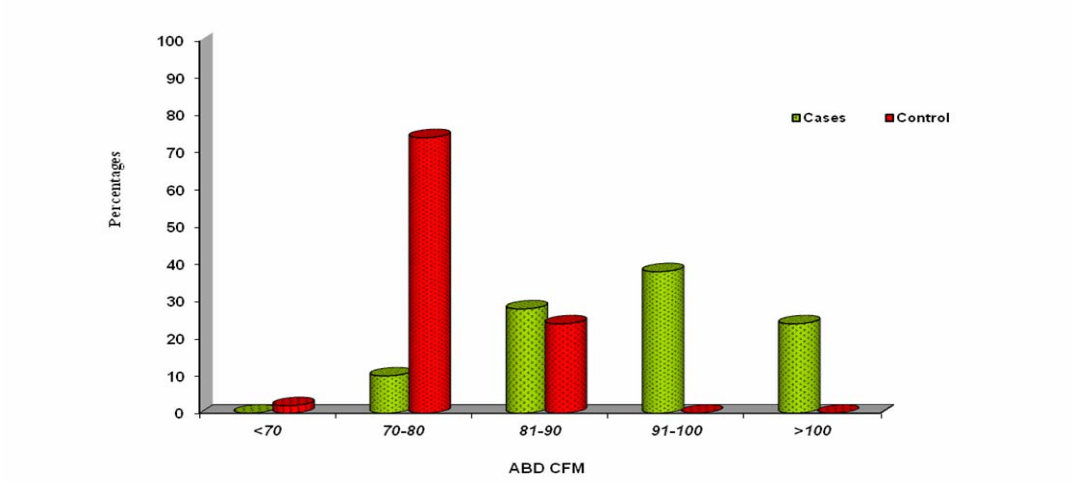


Graph 6 : Gender distribution of patients with subclinical hyperthyroidism

Table 7: Comparison of ABD CFM in two groups studied

ABD CFM	Cases		Control	
	No	%	No	%
<70	0	0.0	1	2.0
70-80	5	10.0	37	74.0
81-90	14	28.0	12	24.0
91-100	19	38.0	0	0.0
>100	12	24.0	0	0.0
Total	**50**	**100.0**	**50**	**100.0**
Mean ± SD	**94.38±8.59**		**78.58±5.17**	

p=<0.001**

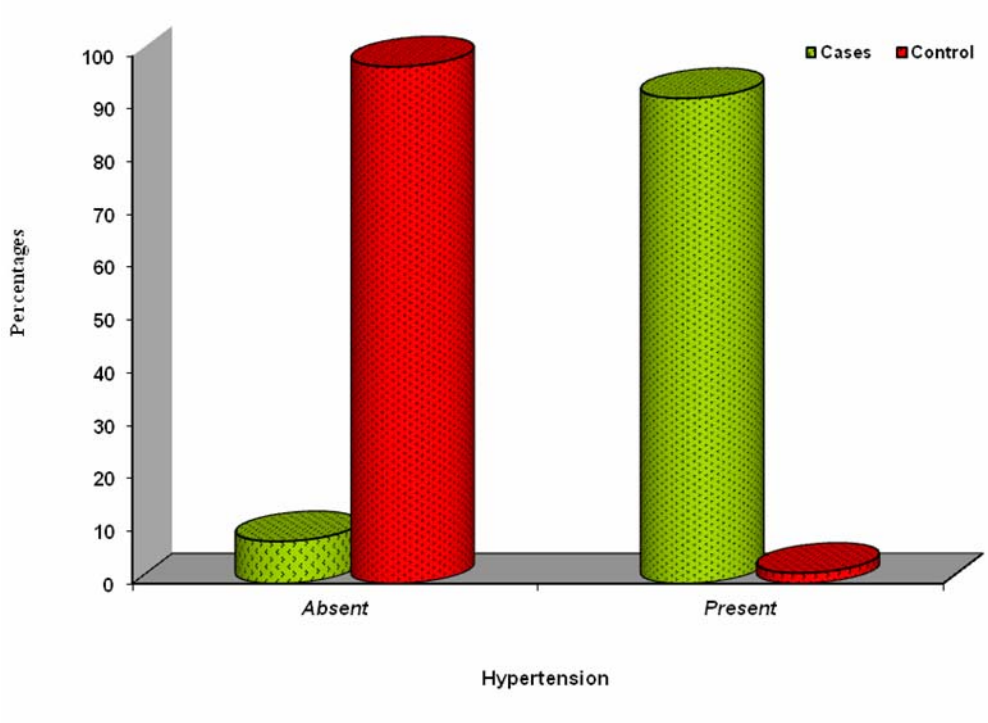


Graph 7 : Comparison of ABD CFM in two groups studied

Table 8: Incidence of Hypertension

Hypertension	Cases		Control	
	No	**%**	**No**	**%**
Absent	4	8.0	49	98.0
Present	46	92.0	1	2.0
Total	**50**	**100.0**	**50**	**100.0**

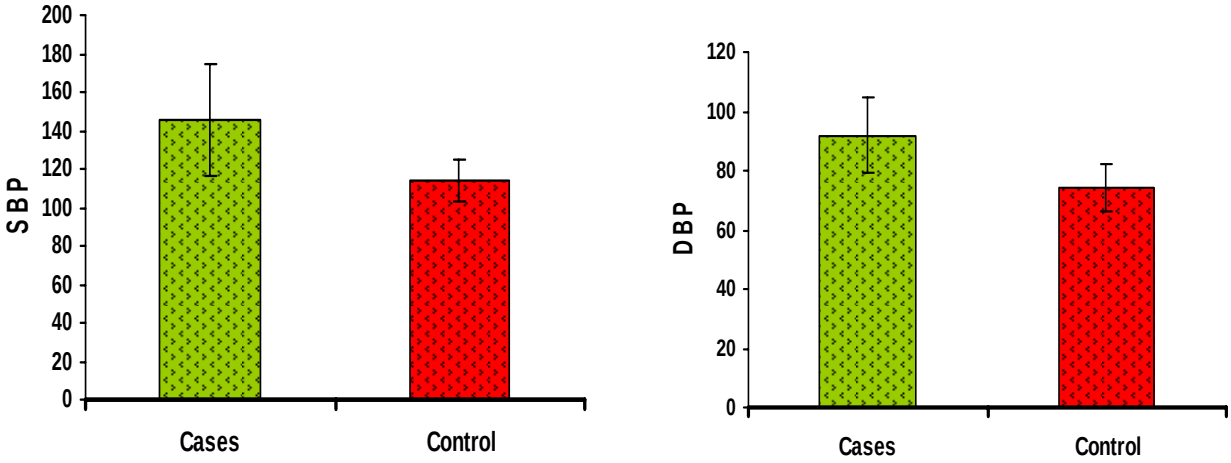
p=<0.001**



Graph 8 : Incidence of Hypertension

Table 9: Comparison of SBP/DBP in two groups studied

	Cases	Control	P value
SBP	145.12±29.31	113.80±11.23	<0.001**
DBP	92.00±13.09	74.00±7.82	<0.001**

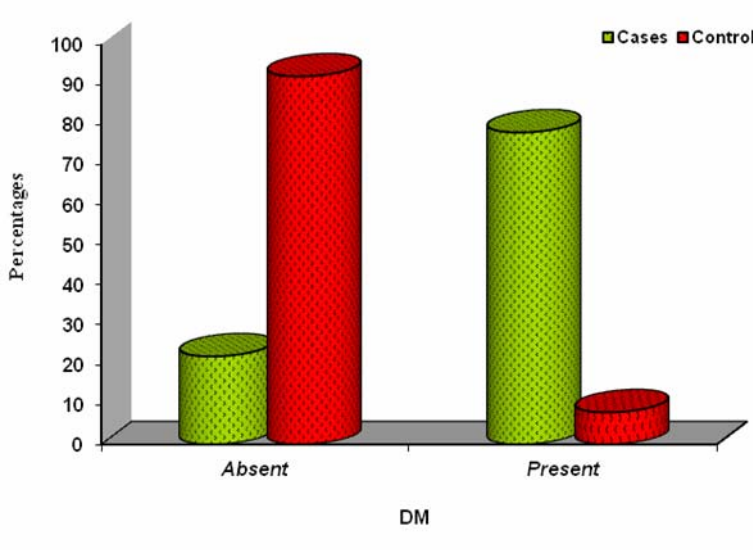


Graph 9 : Comparison of SBP/DBP in two groups studied

Table 10: Incidence of DM

DM	Cases		Control	
	No	**%**	**No**	**%**
Absent	11	22.0	46	92.0
Present	39	78.0	4	8.0
Total	**50**	**100.0**	**50**	**100.0**

p=<0.001**

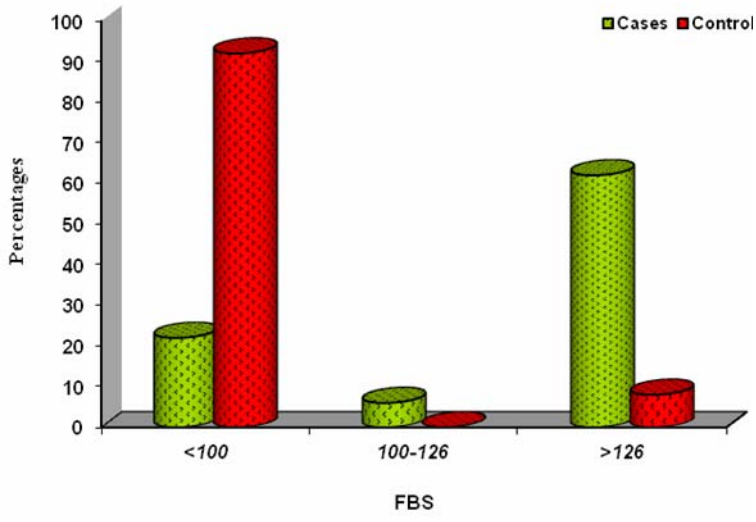


Graph 10 : Incidence of DM

Table 11: Comparison of FBS (mg/dl) in two groups studied

FBS	Cases		Control	
	No	%	No	%
<100	11	22.0	46	92.0
100-126	3	6.0	0	0.0
>126	36	62.0	4	8.0
Total	**50**	**100.0**	**50**	**100.0**
Mean ± SD	**216.66±136.97**		**101.12±68.79**	

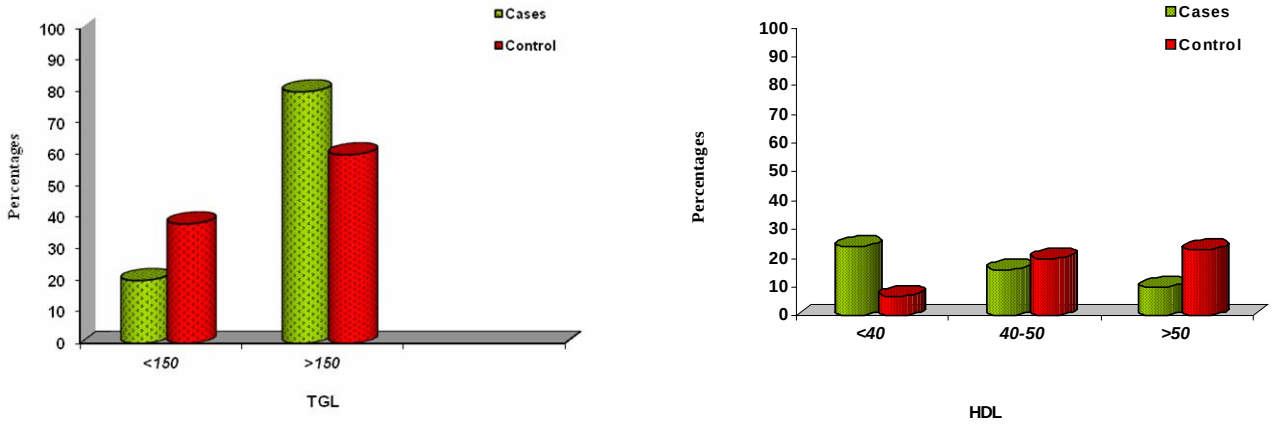
p=<0.001**



Graph 11 : Comparison of FBS (mg/dl) in two groups studied

Table 12: Comparison of Lipids parameters in two groups studied

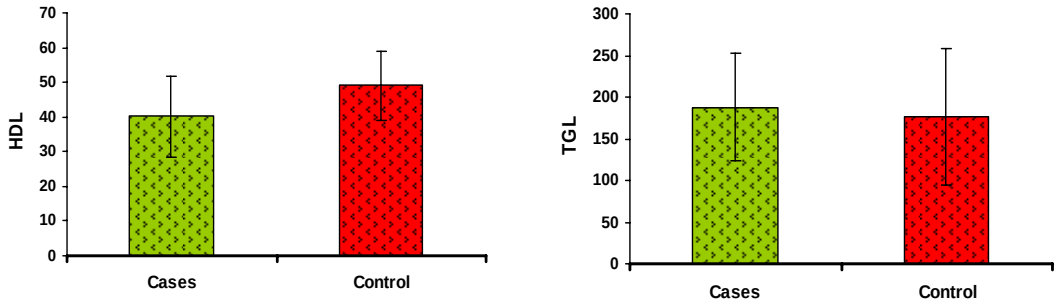
Lipid profile	Cases (n=50)		Control (n=50)	
	No	%	No	%
HDL				
>40	24	48.0	7	14.0
40-50	16	32.0	20	40.0
>50	10	10.0	23	46.0
TGL				
<150	10	20.0	19	38.0
>150	40	80.0	31	62.0



Graph 12 : Comparison of Lipids parameters in two groups studied

Table 13: Comparison of Lipids parameters in two groups studied

Lipids parameters	Cases	Control	P value
HDL	40.13±11.71	49.04±10.09	<0.001**
TGL	188.10±64.16	175.82±81.83	0.406



Graph 13 : Comparison of Lipids parameters in two groups studied

TABLE 14: Gender distribution with Low HDL levels and thyroid status.

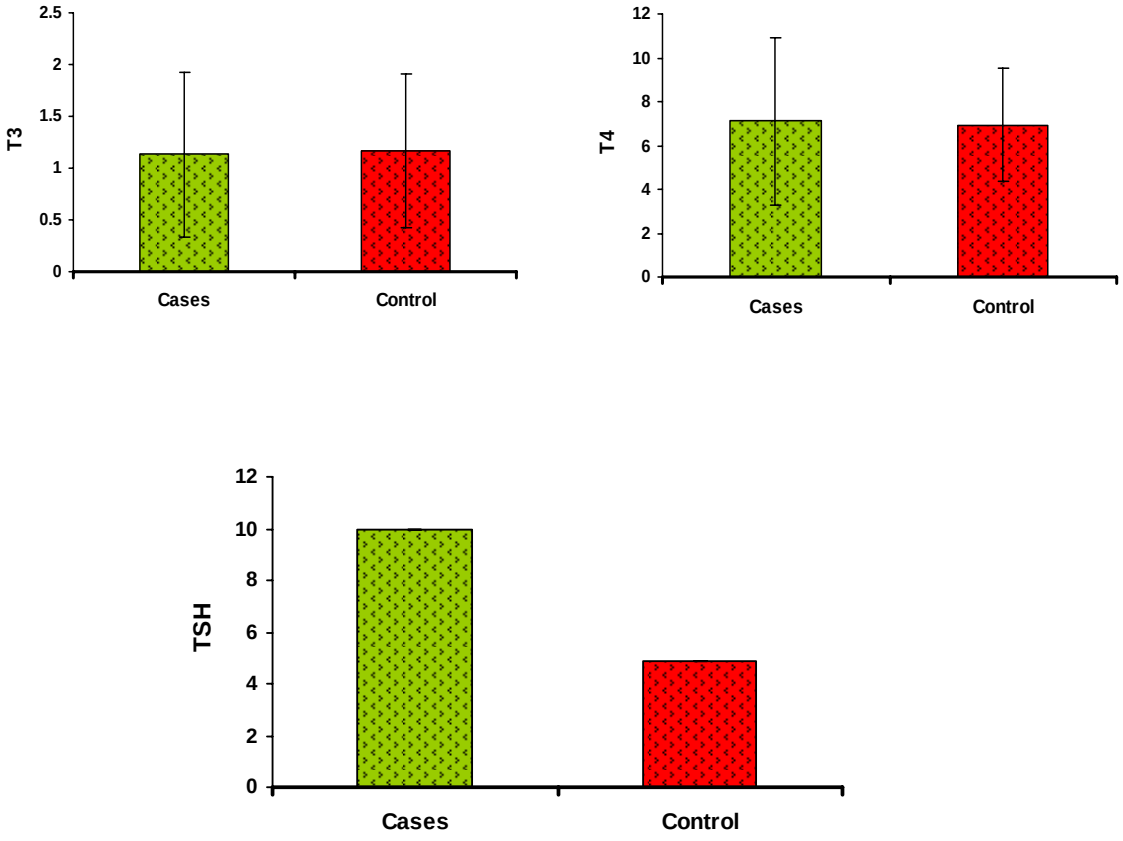
SEX	HDL (< 50 FEMALES, <40 MALES)	HYPOTHYROIDISM	HYPERTHYROIDISM
MALES	13	3	1
FEMALES	21	4	3

TABLE 15: Gender distribution with High TGL levels and thyroid status.

SEX	TGL (>150)	HYPOTHYROIDISM	HYPERTHYROIDISM
MALES	20	4	1
FEMALES	20	5	2

Table 16: Thyroid functions

Thyroid functions	Cases	Control	P value
TSH	9.98±21.73	4.90±7.32	0.120
T4	7.10±3.84	6.94±2.60	0.817
T3	1.13±0.80	1.17±0.74	0.772



Graph 14 : Thyroid functions

DISCUSSION

Epidemiological studies have shown that the metabolic syndrome occurs in a wide variety of ethnic groups including Asian Indians. The Mets is common in adult Asian Indians.[83]

The present study was conducted to study the association between metabolic syndrome and subclinical thyroid dysfunction. The study included 100 subjects, of whom 50 non-metabolic syndrome subjects (controls) and 50 were were metabolic syndrome subjects (cases) presenting to R.L.Jalappa Hospital and Research Centre, Kolar, between January 2012 to January 2013.

TABLE 17: MEAN AGE

STUDIES	**MEAN AGE (MALES)**	**MEAN AGE (FEMALES)**
Agarwal et al[6]	-	52.68 ± 10.20
Lai et al[8]	70.0 ± 4.4	69.7±4.6
Uzunlulu et al[84]	48.5± 11.5 (both M and F)	48.5± 11.5 (both M and F)
Present study	**61.18±12.67**	**61.14±10.79**

THYROID DYSFUNCTION AND METABOLIC SYNDROME

Our study shows that 32% of subjects with metabolic syndrome had subclinical thyroid dysfunction. Incidence of subclinical Hypothyroidism are more in Cases (22.0%) compared to Controls (8.0%) with P=0.091. Incidence of subclinical Hyperthyroidism are more in Cases (10.0%) compared to Controls (4.0%) with P=0.436 but not statistically significant

45% of females with metabolic syndrome had subclinical hypothyroidism and 55% of males with metabolic syndrome had subclinical hypothyroidism.

According to a study done by Uzunlulu et al[84] 16% of patients with metabolic syndrome had subclinical hypothyroidism whereas only 5.8% had in control group. Agarwal et al reported 53% incidence of subclinical hypothyroidism in females.[6]In a study by RV Jayakumar et al[9], it was reported that 60 percent of the cases with metabolic syndrome had thyroid function abnormalities in their case series.

In our study subclinical hypothyroidism was maximum in age group between 50-70 years in males and 30-50 years in females.

In a study by Punia VPS[83] done in urban population in Delhi, it was reported TSH levels were high in 30% of women and 26% men. The prevalence of the abnormality was common in 30 – 39 years of age in women where the levels were high in 70% of the cases, while in men the prevalence was high in the age group of 50 - 59 years, which is comparable to our study.

Similar observations were made in the study by Agarwal et al[6] which they reported more incidence of subclinical thyroid dysfunction in age between 40-60 years in females.

In a study done by Lai CC et al[8] in Taiwanese elderly population, they reported that the association between subclinical thyroid hypo/hyperthyroidism and MetS was 32.8% of subjects with subclinical hypothyroidism and 28.1% of subjects with subclinical hyperthyroidism, which is also comparable to our study.

TABLE 18: ABDOMINAL CIRCUMFERENCE

STUDIES	**MALES (cms)**	**FEMALES (cms)**
Rajeev Gupta et al[32]	102	88
A.Ramachandran et al[31]	90	85
Dongfeng Gu et al[85]	90	80
Agarwal et al[6]	-	95.91± 5.05
Uzunlulu et al[84]	98.9± 8.6(M & F)	98.9± 8.6(M & F)
Present Study	**94.38±8.59**	**78.58±5.17**

In our study out of 50 cases, 29 cases (58%) had increased waist circumference as defined by NCEP-ATPIII criteria earlier. Out of 29 cases, 20 were females (80%) with abdominal circumference more than 88cms and 9 were males (36%) with a waist circumference more than 102 cms. In females with increased waist circumference 4 (80%) had subclinical hypothyroidism whereas only 1 (16.7%) male had increased waist circumference. 3 (18.75%) subjects of metabolic syndrome had increased waist circumference were having subclinical hyperthyroidism. Out of the 3 two were females. None of the controls had increased waist circumference.

In study done by Punia VPS[83] , it was reported that an increase of 65% if waist circumference in metabolic syndrome patients and 28% of these patients were reported to have subclinical hypothyroidism, which was quite significant in our study. In another study by Agarwal et al[6] , they reported among the components of the metabolic syndrome, women with a waist circumference > 35 inches (88 centimeters) had a higher incidence of thyroid hypofunction.

BLOOD SUGARS

Mean fasting blood sugars in our study was 216.66±136.97. 36 cases (62%) had FBS >126 mg/dl. 42 cases (84%) were either known diabetics on antidiabetic medications or were having FBS >126 mg/dl.

4 males and 4 females with subclinical hypothyroidism were either on antidiabetic medication or had FBS>126 mg/dl. 2 males and 2 females had subclinical hyperthyroidism were either on antidiabetic medication or had FBS>126 mg/dl.

In studies by Uzunlulu et al[84] showed a mean FBS of 107±11.7 mg/dl and another study by Agarwal et al[6] also showed a mean FBS 144.06 ± 51.70, which is comparable with our study and infact shows to be quite significant.

TABLE 19: HYPERTENSION

STUDIES	**SBP**	**DBP**
Wang et al	119.85 ± 16.36	70.91 ± 10.43
Agarwal et al[6]	135.26 ± 17.47	87.23 ± 12.02
Lai CC et al[8]	141.6 _27.4	75.7 _ 13.7
Uzunlulu et al[84]	145.6±21.6	116.3±8.3
Present study	**145.12±29.31**	**92.00±13.09**

47 subjects (94%) had hypertension or were on antihypertensive medications. 8 out of 11 subclinical hypothyroid subjects with metabolic syndrome had hypertension (72.7%) and 4 out of 5 subclinical hyperthyroid subjects had hypertension. Male and female incidences were equal in both the thyroid dysfunctions (50% each).

These results were comparable to other studies as compared in the table.

DYSLIPIDEMIA

Low HDL levels were found in 44 cases (88%), 21 females (84%) were having low HDL levels, 13 males (52%) were having low HDL levels. Out of these 21 females, 4 (80% of females with subclinical hypothyroidism had low HDL levels) were having subclinical hypothyroidism and 3 were having subclinical hyperthyroidism. Out of 13 males having low HDL levels, 3 had subclinical hypothyroidism (50% males with subclinical hypothyroidism had low HDL levels) and 1 had subclinical hyperthyroidism.

Mean HDL levels of cases in our study were 40.13±11.71 and in controls were 49.04±10.09, with a p value of < 0.01, which is a significant finding.

In other studies, Agarwal et al[6] , mean HDL was 48.65 ± 25.08, Uzunlulu et al[84] mean HDL was 44.9 ±10.7 in cases and 53± 15.9 in controls, indicating that the findings in our study are indeed very significant.

High TGL levels were found in 40 cases of metabolic syndrome. Both males and females had equal incidence (20 each). 9 subclinical hypothyroid cases had an elevated TGL levels and 3 subclinical hyperthyroid cases had an elevated TGL levels.

Mean TGL levels of cases in our study were 188.10±64.16 and in controls were 175.82±81.83.

In other studies, Agarwal et al[6] , mean HDL was 182 ± 69.63, Uzunlulu et al[84] mean HDL was 199.4 ±100.7 in cases and 11.7± 62.6 in controls, which is comparable finding in our study.

CONCLUSION

In this study we found that 32% of the subjects with metabolic syndrome had subclinical thyroid dysfunction, which is quite a significant number.

22% of metabolic syndrome patients had subclinical hypothyroidism as compared to 8% of the general population, which was statistically significant.

10% of metabolic syndrome patients had subclinical hyperthyroidism as compared to 4% of the general population studied, which is also quite a high number.

Patients with subclinical hypothyroidism are at an enhanced risk for atherosclerosis and myocardial manifestations. The prevalence of hypothyroidism (subclinical and overt) is more with metabolic syndrome as evident from our study, early detection could reduce the significant cardiovascular risk in these patients.

Subclinical thyroid disorders are known to increase blood pressure, lower HDL and raise LDL cholesterol. In our study also supported this fact and these being individual components of metabolic syndrome they can further lead to cardiovascular morbidity and mortality.

In conclusion, investigation for subclinical thyroid dysfunction- both hyperthyroid and hypothyroid prior to initiation of treatment for MetS patient may be a reasonable strategy.

SUMMARY

The present study was conducted to compare the incidence of subclinical thyroid dysfunction in metabolic syndrome subjects. The study included 100 subjects, of whom 50 non-metabolic syndrome subjects (controls) and 50 were were metabolic syndrome subjects (cases) presenting to R.L.Jalappa Hospital and Research Centre, Kolar over a period of one year.

The subjects were studied by detailed history taking, clinical examination, anthropometric measurements and relevant investigations using a proforma specially designed for this study.

The study group (Controls & Cases) was matched with the Age, Gender & BMI, to compare the important variables.

- The age of the patients ranged from 31 to 90 years, with a median age of 61.18 years. Maximum number of cases was in the 51-60 years (34%).
- Male and Females were equal in cases, while males predominated in controls (66%).
- Incidence of subclinical Hypothyroidism are more in Cases (22.0%) compared to Controls (8.0%) with P=0.091.
- Incidence of subclinical Hyperthyroidism are more in Cases (10.0%) compared to Controls (4.0%) with P=0.436 but not statistically significant.
- Subclinical hypothyroidism was maximum in age group between 50-70 years in males and 30-50 years in females.
- Out of 50 cases, 29 cases (58%) had increased waist circumference. In females with increased waist circumference 4 (80%) had subclinical hypothyroidism whereas only 1 (16.7%) male had increased waist circumference. 3 (18.75%) subjects of metabolic

syndrome had increased waist circumference were having subclinical hyperthyroidism.

- Mean fasting blood sugars in our study was 216.66±136.97. 4 males and 4 females with subclinical hypothyroidism had FBS>126 mg/dl. 2 males and 2 females had subclinical hyperthyroidism were either on antidiabetic medication or had FBS>126 mg/dl.
- 8 out of 11 subclinical hypothyroid subjects with metabolic syndrome had hypertension (72.7%) and 4 out of 5 subclinical hyperthyroid subjects had hypertension.
- Mean HDL levels of cases in our study were 40.13±11.71 and in controls were 49.04±10.09, with a p value of < 0.01, which is a significant finding. 80% of females with subclinical hypothyroidism had low HDL levels. 50% males with subclinical hypothyroidism had low HDL levels.
- 9 subclinical hypothyroid cases had an elevated TGL levels and 3 subclinical hyperthyroid cases had an elevated TGL levels.

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ANNEXURES

PROFORMA

Name:

Age:

Sex:

Hospital No.:

Presenting Complaints:

Past History:

a. Diabetes

b. HTN

Personal History

Smoker

Alcoholic

General Examination

Built:

Pallor: Icterus: Clubbing: Pedal Edema:

BP: / mm of Hg Pulse: / min

Temp.: F

Respiratory system:

Cardiovascular system:

Per abdomen:

Central nervous system:

Abdominal circumference:

Clinical Impression:

INVESTIGATIONS

(i) CBC

Hb. - TLC: Plt:

(ii) FBS:

(iii) RFT:

Blood Urea: Serum Creatinine:

(iv) Lipid profile

a) Triglycerides:

b) HDL:

(v) Thyroid Function tests

a) TSH

b) T_4

c) T_3

(vi) ECG:

MASTER CHART : CONTROLS

S. No.	AGE	SEX	HTN/BP (SYSTOLIC/ DIASTOLIC)	DM/FBS	HDL	TGL	ABD. CFM	TSH	T4	T3	IP NO
1	48	F	N/110/70	Y/336	43	384	79	3.61	10	1.44	708050
2	53	F	N/130/80	N/98	32	187	80	2.34	1.57	0.25	712785
3	65	F	N/120/80	N/96	29	73	67	1.13	7.91	1.92	712797
4	65	M	N/140/80	N/87	32	210	78	1.3	7.54	0.92	713396
5	53	M	N/100/60	N/95	31	557	70	2.61	6.3	0.88	713397
6	77	M	N/110/70	Y/283	55	120	78	3.18	9.96	1.33	674453
7	45	M	N/120/80	Y/230	48	167	80	2.96	9.33	1.22	712369
8	55	M	N/110/70	N/83	45	194	82	3.84	7.46	1.11	714563
9	78	M	N/100/60	Y/428	60	177	80	3.4	8.05	1.19	714596
10	55	M	N/120/80	N/89	44	140	77	1.61	4.08	0.7	711688
11	46	M	N/120/80	N/87	46	141	76	4.06	7.97	1.35	718962
12	65	F	N/110/70	N/90	50	367	80	6.21	8.42	0.87	715748
13	45	F	N/120/80	N/88	50	168	77	3.46	8.84	0.9	713366
14	45	F	N/110/80	N/96	56	153	71	1.63	7.45	1.55	717951
15	75	F	N/110/70	N/76	67	176	78	0.99	7.93	1.56	719293
16	40	M	N/130/80	N/80	55	143	86	3.55	8.93	1.06	716918
17	55	M	N/100/60	N/72	41	165	86	0.56	7.42	0.93	714649
18	34	M	N/120/80	N/80	43	220	87	1.68	5.88	0.81	723336
19	45	F	N/110/80	N/77	54	199	80	2.03	5.34	0.8	721863
20	65	F	N/100/70	N/80	59	177	77	4.13	5.69	1.5	720625
21	70	M	N/100/60	N/88	58	201	78	2.43	5.75	1.26	722151
22	65	M	N/120/80	N/79	46	150	73	1.18	4.96	0.54	721480
23	60	M	N/120/80	N/87	60	111	78	1.7	7.29	1.02	780113
24	70	M	N/110/80	N/98	44	133	80	1.65	5.28	0.77	753967
25	70	F	N/100/70	N/97	57	195	86	2.71	10.7	1.19	732884
26	62	F	N/120/80	N/84	62	107	71	1.7	5.74	0.899	743901
27	70	M	N/120/80	N/88	48	106	75	3.78	5.26	1.36	751224
28	63	M	Y/140/80	N/97	60	100	78	30.28	7.34	0.99	674032
29	47	M	N/110/80	N/80	42	163	87	4.93	7.91	1.39	674040
30	75	F	N/110/60	N/75	63	177	80	1.29	5.04	0.861	675160
31	62	M	N/110/60	N/69	66	108	86	5.45	8.3	0.732	705479
32	56	M	N/120/80	N/70	42	170	83	1.81	10.6	1.44	705480
33	60	M	N/110/80	N/70	42	279	85	25.98	7.74	0.98	713284
34	60	M	N/120/80	N/76	53	136	87	4.87	7.25	1.11	678715
35	60	F	N/120/80	N/71	58	154	70	2.21	6.7	0.747	711165
36	62	M	N/110/70	N/70	48	176	80	6.43	5.44	0.768	715377
37	75	M	N/100/60	N/70	49	112	78	3.11	3.62	0.887	715002
38	70	M	N/80/60	N/65	45	193	70	35.83	4.28	0.94	716032
39	74	F	N/120/80	N/70	60	112	72	6.34	8.31	1.21	710140
40	65	M	N/130/80	N/89	67	90	76	3.8	7.57	1.02	624842
41	78	M	N/100/60	N/80	30	210	78	1.12	8.21	1.34	662045
42	80	M	N/120/80	N/78	56	134	76	3.28	0.474	5.84	665228
43	55	M	N/110/70	N/84	44	176	87	21.1	6.21	1.04	663807
44	71	M	N/130/80	N/76	32	166	85	1.75	6.88	0.94	669626
45	65	F	N/120/80	N/88	48	193	70	1.43	5.44	0.99	663422
46	64	M	N/100/70	N/76	52	165	80	5.8	4.32	1.12	666385
47	61	M	N/120/80	N/87	49	134	76	<0.015	13.92	1.49	672048
48	56	F	N/110/70	N/76	55	123	77	5.34	3.11	1.35	672392
49	63	F	N/110/70	N/80	40	112	78	0.21	13.98	1.21	674635
50	59	M	N/110/80	N/87	36	287	80	3.12	3.45	0.78	643139