"PREVALENCE OF PRIMARY HYPOTHYROIDISM IN METABOLIC SYNDROME – A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELGAUM"

REG NO. BG0112004

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"PREVALENCE OF PRIMARY HYPOTHYROIDISM IN METABOLIC SYNDROME – A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELGAUM"** is a bonafide research work done by **CANDIDATE REGISTER NO. BG0112004**

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LIST OF ABBREVIATIONS USED

A1C	-	Glycated
TSH	-	Thyroid stumulating hormone
AACE	-	American Association of Clinical Endocrinologists
apoB	-	Apolipoprotein B
ASCVD	-	Atherosclerotic cardiovascular disease
AT II	-	Angiotensin II
ATP	-	Adult treatment panel
BMI	-	Body mass index
BP	-	Blood pressure
CETP	-	Cholesterol ester transport protein
cm	-	Centimeter
CNS	-	Central nervous system
CRP	-	C-reactive protein
CVD	-	Cardiovascular disease
DBP	-	Diastolic blood pressure
DIT	-	Diiodotyrosine
e.g.	-	For example
NF B	-	Nuclear factor kappa-beta
EGIR	-	European Group for the Study of Insulin Resistance
ET-1	-	Endothelin-1
FFA	-	Free fatty acid
FNA	-	Fine-needle aspiration
GC	-	Glucocorticoid
hCG	-	Human chorionic gonadotropin

HDL	-	High density lipoprotein
HDL-C	-	High density lipoprotein–cholesterol
HOMA	-	Homeostasis Model Assessment
i.e	-	That is
IDF	-	International Diabetes Federation
IFG	-	Impaired fasting glucose
IL1	-	Interleukin 1
IL6	-	Interleukin 6
IL-6	-	Interleukin-6
kg/m^2	-	Kilograms per square meter
LDL	-	Low density lipoprotein
VLDL	-	very low density lipoprotein
LDL-C	-	Low density lipoprotein cholesterol
MAP	-	Mitogen activated protein
MetS	-	Metabolic syndrome
mg/dL	-	Milligram per deciliter
mg/dL	-	Milligram per liter
MI	-	Myocardial infarction
MIT	-	Monoiodotyrosine
mmHg	-	Millimeters of mercury
mmol/l	-	Millimole per liter
MS	-	Metabolic syndrome
n	-	Total number
NCEP	-	National Cholesterol Education Program
ng/dL	-	Nano gram per deci liter
NO	-	Nitric oxide

No.	-	Number
NSAIDs	-	Nonsteroidal anti-inflammatory drugs\
OGTT	-	Oral glucose tolerance test
p	-	Probability
PAI-1	-	Plasminogen activator inhibitor-1
pg/mL	-	Picogram per milliliter
PI3K	-	Phosphoinositide 3-kinase
RAAS	-	Renin angiotensin aldosterone system
RAS	-	Renin angiotensin system
SCH	-	Sub-clinical hypothyroidism
SD	-	Standard deviation
SNS	-	Sympathetic nervous system
T2DM	-	Type 2 diabetes mellitus
TBG	-	Thyroxine-binding globulin
TG	-	Triglycerides
TGs	-	Triglycerides
TNFα	-	Tumor necrosis factor alpha
tPA	-	Tissue plasminogen activator
U.S.	-	United States
vs	-	Versus
WC	-	Waist circumference
WHO	-	World Health Organization
µg/min	-	Microgram per minute

ABSTRACT

Background and objectives

Metabolic syndrome and hypothyroidism are independent risk factors for cardiovascular disease. Patients suffering from both these diseases may have a compounded risk atherosclerotic cardiovascular disease, hyperlipidemia, low grade inflammation and hypercoagulability. The present study was undertaken to investigate the proposed association between these two disease entities.

Methodology

The present one year cross-sectional study was done from January 2013 to December 2013 at Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 117 patients diagnosed to have metabolic syndrome based on NCEP ATP III criteria were studied for thyroid abnormalities.

Results

Males constituted 50.43% and 49.57% were females with male to female ratio of 1:1. Most of the patients presented with age between 51 to 60 years (28.21%) and the mean age was 52.25 ± 13.49 years. Most of the patients had BMI between 25.00 to 29.99 Kg/m^2 (37.61%) and mean BMI was found to be 27.20 ± 4.22 Kg/m^2. History of diabetes mellitus, hypertension and dislipidemia was noted in 63.25%, 76.07% and 65.81%. Abnormal waist circumference was noted in 38.46% of the patients and mean waist circumference was 90.78 ± 9.74 Cms. Majority of the patients had abnormal HDL (86.32%) and triglyceride (52.14%) levels. Based on abnormal fT4B levels in 9.40% and abnormal TSH

levels in 24.79%, thyroid status was abnormal in 24.79% of the patients. Thyroid abnormalities were hypothyroidism in 9.40% and 15.38% had sub-clinical hypothyroidism. Majority of the patients (71.79%) had metabolic syndrome with three components. Positive association of hypothyroidism was noted with female gender ($p<0.050$) while no association was found between hypothyroidism and metabolic syndrome components including waist circumference, hypertension, diabetes, high density lipoprotein and triglycerides.

Conclusion and interpretation

There is high prevalence of primary hypothyroidism in patients with metabolic syndrome and is further high among females compared to males.

Keywords

Hypothyroidism; Metabolic syndrome; Primary hypothyroidism; Subclinical hypothyeroidism;

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INTRODUCTION

Metabolic syndrome constitutes a cluster of risk factors which includes hypertension, atherogenic dyslipidemia, hyperglycemia, prothrombotic and proinflammatory conditions.[1] It was described as early as 1923 by Kylin as the clustering of hyperuricemia, hyperinsulinemia and hypertension.[2] Reaven in 1988 described the central role of insulin resistance in Syndrome X, which has now become known as the metabolic syndrome.[3] It was also called as insulin resistance syndrome by some until 1999, when the WHO named it metabolic syndrome as there was not sufficient evidence to show that all its components were caused by insulin resistance.[4]

Approximately one fourth of the adult European population was estimated to have metabolic syndrome, with a similar prevalence in Latin America.[5] Metabolic syndrome is considered as an emerging epidemic in developing East Asian countries like China, Japan, and Korea. The prevalence of metabolic syndrome ranges from 8 to 13% in men and 2 to 18% in women depending on the population and definitions used.[6-8] Metabolic syndrome now has been recognized as a highly prevalent problem in many other countries worldwide.[9]

Metabolic syndrome (MetS) has affected approximately one quarter of the population in developed countries. In India, studies have reported prevalence of metabolic syndrome ranging from 24.9% in northern India to 41% in Southern India using different definitions.[10]

It was accepted that metabolic syndrome increases the relative risk of cardiovascular disease, though was still debated whether metabolic syndrome adds to global cardiovascular disease risk as assessed by traditional risk factors. It was believed that visceral adiposity lies at the root of the cardiometabolic risk with the consequent syndrome of central obesity/insulin resistance. Clinical definitions of metabolic syndrome by National Cholesterol Education Program-ATP-III[11] or International Diabetes Federation[12] have become enormous value in the diagnosis, management and research on the cluster of metabolic risk factors. Yet, there is increasing recognition that other atherogenic, pro-thrombotic and inflammatory aspects of this syndrome are still not captured by these practical clinical definitions which warrant further investigation, particularly for valuable clinical markers.[13]

Presence of metabolic syndrome poses a major risk for development of both type 2 diabetes mellitus and atherosclerosis. The prevalence of cardiovascular disease increases to two to three times higher in individuals with metabolic syndrome than in age-matched controls.[1]

Sub-clinical hypothyroidism (SCH) and overt hypothyroidism were recognized risk factors for atherosclerotic cardiovascular disease, hyperlipidemia, low grade inflammation and hypercoagulability.[1] Hypothyroidism is known to cause hyperlipidemia, diastolic hypertension, endothelial dysfunction, and cardiovascular disease.[14] Considerable overlap can occur in the pathogenic mechanisms of atherosclerotic cardiovascular disease by MetS and hypothyroidism. The basic pathogenic mechanism in MetS is insulin resistence. The role of insulin resistance in development of dyslipidemia in hypothyroidism has been suggested in recent

studies.[15] Its relationship with insulin resistance can lead to a considerable overlap between the population subsets of MetS and hypothyroidism as well.[14]

However, in the South Indian general population there is scanty data on the prevalence of SCH and overt hypothyroidism. Since metabolic syndrome and hypothyroidism are independent risk factors for the same disease process, namely cardiovascular disease, it is possible that patients suffering from both these disease entities may have a compounded risk.

The present study is an effort to find out the prevalence of primary hypothyroidism in patients with metabolic syndrome so as to know the magnitude of overlap of these two groups and may highlight the importance of thyroid function tests in identifying hypothyroid population from MetS. This could helpful for the proper planning and adequate management strategies which may result in significant reduction in cardiovascular morbidity and mortality due to MetS by effective thyroid replacement therapy in future.

OBJECTIVES

The objectives of the present study is to assess the prevalence of primary hypothyroidism (overt and sub-clinical) in patients with metabolic syndrome.

REVIEW OF LITERATURE

The metabolic syndrome (MetS) has been a major escalating public-health and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits. It confers a 5-fold increased risk of type 2 diabetes mellitus (T2DM) and 2-fold increased risk of developing cardiovascular disease (CVD) over the next 5 to 10 years. Further, patients with the MetS are at 2- to 4-fold increased risk of developing stroke, a 3- to 4-fold increased risk of developing myocardial infarction (MI), and 2-fold risk of dying from such an event compared with those without the syndrome regardless of a previous history of cardiovascular events.[16]

Historical note

MetS initially started as a concept rather than a diagnosis. The metabolic syndrome had its origins in 1920 when Kylin, a Swedish physician, demonstrated the association of high blood pressure (hypertension), high blood glucose (hyperglycemia), and gout.[2] Later on in 1947, a study by Vague described that visceral obesity was commonly associated with the metabolic abnormalities found in CVD and T2DM.[17] Following this, in 1965, an abstract was presented at the European Association for the Study of Diabetes annual meeting by Avogaro and Crepaldi which described a syndrome which comprised of hypertension, hyperglycemia, and obesity.[16] The field moved forward significantly after the 1988 Banting Lecture given by Reaven.[3] He then described “a cluster of risk factors for diabetes and cardiovascular disease” and named it “Syndrome X”. His main contribution was an introduction to the concept of insulin resistance. But he

surprisingly missed obesity or visceral obesity from the definition which was later on added as a crucial abnormality.[3]

In 1989, Kaplan[18] renamed this syndrome as "The Deadly Quartet" for the combination of upper body obesity, glucose intolerance, hypertriglyceridemia, and hypertension and in 1992, it was again renamed as "The Insulin Resistance Syndrome".[16]

Since then several groups have attempted to develop diagnostic criteria for the diagnosis of the MetS and the first attempt in this direction was made by World Health Organization (WHO) diabetes group in 1998 to provide a definition of the MetS.[12]

However, the European Group for the study of Insulin Resistance (EGIR) countered with a modification of the WHO definition in 1999 and then in 2001, the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP) released its definition of metabolic syndrome.[11]

In response, the American Association of Clinical Endocrinologists (AACE) in 2003 offered its views regarding the definition of the syndrome.[19] The proliferation of definitions suggested that a single unifying definition would be desirable.[20]

With the hope of accomplishing this, the International Diabetes Federation (IDF) proposed a new definition of the MetS in April 2005.[21]

Definition

MetS is defined by a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic cardiovascular disease (ASCVD), (T2DM), and all cause mortality.[22] This collection of unhealthy body measurements and abnormal laboratory test results include atherogenic dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and a prothrombotic state.

Though there are several definitions of MetS, the most commonly used criteria for definition at present are from the World Health Organization (WHO),[12] the European Group for the study of Insulin Resistance (EGIR),[23] the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III),[11] American Association of Clinical Endocrinologists (AACE),[19] and the International Diabetes Federation (IDF).[21]

<u>WHO definition</u>[12]

Diabetes mellitus (fasting plasma glucose ≥7.0 mmol/l and/or 2-hour plasma glucose ≥11.1 mmol/l), or impaired glucose regulation (fasting plasma glucose 6.1-6.9 mmol/l and/or 2-hour plasma glucose 7.8-11.0 mmol/l), and/or insulin resistance (below lowest quartile of glucose uptake in the euglycaemic state), and two or more of the following:

- Raised triglycerides (≥1.7 mmol/l or > 150 mg/dL) and/or
- Low HDL-cholesterol (<0.9 mmol/l in men, < 1.0 mmol/l in women).

- Central obesity (waist-to-hip ratio >0.90 in men, >0.85 in women) and/or body mass index (BMI) >30 kg/m^2.
- Raised blood pressure (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg).
- Micro albuminuria (urinary albumin excretion rate ≥20 μg/min or albumin/creatinine ratio ≥30 mg/g).

EGIR definition for non-diabetic individuals [23]

Hyperinsulinemia (fasting insulin concentrations in the highest quartile) and at least two of the following:

- Hyperglycemia (fasting plasma glucose ≥6.1 mmol/l or 110 mg/dL).
- Central obesity (waist circumference ≥94 cm in men, ≥80 cm in women).
- Hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treated for hypertension).
- Dyslipidemia (triglycerides >2.0 mmol/l [>178 mg/dL] or low HDL-cholesterol < 1.0 mmol/l [<39 mg/dL] or treated for dyslipidemia).

NCEP- ATPIII definition[11]

Three or more of the following:

- Abdominal obesity (waist circumference >102 cm in men, >88 cm in women).
- Triglycerides ≥1.7 mmol/l (> 150 mg/dL).
- HDL-cholesterol < 1.03 mmol/l in men (< 40 mg/dL), <1.29 mmol/l in women (< 50 mg/dL).

- Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg.
- Fasting plasma glucose ≥6.1mmol/l (≥ 110 mg/dL).

AACE definition for non-diabetic individuals[19]

Two or more of the following:

- Triglycerides ≥1.7 mmol/l (≥ 150 mg/dL).
- HDL-cholesterol < 1.03 mmol/l (< 40 mg/dL) in men, <1.29 mmol/l (< 50 mg/dL) in women.
- Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or current use of antihypertensive medications.
- 2-hour plasma glucose 7.8-11.0 mmol/l or fasting plasma glucose 6.1-6.9 mmol/l (IFG) (IFG was added in updated AACE criteria).

IDF definition[21]

Central obesity defined as ethnicity specific values of waist circumference (≥ 90cm for South Asian men and ≥80cm for South Asian women) and at least two of the following:

- Raised triglycerides levels (≥1.7 mmol/l or > 150 mg/dL), or specific treatment for this lipid abnormality.
- Reduced HDL-cholesterol (< 1.03 mmol/l or <40mg/dl in men, <1.29 mmol/l or <50mg/dl in women), or specific treatment for this lipid abnormality.

- Raised blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg), or treatment of previously diagnosed hypertension.

- Raised fasting plasma glucose (≥5.6 mmol/l or 100mg/dl), or previously diagnosed type 2 diabetes.

If above 5.6 mmol/l, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Although each definition possessed common features, there were several parameters that differed which resulted in difficulty in terms of applicability, uniformity, and positive predictive value with all these definitions. The AACE, WHO, and EGIR definitions were largely focused on insulin resistance, which is determined by an oral glucose tolerance test and hyperinsulinemic-euglycemic clamp. However, this labour intensive method was primarily used in a research environment.[24] In contrast, the ATPIII definition uses the measurements and laboratory results that are readily available to physicians, facilitating their clinical and epidemiological application and therefore has remained a backbone for subsequent classifications such as the IDF diagnostic criterion.[24] But the major problem with WHO and NCEP ATP III definitions has been their applicability to the different ethnic groups, especially when trying to define obesity cut-offs. This is particularly evident for the risk of T2DM, which is noted at much lower levels of obesity in Asians compared to Europeans. The IDF then recognized the difficulties in identifying unified criteria for MetS that was applicable across all the ethnicities and has then proposed a new set of criteria with ethnic/racial specific cut-offs.[25]

Gender and age-specific waist circumference cut-offs.[25]

Country /Ethnic group		Waist circumference
Europids: In USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥ 94 cms
	Female	≥ 80 cms
South Asians: Based on Chinese, Malay and Asian Indian population	Male	≥ 90 cms
	Female	≥ 80 cms
Chinese	Male	≥ 90 cms
	Female	≥ 80 cms
Japanese	Male	≥ 90 cms
	Female	≥ 80 cms
Ethnic South and Central Americans	Use South Asian recommendation until more specific data are available	
Sub Saharan Africans	Use European data until more data are available	
Eastern Mediterranean and middle east (Arab) populations	Use European data until more data are available	

This could account for the fact that the different populations, ethnicities, and nationalities have the different distributions of norms for body weight and waist circumference. It also recognized the relationship between these values and the risk of T2DM or CVD which differed in different populations.

Epidemiology

Worldwide prevalence of MetS ranges from <10% to 84%, depending on the region, urban or rural environment, composition (sex, age, race, and ethnicity) of the population studied as well as the definition of the syndrome used. In general, the IDF has estimated that one-quarter of the world's adult population has MetS.[16]

When the NCEP-ATP III[11] definition of metabolic syndrome was applied to a representative U.S. sample of 8,814 men and women aged 20 years and older from

the Third National Health and Nutrition Examination Survey (1988-1994), the unadjusted and age-adjusted prevalence of metabolic syndrome was 21.8% and 23.7%, respectively. The prevalence of metabolic syndrome increased from 6.7% among participants aged 20 - 29 years to 43.5% and 42.0% for participants aged 60-69 years and aged 70 years or older, respectively. Amongst the subgroup analysis, Mexican Americans had the highest age-adjusted prevalence of metabolic syndrome (31.9%). The age-adjusted prevalence was however similar for men (24.0%) and women (23.4%). But African American women had a 57% higher prevalence than African American men did, and Mexican American women had a 26% higher prevalence than Mexican American men did. According to the 2000 census data, about 47 million U.S. residents have metabolic syndrome.[26]

Yet another data from eight European studies, which included 8,200 men and 9,363 women, showed that in non-diabetic subjects, the frequency of the WHO-defined syndrome[12] varied between 7% and 36% for men aged 40 to 55 years, and for women of the same age, between 5% and 22%; however the EGIR-defined syndrome was less frequent than the WHO-defined syndrome (1% to 22% in men, 1% to 14% in women 40-55 years).[27]

In another study based on 11 prospective European cohort studies including 6,156 men and 5,356 women without diabetes, and aged from 30 to 89 years, the age-standardized prevalence of metabolic syndrome defined by the modified WHO[12] definition was slightly higher in men (15.7%) than in women (14.2%). However the overall prevalence of the WHO defined metabolic syndrome in non-diabetic adult Europeans is 15%.[28]

A study done in the city of Nizwa, among the Omani adults aged 20 years and over the age-adjusted prevalence of the NCEP-defined metabolic syndrome[13] was 21.0% (men: 19.5%, women: 23.0%).[29]

A study conducted on 40,698 Korean metropolitan subjects (26,528 men, 14,170 women) aged 20-82 years, the age-adjusted prevalence of the NCEP-defined metabolic syndrome[11] was 6.8% in total (5.2% male, 9.0% female). After using the Asia-Pacific criteria (APC) for abdominal obesity based on waist circumference (WC) (APC-WC: ≥ 90 cm in men, ≥ 80 cm in women), the prevalence rates of metabolic syndrome increased to 10.9% (9.8% male, 12.4% female). The subjects over 70 years of age had a 14-fold increased risk for metabolic syndrome compared to those aged 20-29 years, and females had higher prevalence rates than males in age groups older than 50 years.[30]

The 1998 Singapore National Health Survey which involved 4,723 men and women of Chinese, Malay, and Asian-Indian ethnicity aged 18-69 years, demonstrated that the age-adjusted prevalence rates of the NCEP-defined metabolic syndrome[13] were 9.4%, 18.7%, and 20.4% for Chinese, Malays, and Asian-Indians, respectively. After using the APC criteria, the analogous prevalence rates increased to 14.8%, 24.2%, and 28.8% for the three ethnic groups, respectively.[31]

The prevalence of the metabolic syndrome depends on multiple factors like age, ethnic background, and gender and rises linearly from 20 to 50 years and plateaus thereafter. Looking at other studies done around the world, which included population samples, aged from 20 to 25 and upwards, the prevalence varies from 8%

(India) to 24% (United States) in men and from 7% (France) to 46% (India) in women.[32]

The two Indian studies on metabolic syndrome differed in their definition of obesity, the first[33] used the obesity criteria suitable for Indians, while the second[34] used the standard ATP III definition of obesity. Both the studies used population based samples within the age range and reported a prevalence of 13% in Jaipur[45] and 41% in Chennai.[33] Though, the prevalence of obesity in the two study groups were quite similar (31% versus 33%), despite the different definitions used, more larger differences were observed between the two studies for the prevalence of elevated triglycerides (46% vs. 30%), hypertension (55% vs. 39%) and elevated fasting plasma glucose (27% vs. 5%); indicating a larger impact of these risk factors than obesity alone.

Many factors contributing to increasing prevalence of metabolic syndrome have been identified like atherogenic dyslipidemia, elevated triglycerides, apolipoprotein B and small low-density lipoprotein, low HDL, elevated plasma glucose, blood pressure, pro-thrombotic and pro-inflammatory state.

The low socio-economic status is associated with a higher mortality rate due to cardiovascular disease.[35] A low education level is linked to cardiovascular disease with risk factors such as smoking, hypertension, impaired glucose tolerance, diabetes mellitus, physical inactivity and overweight associated with other metabolic abnormalities.

Pathophysiology

MetS has been considered a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors. Several factors which constitute this syndrome include insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress.[16]

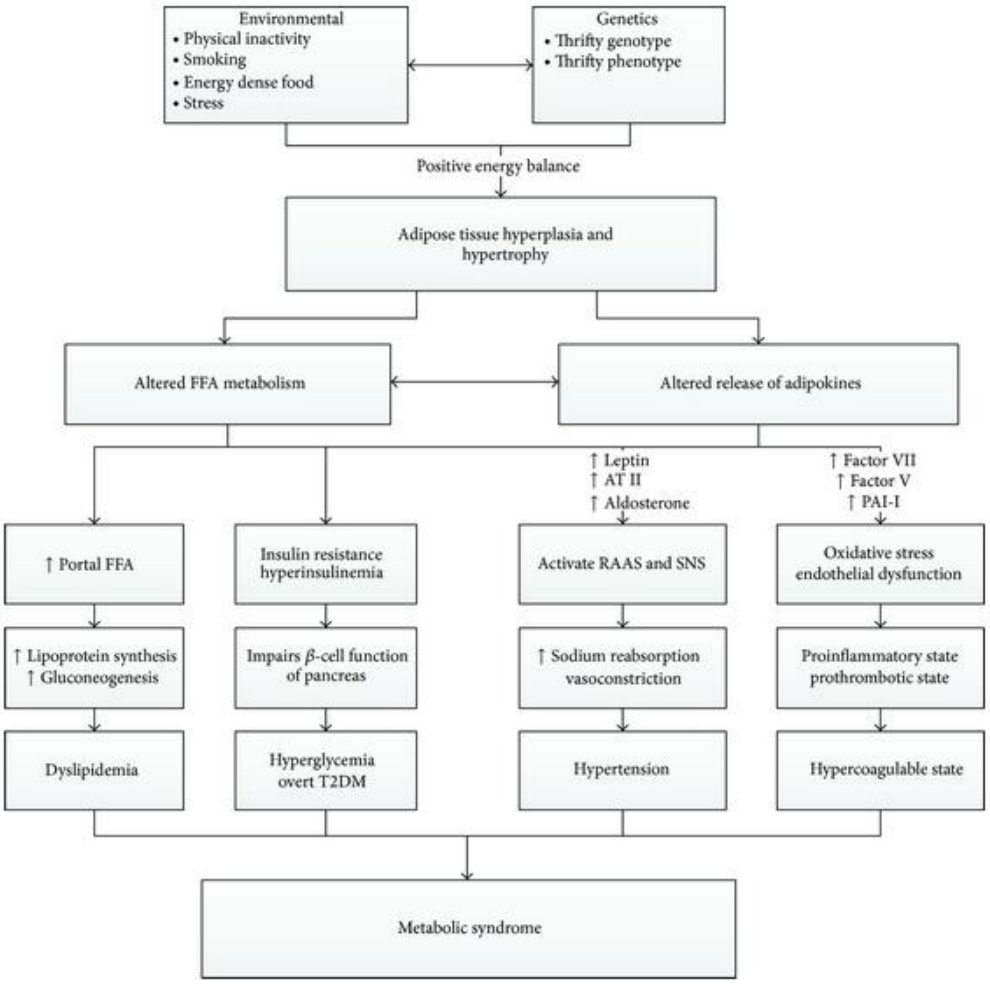


Figure 1. Schematic presentation of MetS (FFA: free fatty acid, ATII: angiotensin II, PAI-1: plasminogen activator inhibitor-1, RAAS: renin angiotensin aldosterone system, SNS: sympathetic nervous system.)

Abdominal Obesity

The “obesity epidemic” is mainly driven by an increased consumption of cheap, calorie-dense food and reduced physical activity. Adipose tissue is a heterogeneous mix of adipocytes, stromal preadipocytes, immune cells, and endothelium which can respond rapidly and dynamically to alterations in nutrient excess through adipocytes hypertrophy and hyperplasia. With obesity and progressive adipocytes enlargement, the blood supply to adipocytes is reduced with consequent hypoxia. Hypoxia has now been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as adipocytokines which includes glycerol, free fatty acids (FFA), proinflammatory mediators (tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6)), plasminogen activator inhibitor-1 (PAI-1), and C-reactive protein (CRP). This could result in a localized inflammation in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity related comorbidities. Adipocytokines integrate the endocrine, autocrine, and paracrine signals in order to mediate the multiple processes including insulin sensitivity, oxidant stress, energy metabolism, blood coagulation, and inflammatory responses which are thought to accelerate atherosclerosis, plaque rupture, and atherothrombosis. This shows that the adipose tissue is not only specialized in the storage and mobilization of lipids but also a remarkable endocrine organ releasing the numerous cytokines.[16]

FFA

Upper body subcutaneous adipocytes generate a majority of circulating FFA compared to the intra-abdominal fat content which has been positively correlated with the splanchnic FFA levels which may contribute to the liver fat accumulation commonly found in abdominal obesity.[36] In addition, an acute exposure of skeletal muscle to the elevated levels of FFA induces insulin resistance by inhibiting the insulin-mediated glucose uptake, while, a chronic exposure of the pancreas to the elevated FFA impairs a pancreatic β-cell function. FFAs may increase the fibrinogen and PAI-1 production.[16]

TNFα

It is a paracrine mediator in adipocytes and appears to act locally in order to reduce the insulin sensitivity of adipocytes.[16] Evidence suggests that TNF-α could induce adipocytes apoptosis[37] and promote insulin resistance by the inhibition of the insulin receptor substrate 1 signalling pathway.[38] The paracrine action further tends to exacerbate the FFA release, inducing an atherogenic dyslipidemia. Plasma TNFα has been positively associated with body weight, WC, and triglycerides (TGs), while, a negative association exists between the plasma TNFα and High density lipoprotein–cholesterol (HDL-C).[37]

CRP

Elevated levels of CRP are also associated with an increased WC, insulin resistance, BMI, and hyperglycemia and are increased with the number of the MetS components. Further it is more likely elevated in obese insulin-resistant, but, not in obese insulin-sensitive subjects.[16] In addition, it has also been demonstrated that

regardless of the presence or degree of the MetS in an individual, CRP levels independently predicted the occurrence of future CVD events.[39] Because the MetS has been linked with a greater chance of future CVD events,[40] CRP levels is an important independent predictor of unfavourable outcomes in the MetS.

IL-6

It is released by adipose tissue and skeletal muscle in humans and has both an inflammatory and an anti-inflammatory action. IL-6 receptor is expressed in several regions of the brain, such as the hypothalamus, in which it controls the appetite and energy intake.[16] Since it is a systemic adipokine, it not only impairs insulin sensitivity but is also a major determinant of the hepatic production of CRP.[41] IL-6 is also capable of suppressing lipoprotein lipase activity. It is positively associated with BMI, fasting insulin, and the development of T2DM and negatively associated with HDL-C.[16]

PAI-1

It is a serine protease inhibitor secreted from intra-abdominal adipocytes, platelets, and the vascular endothelium which exerts its effects by inhibiting the tissue plasminogen activator (tPA) and thus is considered as a marker of an impaired fibrinolysis and atherothrombosis. Plasma PAI-1 levels are increased in obese subjects and inflammatory states, thus, increasing the risk of an intravascular thrombus and adverse cardiovascular outcomes.[16]

Adiponectin

It regulates lipid and glucose metabolism, increases insulin sensitivity, regulates food intake and body weight. It also protects against chronic inflammation. It inhibits hepatic gluconeogenic enzymes and also the rate of endogenous glucose production in the liver. It can increase glucose transport in muscles and enhance fatty acid oxidation. It has a multifactorial antiatherogenic action like inhibition of endothelial activation, a reduced conversion of macrophages to foam cells, and inhibition of the smooth muscle proliferation and arterial remodelling that characterizes the development of the mature atherosclerotic plaque.[16]

However, adiponectin is inversely associated with CVD risk factors such as blood pressure, low density lipoprotein cholesterol (LDL-C), and TGs.[42] Moreover, a study by Pischon et al. have shown adiponectin to be a strong inverse independent risk factor for CVD.[43]

Further, Fumeron et al. showed that hypoadiponectinemia is associated with insulin resistance, hyperinsulinemia, and the possibility of developing T2DM, independent of fat mass.[44]

The anti-inflammatory molecule, adiponectin, has been negatively associated with the body weight, WC, TGs, fasting insulin, insulin resistance (HOMA-Homeostasis Model Assessment), BMI, and blood pressure, whereas a positive association exists between adiponectin and HDL-C. Its expressions and secretions are reduced by TNFα, through a stimulated production of IL-6, which also inhibits adiponectin secretion. Adiponectin is “protective,” not only in its inverse

relationship with the features of MetS but also through its antagonism of TNFα action.[16]

Leptin

It is an adipokine which is involved in the regulation of satiety and energy intake. Levels of leptin in the plasma can increase during the development of obesity and decline during the weight loss. Leptin receptors are located principally in the hypothalamus and the brain stem and signals through these receptors controls satiety, energy expenditure, and neuroendocrine function. Most of the overweight and obese individuals have an elevated level of leptin that do not suppress appetite, or in other words ,have leptin resistance. Leptin resistance has been considered to be a fundamental pathology in obesity.[16]

In addition to its effect on appetite and metabolism, leptin acts in the hypothalamus to increase the blood pressure through activation of the sympathetic nervous system (SNS).[16] High circulating levels of leptin are associated with an increase in the renal sympathetic tone observed in obese human subjects.[45] Leptin-induced increase in renal sympathetic activity and blood pressure is considered to be mediated by the ventromedial and dorsomedial hypothalamus. Leptin is an nitric oxide (NO) dependent vasodilator but can also increase the peripheral vascular resistance and the sympathetic nerve activity.[16] The concentration of plasma leptin is associated with adiposity, and hyperleptinemia is indeed considered an independent cardiovascular disease risk factor.[46]

Insulin Resistance

Characteristics of the insulin-sensitive phenotype are a normal body weight without abdominal or visceral obesity, being moderately active, and consuming a diet low in saturated fats.[16] In contrast, insulin-resistant individuals demonstrate an impaired glucose metabolism or tolerance by an abnormal response to a glucose challenge, an elevated fasting glucose levels and/or overt hyperglycemia, or a reduction in insulin action after intravenous administration of insulin (euglycemic clamp technique) with decreased insulin-mediated glucose clearance and/or reductions in the suppression of endogenous glucose production. It can be defined as a pathophysiological condition in which a normal insulin concentration does not adequately produce a normal insulin response in the peripheral target tissues such as adipose, muscle, and liver. In this condition, pancreatic beta cell secretes more insulin (i.e., hyperinsulinemia) to overcome the hyperglycemia among insulin-resistant individuals. Though hyperinsulinemia can compensate for insulin resistance to some biological actions of insulin, that is, maintenance of normoglycemia, however, it may cause an overexpression of insulin activity in some normally sensitive tissues. This accentuation of insulin actions coupled with a resistance to other actions of insulin results in the clinical manifestations of MetS.[47]

The inability of the pancreatic beta cells over time to produce sufficient insulin to correct the worsening tissue insulin resistance leads to hyperglycemia and overt T2DM. Physiological insulin signalling occurs after the binding of insulin to the insulin receptor, a ligand-activated tyrosine kinase. Binding of insulin to its receptor results in tyrosine phosphorylation of downstream substrates and activation of two parallel pathways: the phosphoinositide 3-kinase (PI3K) pathway and the

mitogen activated protein (MAP) kinase pathway. Though the PI3K-Akt pathway is affected, the MAP kinase pathway functions normally in insulin resistance which leads to a change in the balance between these two parallel pathways. Inhibition of the PI3K-Akt pathway could lead to a reduction in endothelial NO production, resulting in an endothelial dysfunction, and a reduction in GLUT4 translocation, leading to a decreased skeletal muscle and fat glucose uptake. In contrast, the MAP kinase pathway is unaffected, so there is a continued endothelin-1 (ET-1) production, an expression of vascular cell adhesion molecules, and a mitogenic stimulus to vascular smooth muscle cells. In these ways, insulin resistance results in vascular abnormalities that predispose to atherosclerosis. Although insulin-resistant individuals need not be clinically obese, they commonly have an abnormal fat distribution that is characterized by a predominant upper body fat. Regardless of the relative contributions of visceral fat and abdominal subcutaneous fat to insulin resistance, a pattern of abdominal (or upper body) obesity also correlates more strongly with the insulin resistance and MetS than does lower body obesity.[16,48]

Dyslipidemia

Characterised by a spectrum of qualitative lipid abnormalities reflecting perturbations in the structure, metabolism, and biological activities of both atherogenic lipoproteins and antiatherogenic HDL-C which includes an elevation of lipoproteins containing apolipoprotein B (apoB), elevated TGs, increased levels of small particles of LDL, and low levels of HDL-C. Insulin resistance could lead to an atherogenic dyslipidemia in several ways. First, insulin normally suppresses lipolysis in adipocytes, so an impaired insulin signalling increases lipolysis, resulting in increased circulating FFA levels. In the liver, FFAs act as a substrate for

the synthesis of TGs. Also, FFAs stabilize the production of apoB, the major lipoprotein of very low density lipoprotein (VLDL) particles, resulting in increased VLDL production. Second, insulin degrades apoB through PI3K-dependent pathways, so an insulin resistance directly increases VLDL production. Third, insulin also regulates the activity of lipoprotein lipase, the rate-limiting step and major mediator of VLDL clearance. Thus, hypertriglyceridemia in insulin resistance is due to both an increase in VLDL production and a decrease in VLDL clearance. VLDL is then metabolized to remnant lipoproteins and small dense LDL, both of which can promote an atheroma formation. The TGs in VLDL are transferred to HDL by the cholesterol ester transport protein (CETP) in exchange for cholesteryl esters, resulting in the production of TG-enriched HDL and cholesteryl ester-enriched VLDL particles. In addition, the TG-enriched HDL is a better substrate for hepatic lipase, so it is cleared rapidly from the circulation, leaving a fewer HDL particles to participate in a reverse cholesterol transport from the vasculature. Hence in the liver of insulin-resistant patients, FFA flux is high, TGs synthesis and storage are increased, and excess TG is secreted as VLDL.[49]

But for the most part, it is believed that the dyslipidemia associated with insulin resistance is a direct consequence of increased VLDL secretion by the liver.[50] These abnormalaties are closely associated with an increased oxidative stress and an endothelial dysfunction, thereby reinforcing the proinflammatory nature of macrovascular atherosclerotic disease.[16]

Hypertension

Essential hypertension is associated with several metabolic abnormalities, of which obesity, glucose intolerance, and dyslipidemia are the most common.[16] Studies have reported that both hyperglycemia and hyperinsulinemia activate the Renin angiotensin system (RAS) by increasing the expression of angiotensinogen, Angiotensin II (AT II), and the AT1 receptor, which, in concert, contribute to the development of hypertension in patients with insulin resistance.[51] There is also evidence that insulin resistance and hyperinsulinemia can lead to SNS activation, and, as a result, the kidneys increase sodium reabsorption, the heart increases cardiac output, and arteries respond with vasoconstriction resulting in hypertension.[52] It has been recently reported that adipocytes also produce aldosterone in response to ATII.[53] In this regard, the adipocyte are considered a miniature renin-angiotensin-aldosterone system.[16]

Genetics

The variations in the susceptibility and age of onset in individuals with a very similar risk profile suggest a major interaction between genetic and environmental factors. It is recognized that some people who are not obese by traditional measures are insulin-resistant and have abnormal levels of metabolic risk factors.[16] Examples are seen in individuals with 2 diabetic parents or 1 parent and a first- or second-degree relative;[54] the same is true for many individuals of South Asian ethnicity.[55] Also considerable ethnic variations also exist in the clinical pattern of metabolic risk factors in obese/insulin-resistant subjects. It is likely that the expression of each metabolic risk factor falls partially under its own genetic

control, which then influences the response to different environmental exposures. For example, a variety of polymorphisms in genes affecting lipoprotein metabolism are associated with the worsening of dyslipidemia among obese people. Similarly, a genetic predisposition to the defective insulin secretion when combined with insulin resistance can raise the plasma glucose to abnormal levels.[16]

According to the thrifty genotype hypothesis proposed by Neel in 1962, individuals living in a harsh environment with an unstable food supply would maximize their probability of survival if they could maximize a storage of surplus energy. Genetic selection thus favours the energy-conserving genotypes in such environments. However, the selected genetic variations that were favoured during malnutrition would become unfavourable when nutrition improved. This hypothesis thus assumes that the common genetic variants of thrifty genes predispose to MetS.[56]

Another thrifty phenotype hypothesis was introduced by Hales and Barker in 1992.[57] According to this hypothesis, babies who experienced an intrauterine malnutrition may have adapted to a poor nutrition by reducing energy expenditure and becoming "thrifty." Therefore these metabolic adaptations are beneficial when individuals are poorly nourished during childhood and adult life; however, with an increased food intake, these adaptations are no longer beneficial and would lead to an increased risk of MetS in a later life. Support for this hypothesis comes from the observed associations of low birth weight with later development of insulin resistance and T2DM in several populations.[58]

Endothelial Function

It is mainly characterized by an impaired endothelium-dependent vasodilatation, a reduced arterial compliance, and an accelerated process of atherosclerosis. Many factors like oxidative stress, hyperglycemia, advanced glycation products, FFAs, inflammatory cytokines, or adipokines cause an inability of endothelium to serve its normal physiological and protective mechanisms. A study by Hansson et all has shown that immune cells play an important role in all the stages of the atherosclerotic process; in addition, a reduction in NO, a key regulator of endothelial homeostasis, and an increase in reactive oxygen species result in an endothelial dysfunction and a proatherogenic vascular bed.[59]

Hypercoagulable State

It is a proinflammatory state is characterized by elevated circulating cytokines and acute-phase reactants (e.g., CRP). Further, a prothrombotic state signifies anomalies in the procoagulant factors, that is, an increase in fibrinogen, factor VII and factor VIII as well as the antifibrinolytic factor (PAI-1), platelet abrasions, and endothelial dysfunctions.[16]

Grundy has shown that a fibrinogen, an acute-phase reactant protein like CRP, rises in response to a high-cytokine state. Hence the prothrombotic and proinflammatory states may be metabolically interconnected.[60]

Diet

A study by Aljada et al. has shown that a high dietary fat intake is associated with an oxidative stress and an activation of the proinflammatory transcription factor,

that is, nuclear factor kappa-beta (NF B).[61] In contrast, a diet rich in fruits and fibres has no inflammation-inducing capacity compared with a high-fat diet even if it has the same calories content.[16]

Chronic Stress and Glucocorticoid (GC) Action

Chronic hypersecretion of stress mediators, like cortisol, in individuals with a genetic predisposition exposed to a permissive environment, leads to the visceral fat accumulation as a result of chronic hypercortisolism, low growth hormone secretion, and hypogonadism. GCs may increase the activities of enzymes involved in fatty acid synthesis and promote the secretion of lipoproteins; induce the hepatic gluconeogenic pathway; promote the differentiation of preadipocytes to adipocytes, which could lead to an increased body fat mass; inhibit an insulin-stimulated amino acid uptake by adipocytes; and increase lipolysis or lipid oxidation which leads to the peripheral insulin resistance. Also a good correlation was observed between plasma cortisol levels, total urinary GC metabolites, and the number of features of the MetS among these patients. Both the secretion rate and the peripheral clearance of cortisol in these patients were positively correlated with the systolic blood pressure, and fasting glucose and insulin. These hormonal alterations leads to a reactive insulin hypersecretion, an increasing visceral obesity, and sarcopenia, resulting in dyslipidemia, hypertension, and T2DM.[16]

Presentation

History

As with other diseases, careful history taking is important in metabolic syndrome. Although the condition is diagnosed based on physical and laboratory

features, it may be suspected if symptoms of any of the component disorders are present, such as increased hunger, thirst, or urination that may accompany hyperglycemia. Patients reporting a history of hypertension, dyslipidemia warrant screening for metabolic syndrome. Symptoms suggesting the rise of cardiovascular and other complications, such as chest pain or shortness of breath, must be investigated carefully. Since lifestyle changes can ameliorate the condition, attention should be paid to the patient's dietary habits and exercise routines so that areas for improvement can be identified.

The social history is important for identifying additional risks, such as tobacco use, which may exacerbate the increased cardiovascular complications associated with metabolic syndrome. A family history should be obtained as genetics may play an important role in metabolic syndrome. This feature of the disease is under active investigation; though, currently no gene or group of genes has been implicated consistently, suggesting that the environment exerts substantial influence.[62] Finally, a thorough review of systems may help identify related problems, such as menstrual irregularities that can be seen in polycystic ovarian syndrome.

Physical examination

The physical examination is crucial in patients with metabolic syndrome as the findings of elevated blood pressure and abdominal obesity are 2 of the 5 diagnostic criteria. Measurement and documentation of waist circumference are important routines when screening for metabolic syndrome. Further it may reveal findings reflective of the other criteria. For example, patients with insulin resistance

and hyperglycemia or diabetes mellitus may have acanthosis nigricans, hirsutism, peripheral neuropathy, and retinopathy. Patients with severe dyslipidemia may have xanthomas or xanthelasmas. The presence of arterial bruits may pose a higher risk of cardiovascular complications.

Diagnosis

Initial laboratory studies in patients suspected of having metabolic syndrome should include standard chemistries to assess for hyperglycemia and renal dysfunction and lipid studies to assess for hypertriglyceridemia or low HDL levels.

If a family history of early coronary or other atherosclerotic disease is present, consider including, in addition to HDL-C and low-density lipoprotein cholesterol (LDL-C), studies of lipoprotein(a), apolipoprotein-B100, high-sensitivity C-reactive protein (CRP), and (if the patient does not already merit the lowest LDL-C target [< 70]), homocysteine and fractionated LDL-C.

In view of the various associations between metabolic syndrome and other conditions discussed, additional helpful blood tests include thyroid and liver studies, hemoglobin-A1C levels, and uric acid. Hyperuricemia appears to be more common in patients with metabolic syndrome than in the general population, and this is attributed to the inflammatory effects of metabolic syndrome.[63]

Thyroid function and metabolic syndrome

Obesity, a key component of metabolic syndrome, occurs because of increased energy intake, decreased energy expenditure, or a combination of both, thus leading to positive energy balance. Thyroid hormones up-regulate metabolic

pathways relevant to resting energy expenditure, hence, obesity and thyroid functions are often correlated. On one hand, obesity *per se* causes alterations in thyroid hormones, i.e. increased thyroid hormone levels, increased TSH with no effect on T_3 and T_4, or increase in TSH and T_3 with no effect on T_4; on the other hand, subclinical hypothyroidism due to slow metabolism can lead to the obesity. It is still not clear whether these alterations in thyroid hormones are a cause or an effect of obesity (metabolic syndrome).[64]

One fact that is clear is that clinicians often interpret increased TSH levels with normal thyroid hormone levels in obese persons as an evidence of subclinical hypothyroidism and prescribe thyroxine replacement therapy to reinforce the euthyroid status which already exists. Studies have shown that the unnecessary use of thyroxine replacement can lead to its toxicity. The mechanism of normal levels of T_3, T_4 with increased TSH in metabolic syndrome is not defined, but has been hypothesized that metabolic syndrome is associated with insulin resistance due to the defect in postreceptor signal transduction in target tissue, a similar mechanism of thyroid receptor resistance might be operating in these obese persons.[65]

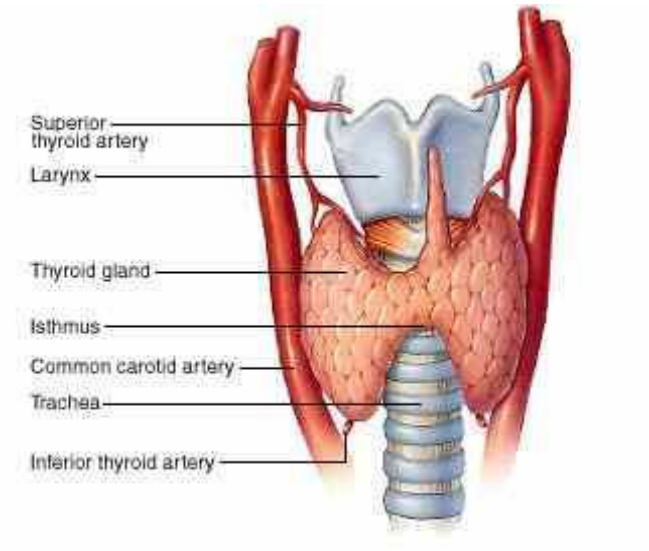


Figure 2. Anatomy, development and histology of thyroid gland

The thyroid name was derived from Greek (thyreos- shield, eidos-form). Thyroid gland weighs 15 to 20 gm. Normal thyroid gland is made up of two lobes joined together by a thin band of tissue, the isthmus. It is 0.5 cm thick, 2cm wide, and 2cm in height. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch. 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 that is in the neck. Each lobe is approximately 2 to 2.5 cm thickness and width at its largest diameter is approx 4cm in length. Right lobe is normally more vascular than left, and is often the larger of the two.[66,67]

Blood supply

- The superior thyroid artery, arising from external carotid artery.
- The inferior thyroid artery, arising from subclavian artery.

- Blood flow rate is 4-6 ml /min per gm.

Histology

The gland is mainly composed of closely packed spherical units called follicles. The interior of the follicle is filled with clear, proteinaceous colloid. The thyroid tissue also contains parafollicular cells (c cells), that is a source of calcitonin. The principal function of thyroid is production of the hormones thyroxin (T4), triiodothyronine (T3) and calcitonin. Upto 40% of the T4 is converted to T3 by peripheral organs such as the liver, kidney and spleen.[66]

Physiology of thyroid hormones

Thyroxine (T4) and triiodothyronine(T3) are the principle hormones produced by thyroid gland. Initially iodine is absorbed in the gut and is converted to iodide and transported in the blood. It is then actively transferred into the thyroid cell by "iodide trapping". The trapped iodine is then oxidised to iodine and combines with tyrosine to form monoiodotyrosine (MIT) and Diiodotyrosine (DIT). MIT and DIT are coupled to form T3, where as two DIT couple to form T4. Oxidation, Iodination and coupling reactions are catalyzed by "thyroid peroxidise". Thyroid hormones thus produced rebound with thyroglobulin until secreted.[68]

T4 secreted from the thyroid gland is about twentyfold excess over T3. 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 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 (T4> T3), it carries about 80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones, but has a high plasma concentration (3.5g/dl), and can bind upto 10% of T4 and 30% of T3. TTR carries about 10% of T4 but little T3.[68]

In the periphery T4 is converted to T3 by the deiodinase enzymes. Type I deiodinase, which is located primarily in thyroid, liver, and kidneys, has low affinity for T4. Type II deiodinase has a higher affinity for T4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Expression of type II deiodinase allows it to regulate T3 concentrations locally, a property that may be important in the context of levothyroxine (T4) replacement. Type III deiodinase inactivates T4 and T3 and is the most important source of reverse T3 (rT3). Only about 13% of T3 is produced from thyroid gland and remaining 87% is formed from T4.[68]

Mechanism of action

Thyroid hormones enter cells, and T3 binds to thyroid receptors (TR) in the nuclei. The nuclear thyroid hormone receptors (TRs), Both TR-alpha and TR-beta are expressed in most tissues, but their relative expression levels vary among organs; TR alpha is particularly abundant in brain, kidneys, gonads, muscle, and heart, but TR beta expression is relatively high in the pituitary and liver. T4 can also bind, but not as avidly. The hormone-receptor complex then binds to DNA via zinc fingers and can increase or in some cases decrease the expression of variety of different genes that code for enzymes which regulate cell function. For example, the activated receptor, stimulate gene transcription (e.g., myosin heavy chain -alpha) or inhibit transcription (e.g., TSH beta-subunit gene).[68]

Thyroid hormones (T3 and T4) bind with similar affinities to TR-alpha and TR-beta. However, structural differences in the ligand binding domains provide the potential for developing receptor-selective agonists or antagonists. T3 is bound 10–15 times with greater affinity than T4, which explains its increased hormonal potency. Although T4 is produced in excess of T3, receptors are occupied mainly by T3, reflecting T4 to T3 conversion by peripheral tissues, greater T3 bioavailability in the plasma, and receptors' greater affinity for T3. After binding to TRs, thyroid hormone induces conformational changes in the receptors which modify its interactions with accessory transcription factors.[68]

Regulation of the Thyroid Axis

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 alpha and betasubunits; the alpha subunit is common to the other glycoprotein hormones [luteinizing hormone, follicle-stimulating hormone, human chorionic gonadotropin (hCG)], whereas the TSH beta subunit is unique to TSH.[68]

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-beta (TR beta), 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.[68]

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). Thus 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).[68]

The TSH is extremely sensitive to the levels of thyroid hormones in circulation and can be used as a useful tool in detection of thyroid abnormalities rather than using T4 or T3 levels. The thyroid dysfunction is simply classified as hypothyroidism, hyperthyroidism, subclinical hyperthyroidism depending upon the TSH and thyroid hormone levels.[68]

Clinical status	TSH level	Thyroid hormones
Normal	Normal	Normal
Hypothyroid	High	Low
Hyperthyroid	Low	High
Subclinical hypothyroid	High	Normal
Subclinical hyperthyroid	Low	Normal

Hypothyroidism

Hypothyroidism resulting from lack of the effects of thyroid hormones on body tissues. Hypothyroidism is a common condition.[69] The overall incidence in the population is approximately 1% to 2%.[70,71] The serum TSH levels more than 10mU/L and associated with low values of thyroid hormones. Florid hypothyroidism can be diagnosed clinically.

Causes of hypothyroidism[68]

Hypothyroidism is due to primary disease of the thyroid gland itself or lack of pituitary TSH. Iodine deficiency remains the most common cause of hypothyroidism worldwide. In areas of iodine sufficiency, autoimmune disease (Hashimoto's thyroiditis) and iatrogenic causes (treatment of hyperthyroidism) are most common.

Primary

- Autoimmune Hypothyroidism - Hashimoto's thyroiditis, atrophic thyroiditis.
- Iodine deficiency

- Iatrogenic - Iodine 131 treatment, subtotal or total thyroidectomy, external irradiation of neck for lymphoma or cancer.
- Drugs - Iodine excess (including iodine-containing contrast media and amiodarone),lithium, antithyroid drugs, p-aminosalicyclic acid, interferonalpha and other cytokines,aminoglutethimide.
- Congenital - Absent or ectopic thyroid gland, dyshormonogenesis, TSH-R mutation.
- Infiltrative disorders - Amyloidosis, sarcoidosis, hemochromatosis, scleroderma, cystinosis, Riedel's thyroiditis
- Over expression of type 3 deoiodinase in infantile hemangioma
- **Transient**
    - Silent thyroiditis, including postpartum thyroiditis
    - Subacute thyroiditis
    - Withdrawal of thyroxine treatment in individuals with an intact thyroid
    - After treatment or subtotal thyroidectomy for Graves' disease

Secondary

- Hypopituitarism: tumors, pituitary surgery or irradiation, infiltrative disorders, Sheehan's syndrome, trauma, genetic forms of combined pituitary hormone deficiencies
- Isolated TSH deficiency or inactivity
- Bexarotene treatment
- Hypothalamic disease: tumors, trauma, infiltrative disorders, Idiopathic

Symptoms of hypothyroidism[68]

- Tiredness, weakness
- Dry skin
- Feeling cold
- Hair loss
- Difficulty in concentrating and poor memory
- Constipation
- Weight gain with poor appetite
- Dyspnea
- Hoarse voice
- Menorrhagia (later amenorrhea)
- Parasthesia
- Impaired hearing

Signs of hypothyroidism

- Tiredness, weakness
- Dry coarse skin
- Cool peripheral extremities
- Puffy face, hands, and feet(myxedema)
- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpel tunnel syndrome

- Serous cavity effusion

Subclinical hypothyroidism

According to the latest consensus statement by the American association of clinical endocrinologists, the American thyroid association and the endocrine society, subclinical hypothyroidism is defined as an elevated serum TSH level (4.5mU/L to 10mU/L) associated with normal total or free T4 and T3 levels.[72] Several alternative names have been proposed to describe this condition and include compensated hypothyroidism, mild thyroid failure, and mild Hypothyroidism. The overall prevalence is 2% to 8% in the general population.[70,71,73]

Laboratory evaluation

Measurement of Thyroid Hormones

Because TSH levels change dynamically in response to changes in the level of T4 and T3a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated. The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH). Radioimmunoassays are widely available for serum total T4 and total T3. T4 and T3 are highly protein-bound, and numerous factors (illness, medications, genetic factors) can influence protein binding. It is useful, therefore, to measure the free, or unbound, hormone levels, which correspond to the biologically available hormone pool.

- Total thyroid hormone levels are elevated when TBG is increased (due to pregnancy, oral contraceptives, hormone therapy, tamoxifen).

- Total thyroid hormone levels are decreased, when TBG binding is reduced (androgens, nephrotic syndrome).

Genetic disorders and acute illness can also cause abnormalities in thyroid hormone binding proteins, and various drugs [phenytoin, carbamazepine, salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs)] can interfere with thyroid hormone binding. Because unbound thyroid hormone levels are normal and the patient is euthyroid in all of these circumstances.

Tests to Determine the Etiology of Thyroid Dysfunction

TPO antibodies

Autoimmune thyroid disease is detected by measuring circulating antibodies against TPO and Tg. As antibodies to Tg alone are uncommon, it is reasonable to measure only TPO antibodies. About 5–15% of euthyroid women and up to 2% of euthyroid men have thyroid antibodies; such individuals are at increased risk of developing thyroid dysfunction. Almost all patients with autoimmune hypothyroidism, and up to 80% of those with Graves' disease, have TPO antibodies, usually at high levels.

Thyroid stimulating antibodies

TSI are antibodies that stimulate the TSH-R in Graves' disease. They can be measured in bioassays or indirectly in assays for TSH-binding inhibiting immunoglobulins (TBII) that detect antibody binding to the receptor. The main use

of these assays is to predict neonatal thyrotoxicosis caused by high maternal levels of TSI in the last trimester of pregnancy.

Serum thyroglobulin levels

Serum Tg levels are increased in all types of thyrotoxicosis except thyrotoxicosis factitia caused by self administration of thyroid hormone. Tg levels are particularly increased in thyroiditis, reflecting thyroid tissue destruction and release of Tg. The main role for Tg measurement, however, is in the follow-up of thyroid cancer patients. After total thyroidectomy and radioablation, Tg levels should be undetectable; in the absence of anti-Tg antibodies, measurable levels indicate incomplete ablation or recurrent cancer.

Radioiodine Uptake and Thyroid Scanning

The thyroid gland selectively transports radioisotopes of iodine (123I, 125I, 131I) and 99mTc pertechnate, allowing thyroid imaging and quantitation of radioactive tracer fractional uptake.

Nuclear imaging of Graves' disease is characterized by an enlarged gland and increased tracer uptake that is distributed homogeneously. Toxic adenomas appear as focal areas of increased uptake, with suppressed tracer uptake in the remainder of the gland. In toxic MNG, the gland is enlarged—often with distorted architecture and there are multiple areas of relatively increased or decreased tracer uptake. Subacute thyroiditis is associated with very low uptake because of follicular cell damage and TSH suppression. Thyrotoxicosis factitia is also associated with low uptake. Thyroid scanning is also used in the follow-up of thyroid cancer. After thyroidectomy and ablation using 131I, there is diminished radioiodine uptake in the

thyroid bed, allowing the detection of metastatic thyroid cancer deposits that retain the ability to transport iodine.

Thyroid Ultrasound

Ultrasonography is used to assist in the diagnosis of nodular thyroid disease, a reflection of the limitations of the physical examination and improvements in ultrasound technology. In addition to detecting thyroid nodules, ultrasound is useful for monitoring nodule size and for the aspiration of nodules or cystic lesions. Ultrasound-guided FNA biopsy of thyroid lesions lowers the rate of inadequate sampling. Ultrasonography can also be used in the evaluation of recurrent thyroid cancer, including possible spread to cervical lymph nodes.

FNAB

The use of fine-needle aspiration (FNA) biopsy has diminished the use of thyroid scans in the evaluation of solitary thyroid nodule.

Thyroid functions and the metabolic syndrome

It is well documented that hypothyroidism is associated with all parameters of metabolic syndrome,37expect increase in fasting blood glucose.

Obesity

The obesity (increase in waist circumference) is the important symptom and sign of hypothyroidism. More than 60% of hypothyroid patients have obesity (increase in waist circumference).[74] There is decrease in basal metabolic rate and energy metabolism in hypothyroidism.

Hypertension

In hypothyroidism, the haemodynamic alterations causes narrowing of pulse pressure, prolongation of circulatory time and decrease in blood flow to the tissues.[75] Systemic vascular resistance is increased in hypothyroidism and results in hypertension.[76] Rotterdam study[77] suggested that there was a two fold increase in risk of atherosclerosis in hypothyroid patients.

Lipid profile

Both the synthesis and degradation of lipids are depressed in hypothyroidism, the latter especially so, the net effect being one of the lipid accumulation, especially of LDL cholesterol and triglyceride.[78] The increase in serum cholesterol in hypothyroidism is accompanied by increased levels of serum phospholipids, serum triglycerides and LDL cholesterol.The activity of cholesterol ester transfer protein is decreased in hypothyroidism, thus HDL cholesterol level reduced in hypothyroidism.[79]

Glucose intolerance

Glucose intolerance in hypothyroidism is not proved in latest studies though Shah et al. published insulin metabolism in hypothyroidism in 1975 indicating that glucose intolerance of the hypothyroid state is not characterized by insulin resistance.[80] Aneemieke Ross et al.[79] in 2007 found that free T4 was significantly associated with insulin resistance and with four of five components of the metabolic syndrome (except glucose intolerance).

Literature review

Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects.[81] In this population based study there was negative correlation between thyroid hormone levels (free T3 and free T4) and the metabolic components, Apo B and insulin resistance levels in people with euthyroid state. Free T4 was very significantly related to four of five metabolic components – waist circumference, fasting glucose, high density cholesterol and triglycerides and insulin resistance levels, which assessed by the homeostasis model assessment (HOMA) model. i.e .low normal free T4 was associated with higher triglycerides, lower high density lipoprotein cholesterol, increased fasting glucose and higher waist circumference. Free T3 levels correlated well with systolic blood pressure, triglycerides and Apo- B levels. In insulin resistance individuals are more susceptible to the associated of TSH with higher low density lipoprotein cholesterol and lower high density lipoprotein cholesterol. The morbid obese subjects have higher level of T3, T4 and TSH, probably of the reset of their central thyrostat at higher levels.[82]

In a study done by Uzunulu et al, at Japan they have analysed the prevalence of sub clinical hypothyroidism among 220 metabolic syndrome patients. They found that subclinical hypothyroidism was 16.4% prevalent in metabolic syndrome patients. One sixth of metabolic syndrome patients had subclinical hypothyroism and more prevalent in female gender.[83]

In a study from Nepal, done by Chandra L et al, found that the metabolic syndrome prevalent in 21.1 % of thyroid dysfunction patients. They have assessed

the association of metabolic syndrome and its components with thyroid dysfunction in 100 female patients.This study found that the prevalence of overall metabolic syndrome was 32%, more in euthyoid group (21/48) than hyperthyroid group(5/24) and hypothyroid group (6/28).[84]

In a study of more than 1,500 subjects, researchers found that those with metabolic syndrome had statistically significantly higher TSH levels (meaning lower thyroid hormone output) than healthy control subjects. Subclinical hypothyroidism was also correlated with elevated triglyceride levels and increased blood pressure. Slight increases in TSH may put people at higher risk for metabolic syndrome.[85]

In a study by Bauer DC et al, it was shown that among older white women, high TSH levels were associated with deleterious changes in serum lipids and that women with multiple lipid abnormalities were twice as likely to have increased TSH levels.[86]

The Tromso Study and the Basel Thyroid Study have shown that L-thyroxine replacement in patients with sub-clinical hypothyroidism has a beneficial effect on low density lipoprotein cholesterol levels and clinical symptoms of hypothyroidism. Also an important risk reduction in cardiovascular mortality of 9–31% can be estimated from the observed improvement in low density lipoprotein cholesterol.[87]

The HUNT study concluded that "Within the range of TSH that is considered clinically normal, increasing level of TSH was associated with less favorable lipid concentrations. The association with serum lipids was linear across the entire reference range of TSH, in a research published during February 2007 and reported connection between thyroid function.[88]

In those with normal TSH levels, the thyroid hormone level known as free T4 was important. Free T4 levels that were slightly low, but still within the normal range, significantly increased the risk of many risk factors for metabolic syndrome.[89]

In hypothyroidism, energy metabolism is reduced leading to a decreased in appetite, cold in tolerance, reduced protein synthesis, lipid accumulation(elevated TG and LDL-Cholesterol).[90]

Atherogenic lipid abnormalities were observed in adult subjects with Subclinical hypothyroidism-2 (TSH > 10.0 mIU/L), and not in subjects with Subclinical hypothyroidism-1 who had TSH ≤ 10.0 mIU/L in Indian population.[91]

The Jaipur Heart Watch Studies have reported that in urban Indian populations, age-adjusted prevalence of metabolic syndrome was 18.4% in men, 30.9% in women, and 24.9% overall.[92]

According to CURES 52 study, hypertension is prevalent in 20% of Chennai urban population. Among these hypertensive patients, the prevalence of other components of metabolic syndrome was: diabetes in 31.8%, impaired glucose tolerance in 17.9%, hypercholesterolemia in 38.8%, hypertryglyceridemia.[93]

METHODOLOGY

This study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients with metabolic syndrome during the period of January 2013 to December 2013.

Study design

The study design was cross sectional study.

Study period and duration

The present one year study was conducted from January 2013 to December 2013.

Source of Data

Patients diagnosed to have metabolic syndrome based on NCEP ATP III criteria attending Medicine Department at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied.

Sample size

A total of 117 patients with metabolic syndrome were selected for the study.

Sampling procedure

The sample size was calculated based on the formula as mentioned below.

$n = 4 \times p \times q / d^2$

Where, p = Prevalence of the disease was considered as 25%

due to scarcity of data on metabolic syndrome from hospital records

q = 100 – p

d = Absolute error taken as 8%

Therefore, $n = 4 \text{ X } 25 \text{ X } 75 / 8^2$

n = 117

Sampling method

Patients fulfilling the inclusion criteria were enrolled considering simple random sampling.

Selection criteria

Inclusion Criteria

- Patients who fulfill the National Cholesterol Education Program-ATP-III criteria for metabolic syndrome[11] that is, three or more of the following components:
    - Abdominal obesity (waist circumference >102 cm in men, >88 cm in women).
    - Triglycerides ≥ 150 mg/dL.
    - HDL-cholesterol < 40 mg/dL in men, < 50 mg/dL in women.
    - Systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mm Hg.
    - Fasting plasma glucose ≥ 110 mg/dL.

Exclusion Criteria

- Patients with;
    - Liver disorders.
    - Renal disorders.
    - Congestive cardiac failure.
    - Hypothyroidism.
    - Statins and other medications that alter thyroid functions and lipid levels
    - Under treatment of any thyroid related disorder.
- Pregnant women.
- Women on oral contraceptive pills

Ethical clearance

Prior to the commencement, the study was approved by the Institutional Ethics Committee of Jawaharlal Nehru Medical College, Belgaum.

Informed consent

Patients attending the OPD, Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were evaluated based on selection criteria. Those who fulfill the selection criteria were briefed about the nature of the study and a written informed consent was obtained (Annexure–I).

Data collection

Demographic data like gender and age were collected and the patients were interviewed for the relevant history such as diabetes mellitus, hypertension, heart

disease, personal history and family history. A thorough general physical examination was conducted followed by systemic examination and the findings were noted on a predesigned and pretested proforma (Annexure-II).

Body mass index

Body mass index was calculated based on formula;

$$\text{Body Mass Index} = \frac{\text{Weight (Kg)}}{\text{Height}^2 \text{ (m)}}$$

Body mass index in the range of less than 18.5 kg/m^2 were considered as underweight, 18.5 to 24.9 kg/m^2 were considered as normal, 25.0 to 29.9 kg/m^2 were considered as overweight and more than 30 kg/m^2 were considered as obese.[94-96]

Waist circumference

The waist circumference was measured using a standard measuring tape in cms and waist circumference of > 102 cms in males and > 88 cms in females was considered abnormal.

Hypertension

Blood pressure was recorded in the sitting position after five minutes of rest using standard mercury manometer and three readings were taken at an interval of one minute and mean BP was calculated.

Investigations

Fasting blood samples were then drawn for following investigations

- Fasting blood sugar
- Lipid profile (total cholesterol, triglycerides, HDL and LDL)
- Serum TSH and fT4

Thyroid profile

The thyroid profile was assessed by withdrawing venous blood under aseptic precautions and estimation of TSH and fT4 was done using a fully automated electrochemiluminescence immunoassay analyser (Make: Roche Cobas E 601from Roche Hitachi). The results obtained were interpreted as below;[97,98]

Thyroid stimulating hormone

- Normal range – 0.34 to 4.25µIU/mL.
- Abnormal - < 0.34 or > 4.25 µIU/mL.

Free thyroxine :

- Normal range – 0.7 to 1.24 ng/dl
- Abnormal - < 0.7 or > 1.24 ng/dl

Free Triiodothyronine :

- Normal range – 2.4 -4.2 pg/ml
- Abnormal - < 2.4 or > 4.2 pg/ml

Statistical analysis

The data thus obtained was tabulated on Microsoft Excel spreadsheet. The categorical data was expressed as rates, ratios and percentages. Chi-square test was used to assess the association of primary hypothyroidism. Continuous data was expressed as mean ± standard deviation (SD) and then the comparison was done using independent sample‘t’ test. A probability value (‘p’ value) of less than or equal to 0.050 was considered to be statistically significant.

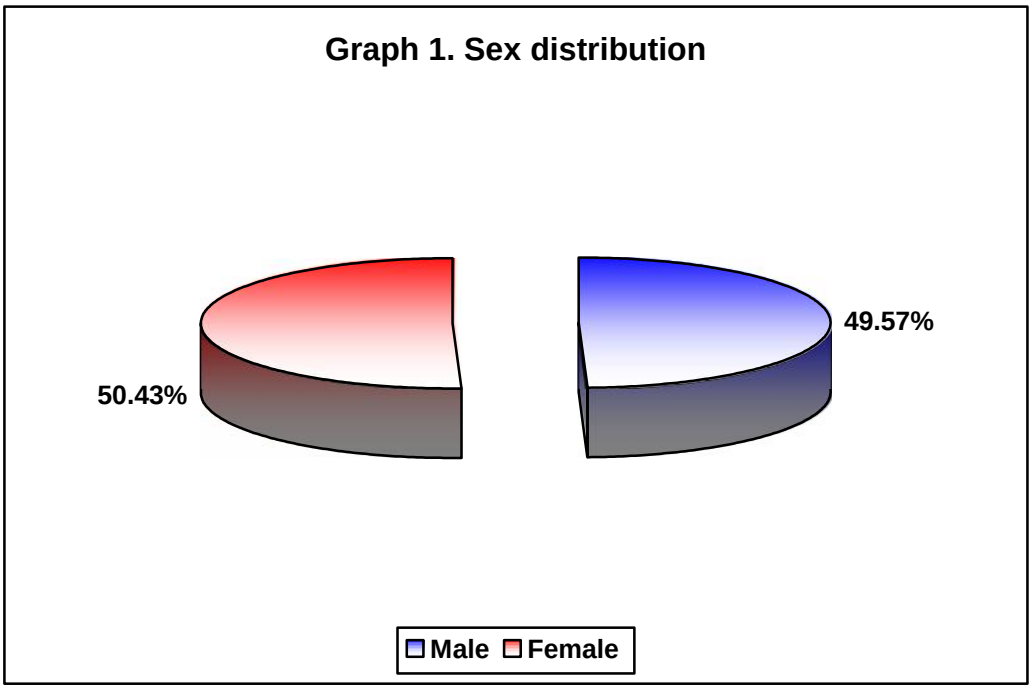
RESULTS

The present study was conducted in the Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 117 patients with metabolic syndrome based on NCEP ATP III criteria were studied for the presence of thyroid abnormalities.

The data obtained was analysed and the final results and observations were tabulated as below.

Table 1. Sex distribution

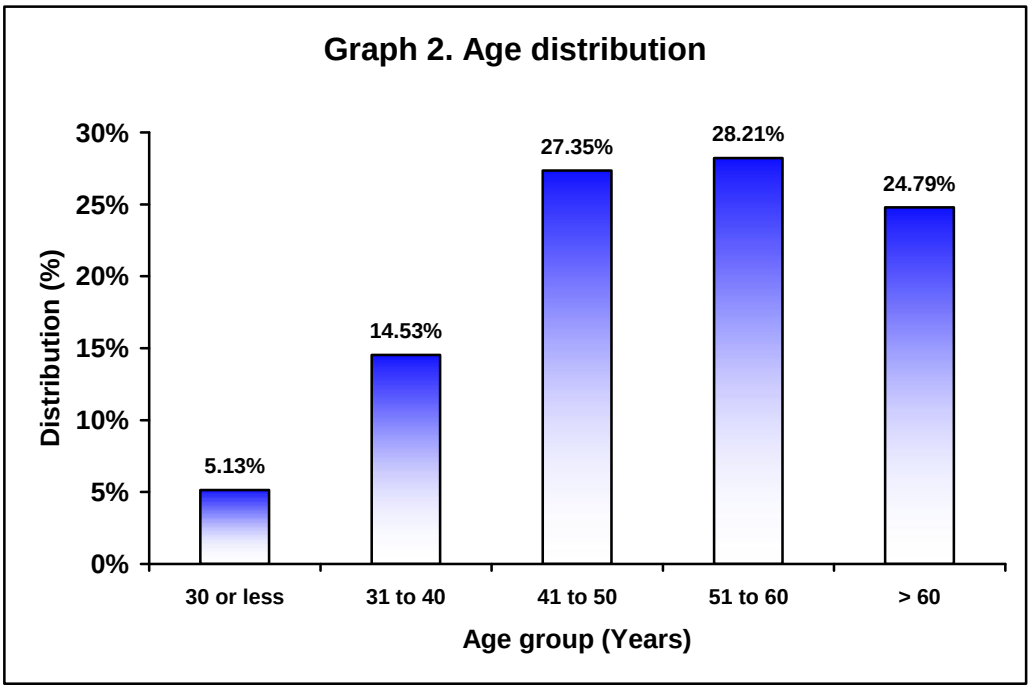
Sex	Distribution (n=117)	
	Number	**Percentage**
Male	58	49.57
Female	59	50.43
Total	**117**	**100.00**



In the present study 50.43% were females and 49.57% were males. The male to female ratio was 1:1.

Table 2. Age distribution

Age group (Years)	Distribution (n=117)	
	Number	**Percentage**
30 or less	6	5.13
31 to 40	17	14.53
41 to 50	32	27.35
51 to 60	33	28.21
> 60	29	24.79
Total	**117**	**100.00**

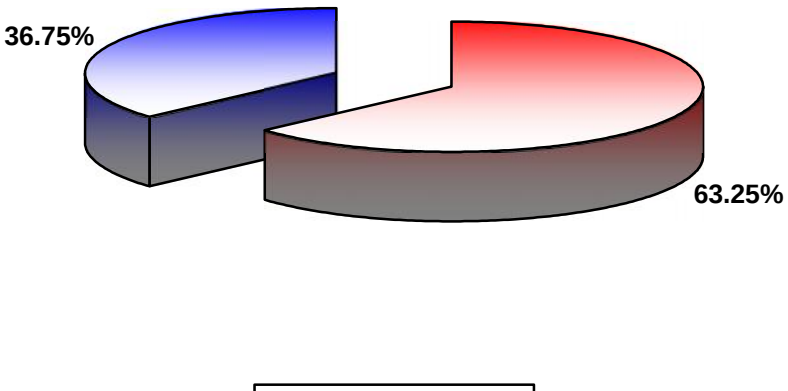


In this study most of the patients presented with age between 51 to 60 years (28.21%) followed by 41 to 50 years (27.35%), more than 60 years (24.79%), 31 to 40 years (14.53%) and less than or equal to 30 years (5.13%). The mean age was found to be 52.25 ± 13.49 years.

Table 3. History of diabetes mellitus

History	Distribution (n=117)	
	Number	**Percentage**
Present	74	63.25
Absent	43	36.75
Total	**117**	**100.00**

Graph 3. History of diabetes mellitus



In the present study history of diabetes mellitus was noted among 74 (63.25%) patients.

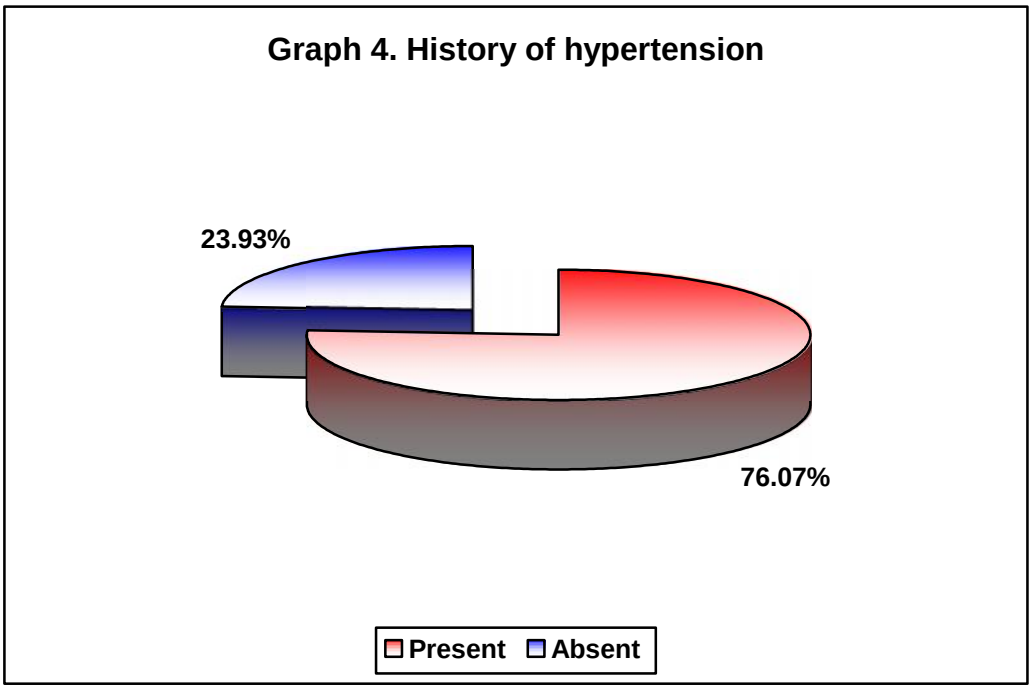
Table 4. Duration of diabetes mellitus

Duration	Distribution (n=74)	
	Number	**Percentage**
3 years or less	30	40.54
> 3 to 6 years	14	18.92
> 6 to 9 years	12	16.22
> 9 years	9	12.16
Newly detected	9	12.16
Total	**74**	**100.00**

In this study of the 74 patients with history of diabetes, nine (12.16%) were newly detected and in the remaining 30 patients (40.54%) presented with the duration of three years or less.

Table 5. History of hypertension

History	Distribution (n=117)	
	Number	**Percentage**
Present	89	76.07
Absent	28	23.93
Total	**117**	**100.00**



In the present study, the history of hypertension was noted in 89 (76.07%) patients.

Table 6. Duration of hypertension

Duration	Distribution (n=89)	
	Number	**Percentage**
3 years or less	39	43.82
> 3 to 6 years	28	31.46
> 6 to 9 years	8	8.99
> 9 years	8	8.99
Newly detected	6	6.74
Total	**89**	**100.00**

In this study, of the 89 patients who had history of hypertension, most of the patients reported duration of three year or less (43.82%). However, six (6.74%) of the patients were newly detected.

Table 7. History of other comorbid conditions

Comorbid conditions	Distribution (n=117)	
	Number	**Percentage**
Dyslipidemia	77	65.81
Renal disorders	0	0.00
Congestive cardiac failure	0	0.00
Pregnancy (Urine test)	0	0.00
Oral contraceptive pills	0	0.00
Liver disorders	0	0.00
Known case of hypothyroidism	0	0.00
Hyperthyroidism	0	0.00
Treatment of thyroid disorder	0	0.00

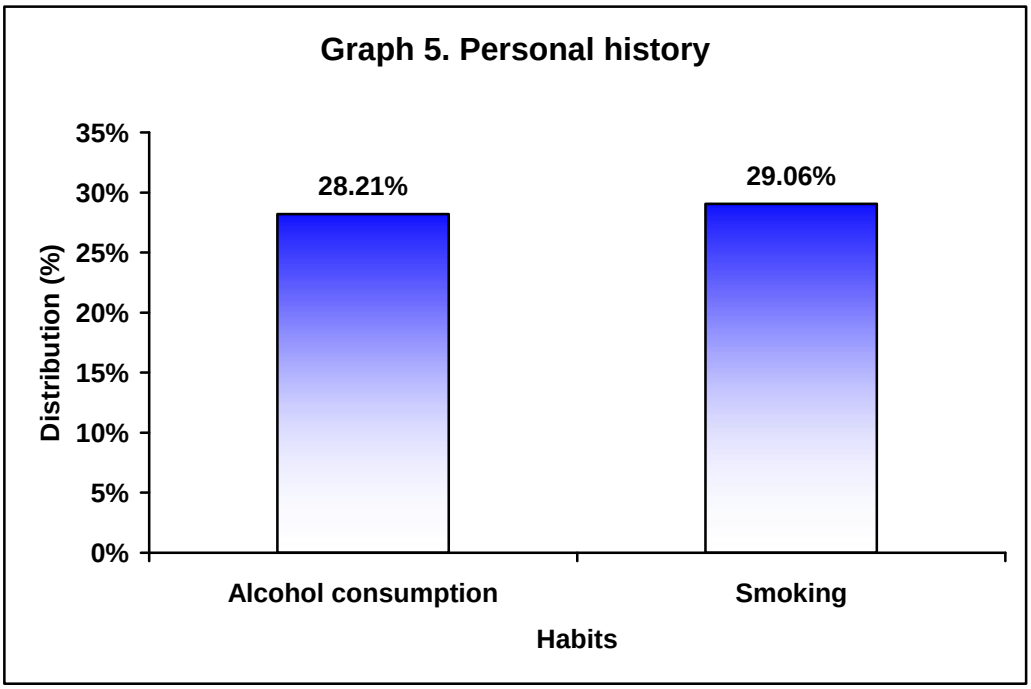
Multiple conditions hence total not shown

In the present study, history of dyslipidemia was noted in 65.81% of the patients.

Table 8. Personal history

Habits	Distribution (n=117)	
	Number	Percentage
Alcohol consumption	33	28.21
Smoking	34	29.06

Multi conditions hence total not shown



In this study personal history revealed alcohol consumption in 28.21% of the patients while 29.06% reported smoking.

Table 9. Family history

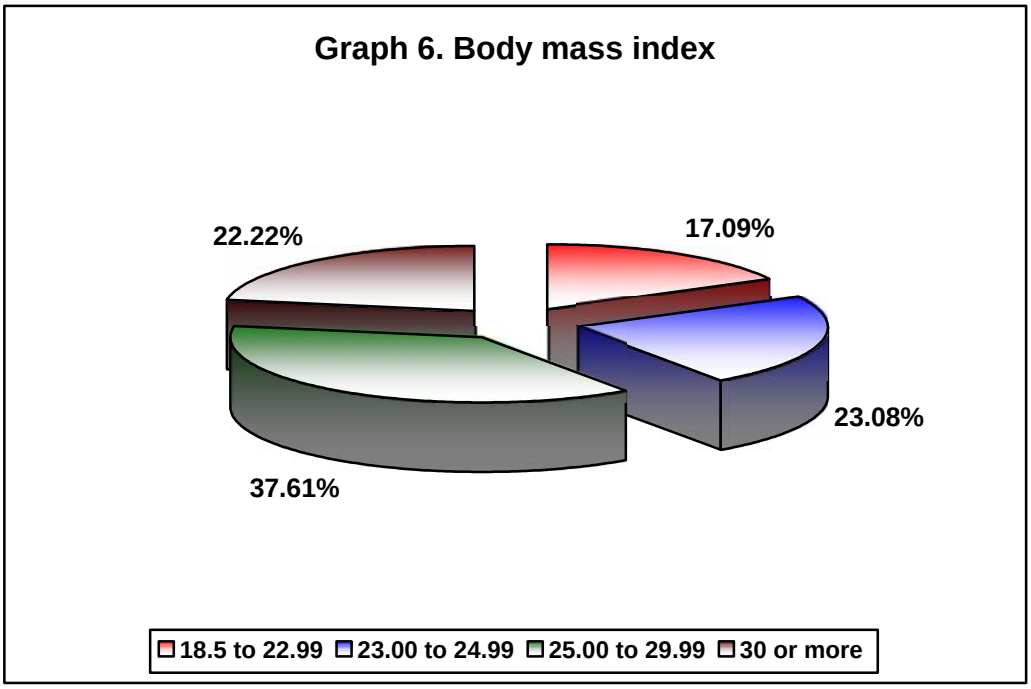
Conditions	Distribution (n=117)	
	Number	**Percentage**
Hypertension	63	53.85
Diabetes mellitus	71	60.68
Obesity	43	36.75
Hypothyroidism	2	1.71
Dyslipidemia	23	19.66

Multi conditions hence total not shown

In the present study most of the patients reported family history of diabetes mellitus (60.68%) and the next common condition was hypertension (53.85%).

Table 10. Body mass index

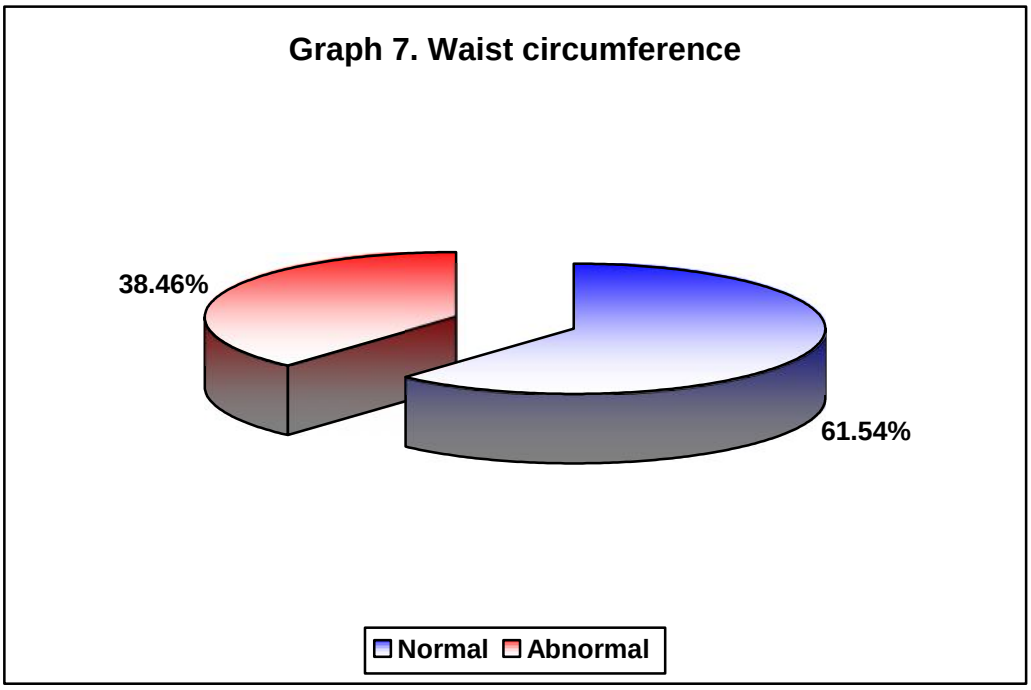
Body mass index (Kg/m^2)	Distribution (n=117)	
	Number	**Percentage**
18.5 to 22.99	20	17.09
23.00 to 24.99	27	23.08
25.00 to 29.99	44	37.61
30 or more	26	22.22
Total	**117**	**100.00**



In this study most of the patients had BMI between 25.00 to 29.99 Kg/m^2 (37.61%). The mean BMI was found to be 27.20 ± 4.22 Kg/m^2.

Table 11. Waist circumference

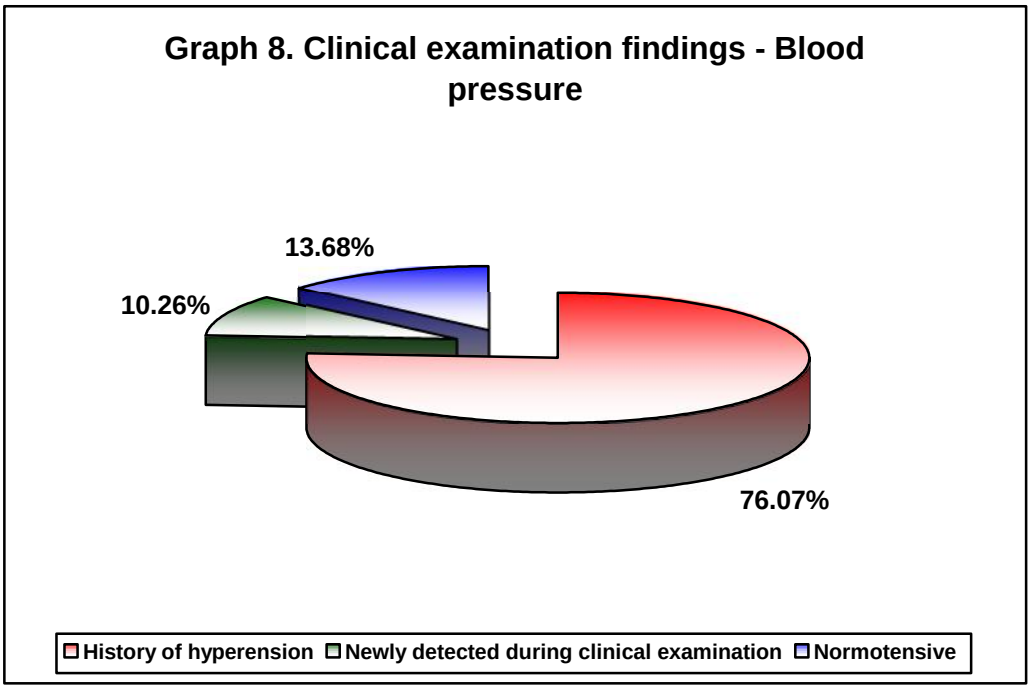
Findings	Distribution (n=117)	
	Number	**Percentage**
Normal	72	61.54
Abnormal	45	38.46
Total	**117**	**100.00**



In the present study, based on NCEP ATP III criteria, 38.46% of the patients has abnormal waist circumference. The mean waist circumference was noted as 90.78 ± 9.74 cms.

Table 12. Clinical examination findings – Blood pressure

Findings	Distribution (n=117)	
	Number	**Percentage**
History of hypertension	89	76.07
Newly detected during clinical examination	12	10.26
Normotensive	16	13.68
Total	**117**	**100.00**



In this study of the 117 patients, 89 (76.07%) had history of hypertension. In the remaining, 10.26% were newly detected to have hypertension while 13.68% were normotensive.

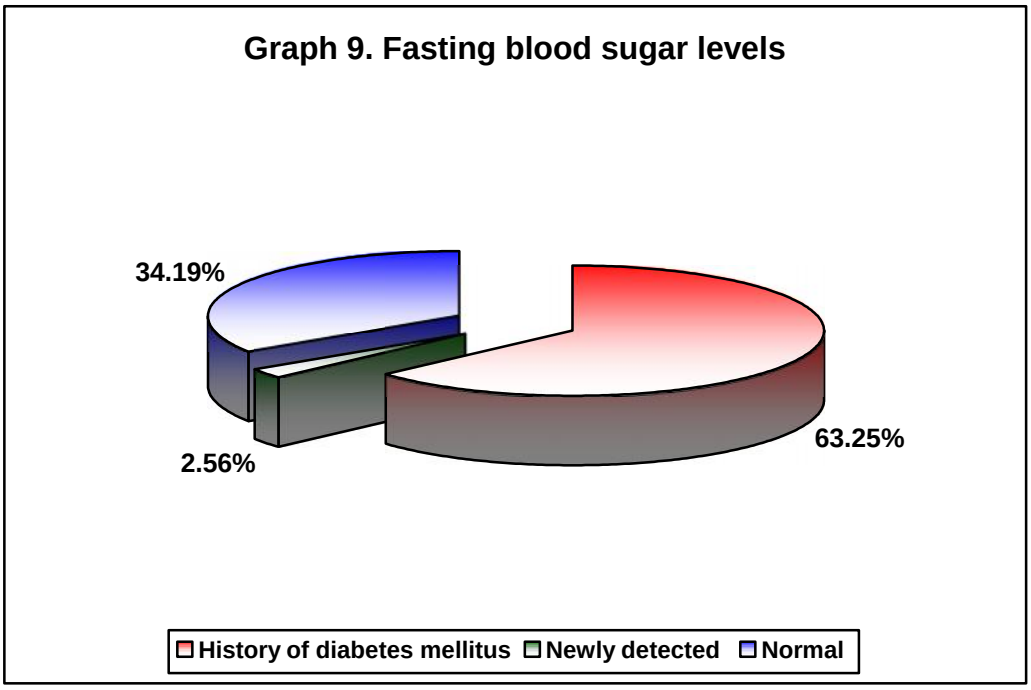
Table 13. Systemic examination findings - CNS

Findings	Distribution (n=117)	
	Number	**Percentage**
Peripheral neuropathy	15	12.82
Normal	102	87.18
Total	**117**	**100.00**

In the present study, systemic examination with respect to central nervous system revealed peripheral neuropathy in 12.82% of the patients.

Table 14. Fasting blood sugar levels

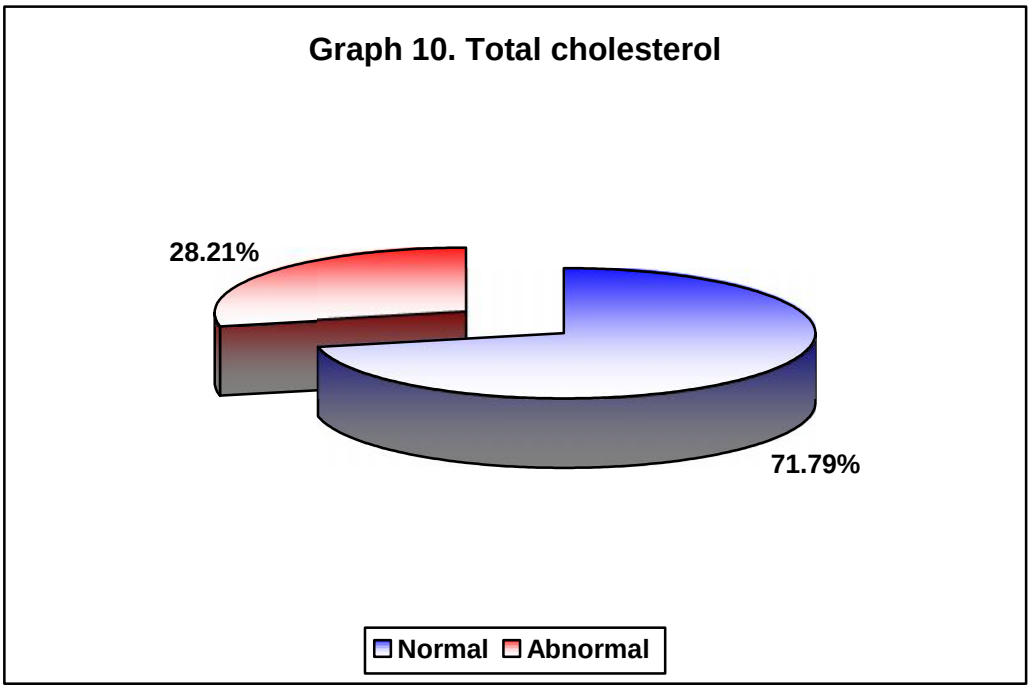
Findings	Distribution (n=117)	
	Number	**Percentage**
History of diabetes mellitus	74	63.25
Newly detected	3	2.56
Normal	40	34.19
Total	**117**	**100.00**



In this study of the 117 patients, 74 (63.25%) had history of diabetes. In the remaining, 2.56% were newly detected with diabetes while in 34.19% of the patients the fasting blood sugar levels were normal.

Table 15. Total cholesterol

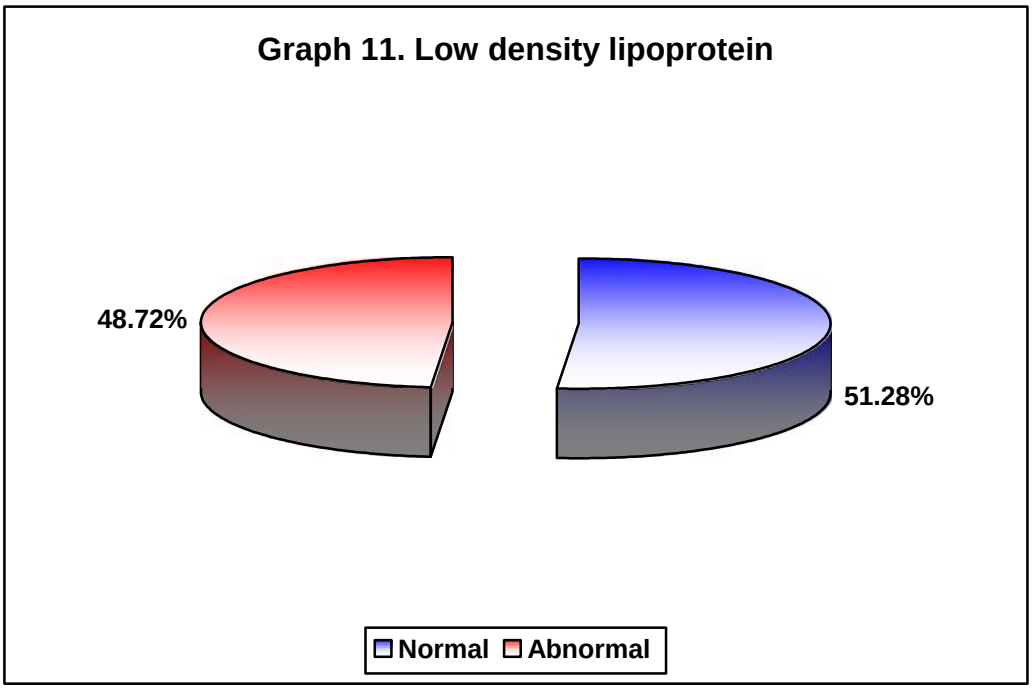
Findings	Distribution (n=117)	
	Number	**Percentage**
Normal (200 mg/dL or less)	84	71.79
Abnormal (> 200 mg/dL)	33	28.21
Total	**117**	**100.00**



In the present study 28.21% of the patients had abnormal total cholesterol levels (> 200 mg/dL). The mean cholesterol level was noted was 172.7 ± 53.3 mg/dL.

Table 16. Low density lipoprotein

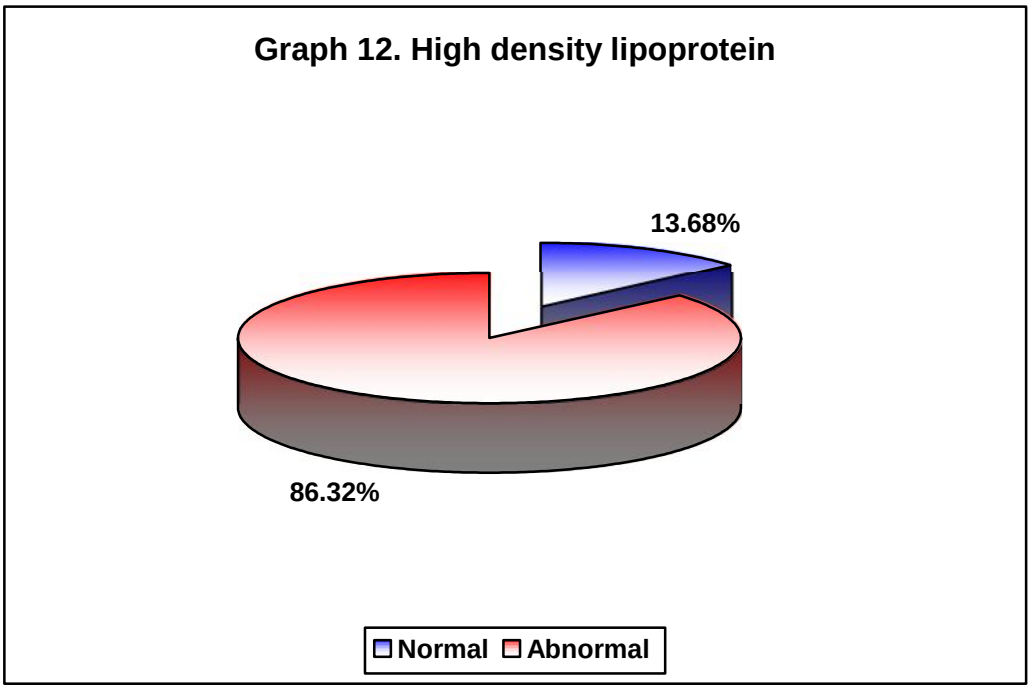
Findings	Distribution (n=117)	
	Number	**Percentage**
Normal (100 mg/dL or less)	60	51.28
Abnormal (> 100 mg/dL)	57	48.72
Total	**117**	**100.00**



In this study abnormal LDL levels (> 100 mg/dL) were present in 48.72% of the patients. The mean LDL level was noted as 107.2 ± 48.8 mg/dL.

Table 17. High density lipoprotein

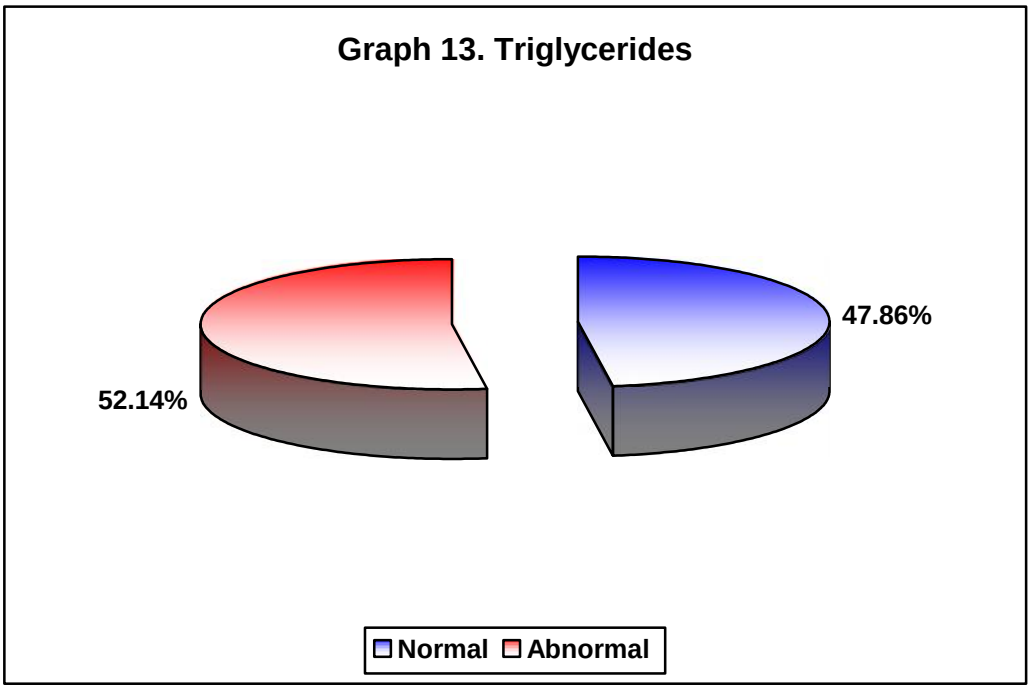
Findings	Distribution (n=117)	
	Number	**Percentage**
Normal (Male: > 40 or Female: > 50 mg/dL)	16	13.68
Abnormal (Male: ≤ 40 mg/dL; Female: ≤50 mg/dL)	101	86.32
Total	**117**	**100.00**



In the present study majority (86.32%) of the patients had abnormal HDL levels that is ≤ 40 mg/dL in males and ≤50 mg/dL in females. The mean HDL level was noted as 34.71 ± 10.16 mg/dL.

Table 18. Triglycerides

Findings	Distribution (n=117)	
	Number	**Percentage**
Normal (150 mg/dL or less)	56	47.86
Abnormal (> 150 mg/dL)	61	52.14
Total	**117**	**100.00**

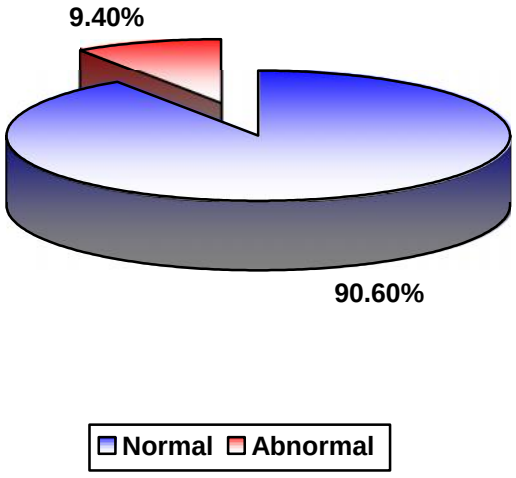


In this study abnormal triglyceride levels (≥ 150 mg/dL) were noted in 52.14% of the patients and the mean triglyceride level was 144.7 ± 65.09 mg/dL.

Table 19. Assessment of fT4

fT4	Distribution (n=117)	
	Number	**Percentage**
Normal (≥0.7)	106	90.60
Abnormal (<0.7)	11	9.40
Total	**117**	**100.00**

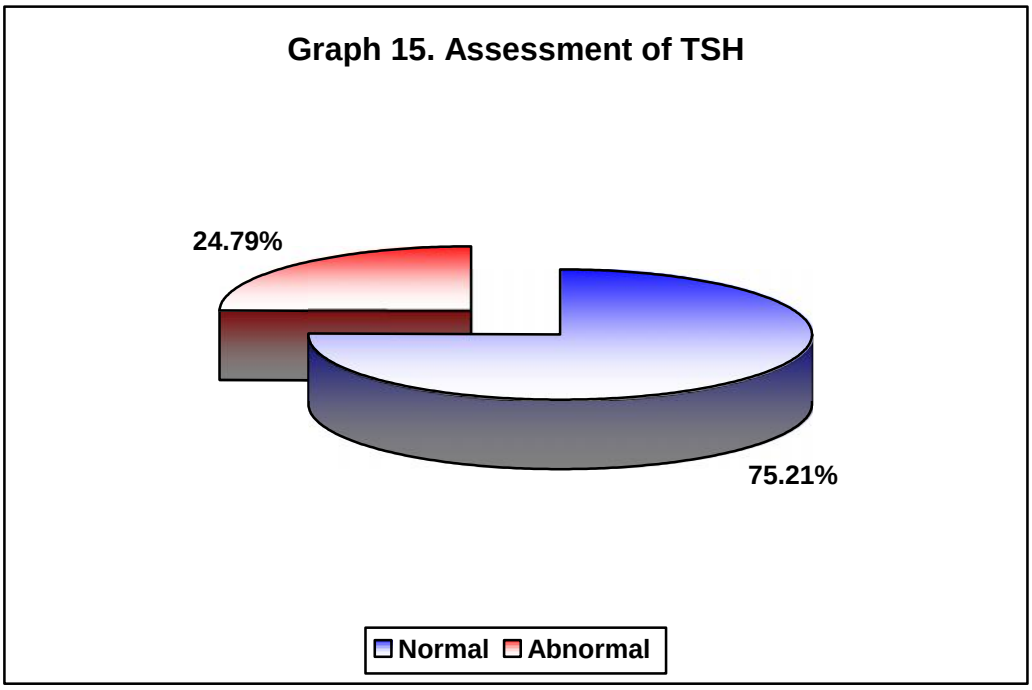
Graph 14. Assessment of fT4



In the present study fT4 levels were normal in 90.60% of the patients and abnormal in 9.40% of the patients.

Table 20. Assessment of TSH

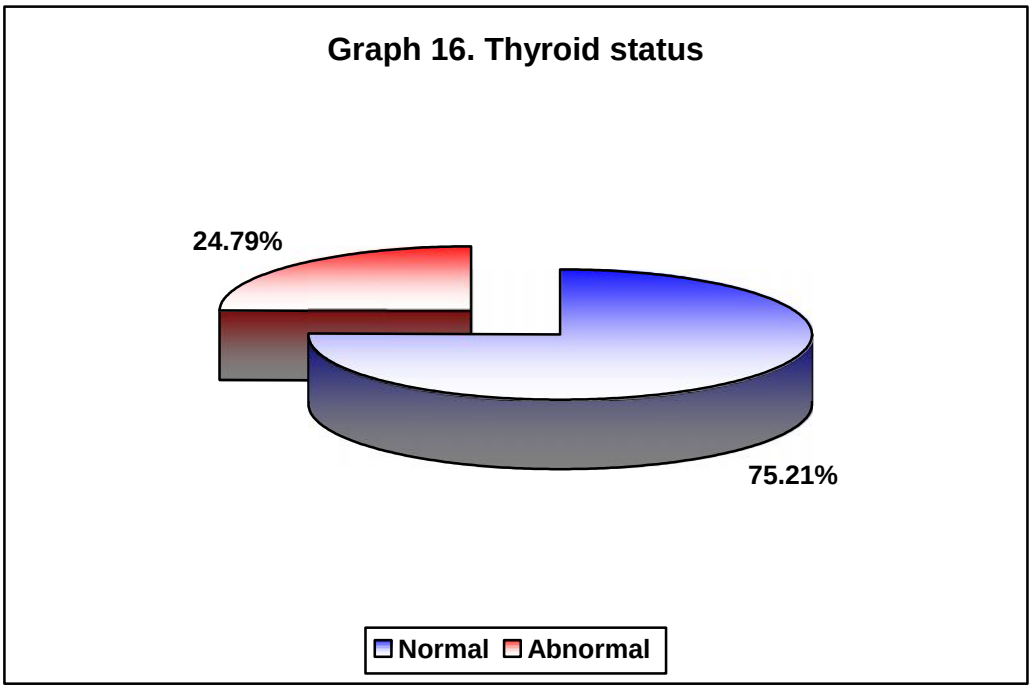
TSH	Distribution (n=117)	
	Number	**Percentage**
Normal (≤4.25)	88	75.21
Abnormal (>4.25)	29	24.79
Total	**117**	**100.00**



In the present study TSH levels were normal in 75.21% of the patients while in 24.79% the TSH levels were abnormal.

Table 21. Thyroid status

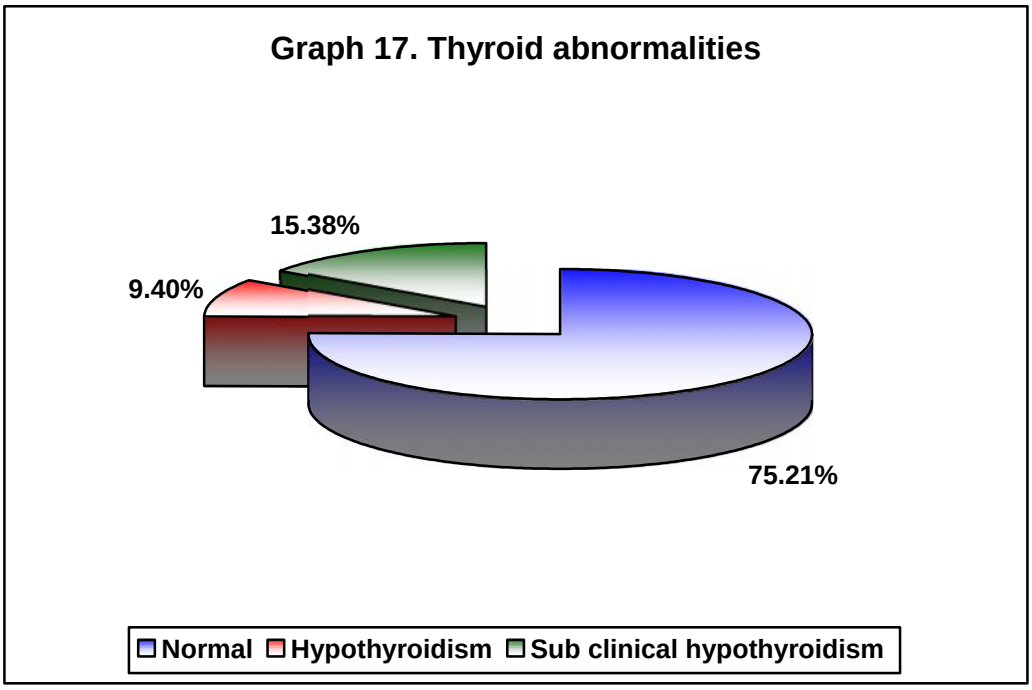
Status	Distribution (n=117)	
	Number	**Percentage**
Normal	88	75.21
Abnormal	29	24.79
Total	**117**	**100.00**



In the present study based on TSH and fT4 levels thyroid status was normal in 75.21% and abnormal in 24.79% of the patients.

Table 22. Thyroid abnormalities

Findings	Distribution (n=117)	
	Number	**Percentage**
Normal	88	75.21
Hypothyroidism	11	9.40
Sub clinical hypothyroidism	18	15.38
Total	**117**	**100.00**

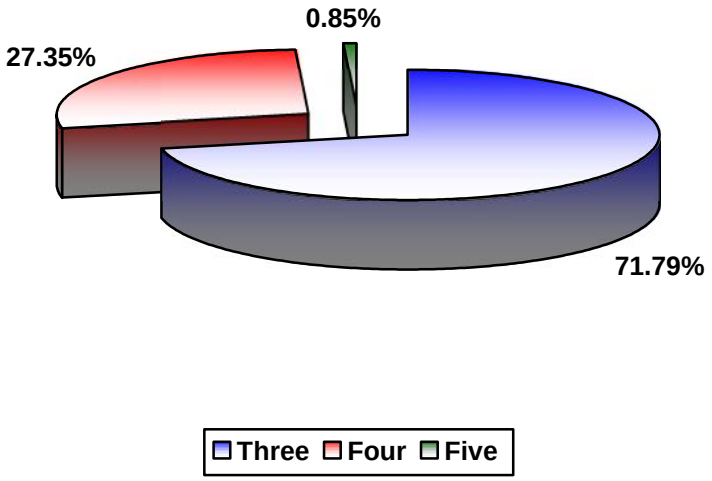


In this study thyroid abnormalities were noted as hypothyroidism in 9.40% of the patients and 15.38% had sub-clinical hypothyroidism.

Table 23. Components of metabolic syndrome

Components	Distribution (n=117)	
	Number	**Percentage**
Three	84	71.79
Four	32	27.35
Five	1	0.85
Total	**117**	**100.00**

Graph 18. Components of metabolic syndrome



In the present study based on the NCEP ATP III criteria, 71.79% of the patients had metabolic syndrome with three components while four components were noted in 27.35% of the patients. However one patient had five components (0.85%)

Table 24. Association of hypothyroidism with metabolic syndrome components

Components	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
Three	20	23.81	64	76.19	84	100.00
Four	8	25.00	24	75.00	32	100.00
Five	1	100.00	0	0.00	1	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.316 (Fischer exact test)

In this study 84 patients had three components of metabolic syndrome. Of these 23.81% had hypothyroidism while the in those with four and five components, hypothyroidism was noted among 25% and 100%. However this difference was statistically not significant (p=0.316).

Table 25. Association of hypothyroidism with sex

Sex	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
Male	8	13.56	51	86.44	59	100.00
Female	21	36.21	37	63.79	58	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.005 (Chi-square test)

In the present study 58 patients were females. Among these, 36.21% had hypothyroidism. It was observed that significantly higher number of females had hypothyroidism compared to males (36.21% vs 13.56%; p=0.005)

Table 26. Association of hypothyroidism with age

Age group (Years)	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
30 or less	3	50.00	3	50.00	6	100.00
31 to 40	3	17.65	14	82.35	17	100.00
41 to 50	11	34.38	21	65.63	32	100.00
51 to 60	5	15.15	28	84.85	33	100.00
> 60	7	24.14	22	75.86	29	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.216 (Fischer exact test)

Table 24 shows association between hypothyroidism with age group. It was observed that, maximum patients aged 30 years or less had hypothyroidism (50%) compared to other age groups but the difference was statistically not significant (p=0.216).

Table 27. Association of hypothyroidism with waist circumference

Waist circumference	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
Normal	18	25.00	54	75.00	72	100.00
Abnormal	11	24.44	34	75.56	45	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.946 (Chi-square test)

In the present study abnormal waist circumference was noted in 45 patients and of these 24.44% had hypothyroidism compared to 25% of the patients who had normal waist circumference (p=0.946).

Table 28. Association of hypothyroidism with hypertension

Hypertension	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
Present	26	25.74	75	74.26	101	100.00
Absent	3	18.75	13	81.25	16	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.401 (Fisher's exact test)

In this study hypertension was present in 101 patients. Among them 25.74% of the patients had hypothyroidism compared to 18.75% normotensives but the difference was statistically not significant (p=0.401).

Table 29. Association of hypothyroidism with diabetes mellitus

Diabetes mellitus	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
Present	20	25.97	57	74.03	77	100.00
Absent	9	22.50	31	77.50	40	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.680 (Chi-square test)

In the present study diabetes mellitus was present in 77 patients. Hypothyroidism was present in 25.97% of the diabetics compared to 22.5% non-diabetics. The difference was statistically not significant (p=0.680).

Table 30. Association of hypothyroidism with high density lipoprotein

HDL levels	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
Normal	3	18.75	13	81.25	16	100.00
Abnormal	26	25.74	75	74.26	101	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.401 (Fisher's exact test)

In this study, no statistically significant difference was noted in patients with normal (18.75%) and abnormal HDL levels (25.74%) with regard to presence of hypothyroidism (p=0.401).

Table 31. Association of hypothyroidism with triglycerides

Triglyceride levels	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
Normal	15	26.79	41	73.21	56	100.00
Abnormal	14	22.95	47	77.05	61	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.631 (Chi-square test)

In this study hypothyroidism was present in 26.79% of the patients with normal triglyceride levels compared to 22.95% of the patients with abnormal triglyceride levels. However this difference was statistically not significant (p=0.631).

Table 32. Association of hypothyroidism with body mass index

Body mass index (Kg/m^2)	Hypothyroidism				Total (n=117)	
	Present		Absent			
	No.	%	No.	%	No.	%
18.5 to 22.99	3	15.00	17	85.00	20	100.00
23.00 to 24.99	9	33.33	18	66.67	27	100.00
25.00 to 29.99	13	29.55	31	70.45	44	100.00
30 or more	4	15.38	22	84.62	26	100.00
Total	**29**	**24.79**	**88**	**75.21**	**117**	**100.00**

p = 0.292 (Fisher's exact test)

In this study the higher proportion of patients (33.33%) with hypothyroidism had BMI between 23 to 24.99 Kg/m^2 and the distribution of body mass index in patients with hypothyroidism was comparable (p=0.292).

DISCUSSION

Metabolic syndrome is a cluster of risk factors which includes hypertension, atherogenic dyslipidemia, hyperglycemia, prothrombotic and proinflammatory conditions. In developed countries, metabolic syndrome affects nearly one quarter of the population and a major risk for development of diabetes mellitus and atherosclerosis. The prevalence of cardiovascular disease is considered to be three times higher in individuals with metabolic syndrome than in age-matched controls.[1]

According to CURES 52 study, hypertension was prevalent in 20% of Chennai urban population.[93] Among these hypertensive patients, the prevalence of other components of metabolic syndrome were: diabetes in 31.8%, impaired glucose tolerance in 17.9%, hypercholesterolemia in 38.8%, hypertriglyceridemia in 38%, abdominal obesity in 64.3% and general obesity in 40%.[93]

The Jaipur Heart Watch Studies have reported that in urban Indian populations, age-adjusted prevalence of metabolic syndrome is 18.4% in men, 30.9% in women, and 24.9% overall.[92]

Further sub-clinical hypothyroidism (SCH) and overt hypothyroidism have been recognized risk factors for atherosclerotic cardiovascular disease, hyperlipidemia, low grade inflammation and hypercoagulability.[1] However, there is little data on the prevalence and the associations of SCH and overt hypothyroidism in the South Indian general population. Since metabolic syndrome and hypothyroidism are independent risk factors for cardiovascular disease, it is possible that the patients suffering from both these diseases may have a compounded risk.

Hence the present study is an effort to investigate the proposed association between these two disease entities.

This one year cross-sectional study was carried out in the Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 117 patients diagnosed to have metabolic syndrome based on NCEP ATP III criteria from January 2013 to December 2013 were studied for thyroid abnormalities.

In the present study based on abnormal fT4 (9.40%) and TSH (levels 24.79%) thyroid status was found to be abnormal in as high as almost one fourth of the study population (24.79%) with 9.40% patient having hypothyroidism and 15.38% having sub-clinical hypothyroidism. Also another study from South India showed prevalence of SCH as 21.9% and overt hypothyroidism as 7.4% in patients with metabolic syndrome.[1] Yet an another study from Orissa, showed prevalence of subclinical hypothyroidism in 22% and overt hypothyroidism in 4% in patients with MetS.[99] In India, a recent population-based study among adult population showed the prevalence of hypothyroidism as 3.9% while that of subclinical hypothyroidism as 9.4%.[100] The proportion of patients with thyroid dysfunction in the present study was 24.79% which was comparable with Chandra L et al[84] who reported thyroid dysfunction in 21.1% of the patients with metabolic syndrome. In contrast, a study by Unuzula et al[83] reported lower prevalence of thyroid dysfunction in patients with metabolic syndrome that is, 16.4% whereas Gyawali P et al[101] found prevalence of thyroid abnormalities in 31.25% of the patients with metabolic syndrome. The findings of the present study with regard to sub-clinical hypothyroidism and overt hypothyroidism among metabolic syndrome patients were consistent with the

finding of the study from South India. But the concordance noted in the prevalence of thyroid abnormalities could be attributed to the patient selection that is different criterion of metabolic syndrome and the method of assessment for the thyroid dysfunction.

In this study by applying NCEP ATP III criteria[11] majority of the patients (71.79%) were diagnosed to have metabolic syndrome with three components. Among them, 23.81% of the patients had hypothyroidism and in those with four and five components hypothyroidism was noted among 25% and 100%. However the distribution of patients with hypothyroidism was comparable in different subset of patients with components of Mets (p=0.316). These findings suggest that hypothyroidism was prevalent irrespective of the metabolic syndrome components. In contrast, a study[102] conducted in Pakistan in 2011 demonstrated that thyroid function decreased as the number of components of metabolic syndrome increased. This implies that patients with lower thyroid function had greater number of components of metabolic syndrome. Hence thyroid function in the low-normal range was related to increased presence of metabolic syndrome. Also a relationship between thyroid function (free T4) and number of components of metabolic syndrome was shown by Lin et al[103] in Chinese population. But the lack of association between metabolic syndrome components and thyroid dysfunction may be attributed to smaller subset of patients with four and five components.

In the present study the prevalence metabolic syndrome was comparable among males and females with 50.43% males and 49.57% females. The male to female ratio was 1:1. Of the 58 females, 36.21% had hypothyroidism compared to 13.56% males and the difference was statistically significant (p=0.005). The

findings show higher prevalence of hypothyroidism among females with metabolic syndrome. Another cross-sectional study on South Indian patients demonstrated an association between hypothyroidism (overt and sub-clinical) and metabolic syndrome and showed that women with metabolic syndrome are at a greater risk of developing hypothyroidism.[1] In post-menopausal Korean women TSH levels were found to be significantly associated with metabolic syndrome.[104] Also the study done by Uzunlulu et al.[83] showed that females were more commonly associated with SCH and MetS. The findings of the present study is consistent with the study from South India and Uzunlulu et al.[83] Therefore it may be a good practice to screen females with metabolic syndrome for hypothyroidism.

In this study 28.21% of the patients presented with age between 51 to 60 years, 27.35% were aged between 41 to 50 years and 24.79% had age more than 60 years. A small subset of patients that is, 14.53% of the patients presented with age from 31 to 40 years and 5.13% with less than or equal to 30 years. The mean age of the study population was found to be 52.25 ± 13.49 years. The prevalence of hypothyroidism was high in patients aged 30 years or less (50%) compared to other age groups but the same was not true statistically (p=0.216). A study[99] from Orissa reported the mean age was 47.30 ± 4.85 years in patients with metabolic syndrome. Another study[1] from South India reported mean age was 51 ± 9.4 years among metabolic syndrome patients. Though the mean age observed in the present was close to South Indian study,[1] the study was carried out under case control design.

In the present study 63.25% of the patients presented with history of diabetes mellitus and based on FBS 2.56% were newly detected with diabetes summing up to 65.81% of the patient with diabetes mellitus. In these patients the prevalence of

hypothyroidism was noted as 25.97% compared to 22.5% who were non-diabetics but the difference was statistically not significant (p=0.680). These findings propose no association of hypothyroidism in patients with diabetes mellitus.

Low thyroid function increases the peripheral vascular resistance and activate the sympatho-adrenal system, leading to an increase in BP, particularly DBP.17 In this study, 76.07% of the patients reported history of hypertension. On examination, 10.26% were newly detected to have hypertension summing up to 86.33%. The prevalence of hypothyroidism among hypertensives and normotensives was comparable (25.74% and 18.75% respectively; p=0.401). A study[102] from Pakistan showed that TSH levels significantly correlated with DBP in men. In the study done by Park et al[104] among post menopausal women, correlation analysis showed a positive relationship of TSH with BP.

Thyroid hormones affect thermogenesis and body energy expenditure. Hence a lower thyroid function (free T4) may potentially lead to obesity and associated increased waist circumference.[102] In the present study, more than one third (38.46%) of the patients presented with abnormal waist circumference and mean waist circumference was 90.78 ± 9.74 cms. However, the prevalence of hypothyroidism was comparable in patients with abnormal (24.44%) and normal waist circumference (25%). (p=0.946). In a study[102] from Pakistan, the TSH levels significantly correlated with the waist circumference in men. Also a study by Roos et al[79] showed a positive relationship of low normal thyroid function with waist circumference in both men and women.

In this study majority (86.32%) of the patients were found to have abnormal HDL levels. The mean HDL levels also tended toward lower values (34.71 ± 10.16 mg/dL). The prevalence of hypothyroidism was slightly high in patients with abnormal HDL levels (25.74%) compared to those having normal HDL levels (18.75%) but the difference was statistically not significant (p=0.401). The findings were consistent with other studies[79,104] which have also shown that thyroid function (free T4 or TSH) is not related to HDL-C.

In the present study nearly half of the study population (52.14%) presented with hypertriglyceridemia and the mean triglyceride levels were 144.7 ± 65.09 mg/dL. However, hypothyroidism was comparable (p=0.631) in patients with normal triglyceride levels (26.79%) and among those who had hypertriglyceridemia (22.95%). In a study from Pakistan, the TSH levels significantly correlated with TG levels in all subject population. However, the study by Kim et al[105] showed that low normal thyroid function (free T4) is negatively related to TG levels.

Overall in the present study none of the metabolic syndrome components showed positive association with hypothyroidism. In contrast, thyroid function has been consistently associated with individual components of metabolic syndrome.

A recent study[1] with case control design from Chennai showed that, mean systolic pressure, diastolic pressure, waist circumference, fasting blood sugar, total cholesterol, LDL cholesterol, triglycerides and TSH values were significantly higher in the MetS group compared to the control group. Also, Uzunlulu et al.,[83] reported that, the MetS group in their study had significantly higher levels of mean systolic pressure, diastolic pressure, waist circumference, body mass index, fasting blood

sugar, total cholesterol, LDL cholesterol, triglycerides and TSH values and SCH was significantly associated with MetS group (p=0.001).

Recently, many studies have established the association between fT4 levels and total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.[1] Yet another study called the HUNT study concluded that "Within the range of TSH that is considered clinically normal, increasing level of TSH was associated with less favorable lipid concentrations. The association with serum lipids was linear across the entire reference range of TSH".[106]

The disparity observed between present study and other studies with regard to association between metabolic syndrome components could be attributed to the fact that majority of the patients with metabolic syndrome presented with three components. Further in those patients who presented with history of hypertension and diabetes reported shorter duration that is 40.54% with diabetes and 43.82% with hypertension had duration less than three years and even few cases were diagnosed on examination that is 12.16% and 6.64% respectively. Also a recent study from Orissa showed no statistically significant association with total cholesterol, triglycerides, LDL-C and HDL-C in patients with sub-clinical hypothyroidism with metabolic syndrome.

In the present study no statistically significant association was observed between abnormal thyroid function and body mass index. A study by Kota *et al*, recently demonstrated the absence of significant relation between severity of obesity and serum TSH level.[107] In contrast, a study from Orissa, showed significant association of BMI with subclinical hypothyroidism in patients with MetS.

The present study has certain limitations. Since it is cross-sectional in design, a causal relationship between low-normal thyroid function and metabolic syndrome cannot be ascertained. Also the sample size was relatively small which restricted from sub-group analysis. Although metabolic syndrome is a well known clinical expression of insulin resistance, direct measures of insulin resistance have not been undertaken in this study since it is beyond the scope of this study. Systemic inflammatory markers like IL1, IL6 and TNF-α also were not measured.

Further studies with large sample size and specific cluster of metabolic syndrome components like insulin resistance, systemic inflammatory markers would further focus the epidemiology of hypothyroidism in patients with metabolic syndrome.

CONCLUSION

The present study showed higher prevalence of primary hypothyroidism (overt and sub-clinical) in patients with metabolic syndrome based on NCEP ATP III criteria. The prevalence was higher among females. No positive association was found between hypothyroidism and metabolic syndrome components including waist circumference, hypertension, diabetes, high density lipoprotein and triglycerides.

The association of hypothyroidism with metabolic syndrome might result in a compounded cardiovascular risk which needs to be addressed by prompt evaluation and management in order to reduce the cardiovascular risk in these patients.

SUMMARY

Metabolic syndrome and hypothyroidism are independent risk factors for cardiovascular disease. Patients suffering from both these diseases may have a compounded risk atherosclerotic cardiovascular disease, hyperlipidemia, low grade inflammation and hypercoagulability. The present study was undertaken to investigate the proposed association between these two disease entities.

The present one year cross-sectional study was done from January 2013 to December 2013 at Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 117 patients diagnosed to have metabolic syndrome based on NCEP ATP III criteria were studied for thyroid abnormalities.

Males constituted 50.43% and 49.57% were females with male to female ratio of 1:1. Most of the patients presented with age between 51 to 60 years (28.21%) and the mean age was 52.25 ± 13.49 years. Most of the patients had BMI between 25.00 to 29.99 Kg/m^2 (37.61%) and mean BMI was found to be 27.20 ± 4.22 Kg/m^2. History of diabetes mellitus, hypertension and dislipidemia was noted in 63.25%, 76.07% and 65.81%. Abnormal waist circumference was noted in 38.46% of the patients and mean waist circumference was 90.78 ± 9.74 Cms. Majority of the patients had abnormal HDL (86.32%) and triglyceride (52.14%) levels. Based on abnormal fT4B levels in 9.40% and abnormal TSH levels in 24.79%, thyroid status was abnormal in 24.79% of the patients. Thyroid abnormalities were hypothyroidism in 9.40% and 15.38% had sub-clinical hypothyroidism. Majority of the patients (71.79%) had metabolic syndrome with

three components. Positive association of hypothyroidism was noted with female gender ($p<0.050$) while no association was found between hypothyroidism and metabolic syndrome components including waist circumference, hypertension, diabetes, high density lipoprotein and triglycerides.

There is high prevalence of primary hypothyroidism in patients with metabolic syndrome and is further high among females compared to males.

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ANNEXURE I – CONSENT FORM

PREVALENCE OF PRIMARY HYPOTHYROIDISM IN METABOLIC SYNDROME – A ONE YEAR CROSS SECTIONAL STUDY AT KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELGAUM

This study is conducted by Dr. **** *****, Post graduate student in M.D. General Medicine under guidance of Dr. **** ******, Professor, General Medicine, J. N. Medical College, Belgaum.

Respected Sir/Madam, we invite you to participate in our study as you are eiligible for the same. During the study you will be asked some questions in detail regarding your present complaints.

Purpose of the study

The purpose of this study is to find out the prevalence of primary hypothyroirism in metabolic syndrome. You are being asked to participate in this research because you have been diagnosed to have metabolic syndrome.

Procedure and treatment

You may undergo some amount of discomfort during the process of investigation, which may include slight pain and following thyroixine replacements. The overdose may lead to atrial fibrillation and reduced bone density which is very rare entity. However all necessary steps and precautions will be taken to ensure your safety. The result of you taking part in this research would help health care providers towards a better understanding of this disease, and thus we will be able to provide improved patient care.

Alternatives

If you decide not to participate in this study, you will still be receiving the standard care for your disease.

Privacy and Confidentiality

Your privacy will be respected and all the information collected about you during the course of this study will be kept confidential your identity will remain undisclosed.

Relations with the institutional policy

The J N M C will provide within the limitations of the laws of the State of Karnataka, facilities and medical attention to patients who suffer injuries as a result of participating in this project.

Financial incentives

You shall not be receiving any payment or any financial incentives for participating in this study.

Authorization to publish the results

The results of the study may be published for scientific purpose or presented to a scientific group. You identity, however will be maintained confidential at all times.

Voluntary participation

Your participation in this study is voluntary. Your decision whether or not to participate will neither affect the care of your current disease, nor your relations with the doctor or the hospital. In the event if you suffer any physical injury as the result of your participation in this study, you may contact Dr. *** ****** Telephone No. ****** ****** or Dr. ***** *******, Telephone No. in the event of emergency,

you should contact KLES Dr. Prabhakar Kore Hosptial and MRC on Telephone No. **** *******.

In case you need further information regarding your rights as a participant, you may please contact Dr. **** ***** Chairman of the ethical committee, J. N. Medical College, Belgaum.

Statement of consent

I Mr / Ms / Mrs _____volunteer and consent to take participate in this study. I have read the consent document or it has been red to me in my vernacular language. I accept to participate in the study. All the information regarding this study is provided to me and I have understood the same. I have been given the opportunity to ask questions and obtained appropriate answers.

Name of the Participant: _____

Signature / Thumb print _____

Name of the Witness _____

Signature / Thumb print _____

Signature of investigator _____

Date:

ANNEXURE II – PROFORMA

Case No:

NAME: AGE/SEX:

IP No.

OCCUPATION:

COMPLAINTS AT PRESENTATION:

HISTORY PERTAINING TO METABOLIC SYNDROME :

k/c/o Type 2 diabetes mellitus yes ☐ no ☐

If yes,

Duration of illness -

Details of treatment –

H/o peripheral neuropathy - yes ☐ no ☐

Documented Diabetic retinopathy/surgical management of retinopathy in the past

Diabetic nephropathy yes ☐ no ☐

Diabetic foot yes ☐ no ☐

Autonomic neuropathy yes ☐ no ☐

K/c/o Hypertension or on specific anti-hypertensive medication and duration yes ☐ no ☐

H/o Peripheral vasucular disease/past h/o treatment for the same yes ☐ no ☐

K/c/o of dyslipidemia or on any specific medication yes ☐ no ☐

Past history

History of angina pain / Myocardial infarction / ischaemic heart disease or on any specific medication	Yes/No
History of cerebrovascular accidents	Yes/No
History of chronic kidney disease apart from diabetic retinopathy	Yes/No
History of hyperthyroidism or under treatment	Yes/No
For any thyroid related disorder	Yes/No

If female,

History of use of oral contraceptive pills	Yes/No
Presently pregnant	Yes/No

Personal history

History of alcohol consumption	Yes/No
History of smoking	Yes/No

Family history

Hypertension / Type 2 DM / Obesity / Dyslipidemia	Yes/No
Hypothyroidism	Yes/No

ON EXAMINATION :

- NUTRITION :

  HEIGHT :

  WEIGHT:

  BMI :

  <u>WAIST CIRCUMFERENCE</u> :

- <u>BLOOD PRESSURE :</u>

VITALS

- Temperature
- Pulse
- Respiratory rate
- Blood pressure

SYSTEMIC EXAMINATION

- Cardiovascular system
- Respiratory system
- Per abdominal examination
- Central nervous system

INVESTIGATIONS:

- FBS (Fasting Blood Sugar)
- Fasting lipid profile
    - Total cholesterol-
    - Triglycerides level –
    - Total HDL –
    - Estimated LDL –
- Serum TSH and fT4B
- Miniremal profile
- Liver function tests
- ECG and 2D ECHO (If necessary)
- Urine pregnancy test (In women who are in reproductive age group)

Diagnosis:

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
0C	-	Degree centigrade
BP	-	Blood pressure
Cms	-	Centimeters
dL	-	Deciliter
DM	-	Diabetes mellitus
F	-	Female
HPO	-	Hypothyroidism
HTN	-	Hypertension
Kgs	-	Kilograms
M	-	Male
m	-	Meter
mg	-	Milligram
mm	-	Millimeters of mercury
N	-	No
ND	-	Newly detected
SHPO	-	Sub-clinical hypothyroidism
TSH	-	Thyroid regulating hormone
Y	-	Yes

ANNEXURE III - MASTER CHART

				History													Personal history		Family History					General physical examination												Systemic examination				Investigation								
				DM		HTN																					BP																							
Serial Number	In / out patient number	Age (Years)	Sex	Diabetes	Duration (Years)	Hypertension	Duration (Years)	Liver disorders	Renal disorders	Congestive cardiac failure	Pregnancy (Urine test)	Oral contraceptive pills	Dyslipidemia	Known case of hypothyroidism	Hyperthyroidism	Treatment of thyroid disorder	Alcohol consumption	Smoking	Hypertension	Diabetes mellitus T2	Obesity	Hypothyroidism	Dyslipidemia	Height (Cms)	Weight (Kg)	Body mass index (Kg/m2)	Waist circumference (Cms)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic (mm Hg)	Diastolic (mm Hg)	Temperature (0C)	Cardiovascular system	Respiratory system	Per abdomen	Central nervous system	Fasting blood sugar (mg/dL)	HbA1c	Total cholesterol (mg/dL)	Low density lipoprotien (mg/dL)	High density lipoprotein (mg/dL)	Triglycerides (mg/dL)	Serum TSH	fT4B	Thyroid status
1	2355401	58	F	N	-	Y	8	-	-	-	-	-	N	N	N	-	N	N	+	+	+	-	+	151	90	39.47	92	96	21	150	96	98.6	-	-	-	-	85	-	163	89	62	157	1.07	1.26	-
2	2520076	57	M	Y	2	N	-	-	-	-	-	-	N	N	N	-	Y	Y	+	+	-	-	-	167	78	27.96	88	102	24	150	100	98.6	-	-	-	PN	146	9	210	146	36	78	1.02	1.71	-
3	2487926	22	M	N	-	N	-	-	-	-	-	-	N	N	N	-	N	Y	+	-	+	-	+	156	95	39.03	104	76	16	130	86	98.6	-	-	-	-	106	-	196	113	29	269	3.24	0.89	-
4	520181	53	M	Y	0.5	N	-	-	-	-	-	-	N	N	N	-	Y	Y	+	+	-	-	-	171	86	29.01	96	106	26	140	90	98.6	-	-	-	-	146	8.6	106	31	22	266	5.91	1.01	SHPO
5	563472	54	M	Y	4.5	Y	6	-	-	-	-	-	N	N	N	-	Y	N	+	+	-	-	-	172	78	26.36	98	86	20	120	70	98.6	-	-	-	-	117	6.9	122	87	23	59	2.32	1.82	-
6	559858	88	M	Y	12	Y	20	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	181	72	22.22	82	114	36	100	70	98.6	-	-	-	-	124	9.6	106	68	23	75	0.90	1.44	-
7	2198025	47	M	N	-	Y	ND	-	-	-	-	-	N	N	N	-	Y	N	+	+	-	-	-	176	82	26.47	104	84	20	150	96	98.6	-	-	-	-	106	-	173	124	34	74	1.50	1.5	-
8	2569754	60	M	Y	12	Y	8	-	-	-	-	-	N	N	N	-	N	Y	-	+	+	-	+	162	84	32	106	80	22	146	90	98.6	-	-	-	-	152	9.6	167	98	50	96	1.22	1.47	-
9	565521	58	M	Y	2	Y	6	-	-	-	-	-	N	N	N	-	Y	Y	+	+	+	-	-	182	92	27.77	98	96	24	150	90	98.6	-	-	-	-	111	9.6	126	84	32	46	2.27	1.47	-
10	2125815	39	F	N	-	Y	1	-	-	-	-	-	N	N	N	-	N	N	-	+	-	-	-	158	77	30.84	90	70	14	136	86	98.6	-	-	-	-	80	-	171	95	59	185	7.68	1.22	SHPO
11	2501475	44	F	Y	0.5	Y	0.41	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	154	56	23.61	72	68	16	138	90	98.6	-	-	-	-	162	9.6	202	146	42	69	5.40	1.04	SHPO
12	2195580	54	F	Y	6	Y	6	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	156	82	33.69	96	78	16	136	80	98.6	-	-	-	-	170	8.8	258	186	38	140	1.10	0.9	-
13	552082	45	F	Y	ND	Y	5	-	-	-	-	-	N	N	N	-	N	N	+	+	+	-	+	158	78	31.24	88	90	18	126	80	98.6	-	-	-	-	134	7.4	239	179	29	156	0.57	0.8	-
14	555456	50	F	Y	0.25	N	-	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	162	69	26.29	90	62	14	110	76	98.6	-	-	-	-	132	6.8	258	192	37	146	7.99	0.5	HPO
15	558243	38	M	N	-	Y	0.25	-	-	-	-	-	N	N	N	-	N	N	+	+	+	-	-	154	82	34.57	104	80	16	140	80	98.6	-	-	-	-	87	-	121	71	10	200	1.07	1.13	-
16	493672	81	M	Y	ND	Y	20	-	-	-	-	-	N	N	N	-	N	Y	-	-	-	-	-	164	78	29	96	80	16	136	80	98.6	-	-	-	-	176	7.2	126	64	32	46	1.00	0.96	-
17	561038	37	M	Y	0.25	N	-	-	-	-	-	-	N	N	N	-	N	Y	+	+	+	-	+	172	96	32.44	104	90	20	120	70	98.6	-	-	-	-	185	8.7	80	51	10	96	2.60	1.13	-
18	562355	60	M	Y	0.16	Y	8	-	-	-	-	-	Y	N	N	-	N	Y	+	+	-	-	-	166	82	29.75	98	86	16	140	80	98.6	-	-	-	-	141	6.8	100	48	11	203	0.98	1.01	-
19	554879	45	M	Y	0.5	Y	1	-	-	-	-	-	N	N	N	-	N	N	-	+	+	-	-	158	70	28.04	92	82	14	120	66	98.6	-	-	-	-	123	6.9	126	64	32	46	0.79	1.19	-
20	561558	76	F	N	-	Y	12	-	-	-	-	-	N	N	N	-	N	N	-	+	+	-	-	156	72	29.58	101	92	20	140	90	98.6	-	-	-	-	99	-	110	53	46	156	1.90	1.03	-
21	2436266	54	M	Y	4	N	-	-	-	-	-	-	N	N	N	-	Y	N	-	+	-	-	-	160	82	32.03	103	72	16	120	80	98.6	-	-	-	-	116	6.9	126	64	32	46	2.92	1.13	-
22	2457295	67	F	Y	12	Y	6	-	-	-	-	-	N	N	N	-	N	N	-	+	-	-	+	162	66	25.14	90	76	14	130	86	98.6	-	-	-	-	155	7.7	126	64	32	46	4.20	1.34	-
23	2454729	29	F	Y	ND	Y	0.08	-	-	-	-	-	N	N	N	-	N	N	+	+	+	-	-	152	68	29.43	92	80	16	136	90	98.6	-	-	-	-	156	10	150	66	75	44	2.70	1.47	-
24	2520076	57	M	Y	7	Y	1	-	-	-	-	-	N	N	N	-	Y	Y	+	+	-	-	-	162	98	37.34	104	80	16	140	96	98.6	-	-	-	PN	146	9.8	110	53	46	56	1.02	1.71	-
25	562956	70	M	Y	23	Y	ND	-	-	-	-	-	N	N	N	-	Y	Y	-	+	+	-	-	160	88	34.37	103	82	16	170	110	98.6	-	-	-	PN	150	13	154	113	17	119	1.33	1.17	-
26	2549158	47	M	Y	0.16	Y	5	-	-	-	-	-	N	N	N	-	N	Y	-	+	+	-	-	176	70	22.59	90	88	18	138	90	98.6	-	-	-	-	170	12	126	24	32	46	1.18	0.93	-
27	2539561	58	M	Y	ND	Y	6	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	180	72	22.22	88	80	16	160	100	98.6	-	-	-	-	137	7.6	109	50	36	112	2.11	1.47	-
28	565517	28	M	N	-	Y	5	-	-	-	-	-	N	N	N	-	Y	N	+	+	-	-	-	170	92	31.83	104	84	18	180	100	98.6	-	-	-	-	108	-	137	79	33	128	5.42	1.24	SHPO
29	562381	57	F	Y	6	Y	6	-	-	-	-	-	N	N	N	-	N	N	+	-	-	-	+	166	58	22.65	86	68	14	136	90	98.6	-	-	-	PN	104	-	144	90	35	96	1.30	1.4	-
30	2134725	64	M	Y	4	N	-	-	-	-	-	-	N	N	N	-	Y	Y	-	+	+	-	-	162	96	36.57	105	80	16	120	70	98.6	-	-	-	-	121	9.6	242	159	29	156	1.69	1.26	-

ANNEXURE III - MASTER CHART

Serial Number	In / out patient number	Age (Years)	Sex	History														Personal history		Family History					General physical examination										Systemic examination				Investigation								Thyroid status
				DM		HTN																						BP																			
				Diabetes	Duration (Years)	Hypertension	Duration (Years)	Liver disorders	Renal disorders	Congestive cardiac failure	Pregnancy (Urine test)	Oral contraceptive pills	Dyslipidemia	Known case of hypothyroidism	Hyperthyroidism	Treatment of thyroid disorder	Alcohol consumption	Smoking	Hypertension	Diabetes mellitus T2	Obesity	Hypothyroidism	Dyslipidemia	Height (Cms)	Weight (Kg)	Body mass index (Kg/m2)	Waist circumference (Cms)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic (mm Hg)	Diastolic (mm Hg)	Temperature (0C)	Cardiovascular system	Respiratory system	Per abdomen	Central nervous system	Fasting blood sugar (mg/dL)	HbA1c	Total cholesterol (mg/dL)	Low density lipoprotien (mg/dL)	High density lipoprotein (mg/dL)	Triglycerides (mg/dL)	Serum TSH	fT4B	
31	2281837	31	M	N	-	Y	2	-	-	-	-	-	Y	N	N	-	Y	N	+	-	+	-	-	170	98	33.91	103	78	14	170	90	98.6	-	-	-	-	80	-	126	84	32	46	0.70	0.96	-
32	2228744	55	M	Y	ND	Y	2	-	-	-	-	-	N	N	N	-	N	N	+	-	-	-	-	166	92	33.38	103	66	16	140	90	98.6	-	-	-	-	224	9.8	161	95	44	108	1.20	1.47	-
33	2314999	65	F	N	-	Y	3	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	151	60	26.31	86	80	16	130	80	98.6	-	-	-	-	103	-	293	163	33	246	8.80	0.6	HPO
34	2310969	46	F	N	-	Y	2	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	153	72	30.75	92	80	16	150	90	98.6	-	-	-	-	88	-	181	112	48	205	2.16	1.02	-
35	2304693	52	F	Y	0.5	Y	4	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	+	152	52	22.5	86	78	16	136	90	98.6	-	-	-	-	119	9.6	238	171	32	175	1.75	1.13	-
36	2304566	66	F	Y	8	Y	3	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	172	65	21.97	86	68	16	140	90	98.6	-	-	-	PN	149	7.7	144	90	35	96	9.22	1.4	SHPO
37	2390445	55	F	Y	8	Y	4	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	156	70	28.76	92	62	16	156	96	98.6	-	-	-	-	186	9.6	172	102	45	126	21.80	0.2	HPO
38	2386069	58	F	N	-	Y	6	-	-	-	-	-	Y	N	N	-	N	N	-	+	+	-	-	162	88	33.53	96	78	16	160	90	98.6	-	-	-	-	86	-	247	172	56	197	0.98	1.4	-
39	2382522	65	F	Y	5	Y	5	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	156	72	32	90	76	18	146	90	98.6	-	-	-	-	116	8.8	167	98	50	96	0.99	1.47	-
40	2349556	22	F	N	-	Y	0.25	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	153	68	29.04	94	66	18	126	70	98.6	-	-	-	-	130	6.9	144	90	35	96	12.09	0.56	HPO
41	2351009	59	F	N	-	Y	8	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	+	151	55	24.12	84	78	14	150	90	98.6	-	-	-	-	94	-	236	168	33	177	2.00	1.4	-
42	2346782	76	F	Y	8	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	+	157	60	24.34	80	88	18	158	98	98.6	-	-	-	-	140	11	92	49	39	170	0.69	1.5	-
43	2515019	52	F	N	-	Y	9	-	-	-	-	-	Y	N	N	-	N	N	-	+	+	-	-	160	62	24.21	86	64	18	138	90	98.6	-	-	-	-	74	-	110	53	36	156	4.34	1.16	SHPO
44	2184657	56	F	Y	0.66	Y	6	-	-	-	-	-	Y	N	N	-	N	N	-	+	-	-	-	162	66	25.14	82	68	14	170	100	98.6	-	-	-	PN	105	-	231	131	36	319	16.50	0.5	HPO
45	2178873	34	F	Y	ND	Y	2	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	152	64	27.7	94	88	16	146	90	98.6	-	-	-	-	136	8.3	161	98	50	96	6.90	0.9	SHPO
46	2156596	43	M	Y	1	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	+	+	-	-	172	70	23.66	94	78	16	156	96	98.6	-	-	-	-	137	6.6	96	59	39	172	1.58	1.7	-
47	2133086	51	F	Y	6	Y	1	-	-	-	-	-	Y	N	N	-	N	N	-	+	+	-	-	156	58	23.83	80	88	14	126	80	98.6	-	-	-	PN	127	8.4	144	90	35	96	2.02	1.03	-
48	2127917	82	M	Y	20	Y	4	-	-	-	-	-	Y	N	N	-	Y	Y	+	+	-	-	-	176	82	26.47	96	68	14	156	90	98.6	-	-	-	PN	129	12	231	131	36	31	0.84	1.9	-
49	2127520	49	F	Y	ND	N	-	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	162	60	22.86	82	68	12	140	90	98.6	-	-	-	-	182	14	156	78	36	176	1.46	1.6	-
50	2123363	51	F	Y	6	Y	5	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	162	56	21.3	82	78	14	134	76	98.6	-	-	-	-	117	8.5	206	139	39	138	3.19	1.2	-
51	2123348	55	M	N	-	Y	10	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	152	55	29.2	86	68	14	150	90	98.6	-	-	-	-	109	7	203	112	35	279	2.63	1.36	-
52	2120628	41	F	N	-	Y	0.33	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	160	56	21.36	80	70	16	140	90	98.6	-	-	-	-	100	-	92	39	29	170	1.76	1.47	-
53	2466258	44	F	N	-	Y	2	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	155	65	27.01	100	68	16	160	100	98.6	-	-	-	-	104	-	110	53	46	156	1.59	0.98	-
54	546980	64	M	Y	10	N	-	-	-	-	-	-	Y	N	N	-	Y	Y	+	+	-	-	-	164	70	26.02	96	76	18	100	70	98.6	-	-	-	-	176	9.3	210	39	36	170	0.86	1.44	-
55	498231	57	M	Y	8	Y	6	-	-	-	-	-	N	N	N	-	N	N	-	-	+	-	+	168	96	34.01	106	88	16	170	100	98.6	-	-	-	-	164	8.6	110	53	46	56	1.30	1.35	-
56	546241	44	F	N	-	Y	3	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	+	160	62	24.21	82	66	14	140	100	98.6	-	-	-	-	85	-	239	88	36	206	147.49	0.48	HPO
57	546728	50	F	Y	10	Y	10	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	155	60	24.9	78	80	16	116	76	98.6	-	-	-	-	169	9.6	82	50	23	50	1.01	0.97	-
58	2103325	48	M	Y	8	N	-	-	-	-	-	-	Y	N	N	-	Y	Y	+	+	-	-	-	172	82	28.37	96	88	18	110	70	98.6	-	-	-	-	120	11	276	234	12	158	2.20	1.22	-
59	2728221	39	F	N	-	Y	0.5	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	156	68	27.94	90	64	16	138	90	98.6	-	-	-	-	88	-	140	91	30	95	4.20	0.9	-
60	2662359	44	M	Y	0.16	Y	4	-	-	-	-	-	N	N	N	-	Y	Y	-	+	+	-	-	166	95	34.47	105	76	14	156	90	98.6	-	-	-	-	125	8.6	239	109	48	96	1.00	1.35	-

ANNEXURE III - MASTER CHART

Serial Number	In / out patient number	Age (Years)	Sex	History														Personal history		Family History					General physical examination									Systemic examination				Investigation									Thyroid status
				DM		HTN																						BP																			
				Diabetes	Duration (Years)	Hypertension	Duration (Years)	Liver disorders	Renal disorders	Congestive cardiac failure	Pregnancy (Urine test)	Oral contraceptive pills	Dyslipidemia	Known case of hypothyroidism	Hyperthyroidism	Treatment of thyroid disorder	Alcohol consumption	Smoking	Hypertension	Diabetes mellitus T2	Obesity	Hypothyroidism	Dyslipidemia	Height (Cms)	Weight (Kg)	Body mass index (Kg/m2)	Waist circumference (Cms)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic (mm Hg)	Diastolic (mm Hg)	Temperature (0C)	Cardiovascular system	Respiratory system	Per abdomen	Central nervous system	Fasting blood sugar (mg/dL)	HbA1c	Total cholesterol (mg/dL)	Low density lipoprotien (mg/dL)	High density lipoprotein (mg/dL)	Triglycerides (mg/dL)	Serum TSH	fT4B	
61	546388	66	F	Y	6	N	-	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	153	58	24.8	82	78	18	110	70	98.6	-	-	-	-	144	7.3	196	130	36	156	0.82	1.75	-
62	2130314	48	M	N	-	Y	1	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	158	74	29.64	106	70	14	140	90	98.6	-	-	-	-	105	-	191	124	24	130	3.31	1.6	-
63	545598	57	M	Y	1	Y	2	-	-	-	-	-	Y	N	N	-	Y	Y	+	+	-	-	-	172	68	22.98	92	68	14	130	80	98.6	-	-	-	-	136	6.9	182	126	32	122	0.64	1.58	-
64	562522	57	M	Y	0.66	Y	1	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	176	82	26.47	98	78	16	138	90	98.6	-	-	-	-	112	6.6	242	114	28	498	3.25	1.06	-
65	2683410	55	F	Y	9	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	+	152	68	29.43	98	66	16	100	70	98.6	-	-	-	PN	116	11	144	90	35	96	1.01	1.54	-
66	215181	69	M	Y	10	Y	6	-	-	-	-	-	Y	N	N	-	N	Y	+	-	+	-	-	178	82	26.47	96	70	14	170	90	98.6	-	-	-	PN	131	12	173	118	35	98	156.00	0.67	HPO
67	2415833	51	F	Y	0.33	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	+	+	-	-	160	66	25.7	78	76	18	140	90	98.6	-	-	-	-	178	7.2	118	60	28	150	1.93	0.96	-
68	565516	50	F	Y	0.16	N	-	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	153	53	22.64	80	82	16	106	76	98.6	-	-	-	-	133	8.3	92	39	19	170	1.46	1.33	-
69	564374	66	F	N	-	Y	0.41	-	-	-	-	-	Y	N	N	-	N	N	+	-	+	-	-	152	54	23.37	78	72	16	100	70	98.6	-	-	-	-	72	-	121	71	10	200	12.63	1.13	SHPO
70	564475	36	M	N	-	Y	2	-	-	-	-	-	Y	N	N	-	Y	Y	-	+	+	-	-	156	72	29.58	105	68	14	126	76	98.6	-	-	-	-	103	-	110	53	46	186	3.51	1.35	-
71	947144	47	F	N	-	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	-	158	74	29.64	94	70	14	140	90	98.6	-	-	-	-	111	6.8	258	192	37	146	8.71	1.14	SHPO
72	562475	55	F	Y	5	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	+	-	-	-	162	63	24.25	84	68	16	126	80	98.6	-	-	-	-	137	10	239	179	29	156	1.32	1.4	-
73	523749	28	F	N	-	Y	0.25	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	+	154	55	23.91	78	68	14	130	80	98.6	-	-	-	-	106	-	92	39	29	170	6.46	1.13	SHPO
74	523420	48	F	N	-	Y	3	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	-	166	78	28.03	86	80	16	176	100	98.6	-	-	-	-	93	-	118	60	28	160	1.93	0.96	-
75	523746	44	M	Y	0.33	N	-	-	-	-	-	-	Y	N	N	-	N	Y	+	-	-	-	-	176	62	20.01	90	88	18	110	70	98.6	-	-	-	-	112	6.7	173	118	35	198	4.60	0.91	SHPO
76	523745	60	F	Y	6	Y	10	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	162	66	25.14	80	76	16	136	90	98.6	-	-	-	PN	110	7.7	134	90	38	196	1.10	1.44	-
77	523424	42	M	Y	0.33	Y	2	-	-	-	-	-	Y	N	N	-	Y	N	-	+	+	-	-	180	92	28.39	100	70	16	136	90	98.6	-	-	-	-	159	8.6	242	114	28	146	4.25	1.16	-
78	527441	30	M	N	-	Y	0.41	-	-	-	-	-	Y	N	N	-	Y	Y	+	+	-	-	-	178	86	27.14	98	68	16	180	100	98.6	-	-	-	-	95	-	193	126	37	158	1.22	1.1	-
79	523702	42	M	Y	4	Y	1	-	-	-	-	-	Y	N	N	-	Y	Y	-	-	+	-	+	166	65	24.47	90	68	14	150	96	98.6	-	-	-	-	144	8.6	192	126	36	132	0.64	1.54	-
80	523699	70	F	Y	8	Y	10	-	-	-	-	-	Y	N	N	-	N	N	+	+	-	-	-	153	54	23.06	76	70	14	140	90	98.6	-	-	-	-	166	9.6	182	126	32	152	5.89	1.58	SHPO
81	523697	46	M	N	-	Y	ND	-	-	-	-	-	Y	N	N	-	Y	N	-	+	+	-	-	162	78	29.7	104	78	16	160	90	98.6	-	-	-	-	94	-	191	124	24	130	3.31	1.6	-
82	523434	45	M	N	-	Y	2	-	-	-	-	-	Y	N	N	-	Y	Y	+	+	-	-	-	182	82	24.75	88	80	18	146	100	98.6	-	-	-	-	90	-	196	130	36	156	0.82	1.75	-
83	523691	60	M	N	-	Y	4	-	-	-	-	-	Y	N	N	-	N	Y	+	+	-	-	-	166	76	27.58	86	78	16	130	76	98.6	-	-	-	-	99	-	239	109	38	196	5.02	0.56	HPO
84	523684	49	F	N	-	Y	1	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	156	86	35.33	102	90	20	140	90	98.6	-	-	-	-	107	-	140	91	30	95	4.20	0.9	-
85	523679	39	M	Y	0.33	Y	0.5	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	-	168	68	24.09	88	68	12	130	80	98.6	-	-	-	-	118	7.7	126	64	32	46	2.92	1.13	-
86	523670	73	M	Y	8	Y	10	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	-	166	58	22.65	86	78	16	136	90	98.6	-	-	-	-	127	9.6	170	112	38	105	2.16	1.03	-
87	523669	66	F	Y	6	Y	8	-	-	-	-	-	Y	N	N	-	N	N	-	+	-	-	-	170	76	26.29	80	78	16	126	70	98.6	-	-	-	PN	136	10	142	154	39	166	1.69	1.26	-
88	523770	31	F	Y	ND	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	-	156	60	24.65	76	70	16	120	70	98.6	-	-	-	-	128	7.9	176	234	12	168	2.20	1.22	-
89	523657	43	F	Y	0.58	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	+	162	64	24.38	78	80	18	140	90	98.6	-	-	-	-	122	12	182	50	26	150	1.01	0.98	-
90	523446	50	F	Y	0.66	Y	4	-	-	-	-	-	N	N	N	-	N	N	-	-	+	-	-	158	65	26.03	90	68	14	130	96	98.6	-	-	-	-	123	8.8	139	88	46	106	4.50	0.96	SHPO

ANNEXURE III - MASTER CHART

Serial Number	In / out patient number	Age (Years)	Sex	History														Personal history		Family History					General physical examination										Systemic examination				Investigation								Thyroid status
				DM		HTN																						BP																			
				Diabetes	Duration (Years)	Hypertension	Duration (Years)	Liver disorders	Renal disorders	Congestive cardiac failure	Pregnancy (Urine test)	Oral contraceptive pills	Dyslipidemia	Known case of hypothyroidism	Hyperthyroidism	Treatment of thyroid disorder	Alcohol consumption	Smoking	Hypertension	Diabetes mellitus T2	Obesity	Hypothyroidism	Dyslipidemia	Height (Cms)	Weight (Kg)	Body mass index (Kg/m2)	Waist circumference (Cms)	Pulse rate (/Minute)	Respiratory rate (/Minute)	Systolic (mm Hg)	Diastolic (mm Hg)	Temperature (0C)	Cardiovascular system	Respiratory system	Per abdomen	Central nervous system	Fasting blood sugar (mg/dL)	HbA1c	Total cholesterol (mg/dL)	Low density lipoprotien (mg/dL)	High density lipoprotein (mg/dL)	Triglycerides (mg/dL)	Serum TSH	fT4B	
91	523653	35	F	Y	0.16	Y	0.25	-	-	-	-	-	Y	N	N	-	N	N	-	+	-	-	-	164	58	21.56	82	78	16	120	70	98.6	-	-	-	-	168	9.4	110	53	46	156	1.30	1.35	-
92	536411	62	F	Y	6	N	-	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	+	-	162	68	25.91	80	72	16	140	90	98.6	-	-	-	PN	120	7.2	210	39	33	70	9.60	0.76	SHPO
93	523615	70	M	N	-	Y	6	-	-	-	-	-	Y	N	N	-	Y	Y	-	+	+	-	-	178	82	25.88	104	80	16	136	90	98.6	-	-	-	-	106	-	110	53	46	256	1.59	0.9	-
94	523610	62	M	N	-	Y	4	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	168	64	22.67	80	70	16	140	90	98.6	-	-	-	-	102	-	192	39	32	160	1.76	1.56	-
95	523591	60	F	N	-	Y	4	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	160	62	24.2	72	72	16	136	88	98.6	-	-	-	-	90	-	213	112	37	179	2.53	1.24	-
96	560565	35	M	Y	0.41	N	-	-	-	-	-	-	Y	N	N	-	N	Y	+	+	-	-	-	162	86.5	32.95	105	96	20	130	80	98.6	-	-	-	-	111	6.8	206	140	36	148	3.40	1.26	-
97	523544	35	M	N	-	Y	0.08	-	-	-	-	-	Y	N	N	-	Y	Y	-	-	+	-	+	178	70	22.093	86	68	14	150	96	98.6	-	-	-	-	103	-	156	78	36	186	1.56	1.16	-
98	523525	43	F	Y	0.25	Y	0.16	-	-	-	-	-	N	N	N	-	N	N	-	+	+	-	-	158	83	33.24	90	70	14	140	100	98.6	-	-	-	-	130	7.6	161	95	44	108	8.60	0.56	HPO
99	523520	38	M	N	-	Y	0.5	-	-	-	-	-	Y	N	N	-	Y	Y	-	-	-	+	+	170	70	24.22	86	72	16	130	80	98.6	-	-	-	-	100	-	293	164	36	246	0.88	1.09	-
100	523516	50	F	Y	0.5	Y	4	-	-	-	-	-	Y	N	N	-	N	N	+	-	+	-	-	158	62	24.83	78	82	18	140	90	98.6	-	-	-	-	116	9.3	126	84	36	106	5.60	0.69	HPO
101	595177	70	M	N	-	Y	3	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	+	174	74	24.44	86	76	16	136	98	98.6	-	-	-	-	98	-	258	192	33	160	2.90	1.14	-
102	566522	33	M	Y	0.33	Y	ND	-	-	-	-	-	N	N	N	-	Y	Y	-	-	+	-	+	160	81	31.64	105	86	18	140	90	98.6	-	-	-	-	116	7.3	180	170	32	158	5.01	0.9	SHPO
103	566271	35	M	N	-	Y	0.16	-	-	-	-	-	Y	N	N	-	Y	Y	-	+	-	-	-	170	85	29.41	104	86	18	136	90	98.6	-	-	-	-	90	-	190	76	46	166	3.60	0.96	-
104	561344	31	F	Y	0.41	Y	ND	-	-	-	-	-	Y	N	N	-	N	N	-	+	-	-	-	155	55	22.89	78	82	16	150	90	98.6	-	-	-	-	116	8.2	116	170	32	160	2.80	1.1	-
105	561502	85	M	N	-	Y	6	-	-	-	-	-	Y	N	N	-	Y	Y	-	-	-	-	+	168	86	30.47	106	88	18	106	90	98.6	-	-	-	-	102	-	212	172	24	176	3.60	1.01	-
106	532609	60	M	N	-	Y	8	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	+	166	72	26.18	103	98	20	120	90	98.6	-	-	-	-	106	-	292	168	41	178	4.09	0.96	-
107	566086	72	M	Y	7	N	-	-	-	-	-	-	Y	N	N	-	Y	Y	-	-	+	-	+	178	68	21.46	76	76	16	130	90	98.6	-	-	-	PN	161	8.6	192	160	32	160	2.30	0.92	-
108	566286	65	F	Y	8	Y	7	-	-	-	-	-	Y	N	N	-	N	N	-	-	+	-	-	174	76	25.1	82	78	18	140	90	98.6	-	-	-	PN	120	9.6	190	160	32	166	3.60	1.1	-
109	567818	54	M	N	-	Y	4	-	-	-	-	-	Y	N	N	-	Y	N	-	+	-	-	-	176	72	23.24	80	78	16	130	70	98.6	-	-	-	-	102	-	292	160	26	190	3.60	0.92	-
110	571550	50	M	Y	ND	N	-	-	-	-	-	-	N	N	N	-	Y	Y	+	-	-	-	-	172	72	24.33	86	76	16	130	80	98.6	-	-	-	-	133	6.9	192	160	28	172	4.60	0.93	SHPO
111	572491	66	F	Y	3	N	-	-	-	-	-	-	Y	N	N	-	N	N	+	-	-	-	-	162	58	22.1	78	76	16	120	80	98.6	-	-	-	-	116	7.4	180	190	34	176	2.30	1.1	-
112	561319	50	M	Y	0.5	Y	ND	-	-	-	-	-	N	N	N	-	N	N	+	+	-	-	-	174	88	29.06	105	72	16	180	90	98.6	-	-	-	-	123	8.9	196	190	46	144	5.60	0.6	HPO
113	561236	63	F	N	-	Y	0.41	-	-	-	-	-	Y	N	N	-	N	N	-	+	+	-	-	172	65	21.97	76	76	16	130	80	98.6	-	-	-	-	103	-	200	160	36	190	4.30	0.98	SHPO
114	560933	65	F	Y	7	Y	6	-	-	-	-	-	Y	N	N	-	N	N	-	+	-	-	-	166	67	24.31	84	78	18	126	70	98.6	-	-	-	-	121	9.3	160	160	30	132	3.60	0.96	-
115	947144	47	F	N	-	N	-	-	-	-	-	-	Y	N	N	-	N	N	-	-	-	-	-	160	62	24.2	72	72	16	136	88	98.6	-	-	-	-	111	6.8	258	192	37	148	8.71	1.1	SHPO
116	523680	39	M	N	-	Y	0.25	-	-	-	-	-	Y	N	N	-	Y	N	+	+	-	-	-	176	96	31	103	66	121	160	90	98.6	-	-	-	-	96	-	193	126	37	158	1.22	1.1	-
117	512456	64	M	Y	10	N	-	-	-	-	-	-	Y	N	N	-	Y	Y	+	+	-	-	-	164	70	26.02	96	76	18	100	70	98.6	-	-	-	-	176	9.3	210	39	36	170	0.86	1.44	-