METABOLIC SYNDROME IN HYPOTHYROID PATIENTS

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DECLARATION

I solemnly declare that this dissertation entitled "**METABOLIC SYNDROME IN HYPOTHYROID PATIENTS**" was done by me at Madras Medical College and Government General Hospital, during the academic year 2006-2009 under the guidance and supervision of **Prof.K.RAGHAVAN M.D**. This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine (Branch-I).

Place: Chennai Signature of the candidate

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CERTIFICATE

This is to certify that the dissertation entitled "METABOLIC SYNDROME IN HYPOTHYROID PATIENTS" is a bonafide work done by Dr.K.S.VITHYATHARAN, Postgraduate of Internal Medicine, Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D Degree in General Medicine (Branch-1), under my guidance and supervision during the academic year 2006-2009.

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ABBREVIATIONS

MS	**- Metabolic Syndrome**
BMI	**-Body Mass Index**
WC	**- Waist Circumference**
SBP	**- Systolic Blood Pressure**
DBP	**- Diastolic Blood Pressure**
FBS	**- Fasting Blood Sugar**
TC	**- Total Cholesterol**
HDL	**-High Density Lipoprotein**
TGL	**-Triglycerides**
LDL	**-Low Density Lipoprotein**
HTN	**-Hypertension**
Lp	**- Lipoprotein**
TSH	**- Thyroid Stimulating Hormone**
ATP III	**- Adult Treatment Panel III**
AHA/NHLBI	**- American Heart Association/National Heart, Lung, and Blood Institute**
WHO	**- World Health Organization**
IDF	**-International Diabetic Federation**

INTRODUCTION

Primary hypothyroidism is the condition resulting from the inherent inability of the thyroid gland to supply a sufficient amount of the hormone. Overt hypothyroidism and atherosclerotic cardiovascular disease[1–3] is undoubtedly associated, but there is controversy whether this association is also present in subclinical hypothyroidism[2,4,5]. Most studies in subclinical hypothyroidism show comparable but less pronounced associations[6,7]. The association of thyroid disease with atherosclerotic cardiovascular disease may in part be explained by thyroid hormone's regulation of lipid metabolism and its effect on blood pressure (BP)

Metabolic syndrome also known as Syndrome X[8], Deadly Quartet[9], Insulin resistance Syndrome[10,11] consists of a constellation of metabolic abnormalities like central obesity, atherogenic dyslipidemia (elevated triglycerides and apolipoprotein B, small LDL particles and low HDL cholesterol [HDL-C] concentrations) ,elevated blood pressure, elevated plasma glucose, that confers increased risk of cardiovascular disease (CVD). People with metabolic syndrome are twice as likely to die from and three

times as likely to have a heart attack or stroke compared with people without the syndrome[1].

As hypothyroidism is associated with parameters like obesity[12][13], hypertension[13-17],decreased HDL[18][19] and elevated triglycerides[20][21], it may be associated with metabolic syndrome.

The study done by Aneemieke Ross *et al.* , reveals that free T4 was significantly related to four of five components of the metabolic syndrome (abdominal obesity, triglycerides, high-density lipoprotein cholesterol, and blood pressure), independent of insulin resistance[20]. The study done by Lin ST *et al* found that lower serum free thyroxine level are associated with metabolic syndrome in a Chinese population[22]. In a study from Nepal, Chandra L *et al.* found that metabolic syndrome was prevalent in 21. 1% of thyroid dysfunction patients[23].

Poor drug compliance is common in chronic illness like diabetes, hypertension, dyslipidemia, hypothyroidism etc, irrespective of income and educational status of the patient. The study conducted by Mohan *et al.* among the industrial population of south India which provides free health care, reveals that among subjects receiving medication, only 42.1% of

subjects with diabetes and 55.3% of subjects with hypertension had their disease under adequate control[24]. One of the reason for this may be because most of the people are unaware of the complications arising from inadequate control of disease.

Coronary artery atherosclerosis is twice as common in patients with hypothyroidism compared with sex and age-matched controls, and adequate thyroid hormone replacement therapy may protect against the progression[25]. In South East Asia the prevalence of diabetes, premature coronary artery disease and dyslipidemia are higher than the rest of the world due to rapid changes in demography, economic development[26,27] and partly to genetic predisposition[28-30]. Frankly hypothyroid patients with poor drug compliance, Sub clinical hypothyroidism who are not started on levothyroxine as well as late diagnosis of hypothyroidism may have increased risk of metabolic syndrome. As no information is available from Indian literature regarding the prevalence of metabolic syndrome in hypothyroid patients, this study was undertaken.

AIMS AND OBJECTIVES

1) To study the prevalence of metabolic syndrome in female primary hypothyroidism either frankly hypothyroid patients not taking levothyroxine for more than 3 months, sub clinical hypothyroidism not started on levothyroxine as well as newly detected hypothyroidism not started on levothyroxine.

2) To find out the association of hypothyroidism and Metabolic syndrome.

REVIEW OF LITERATURE

ANATOMY AND DEVELOPMENT OF THYROID GLAND

The thyroid name was derived from Greek (*thyreos*- shield, *eidos*-form). It consists of two lobes that are connected by an isthmus. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch. The normal thyroid is 12–20 g in size . The thyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct to reach its final location in the neck.

THYROID HORMONES

The principal hormones secreted by the thyroid are **thyroxine (T_4)** and **triiodothyronine (T_3)**. T_3 is also formed in the peripheral tissues by deiodination of T_4. Small amounts of reverse triiodothyronine (3,3´,5´-triiodothyronine, RT_3) and other compounds are also found in thyroid. T_3 is more active than T_4, whereas RT_3 is inactive. The thyroid gland maintains the level of metabolism in the tissues that is optimal for their normal function.

MECHANISM OF ACTION

Thyroid hormones enter cells, and T_3 binds to thyroid receptors (TR) in the nuclei. T_4 can also bind, but not as avidly. The hormone-receptor complex then binds to DNA via zinc fingers and increases or in some cases decreases the expression of a variety of different genes that code for enzymes which regulate cell function.

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. Beta subunit is unique to TSH. The thyroid axis is a classic example of an endocrine feedback loop. Thyroid hormones are the dominant regulator of TSH production. TSH levels change dynamically in response to alterations of T_4 and T_3

PRIMARY HYPOTHYROIDISM

Primary hypothyroidism is the condition resulting from the inherent inability of the thyroid gland to supply a sufficient amount of the hormone.

PREVALENCE OF HYPOTHYROIDISM

Overt hypothyroidism affects approximately 3% of the adult female Population[31] . It is estimated that as many as 7% to 10% of older women have subclinical hypothyroidism[7].

CAUSES OF HYPOTHYROIDISM

Hypothyroidism may be 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:

- ^{131}I 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, interferon- alpha 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 131I 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

INFLUENCE OF HYPOTHYROIDISM ON CARDIOVASCULAR FACTORS[32]

Risk Factors	***Effect***	***Evidence***
Lipids	Increased total and LDL cholesterol	A
Blood pressure	Diastolic hypertension	A
Smoking	Impaired thyroid hormone actions	B
Homocysteinemia	Mild increase	A
Endothelium	Endothelial dysfunction	C
CRP	Mild increase in moderate and severe hypothyroidism	C

SYMPTOMS OF HYPOTHYROIDISM

(Descending Order of Frequency)

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

SIGNS

- Dry coarse skin; cool peripheral extremities
- Puffy face, hands, and feet (myxedema)

- Diffuse alopecia
- Bradycardia
- Peripheral edema
- Delayed tendon reflex relaxation
- Carpal tunnel syndrome
- Serous cavity effusions

LABORATORY EVALUATION

a) Measurement of Thyroid Hormones

Because TSH levels change dynamically in response to alterations of T_4 and T_3, a 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 hypothyroidism. Unbound hormone are preferable to those for total thyroid hormones as numerous factors (illness,medications, genetic factors) can influence protein binding.

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.

b) TPO antibodies

TPO antibodies present in >90% of patients with autoimmune hypothyroidism and up to 80% of those with Graves' disease.

c) ***Radioiodine uptake and thyroid scanning***

d) Thyroid Ultrasound

e) Fine-needle aspiration (FNA) biopsy

f) Other abnormal laboratory findings

May include, increased creatine phosphokinase, elevated cholesterol and triglycerides, and anemia (usually normocytic or macrocytic). Except when accompanied by iron deficiency, the anemia and other abnormalities

gradually resolve with thyroxine replacement.

MANAGEMENT

Levothyroxine (thyroxine; T_4) is the treatment of choice. It is partially converted in the body to T_3, the more active thyroid hormone. If there is no residual thyroid function, the daily replacement dose of levothyroxine is usually 1. 6 g/kg body weight (typically 100–150 g). In many patients, however, lower doses suffice until residual thyroid tissue is destroyed. Adult patients under 60 without evidence of heart disease may be started on 50-100g levothyroxine (T_4) daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH, ideally in the lower half of the reference range. TSH responses are gradual and should be measured about 2 months after instituting treatment or after any subsequent change in levothyroxine dosage

SUBCLINICAL HYPOTHYROIDISM

By definition, subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism. It is estimated that as many as 7% to 10% of older women have subclinical hypothyroidism[(7)]. Although

subclinical disease is frequently "asymptomatic," many patients have symptoms of thyroid hormone deficiency[33,34]. Lipid metabolism is altered in subclinical hypothyroidism[4,35]. Patients have increased serum lipid levels, and cholesterol levels appear to rise in parallel with serum TSH.[7,34] Impaired endothelium-dependent vasodilatation as a result of a reduction in nitric oxide availability has been demonstrated in subclinical hypothyroidism as well resulting in hypertension[36].

SUBCLINICAL HYPOTHYROIDISM AND RISK FACTORS[32]

Risk Factors	***Effect***	***Evidence***
Lipids	Mild increased in total and LDL Cholesterol Serum	TSH 4.5–10 mU/L- C
Blood pressure	Mild increase in diastolic pressure	C
Homocysteine	None	B

METABOLIC SYNDROME

The metabolic syndrome also known as (**syndrome X**[8], '**Deadly Quartet'**[9] **insulin resistance Syndrome**[10,11].

Metabolic syndrome consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease (ASCVD) and strongly associated with type 2 diabetes mellitus[37]

EPIDEMIOLOGY

Prevalence of the metabolic syndrome varies across the globe. In general, the Prevalence of metabolic syndrome increases with age. The metabolic syndrome was present in 22.8% and 22.6% of US men and women[37] meeting National Cholesterol Education Program, Adult Treatment Panel III (NCEP:ATPIII) criteria. The metabolic syndrome was present in 4. 6%, 22.4% and 59.6% of normal weight, overweight and obese men respectively and similar distribution found in women[38]. Older age, high body mass index, current smoking, low household income, high carbohydrate diet and physical inactivity were associated with increased risk of Metabolic syndrome.

PREVALENCE OF METABOLIC SYNDROME IN INDIA:

Mohan *et al.* in CURES-34 study found the prevalence of MS was 23. 2% by WHO criteria, 18.3% by ATPIII criteria and 25.8% by IDF criteria[39]. Study done by Ramachandran *et al.* shows prevalence of Metabolic syndrome in urban Asian adults was 41.1% based on modified ATP III Criteria. WC was increased in 31. 4%, TG in 45.6%, low HDL-C in 65.5%, hypertension in 55.4% and raised FPG 26.7%. Metabolic syndrome was more common in women than in men and in older people[40]. Study by Gupta *et al.* revealed the Prevalence (%) of cardiovascular risk factors in men and women, hypertension in 37.0 and 37.6, overweight and obesity in 37.8 and 50.3, truncal obesity in 57.3 and 68.0, high cholesterol $\geq$ 200mg/dl in 37.4 and 45.8, high triglycerides $\geq$150 mg/dl in 32.3 and 28. 6 and metabolic syndrome in 22.9 and 31.6%[41].

"Whichever definition is used and whatever the variation in the numbers due to the different criteria, when looking at prevalence data for the metabolic syndrome in different countries and across various ethnic groups, one fact is clear. Universally, the metabolic syndrome is a huge problem and is one that is growing at an alarming rate". ***Professor Sir George Alberti***, co-author of the Consensus Statement[42]

DIAGNOSIS OF METABOLIC SYNDROME

Although Reaven[8] already highlighted the concepts of insulin resistance and the metabolic syndrome in 1988, it lasted until 1998[42] before the first attempt for an internationally accepted definition was put forward.

WHO CLINICAL CRITERIA FOR METABOLIC SYNDROME[43]

Glucose intolerance, impaired glucose tolerance (IGT) or diabetes and/or insulin resistance, together with two or more of the following components:

- Central obesity (males: waist to hip ratio > 0. 90; females: waist to hip ratio >0. 85) and/or BMI > 30 kg/m^2
- Raised plasma triglycerides (≥ 1.7 mmol/L; 150 mg/dL) and/or low HDL cholesterol (< 0.9 mmol/L, 35 mg/dL men; < 1.0 mmol/L, 39 mg/dL women)
- Raised Blood pressure ≥ 140/90 mm Hg
- Microalbuminuria (urinary albumin excretion rate ≥ 20g/min or albumin:creatinine ratio ≥ 30 mg/g)

ATP III CRITERIA FOR METABOLIC SYNDROME [44]

Three or more of the following five risk factors:

- Central obesity: Waist circumference for men > 102 cm (> 40 in)Women > 88 cm (>35 in)
- Triglycerides ≥ 150 mg/dL (1.7 mmol/L)
- HDL cholesterol
  Men < 40 mg/dL (1.03 mmol/L)
  Women < 50 mg/dL (1.29 mmol/L)
- Blood pressure ≥ 135/ ≥ 85 mm Hg
- Fasting glucose ≥ 6.1 mmol/L

AHA/NHLBI CRITERIA FOR METABOLIC SYNDROME 2005[37]

Three or more of the following five risk factors:

- Central obesity: Waist circumference for men > 102 cm (>40in)
  Women > 88cm (> 35 in)

-Modified WC for South Asians- Male ≥ 90 cm, Female ≥ 80 cms

- Triglycerides ≥ 150 mg/dL (1. 7 mmol/L)
- HDL cholesterol

  Men < 40 mg/dL (1. 03 mmol/L)

  Women < 50 mg/dL (1. 29 mmol/L)

- Blood pressure ≥ 130/ ≥ 85 mm Hg
- Fasting glucose ≥ 100 mg/dl

THE NEW INTERNATIONAL DIABETES FEDERATION(IDF) DEFINITION[42]

Central obesity *defined as the waist circumference for* South Asians:

Male ≥ 90 cms Female ≥ 80 cms

Plus any two of the following four factors:

- ***Raised TG level:*** ≥ 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- ***Reduced HDL cholesterol:*** <40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality.
- ***Raised blood pressure***: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
- ***Raised fasting plasma glucose*** (FPG) ≥ 100 mg/dL (5. 6 mmol/L), or previously diagnosed type 2 diabetes

PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME

The central pathophysiological phenomenon underlying the clustering is Insulin Resistance[45]. Major contributor to the development of insulin resistance is an overabundance of circulating fatty acids derived

predominantly from adipose tissue triglyceride stores released by hormone-sensitive lipase. Fatty acids are also derived through the lipolysis of triglyceride-rich lipoproteins in tissues by lipoprotein lipase (LPL). Insulin mediates both antilipolysis and the stimulation of LPL in adipose tissue

INCREASED WAIST CIRCUMFERENCE

With increases in visceral adipose tissue, adipose tissue-derived FFAs are directed to the liver. On the other hand, increases in abdominal subcutaneous fat release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism.

DYSLIPIDEMIA

FFA flux to the liver is associated with increased production of apoB–containing, triglyceride- rich very low density lipoproteins (VLDLs). Hypertriglyceridemia is an excellent marker of the insulin-resistant condition. Reduction of HDL cholesterol is a consequence of changes in HDL composition and metabolism. In the presence of hypertriglyceridemia decrease in the cholesterol content of HDL is a consequence of reduced cholesteryl ester content of the lipoprotein core in combination with cholesteryl ester transfer protein–mediated alterations in triglyceride making the particle small and dense. This change in lipoprotein

composition also results in an increased clearance of HDL from the circulation.

HYPERTENSION

In the setting of insulin resistance, the vasodilatory effect of insulin is lost, but the renal effect on sodium reabsorption is preserved. Insulin also increases the activity of the sympathetic nervous system, an effect that may also be preserved in the setting of the insulin resistance. Finally, insulin resistance is characterized by pathway-specific impairment in phosphatidylinositol 3-kinase signaling. In the endothelium, this may cause an imbalance between the production of nitric oxide and secretion of endothelin-1, leading to decreased blood flow.

GLUCOSE INTOLERANCE

The defects in insulin action lead to impaired suppression of glucose production by the liver and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues, i.e., muscle and adipose tissue. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified to sustain euglycemia. Ultimately, this compensatory mechanism fails and progress from IFG and/or IGT to DM.

PROINFLAMMATORY CYTOKINES

The increases in proinflammatory cytokines, including IL-1,IL-6,IL-18, tumor necrosis factor (TNF alpha) and C-reactive protein (CRP), reflect overproduction by the expanded adipose tissue mass . Adipose tissue-derived macrophages may be the primary source of pro-inflammatory cytokines. FFAs also increase the hepatic production of fibrinogen and adipocyte production of plasminogen activator inhibitor 1 (PAI-1), resulting in a prothrombotic state. Higher levels of circulating cytokines also stimulate the hepatic production of C-reactive protein (CRP)

ADIPONECTIN

Adiponectin is an anti-inflammatory cytokine produced exclusively by adipocytes. It enhances insulin sensitivity and inhibits many steps in the inflammatory process. In the liver, adiponectin inhibits the expression of gluconeogenic enzymes and the rate of glucose production. In muscle, adiponectin increases glucose transport and enhances fatty acid oxidation, partially due to activation of AMP kinase. Adiponectin is reduced in the metabolic syndrome .

MANAGEMENT OF METABOLIC SYNDROME[37,42,]

- ***Primary intervention***

  Healthy lifestyle promotion which includes:

  - Moderate calorie restriction (to achieve a 5–10 per cent loss of body weight in the first year)
  - Moderate increase in physical activity
  - Change in dietary composition

- ***Secondary intervention***

In people for whom lifestyle change is not enough and who are considered to be at high risk for CVD, drug therapy may be required to treat the metabolic syndrome. While mechanisms underlying metabolic syndrome are currently unknown and specific pharmacological agents are therefore not yet available, it is currently recommended to treat the individual components of the syndrome in order to reduce the CVD and diabetes risk.

Selective CBI-receptor blockade drugs like Rimonabant significantly reduces the several metabolic risk factors in metabolic syndrome[46,47]

HYPOTHYROIDISM AND OBESITY

Thyroid function could be one of several factors acting in concert to determine body weight in a population. In a study of elderly subjects, a possible association between mild hypothyroidism and BMI was found among women[48]. Even slightly elevated serum TSH levels are associated with an increase in the occurrence of obesity[12]. Leptin produced by adipocytes has important influences on central regulation of thyroid function through stimulation of TRH. This seems to be important for down-regulation of thyroid function in states of energy deficits . Leptin levels are decreased in the hypothyroid patients. Whether decreased leptin levels may contribute to the decreased energy expenditure in patients with hypothyroidism merits further investigation[49-52]. It has been suggested that thyroid hormones may be a significant determinant of sleeping energy expenditure also in subjects without overt thyroid dysfunction[53]. Prolonged decrease in REE might well lead to increased body weight in he current environment of food plenty and physical inactivity.

HYPOTHYROIDISM AND DYSLIPIDEMIA

Even in the euthyroid range, TSH was positively associated with HDL-C, TG, and Apo A-I[20]. The elevation of TGs in hypothyroidism is caused by a reduced removal rate of TG from plasma due to a decrease in the activity of hepatic TG lipase[54]. Some studies have shown that hypothyroidism is associated with a lower HDL cholesterol level. Althaus *et al*[55],Caron *et al*[56] found a significantly lower HDL cholesterol fraction even in the subclinically hypothyroid patients. Furthermore, Caron *et al.* observed a significant increase in the HDL cholesterol level with T4 therapy, which normalized the serum TSH concentration.

Elevated levels of total cholesterol, LDL cholesterol, and apolipoprotein are well documented features of overt hypothyroidism [57,58]. Early studies in humans with hypothyroidism, using isotopically labeled LDL,demonstrated a prolonged half-life of LDL cholesterol because of decreased catabolism, an effect that was reversible with T4 therapy[59]. T4 therapy in overt hypothyroidism is standard practice, controversy exists regarding the indications for therapy in subclinical hypothyroidism. One rationale for treating subclinical hypothyroidism is to lower levels of LDL cholesterol and thereby decrease atherosclerotic risk. Multiple small,

randomized trials have been performed examining the effect of T4 treatment on lipid parameters in subclinical hypothyroidism, with the majority reporting a tendency toward beneficial effects, without achieving statistical significance[60]. Studies have also shown that hypothyroidism causes qualitative changes in circulating lipoproteins that increase their atherogenicity. Two studies have shown that LDL is more susceptible to oxidation in patients with hypothyroidism, with normalization after restoration of the euthyroid state[61,62]. Several studies have shown decreases in the Lp(a) concentration after T4 treatment of hypothyroid patients[63-66]. However, other reports have not confirmed this relationship[67,68]. Clinical trials have not demonstrated an effect of T4 on Lp(a) levels in subclinical hypothyroidism[66-70], with the exception of one trial, which showed a decrease in Lp(a)[71]. Additional potentially atherogenic effects of hypothyroidism on lipid metabolism include a reversible reduction in clearance of chylomicron remnants[72]; reduced activity of cholesteryl ester transfer protein, which is involved in reverse cholesterol transport pathway [73,74]; and decreased activity of hepatic lipase[75,76] and lipoprotein lipase[75].

HYPOTHYROIDISM AND HYPERTENSION

Potential mechanisms for reversible diastolic and systolic

hypertension in hypothyroidism include increases in peripheral vascular resistance and arterial stiffness[77] respectively. In hypothyroidism, arterial compliance is reduced, which leads to increased SVR. In hypothyroidism, endothelial dysfunction and impaired VSM relaxation lead to increased SVR[78]. These effects lead to diastolic hypertension in approximately 30% of patients, and thyroid hormone replacement therapy restores endothelial-derived vasorelaxation and blood pressure to normal in most[36]. Vasoconstriction may, in turn, reflect the absence of demonstrated vasodilatory T3 effects on vascular smooth muscle[79] or be the result of a higher circulating noradrenaline level and a decrease in the number of vascular beta adrenergic receptors mediating vasodilatation in skeletal muscle[16]. In addition, type II iodothyronine deiodinase has been found in cultured human coronary artery smooth muscle cells and human aortic smooth muscle cells, suggesting a potential direct role of local T3 on vascular smooth muscle[1,80]. The increase in diastolic pressure occurs with low serum renin levels[81]and is a sodium sensitive form of hypertension[82]. Asvold *et al.* report a linear correlation between TSH and both systolic and diastolic blood pressure[14], whereas other studies do not find a correlation[17,31,83]. In one study of 169 women with overt hypothyroidism,

the prevalence of hypertension was nearly 3 times higher than in a euthyroid control group(14.8% *vs.* 5.5%)[16]. Euthyroid normotensive patients in another report had an increase in diastolic blood pressure after thyroidectomy-induced hypothyroidism[5], and hypertension was reversed by T4 treatment. There is less published evidence regarding subclinical hypothyroidism and hypertension. Luboshitzky *et al.* did observe that mean diastolic blood pressure was higher in subclinical hypothyroidism[84]. Impaired endothelium-dependent vasodilatation as a result of a reduction in nitric oxide availability has been demonstrated in subclinical hypothyroidism as well[36].

HYPOTHYROIDISM AND DIABETES

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[85]. Aneemieke Ross *et al.* 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)[20].

MATERIAL AND METHODS

Setting

The study was conducted in the Endocrinology OPD, Department of Endocrinology, Institute of Internal Medicine, Madras Medical College and Government General Hospital, Chennai.

Collaboration Department

Endocrinology OPD, Institute of Internal Medicine.

Ethical Approval

Institute Ethical Committee approved the study.

Study Design

Single Centre

Non randomized cross sectional study.

Study Period

Study was conducted between December 2007 and September 2008 for a period of 10 months.

Sample Sizes

In the study period of 10 months female hypothyroid patients attending the Endocrinology OPD,Institute of Internal Medicine after applying inclusion and exclusion criteria, 55 patients were included in the study.

Selection of Study Subjects

The female primary hypothyroid patient in the age group of 21-55 were eligible for the study. Clinically hypothyroid patient with poor drug compliance who had discontinued levothyroxine for the period of over 3 months, Subclinical hypothyroidism not started on levothyroxine as well as newly diagnosed hypothyroidism not started on levothyroxine were taken into study. It is confirmed that they had not taken levothyroxine for 3 months by detail history.

Inclusion Criteria

- Female Sex.
- Age group between 21-55 years.
- Clinically hypothyroid patient who had discontinued Levothyroxine for period of over 3 months.

- Newly detected hypothyroidism who had not started on levothyroxine.
- Subclinical hypothyroidism not started on Levothyroxine.
- Non Smokers,Non alcoholic.

Exclusion Criteria

- Male sex, pregnant women.
- Age below 21 years or above 55 years.
- Smoker, Alcoholic.
- Primary hypothyroid patient taking levothyroxine < 3 months.
- Severely ill patient.
- Patient taking medication for Diabetes, Hypertension, lipid disorder .
- Patient taking steroids.
- Known metabolic syndrome patients.

Consent

- All participants gave written informed consent.

METHODOLOGY

Detailed history including medication, smoking, alcohol intake

anthropometric measurements like height, weight, waist circumference were noted in a semi structured proforma. Thyroid hormone assay was performed. It was confirmed that they had not taken levothyroxine for the previous 3 months. Waist circumference was measured keeping tape in a horizontal plane around the abdomen at level of iliac crest. Blood Pressure was recorded in sitting position in the right arm, with a mercury sphygmomanometer (Diamond BP apparatus, Pune, India). After eight hours of fasting, blood was drawn for fasting blood sugar lipid profile in a single sitting.

The fasting blood sugar was done by enzymatic method(Glucose Oxidase peroxidase) using fully automated analyzer. The lipid profile(Total cholesterol,HDL,Triglycerides) was done enzymatically on XL-300 ERBA fully automated clinical chemistry analyzer. LDL was calculated by the formula,

LDL=Total Cholesterol-HDL-(Triglceride/5)

Thyroid hormone assay was done by Radio Immuno Assay(RIA) or Indirect Radio Immunoassay(IRMA) using ADVIA centaur Bayer Health care.

DEFINITIONS

Primary Hypothyroidism:

Inherent inability of the thyroid gland to supply a sufficient amount of the hormone most commonly due to the destruction of the thyroid gland by disease or as a consequence of vigorous ablative therapies.

Clinical or overt Hypothyroidism:

Patient with few or apparent clinical features of hypothyroidism with biochemical evidence of thyroid hormone deficiency

Subclinical Hypothyroidism:

Patients who have few or no apparent clinical features of hypothyroidism with biochemical evidence of thyroid hormone deficiency.

Thyroid function tests-Normal values:

Serum T3(Total) = 0. 7-2.0 ng/ ml

Serum T4(Total) = 5. 5-13. 5 µg/dl

Serum TSH = 0. 17-4. 05 uIU/ml

THE NEW INTERNATIONAL DIABETES FEDERATION (IDF) DEFINITION[42]

***Central obesity defined as the wiast circumference for* South Asians:**

Male ≥ 90 cms Female ≥ 80 cms

Plus any two of the following four factors:

- Raised TG level: ≥150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females, or specific treatment for this lipid abnormality
- Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes

AHA/NHLBI CRITERIA FOR METABOLIC SYNDROME [37]

Three or more of the following five risk factors:

- Central obesity: Waist circumference for men > 102 cm (> 40 in)Women > 88 cm (> 35 in) Modified WC for south asians- Male ≥ 90 cm, Female ≥ 80 cms
- Triglycerides ≥ 150 mg/dL (1. 7 mmol/L)

- HDL cholesterol

  Men < 40 mg/dL (1.03 mmol/L)

  Women < 50 mg/dL (1.29 mmol/L)

- Blood pressure ≥ 130/ ≥ 85 mm Hg

- Fasting glucose ≥ 100 mg/dl

STATISTICAL ANALYSIS

SPSS12 and Excel were used for data analysis.

LIMITATIONS

- Small number of study subjects.
- No control subjects
- Cross sectional study

CONFLICT OF INTEREST

- Nil conflict of interest

RESULTS AND OBSERVATION

TABLE-1 POPULATION CHARACTERISTICS

TOTAL NO OF PATIENTS: 55

AGE	*NO OF PATIENTS*	*PERCENTAGE(%)*
<30	**14**	**25. 45**
30-40	**20**	**36. 36**
>40	**21**	**38. 18**

P value > 0. 05 Not significant at 5% level

POPULATION CHARACTERISTICS:

55 Patients were included in our study in the age group between 21 and 55. Patient below 30 were 14 (25.45%) in number. Majority of the patients were above 40 age group and constitutes 38.18% (21 in number). 20 patients were between 30-40 (36.36%). Population characteristics are shown in Table 1. Distribution was statistically not significant

TABLE -2 DISTRIBUTION OF HYPOTHYROID PATIENTS

TOTAL NO OF PATIENTS: 55

HYPOTHYROID	***TOTAL NO***	***PERCENTAGE (%)***
Newly detected Clinical 8 Subclinical 8	16	29. 09
Clinical hypothyroidism not on levothyroxine > 3 Months	23	41. 82
Subclinical hypothyroidism not on levothyroxine	16	29. 09

P value > 0. 05 Not significant at 5% level

Among the 55 patient included in our study, 16 patients(29.09%) were newly detected primary hypothyroid. In newly detected patients, 8 patients had clinical hypothyroidism while 8 were subclinical hypothyroidism.

Clinically hypothyroid patient who had not taken levothyroxine >3months were majority with 23(41.82%) in number. Sub clinical hypothyroidism not on levothyroxine constituted the rest with 16 in number 29.09%. They are statistically not significant (>0.05%) at 5% level.

PREVALENCE OF METABOLIC SYNDROME

TABLE-3 METABOLIC SYNDROME AS PER AHA/NHLBI 2005 CRITERIA

FACTORS	*NO OF PATIENTS*	*PERCENTAGE(%)*
≥ **3**	**27**	**49. 09**
<3	**28**	**50. 91**

P value > 0. 05 Not significant at 5% lev**el**

Among 55 patients 27 patients were diagnosed to have metabolic syndrome(≥ 3 parameters). They constitute 49. 09% of the study population.

TABLE-4 METABOLIC SYNDROME AS PER IDF CRITERIA

METABOLIC SYNDROME	*NO OF PATIENTS*	*PERCENTAGE(%)*
PRESENT	**22**	**40**
ABSENT	**33**	**60**

P value > 0. 05 Not significant at 5% level

Among 55 patients 22 patients were diagnosed to have metabolic syndrome(central obesity plus any 2 of the 4 parameters). They constituted 40% of the study population.

TABLE - 5 DISTRIBUTION OF METABOLIC SYNDROME IN HYPOTHYROID PATIENTS:

TOTAL NO OF PATIENTS: 55

HYPOTHYROID PATIENTS	***NO OF METABOLIC SYNDROME PATIENTS AS PER AHA/NHLBI 2005 CRITERIA n-27***	***NO OF METABOLIC SYNDROME PATIENTS AS PER IDF CRITERIA n-22***
Newly detected n-16	7(43. 75%)	5(31. 25%)
Subclinical hypothyroidism not on levothyroxine n-16	10(62. 5%)	9 (56. 25%)
Clinical hypothyroidism not on levothyroxine > 3 Months n-23	10(43. 48%)	8 (34. 78%)

P value > 0. 05 Not significant at 5% level

62.5% and 56. 5%of the total Sub clinical hypothyroid patients not on levothyroxine had Metabolic syndrome as per AHA/NHABI criteria and IDF criteria respectively.

There was no statistically significant increase of Metabolic syndrome in one group in our study.

TABLE- 6 AGE DISTRIBUTION OF METABOLIC SYNDROME

AGE	***NO OF METABOLIC SYNDROME PATIENTS AS PER AHA/NHLBI 2005 CRITERIA***	***NO OF METABOLIC SYNDROME PATIENTS AS PER IDF CRITERIA***
<30	**4**	**2**
30-40	**6**	**6**
>40	**17**	**14**

s P = 0. 01 Significant at 5% level

Above 40 yrs Metabolic syndrome was diagnosed in 17 patients which constitutes 80.95% (AHA/NHLBI 2005 criteria) and in 14 patients which constitutes 66.66% (IDF criteria). Below 30 age group only 4 patients as per AHA/NHLBI 2005 criteria (28.57%) and 2 patient(14.26%)as per IDF criteria.

The prevalence increased with age and was statistically significant.

OBESITY IN HYPOTHYROIDISM

TABLE-7 WAIST CIRCUMFERENCE IN HYPOTHYROIDISM

WAIST CIRCUMFERENCE in cms	*TOTAL NO OF PATIENTS*	*PERCENTAGE(%)*
≥ **80**	**24**	**43. 64**
<80	**31**	**56. 36**

P value > 0.05 Not significant at 5% level

43. 64% of the study group was having central obesity.

TABLE-8 BODY MASS INDEX IN HYPOTHYROIDISM

BMI in Kg/m²	*TOTAL NO OF PATIENTS*	*PERCENTAGE(%)*
NORMAL <23	**14**	**25. 45**
OVERWEIGHT 23-24. 9	**7**	**12. 73**
OBESE ≥ 25	**34**	**61. 82**

P =0. 001 Significant at 5% level

Majority of the patient were obese with 61.82% with BMI ≥ 25. Over weight patient with BM1 (23-24.9) were 7 in number.

DYSLIPIDEMIA IN HYPOTHYROIDISM

TABLE- 9 TRIGLYCERIDE IN HYPOTHYROIDISM

TRIGLYCERIDE in mgs	*TOTAL NO OF PATIENTS*	*PERCENTAGE (%)*
≥ **150**	**33**	**60**
<150	**22**	**40**

P value > 0. 05 Not significant at 5% level

Nearly 60% of the study group were affected by hypertriglyceridemia (TG ≥ 150mgs).

TABLE -10 HDL IN HYPOTHYROIDISM

HDL in mgs	*TOTAL NO OF PATIENTS*	*PERCENTAGE(%)*
<50	**49**	**89. 09**
≥ **50**	**6**	**10. 91**

P value < 0. 001 Significant at 5% level

The most prevalent lipid abnormalities was reduced HDL (<50 mgs)

with 89.09% of the study group affected. 49 patients out of 55 patients are affected by this abnormality.

TABLE -11 TOTAL CHOLESTEROL IN HYPOTHYROIDISM

TOTAL CHOLESTEROL in mgs	***TOTAL NO OF PATIENTS***	***PERCENTAGE (%)***
≥ **200**	**30**	**54.55**
<200	**25**	**45.45**

P value > 0.05 Not significant at 5% level

Elevated cholesterol (≥ 200mgs) was seen in 54.55% of the study group.

TABLE - 12 LDL IN HYPOTHYROIDISM

LDL in mgs	***TOTAL NO OF PATIENTS***	***PERCENTAGE(%)***
≥ **130**	**24**	**43. 64**
<130	**31**	**56. 36**

P value > 0.05 Not significant at 5% level

Elevated LDL ≥ 130mgs was seen in 43. 64% of the study group.

HYPERTENSION IN HYPOTHYROIDISM

TABLE–13 SYSTOLIC BLOOD PRESSURE IN HYPOTHYROIDISM

SBP in mm of Hg	***TOTAL NO OF PATIENTS***	***PERCENTAGE(%)***
≥ **130**	**18**	**32. 73**
<130	**37**	**67. 27**

P=0. 01 Significant at 5% level

TABLE-14 DIASTOLIC BLOOD PRESSURE IN HYPOTHYROIDISM

DBP in mm of Hg	***TOTAL NO OF PATIENTS***	***PERCENTAGE(%)***
≥ **85**	**18**	**32. 73**
<85	**37**	**67. 27**

P=0. 01 Significant at 5% level

Both systolic and diastolic hypertension was seen in 32. 73% of the study group.

TABLE- 15 IMPAIRED GLUCOSE TOLERANCE IN HYPOTHYROIDISM

FBS in mgs	***TOTAL NO OF PATIENTS***	***PERCENTAGE(%)***
≥ **100**	**26**	**47. 27**
<100	**29**	**52. 73**

P value > 0. 05 Not significant at 5% level

Impaired glucose tolerance with fasting plasma glucose ≥ 100mgs was seen in 47. 27% of the study group.

TABLE-16 DISTRIBUTION OF METABOLIC SYNDROME PARAMETERS (AS PER AHA/NHLBI 2005 CRITERIA) IN HYPOTHYROIDISM

MS PARAMETERS	***METABOLIC SYNDROME***		***NO METABOLIC SYNDROME***		***P VALUE***
	MEAN	*SD*	*MEAN*	*SD*	
WAIST	88. 44	8. 82	74. 61	6. 01	0. 001
TG	260. 44	129. 60	137. 75	66. 73	0. 001
HDL	40. 52	4. 53	44. 86	10. 12	0. 046
SBP	130. 44	9. 91	118. 29	7. 79	0. 001
DBP	84. 44	7. 07	76. 79	4. 50	0. 001
FBG	116. 37	28. 99	91. 50	10. 81	0. 001
BMI	28. 76	4. 20	23. 56	3. 37	0. 001
TC	235. 74	53. 14	191. 46	47. 58	0. 002
LDL	143. 13	50. 88	119. 06	46. 80	0. 07

TABLE- 17 DISTRIBUTION OF METABOLIC SYNDROME PARAMETERS (AS PER IDF CRITERIA) IN HYPOTHYROIDISM

MS PARAMETERS	***METABOLIC SYNDROME***		***NO METABOLIC SYNDROME***		***P VALUE***
	MEAN	SD	MEAN	SD	
WAIST	91. 50	6. 32	74. 67	5. 74	0. 001
TG	276. 73	138. 39	145. 48	64. 78	0. 001
HDL	40. 59	4. 04	44. 15	9. 75	0. 112
SBP	132. 45	9. 19	118. 79	7. 87	0. 001
DBP	85. 55	6. 87	77. 21	4. 82	0. 001
FBG	118. 05	31. 84	94. 15	12. 09	0. 001
BMI	29. 77	3. 79	23. 67	3. 29	0. 001
TC	239. 23	55. 37	195. 85	47. 52	0. 003
LDL	143. 29	53. 72	122. 60	46. 14	0. 113

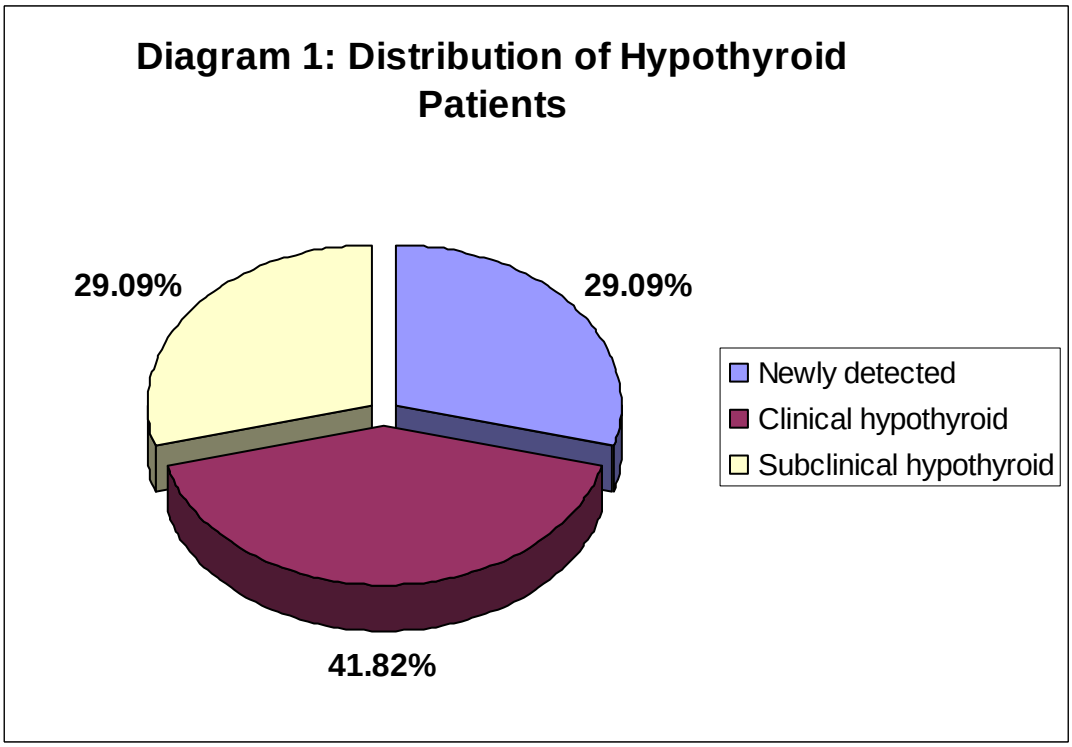
Diagram 1: Distribution of Hypothyroid Patients
29.09%
29.09%
41.82%
Newly detected
Clinical hypothyroid
Subclinical hypothyroid

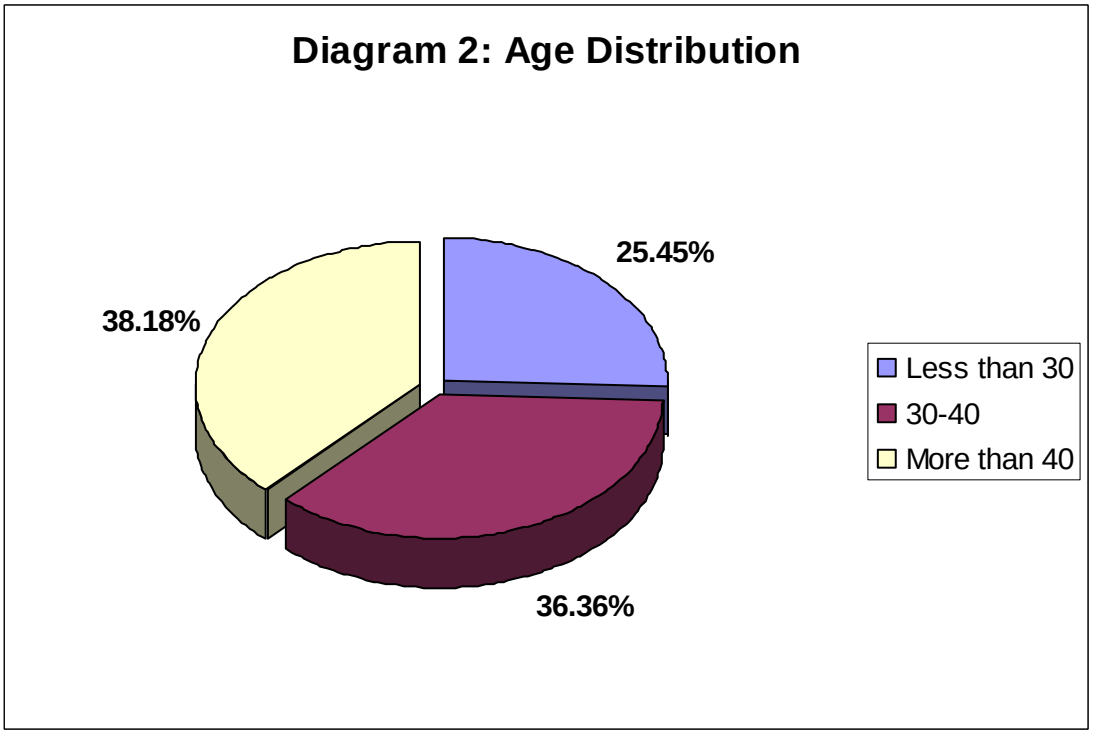
Diagram 2: Age Distribution
25.45%
38.18%
36.36%
Less than 30
30-40
More than 40

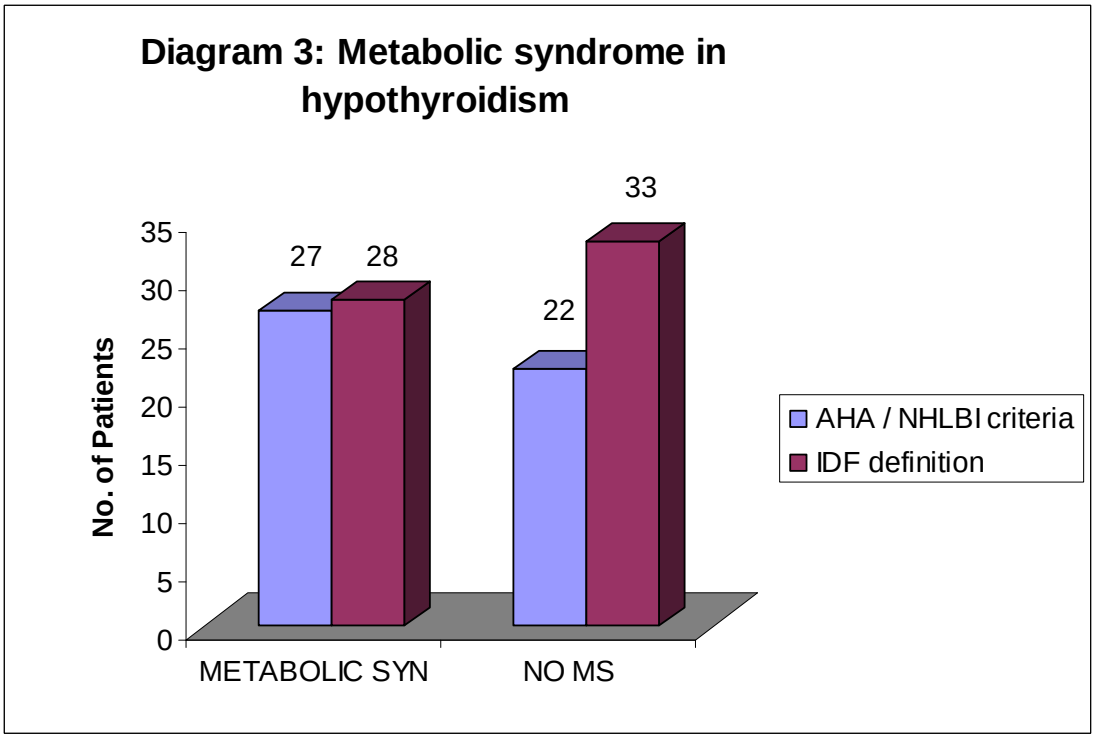
Diagram 3: Metabolic syndrome in hypothyroidism
No. of Patients
35
30
25
20
15
10
5
0
27
28
22
33
METABOLIC SYN
NO MS
AHA / NHLBI criteria
IDF definition

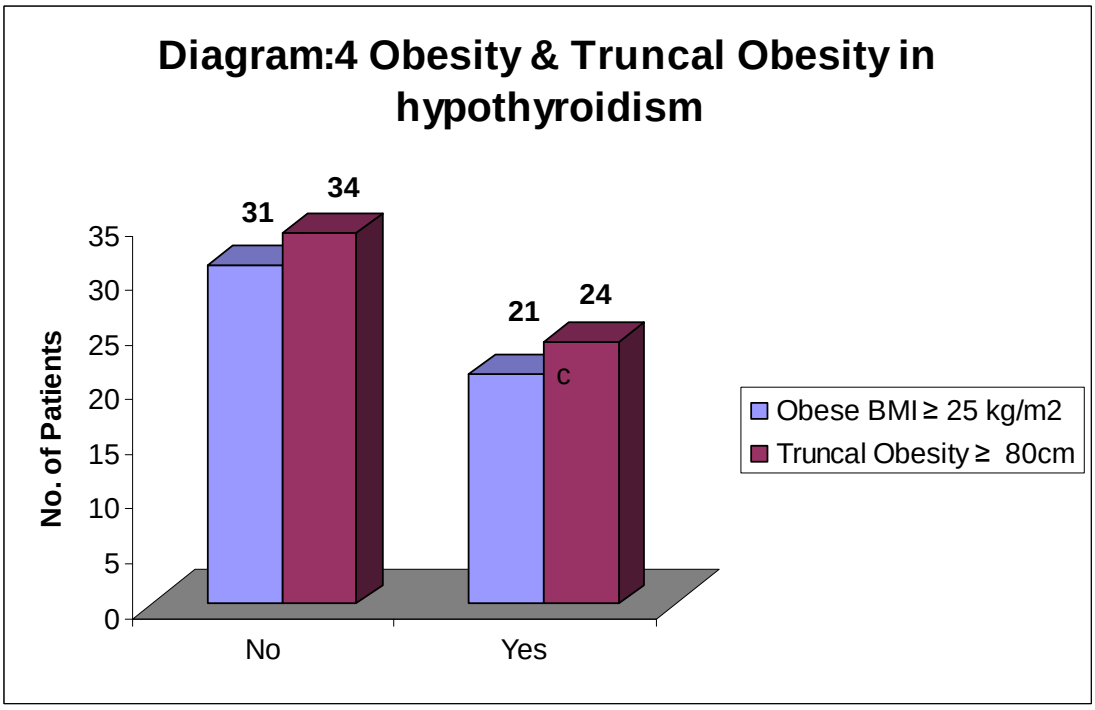
Diagram:4 Obesity & Truncal Obesity in hypothyroidism
No. of Patients
35
30
25
20
15
10
5
0
31
34
21
24
c
No
Yes
Obese BMI ≥ 25 kg/m2
Truncal Obesity ≥ 80cm

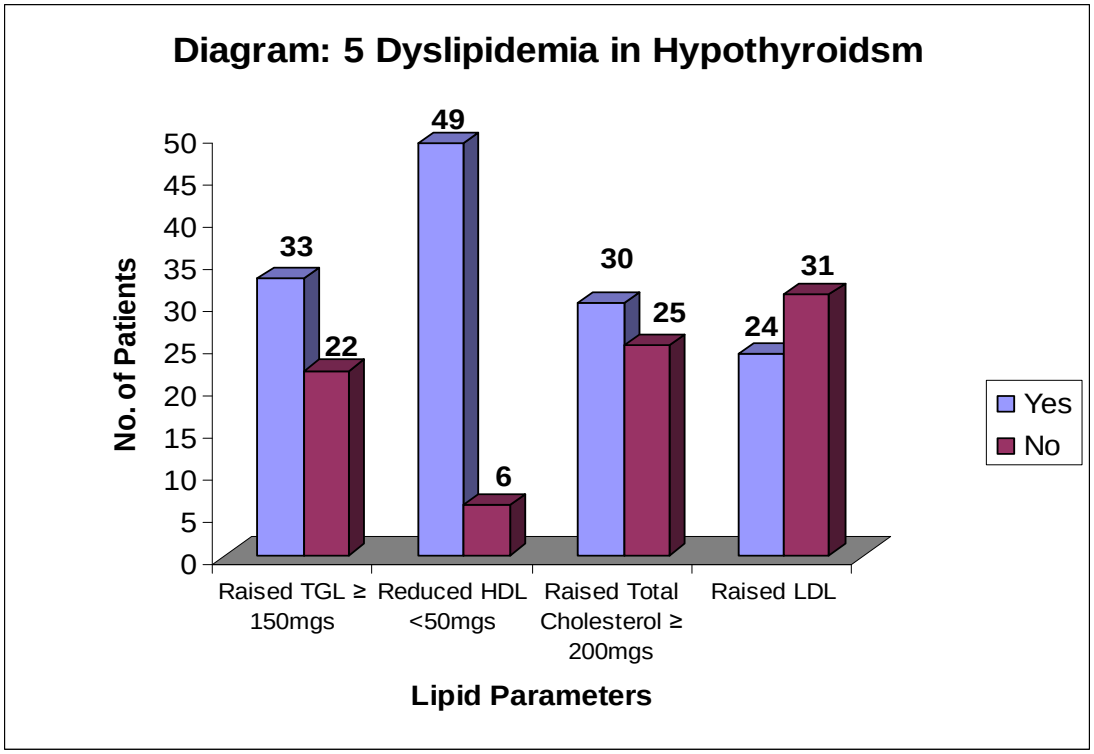
Diagram: 5 Dyslipidemia in Hypothyroidsm
No. of Patients
50
45
40
35
30
25
20
15
10
5
0
33
22
49
6
30
25
24
31
Raised TGL ≥ 150mgs
Reduced HDL <50mgs
Raised Total Cholesterol ≥ 200mgs
Raised LDL
Lipid Parameters
Yes
No

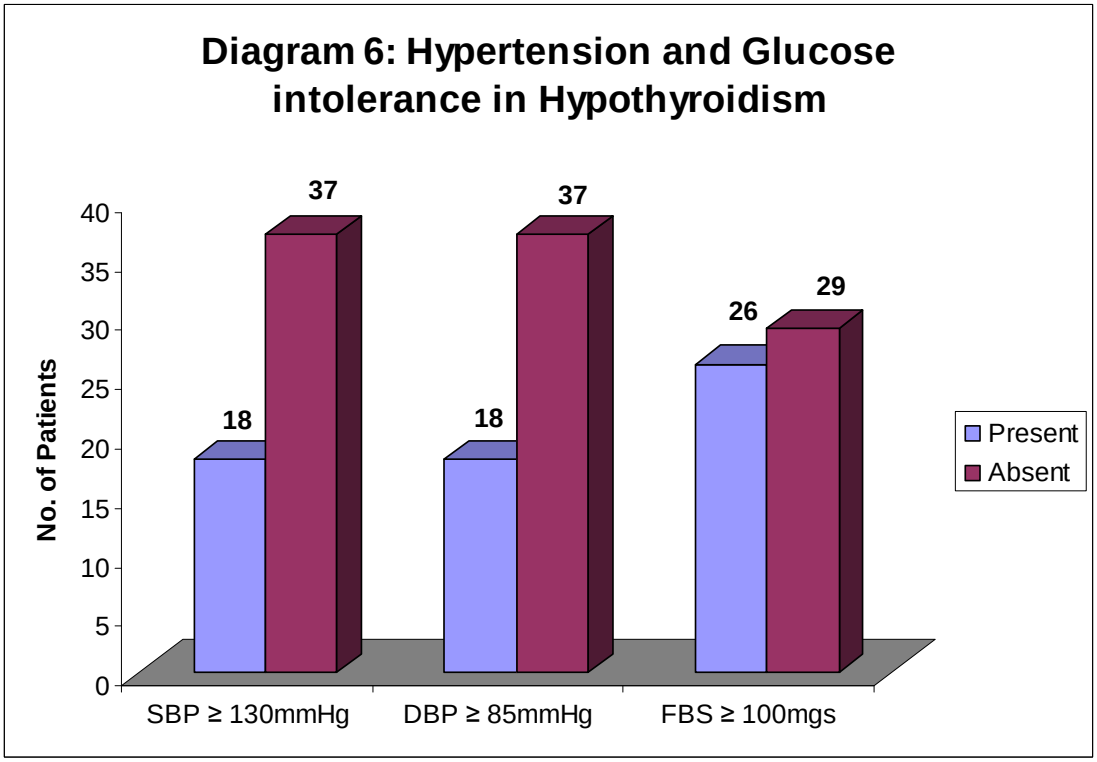
Diagram 6: Hypertension and Glucose intolerance in Hypothyroidism
No. of Patients
40
35
30
25
20
15
10
5
0
18
37
18
37
26
29
SBP ≥ 130mmHg
DBP ≥ 85mmHg
FBS ≥ 100mgs
Present
Absent

DISCUSSION

Overt hypothyroidism affects approximately 3% of the adult female Population. It is estimated that as many as 7% to 10% of older women have subclinical hypothyroidism [(7)]. The prevalence of hypothyroidism increases with age. As early as 1883, Kocher raised the hypothesis of a causal relationship between hypothyroidism and atherosclerosis [(86)].

Metabolic syndrome consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of atherosclerotic cardiovascular disease. The metabolic risk factors consist of atherogenic dyslipidemia (elevated triglycerides and apolipoprotein B, small LDL particles and low HDL cholesterol [HDL-C] concentrations), elevated blood pressure and elevated plasma glucose. The prevalence of metabolic syndrome is estimated to be around 20–25 per cent of the population. The prevalence of metabolic syndrome increases with the age.

As hypothyroidism is associated with parameters like obesity[(12)(13)], hypertension[(13)(15-17)], decreased HDL[(18)(19)], elevated triglycerides[(20)(21)], frankly hypothyroid patients with poor drug compliance, subclinical

hypothyroidism not on levothyroxine, late diagnosis of hypothyroidism may have increased risk of metabolic syndrome.

Enas *et al.*[87] in his study found that South Asians develop metabolic abnormalities at a lower body mass index and waist circumference than other groups, conventional criteria underestimate the prevalence of MS by 25% to 50%. South Asian-specific waist circumference recommended by the International Diabetes Federation appear to be more appropriate in this Population. So in our study waist circumference was adjusted to the south Asians.

In our study 22 patients (40%) and 27 patients(49.09%) of the study group were diagnosed to have metabolic syndrome as per IDF criteria (Waist circumference adjusted to the south Asians) and AHA/NHLBI 2005 criteria(Waist circumference adjusted to the south Asians)respectively. High prevalence of Metabolic syndrome was noted in clinically hypothyroid patient with poor drug compliance, subclinical hypothyroidism not started on levothyroxine as well as newly diagnosed hypothyroid patient. There was no statistically significant difference in prevalence of metabolic syndrome between the three groups. It reveals that all the groups were affected equally.

Metabolic syndrome was higher in study group than in the general population of this region. Mohan *et al.* in his CURES-34 study identified Metabolic syndrome in 23.2% by WHO criteria,18.3% by ATPIII criteria and 25.8% by IDF criteria in this region[88]. Study by Mohan *et al.* in industrial Population found Metabolic syndrome in 34.1% using modified ATPIII criteria[24]. Ramachandran *et al.* showed that the prevalence of Metabolic syndrome in Urban Asian adults was 41.1% using modified ATPIII criteria[40].

It is consistent with the study done by Aneemieke Ross *et al*[20] who reveals that free T4 was significantly associated with insulin resistance and with four out of five components of the metabolic syndrome (except glucose intolerance). The association of lower serum free thyroxine with metabolic syndrome is also proved by Lin SY *et al.* in chinese population[22].

The prevalence of the Metabolic syndrome increases as age advances. Above 40 yrs, 80.95% and 66.66% were Metabolic syndrome based on AHA/NHLBI (2005) criteria & IDF criteria respectively which was higher compared to the individuals below 30 (28.57% & 14.26% based on AHA/NHLBI (2005) criteria & IDF criteria respectively).

Truncal obesity, elevated triglycerides, decreased HDL, hypertension and glucose intolerance were present in 43. 64%, 60%, 89.09%, 32.73% and 47.27% of the study group respectively. Metabolic syndrome parameters were increased in study group than the general population.

Thyroid function could be one of several factors influencing the body weight in a population. Even slightly elevated serum TSH levels are associated with an increase in the occurrence of obesity [(12)]. Leptin levels are decreased in the hypothyroid patients. Whether decreased leptin levels may contribute to the decreased energy expenditure in patients with hypothyroidism merits further investigation [(52)].

It was revealed in our study though 61.82% of patients are obese (BMI $\geq$ 25kg/m^2) only 43. 64% was centrally obese (WC $\geq$ 80cm). Obese individuals were more in the study group compared to the centrally obese individuals indicating that hypothyroid influences obesity than central obesity.

Gupta et al found that truncal obesity was more in the population compared to the obesity (obesity in 50.3%, truncal obesity in 68.0 %[(41)]. In a study by Mohan *et al.* in industrial population it was found that by criteria

(body mass index ≥ 23 kg/m^2) 60.2% was overweight [24]. Ramachandran *et al.* in his study found out truncal obesity (WC≥ 85cms) was 31.4% in this region [40]. It is obvious from this study, that hypothyroid patients are obese than centrally obese. Exact influence of thyroid hormone on the weight of individual in the era of sedentary life style and unbalanced diet needs further evaluation.

Elevated levels of total cholesterol, LDL cholesterol, and apolipoprotein are well documented features of overt hypothyroidism [58]. Asvold *et al.* in HUNT Study (population based study) found the positive relationship of TSH within the reference range and serum lipid concentrations [57]. Subclinical hypothyroid patients have increased serum lipid levels, and cholesterol levels appear to rise in parallel with serum TSH[7,34]. The elevation of TGs in hypothyroidism is caused by a reduced removal rate of TG from plasma due to a decrease in the activity of hepatic TG lipase[54]. Some studies have shown that hypothyroidism is associated with a lower HDL cholesterol level . Althaus *et al.* and Caron *et al* found a significantly lower HDL cholesterol fraction even in the subclinically hypothyroid patients[55,56]. One rationale for treating subclinical hypothyroidism is to lower levels of LDL cholesterol and thereby

decrease atherosclerotic risk. Multiple small, randomized trials have been performed examining the effect of T4 treatment on lipid parameters in subclinical hypothyroidism, with the majority reporting a tendency toward beneficial effects, without achieving statistical significance[60].

Elevated total cholesterol (≥200mg), Hypertriglyceridemia (≥150 mg), Reduced HDL (< 50mg), Elevated LDL (≥130) were present in 54.55% ,60%, 89.09%, 43.64% of the study population respectively. Dyslipidemia was more in study group than the general population. Our study group had a significantly reduced HDL.

Ramachandran *et al.* in his study found that reduced HDL(<40mg) is 65.5% amongst urban Asian adults[40]. In CUPS -5 study by Mohan *et al.* found that mean HDL cholesterol is low in our population (40 mg/dl)[89]. Mohan *et al.* in another study in industrial population found that dyslipidaemia was prevalent in 40.2% of the study group. Hypertriglyceridaemia was seen in 28.3% of the study group[24]; Gupta *et al.* revealed that elevated total cholesterol(≥ 200mg) in 45.8% and hypertriglyceridemia (≥ 150 mg)in 28.6% of the urban female population in this region[41].

It is well known that Asian Indians have low HDL cholesterol levels,

which could be one of the risk factors for premature CAD in this ethnic group[90,91]. Enas *et al.* in his study found dyslipidemia is prevalent in South Asia,which is characterized by high serum levels of apolipoprotein ,triglycerides and low levels of apolipoprotein A1,high-density lipoprotein (HDL) cholesterol. In addition, the HDL particles are small, dense, and dysfunctional[87].

Subclinical hypothyroidism not started on levothyroxine in study group also had dyslipidemia. Hence subclinical hypothyroid should be treated in South Asia where dyslipidemia is widely prevalent to halt the progression of atherosclerosis. Whether hypothyroidism contributes to the dyslipidemia in this region merits further investigation.

In hypothyroidism,endothelial dysfunction and impaired VSM relaxation leads to increased SVR[78]. These effects lead to diastolic hypertension in approximately 30% of patients, and thyroid hormone replacement therapy restores endothelial-derived vasorelaxation and blood pressure to normal in most patients[36]. The increase in diastolic pressure occurs with low serum renin levels[81] and is a sodium sensitive form of hypertension[82]. Asvold *et al.* in his study reports a linear correlation

between TSH and both systolic and diastolic blood pressure[14], whereas other studies do not find a correlation[17,31,83].

Luboshitzky *et al*[84] did observe that mean diastolic blood pressure was higher in subclinical hypothyroidism. Impaired endothelium-dependent vasodilatation as a result of a reduction in nitric oxide availability has been demonstrated in subclinical hypothyroidism as well[36].

In our study hypertension was present in 32.73% of the study group , systolic and diastolic affecting equally. Mohan *et al.* in study found that overall crude prevalence of hypertension (HTN) in this population is 21.1%[92]. Mohan *et al.* in another study in industrial population found that hypertension is prevalent in 25.4%[24]. Hypertension was more in our study group than the general population.

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[85]. Aneemieke Ross *et al.* 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[20].

In our study FBS (≥ 100mg) was 47.7% of the study group. It was increased compared to the general population. Ramachandran *et al.* in his study shows FPG(≥ 110mg) was present in 26.7% in the population[40]. The National Urban Diabetes Survey (NUDS), carried out in six cities in the year 2001, reported the age-standardized prevalence rates of diabetes was 12% in urban India][93]. The age-standardized prevalence of diabetes in Chennai according to this study was 13.5 %. In addition the study also reported that 14% had impaired glucose tolerance (IGT). The large population based study, CURES conducted on 26,001 individuals in the year 2001-2002, showed that according to the ADA criteria 19% had diabetes in Chennai and this scaled down to 16% when WHO criteria was used[94] India with its dubious distinction of being called, "the diabetic capital of the world" is presently estimated to have over 30 million individuals affected by this deadly disease.

Though studies do not associate glucose intolerance with hypothyroidism, this was contrary to the prevalence of increased FBS in our study group. This association needs further evaluation.

In south east asia prevalence of diabetes, premature coronary artery disease and dyslipidemia are higher than the rest of the world though partly attributed due to genetic predisposition. Diabetes and premature coronary artery disease are occurring about 10 years earlier in south east asia than rest of the world population. In India, mortality attributable by CVD is expected to rise by 103% in men and by 90% in women from 1985 to 2015. HEART WATCH STUDY in 1995 and 2002 by Gupta *et al.* reveals that all modifiable risk factors(except hypertension in 36. 9vs. 33.7%) of CVD are increasing in women such as a) leisure time physical inactivity 72.4% vs 75.3%, b) obesity(BMI $\geq$ 25) 19.9%vs 39.4%,c) truncal obesity (waist:hip >0.8) 70.1 vs. 69.2%.d) tobacco use 18.7 vs.20.5%,e)diabetes history 1.0 vs.7.3%.Same increasing trend is seen in males[(95)].

Early diagnosis and aggressive management of modifiable risk factors like diabetes, hypertension, dyslipidemia, hypothyroidism, smoking, sedentary life style, dietary habits would halt this epidemic. Health education plays a vital role in the management. More prospective longitudinal follow up studies are required to throw light on association of hypothyroidism and metabolic syndrome in this region.

SUMMARY

Patients with hypothyroidism are at increased risk of obesity, elevated triglyceride, decreased HDL and hypertension and may have increased risk of Metabolic syndrome.

A non randomized cross sectional Study was conducted in female primary hypothyroid patients who attended the EndocrinologyOPD,Institute of Internal Medicine, Madras Medical College and Government General Hospital,Chennai. The aim of the study was to find the prevalence of Metabolic Syndrome in frankly hypothyroid patients with poor drug compliance for more than 3 months, subclinical hypothyroidism not started on levothyroxine, recently diagnosed hypothyroid patient not started levothyroxine.

After applying inlusion and exclusion criteria, 55 female hypothyroid patients proved by thyroid hormone assay were selected for study after written consent. Detailed history including drug intake, clinical examination including anthropometric measurements were noted. After eight hours of fasting, blood drawn for fasting blood sugar and lipid profile. 22 patients

(40%) and 27 patients (49.09%) of the study group were diagnosed to be metabolic syndrome as per IDF criteria and AHA/NHLBI 2005 criteria respectively. Metabolic syndrome was increased in the study group than the general population. Majority were obese((BMI $\geq$ 25 kg/m^2 - 61.82%) than centrally obese(WC $\geq$ 80 cms-43.64%). Elevated triglycerides, decreased HDL, hypertension and glucose intolerance were present in 60%, 89.09%, 32.73% and 47.27% of the study group respectively. Though studies do not associate glucose intolerance with hypothyroidism, the factors causing increased FBS in this study group remain obscure. Incidence of Metabolic syndrome increases with age and this was also true in our study.

Subclinical hypothyroidism patients be treated in South East Asia where prevalence of diabetes, premature coronary artery disease and dyslipidemia are higher than the rest of the world. Affordable, accessible health care, health education including diet, exercise and drug compliance may halt the progression of diabetes, hypertension, obesity, premature coronary artery disease in this region The study group consists of small number of subjects. The study concludes that larger prospective study has to be performed to confirm the association of hypothyroidism and Metabolic syndrome.

CONCLUSIONS

1) Metabolic syndrome was increased in female frankly hypothyroid patients with poor drug compliance, subclinical hypothyroidism not started on levothyroxine, and newly diagnosed hypothyroid patient.

2) Prevalence of Metabolic syndrome is 40% and 49. 09% as per IDF and AHA/NHLBI 2005 criteria respectively in the study group which was higher than the general Population.

3) All the parameters of Metabolic syndrome like central obesity hypertension, decreased HDL, elevated triglycerides and glucose intolerance are increased in the study group. Majority of patients have generalized obesity rather than central obesity.

4) All clinical and subclinical hypothyroid patients should be screened for metabolic syndrome parameters and if identified should be treated aggressively.

5) Subclinical hypothyroidism should be treated in South East Asia where prevalence of diabetes, premature coronary artery disease and dyslipidemia are higher than the rest of the world though partly attributed due to genetic predisposition.

BIBLIOGRAPHY

1)Cappola AR *et al.* ; 2003 **Hypothyroidism and atherosclerosis**. J Clin Endocrinol Metab 88:2438–2444

2) Hak AE *et al.* ;2000 **Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women:the Rotterdam Study**. Ann Intern Med 132:270–278

3) Klein I, Ojamaa K**;**2001 **Thyroid hormone and the cardiovascular system.** N Engl J Med 344:501–509

4) Duntas LH; 2002 **Thyroid disease and lipids**. Thyroid 12:287–293

5) Fommei E, Iervasi G 2002 **The role of thyroid hormone in blood Pressure homeostasis: evidence from short-term hypothyroidism in humans**. J Clin Endocrinol Metab 87:1996–2000

6) Biondi B, Klein I **;**2004 **Hypothyroidism as a risk factor for cardiovasculardisease**. Endocrine 24:1–13

7) Canaris GJ *et al.* **;** 2000 **The Colorado Thyroid disease prevalence study**. Arch Intern Med 160:526–534

8) Reaven GM; Banting Lecture 1988**. Role of insulin resistance in human disease**. *Diabetes 1988;***37**:1595-607

9) Kaplan NM; **The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension**. *Arch Intern Med 1989*;**149**:1514-20.

10) Alexander CM *et al.* ; **NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older**. *Diabetes 2003*;**52**:1210-4

11) Haffner SM, Cassells HB; **Metabolic syndrome – a new risk factor of coronary heart disease**. *Diabetes, Obesity and Metabolism 2003*;**5**:359-70

12) Nils Knudsen *et al.* ;**Small Differences in Thyroid Function May Be Important for Body Mass Index and the Occurrence of Obesity in the Population (***J Clin Endocrinol Metab* 90: 4019–4024, 2005**)**

13) Zulewski H *et al.* , **Evaluation of patients with various grades of hypothyroidism (***J Clin Endocrinol Metab* 97: 82:771-776

14) Asvold BO *et al.* ;**Association between blood pressure and serum TSH concentration within the reference range: a population-based study**. *J Clin Endocrinol Metab*. 2007;9:841– 845.

15) Danzi S, Klein I. ;**Thyroid hormone and blood pressure regulation** *CurrHypertens Rep*. 2003;5:513–520.

16) Saito I, Saruta T **;**1994 **Hypertension in thyroid disorders.** Endocrinol Metab Clin North Am 23:379–386

17). Walsh JP *et al.* ;**Subclinical thyroid dysfunction and blood pressure:a community-based study**. *Clin Endocrinol*. 2006;65:486–491.

18) Althaus BU *et al.* ; 1988 **LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease**. Clin Endocrinol (Oxf) 28:157–163

19) Caron P *et al.* **;**1990 **Decreased HDL cholesterol in subclinical hypothyroid:the effect of L-thyroxine therapy**. Clin Endo(Ox)33:519–523

20). Annemieke Roos *et al.* ; **Thyroid Function Is Associated with Components of the Metabolic Syndrome in Euthyroid Subjects,** The

Journal of Clinical Endocrinology & Metabolism 92(2):491–496

21),Ito M *et al.* ; 2003 **Serum concentrations of remnant-like particles in hypothyroid patients before and after thyroxine replacement**. Clin Endocrinol (Oxf) 58:621–626

22) Lin SY *et al.* ;**Lower serum free thyroxine level are associated with metabolic syndrome in Chinese population** Metabolism 2005;54:1524-8

23) ChandraL *et al.* ;**Association of metabolic syn and its components with thyroid dysfunction in females.** Int J Diab Dev Ctries 007;27:124-126

24) Mohan *et al.* ;**Surveillance for risk factors of cardiovascular disease among an industrial population in southern India**;Natl MedJ India 2008 Jan-Feb 21(1) 8-13

25). Perk M, O'Neill BJ;**The effect of thyroid hormone therapy on angiographic coronary artery disease progression**. *Can J Cardiol.* 1997;13:273–276.

26). Reddy KS, Yusuf S;**Emerging epidemic of CVD in the developing countries**. Circulation 1998;97:596–601.

27). Dhawan J;**Coronary heart disease risks in Asian Indians**. Curr Opin Lipidol 1996;7:196–8.

28) Anand SS, Yusuf S, Vuksan V, *et al.* ;**Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE).** Lancet 2000;356:279–84.

29) Rajadurai J, Arokiasamy J, Pasamanickam K, *et al.* ;**Coronary artery disease in Asians.** Aust NZ J Med 1992;22:345– 8.

30) Mohan V, Deepa R, Haranath SP, *et al.* ;**Lipoprotein(a) is an independent risk factor for coronary artery disease in NIDDM patients in South India**. Diabetes Care 1998;21:1819 –23.

31) Irwin Klein, MD; Sara Danzi, PhD, **Thyroid Disease and the Heart, (***Circulation*. 2007;116:1725-1735.)

32) A. Squizzato, V. E. A. Gerdes, D. P. M. Brandjes, H. R. Büller

and J. Stam, **Thyroid Diseases& Cerebrovascular Disease,** *Stroke*2005;36;2302 –2310;

33) Evered DC, Ormston BJ, Smith PA, Hall R, Bird T. **Grades of Hypothyroidism**. *BMJ*. 1973;1:657– 662.

34) Althaus BU *et al.* ;**Spectrum of subclinical and overt hypothyroidism :effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues.** *Am J Med*. 1992;92:631– 642.

35) Razvi S *et al.*; **The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: randomised, crossover trial**. *J Clin Endocrinol Metab* 2007;92:1715–1723.

36) Taddei S *et al.*; **Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy.** *J Clin Endocrinol Metab*. 2003;88:3731–3737

37) Scott M. Grundy *et al.* ;**Executive Summary Association/ National Heart, Lung, and Blood Institute Scientific Statement:**

Diagnosis and Management of the Metabolic Syndrome *Circulation* 2005;112;e285-e290

38) yong-woo park *et al.* ; **Prevalence and associated risk factor finding in US population from the Third National Health ans Nutrition Examination Survey**,1988- 1994, Arch Intern Med. 2003;163:427-436

39) Deepa m, Farooqs, Datta M, Deepa R, Mohan V **Prevalence of metabolic syndrome using WHO, ATPIII and IDF definitions in Asian Indians: the Chennai Urban Rural Epidemiology Study(CURES-34)Diabetes Metab Res Rev** 2007 Feb;23(2):127-34

40) A Ramachandran *et al.* ;**Metabolic syndrome in urban Asian Indian adults--a population study using modified ATP III criteria.** Diabetes Res Clin Pract 2003 Jun 60(3)199-40)

41) Gupta *et al.* ;**Fasting glucose and cardiovascular risk factors in an urban population** J Assoc physicians 2007 Oct;55:705-9.

42) The IDF consensus-May 2004 . Worldwide definition of metabolic syndrome. www. idf. org

43) Alberti KG *et al.* ,**Diagnosis and definition-Provisional**

report of WHO consultation. Diabet Med 1998;15:539-553

44) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults 2001 Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection,Evaluation, And Treatment of High Blood Cholesterol In Adults (ATP III). JAMA 285:2486–2497

45). Zimmet PZ *et al.* **The metabolic syndrome**;Lancet 2005:365:1415-1428

46) Jean Pd *et al.* ,RIO-**Lipids study group. effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia**. N Eng J Med 2005:353:2121-34

47) Wierzbicki *et al.* ;**Rimonabant;endocannabinoid inhibition for the metabolic syndrome.** Int J Clin Pract 2006:60:12:1697-1706

48) Lindeman RD *et al.* **;**2003 **Impact of subclinical hypothyroidism on serum total homocysteine concentrations,the prevalence of coronary heart disease (CHD), and CHD risk factors in the New Mexico Elder Health Survey**. Thyroid 13:595–600

49) Chan JL *et al.* ;2003 **The role of falling leptin levels in the neuroendocrine and metabolic adaptation to shortterm starvation in healthy men.** J Clin Invest 111:1409–1421

50) Welt CK *et al.* ; 2004 **Recombinant human leptin in women with hypothalamic amenorrhea.** N Engl J Med 351:987–997

51) Zimmermann-Belsing T *et al.* ; 2003 **Circulating leptin and thyroid dysfunction**. Eur J Endocrinol 149:257–271

52) R. Valcavi *et al.* ; **Influence of Thyroid Status on Serum Immuno reactive Leptin Levels**(*J Clin Endocrinol Metab* **82:** 1632–1634, 1997

53) Astrup A *et al.*; 1992 **The contribution of body composition, substrates, and hormones to the variability in energy expenditure and substrate utilization in premenopausal women.** J Clin Endocrinol Metab 74:279–286

54) Ito M *et al.* **;**2003 **Serum concentrations of remnant-like particles in hypothyroid patients before and after thyroxine replacement.** Clin Endocrinol (Oxf) 58:621–626

55). Althaus BU *et al.* **;**1988 **LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease**. Clin Endocrinol (Oxf) 28:157–163 **56)** Caron P *et al.* **;**1990 **Decreased HDL cholesterol in subclinical hypothyroidism: the effect of L-thyroxine therapy**. Clin Endocrinol (Oxf) 33:519–523

57) Asvold BO *et al.* **;**2007 **The association between TSH within the reference range and serum lipid concentrations in a population based study. The HUNT Study.** Eur J Endocrinol 156:183–188

58) Staub JJ, Althaus BU *et al.* **;**1992 **Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues**. Am J Med 92:631–642

59) Thompson GR *et al.* **;**1981 **Defects of receptor-mediated low density lipoprotein catabolism in homozygous familial hypercholesterolemia and hypothyroidism *in vivo.*** Proc Natl Acad Sci USA 78:2591–2595

60) Danese MD *et al.* **;**2000 Clinical review 115:**Effect of thyroxine**

therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J Clin Endo Metab 85: 2993–3001

61) Sundaram V *et al.* **;**1997 **Both hypothyroidism and hyperthyroidism enhance LDL oxidation.** J Clin EndoMetab 82:3421–3424

62) Diekman T *et al.* **;**1998 **Increased oxidizability of low-density lipoproteins in hypothyroidism.** J Clin Endocrinol Metab 83:1752–1755

63) de Bruin TW *et al.* **;** 1993 **Lipoprotein(a) and apolipoprotein B plasma concentrations in hypothyroid, euthyroid, and hyperthyroid subjects** J Clin Endocrinol Metab 76:121–126

64) Martinez-Triguero ML *et al.* ;1998 **Effect of thyroid hormonereplacement on lipoprotein(a), lipids, and apolipoproteins in subjects with hypothyroidism.** Mayo Clin Proc 73:837–841

65) Becerra A *et al.* ; 1999 **Lipoprotein(a)and other lipoproteins in hypothyroid patients before and after thyroid replacement**

66) Tzotzas T *et al.* **;**2000**Changes in Lp(a) levels in overt and**

subclinical hypothyroidism before and during treatment. Thyroid 10:803–808

67) Arem R *et al.* **;** 1995 **Effect of L-thyroxine therapy on lipoprotein fractions in overt and subclinical hypothyroidism,with special reference to lipoprotein(a).** Metabolism 44:1559–1563

68) Pazos F *et al.* ; 1995 **Long-term thyroid replacement therapy and levels of Lp(a) and other lipoproteins.** J Clin Endo Metab 80:562–566

69) Meier C, Staub *et al.* ; **2001 TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basal Thyroid Study**). J Clin Endocrinol Metab 86:4860–4866

70) Caraccio N, *et al.* **;**2002 **Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study**. J Clin Endocrinol Metab 87:1533–1538

71) Yildirimkaya M *et al.* **;**1996 **Lp(a) concentration in subclinical Hypothyroid before&after levo-thyroxine therapy**Endocr J 43:731–736

72) Weintraub M *et al.* **;**1999 **Thyroxine replacement therapy enhances clearance of chylomicron remnants in patients with hypothyroidism.** J Clin Endocrinol Metab 84:2532–2536

73) Ritter MC *et al.* **;**1996 **The effects of hypothyroidism and replacement therapy on cholesteryl ester transfer**. J Clin Endocrinol Metab 81:797–800

74) Tan KC *et al.* ; 1998 **Plasma cholesteryl ester transfer protein activity in hyper- and hypothyroidism**. J Clin Endocrinol Metab 83:140–143

75) Lam KS, Chan MK, Yeung RT **;**1986 **High-density lipoprotein cholesterol, hepatic lipase and lipoprotein lipase activities in thyroid dysfunction—effects of treatment.** Q J Med 59:513–521

76) Packard CJ *et al.* ; 1993 **Thyroid replacement therapy and its influence on postheparin plasma lipases and apolipoprotein-B metabolism in hypothyroidism**. J Clin Endocrinol Metab 76:1209–1216

77) Obuobie K *et al.* **:**2002 **Increased central arterial stiffness in hypothyroidism**. J Clin Endocrinol Metab 87:4662–4666

78) Napoli R *et al.* ;**Impact of hyperthyroidism and its correction on vascular reactivity in humans**. *Circulation*. 2001;104:3076 –3080

79) Ojamaa K, Klemperer JD, Klein I; 1996 **Acute effects of thyroid hormone on vascular smooth muscle.** Thyroid 6:505–512

80) Mizuma H *et al.* **; Thyroid hormone activation in human vascular smooth muscle cells: expression of type II iodothyronine deiodinase**. Circ Res 88:313–318

81) Laragh JH, Sealey JE. **Relevance of the plasma renin hormonal control system that regulates blood pressure and sodium balance for correctly treating hypertension and for evaluating ALLHAT**. *Am J Hypertens*. 2003;16:407– 415.

82) Marcisz C *et al.* ; **Influence of short-time application of a low sodium diet on blood pressure in patients with hyperthyroidism or hypothyroidism during therapy.** *Am J Hypertens*. 2001;14:995–1002.

83) Volzke H *et al.* ;**The association between subclinical hyperthyroidism and BP in a population-based study**. *J Hypertens*. 2006;24:1947–1953.

84) Luboshitzky R *et al.* ; 2002 **Risk factors for cardiovascular disease in women with subclinical hypothyroidism**. Thyroid 12:421–425

85) JH Shah *et al.* ; **Insulin metabolism in hypothyroidism** Diabetes,1975 Vol 24, Issue 10 922-925

86) Kocher T. **Ueber Kropfexstirpation und ihre Folgen**. *Arch Klein Cir.* 1883;29:254 –337.

87) Enas EA, Mohan V *et al.* ;**The metabolic syndrome and dyslipidemia among Asian Indians: a population with high rates of diabetes and premature coronary artery disease.** J Cardiometab syndrome 2007

88) Mohan V *et al.* ;**Prevalence of Metabolic syndrome using WHO, ATP III,and IDF definitions in asian Indians, CURES-34,** Diabetes Metab. Res Rev 2007 Feb:23(2):127-34

89) Mohan *et al.* ; **Prevalence of Coronary Artery Disease and Its Relationship to Lipids in a Selected Population in South India, (CUPS No. 5)**(J Am Coll Cardiol 2001;38:682–7)

90). Enas EA *et al.* Garg A, Davidson MA, *et al.* ;**Coronary heart disease and its risk factors in first-generation immigrant Asian Indians to the United States of America.** Indian Heart J 1996;48:343–52.

91) Beckles GL *et al.* ;**High total and cardiovascular disease mortality in adults of Indian descent in Trinidad, unexplained by major coronary risk factors**. Lancet 1986;1:1298–301.

92) Mohan V *et al.* ;**Prevalence and risk factors in a selected south Indian Population- CUPS** ,J Assoc Physicians 2003 Jan ;51:20-7

93) Ramachandran A *et al.* ;**Diabetes Epidemiology Study Group in India (DESI): high prevalence of diabetes and impaired glucose tolerance in India. National urban Diabetes Survey**. Diabetologia 2001;44:1094-101

94)Mohan V *et al.* ;**Prevalence of diabetes and impaired fasting glucose in a population based study on 26,001 Individuals in South India using ADA criteria- (CURES)**. Diabetes 2003;Suppl 1:A225.

95) Gupta *et al.* ;**Serial epidemiological surveys in an Urban Indian population demonstrate increasing coronary risk factors among the lower socioeconomic strata** J Assoc Physicians India 2003 May ;51:470-77

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PROFORMA

METABOLIC SYNDROME IN HYPOTHYROID PATIENTS

Name : Age :

Serial No:

Address :

Exclusion Criteria

- Male sex, pregnant women
- Age below 21 years or above 55 years
- Smoker, Alcoholic
- Primary hypothyroid patient taking levothyroxine < 3 months
- Severely ill patient
- Patient taking medication for Diabetes, Hypertension, lipid disorder or taking steroids for any illness.
- Known metabolic syndrome patients.

THYROID PROFILE:

Serum T3(Total) = ng/ ml (0. 7-2. 0)

Serum T4(Total) = µg/dl (5. 5-13. 5)

Serum TSH = uIU/ml (0. 17-4. 05)

Inference : Hypothyroidism - Present/Absent

Height - cms; Weight - kgs; BMI- Kg/m2

Heart rate - per min; Blood pressure - mm Hg;

AHA/NHLBI CRITERIA FOR METABOLIC SYNDROME:

Three or more of the following five risk factors:

•Central obesity

Waist circumference for men >102 cm (> 40 in)Women >88 cm (>35 in)

Modified WC for south asians- Male ≥ 90 cm, Female ≥ 80 cms

•Triglycerides ≥ 150 mg/dL (1. 7 mmol/L)

• HDL cholesterol

Men < 40 mg/dL (1. 03 mmol/L)

Women < 50 mg/dL (1. 29 mmol/L)

•Blood pressure ≥ 130/ ≥ 85 mm Hg

•Fasting glucose ≥ 100 mg/dl

IDF CRITERIA FOR METABOLIC SYNDROME:

S. No	CRITERIA	REFERENCE VALUE	PATIENT'S VALUE	result

1.	Central obesity defined as waist circumference for south asian male ≥ 90 cm female≥ 80 cm Plus any two of the following four criteria	Male ≥ 90 cm Female≥ 80 cm		Yes/No
2.	Raised TG level ≥ 150 mg/dL (1. 7 mmol/L), or specific treatment for this lipid abnormality	≥ 150 mg/dL (1.7 mmol/L),		Yes/No
3.	Reduced HDL cholesterol < 40 mg/dL (1. 03 mmol/L) in males and < 50mg/dL (1. 29 mmol/L) in females, or specific treatment for this lipid abnormality	Male <40mg/dl Female<50mg/dl		Yes/No
4.	Raised blood pressure systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg		Yes/No
5.	Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5. 6 mmol/L), or previously diagnosed type 2 diabetes	FPG≥100mg/dL(5.6 mmol/L)		Yes/No
		Metabolic syndrome		Present/ Absent

INSTITUTIONAL ETHICAL COMMITTEE
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K.Dis.No.16328 P & D3/Ethics/Dean/GGH/08 Dated: 2/9/2008

Title of the work : Metabolic Syndrome in Hypothyroi patients"

Principal Investigator : Dr. K.S. Vithyatharan

Department : General Medicine, MMC, UuH Ch-3

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 10th Sep 2008 at 2 P.M in GGH ..., Deans, Chamber, Chennai-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s)
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH,CHENNAI

CHAIRMAN
IEC, GGH, CHENNAI

DEAN
GGH &MMC, CHENNAI

RKM.5.6(2)

S.NO	Endo no	Category	Name	Age	Sex	Ht	Wt	HT 2	BMI	T3 (ng/ml)	T4 (µg/dl)	TSH uIu/ml)	Waist in cms	TC	TG (mg/dl)	HDL (mg/dl)	VLDL	LDL	SBP	DBP	FPG	ATP	IDF
1	6929/08	New	Parvathi	55	F	151	56	2.28	24.6	0.32	28.5	44.1	86	120	285	40	57	23	134	86	76	4	Y
2	11092/07	Clinical	Ratha	55	F	166	70	2.756	25.4	0.75	102	45.5	94	280	276	41	55.2	183.8	140	92	89	4	Y
3	8473/06	Clinical	Amirthavalli	45	F	147	62	2.161	28.7	0.49	3.9	98.12	81	257	659	34	131.8	91.2	138	88	155	5	Y
4	6678/08	New	Selvi	44	F	152	65	2.31	28.1	0.9	46.9	28.1	85	282	187	44	37.4	200.6	132	86	103	5	Y
5	1128/06	Clinical	Mary	44	F	148	58	2.19	26.5	0.82	2.43	39.8	82	280	396	40	79.2	160.8	128	84	123	4	Y
6	3222/06	Clinical	Kalaiselvi	35	F	154	70	2.372	29.5	0.9	7.28	18.08	92	232	395	42	79	111	124	78	115	4	Y
7	2416/06	Clinical	Mahalakshmi	42	F	155	71	2.403	29.6	0.65	8.54	85.46	103	383	500	38	100	245	150	100	137	5	Y
8	378/07	Clinical	Lakshmi	31	F	150	65	2.25	28.9	1.19	6.57	25.34	94	267	259	42	51.8	173.2	134	86	85	4	Y
9	7148/08	New	Venkatalakshmi	39	F	150	55	2.25	24.4	0.3	41	55.4	87	199	357	37	71.4	90.6	144	90	103	5	Y
10	803/06	Clinical	Susila	42	F	144	60	2.074	28.9	0.28	1.45	100	95	261	320	42	64	155	122	80	104	4	Y
11	7540/08	New	Mohana	55	F	148	70	2.19	32	0.88	10.71	10.07	93	211	130	45	26	140	142	88	102	4	Y
12	7611/07	Clinical	Susheela	50	F	142	54	2.016	26.8	0.5	55	14.5	79	160	107	54	21.4	84.6	136	86	82	1	N
13	9134/07	Clinical	Selvalaxmi	29	F	150	61	2.25	27.1	0.61	4.35	12.02	78	210	189	39	37.8	133.2	120	80	89	2	N
14	4761/05	Clinical	Mohana	38	F	145	55	2.103	26.2	0.64	8.12	40.18	79	200	155	45	31	124	128	82	85	2	N
15	2739/03	Clinical	Yasoda	45	F	144	40	2.074	19.3	0.1	1.28	26.29	68	171	171	32	34.2	104.8	124	80	111	3	N
16	823/07	Clinical	Mohana	35	F	153	58	2.341	24.8	0.74	1.52	102.27	75	220	134	43	26.8	150.2	110	70	81	1	N
17	3188/06	Clinical	Ebsiba	21	F	143	40	2.045	19.6	0.33	3.07	44.15	65	183	109	31	21.8	130.2	112	72	105	2	N
18	4938/07	Clinical	Dilsath	25	F	144	55	2.074	26.5	0.77	5.04	15.36	78	218	278	36	55.6	126.4	120	74	78	2	N
19	9152/07	Clinical	Nagalakshmi	28	F	158	54	2.496	21.6	0.39	2.99	52.65	76	174	64	48	12.8	113.2	108	78	90	1	N
20	877/08	Clinical	Shanthi	43	F	156	55	2.434	22.6	1.06	5	33.95	77	157	206	34	41.2	81.8	126	70	93	2	N
21	7089/06	Clinical	Parvathi	25	F	148	62	2.19	28.3	0.73	5.43	83.06	76	150	110	42	22	86	120	70	65	1	N
22	3962/07	Clinical	Damayanthi	45	F	148	65	2.19	29.7	0.45	4.15	31.85	91	266	187	51	37.4	177.6	130	86	82	3	Y
23	6079/08	New	Dhanalakshmi	46	F	148	55	2.19	25.1	0.69	3.8	63.24	76	290	206	40	41.2	208.8	110	80	102	3	N
24	6813/08	New	Vasanthi	28	F	147	46	2.161	21.3	0.43	0.3	150	77	181	152	45	30.4	105.6	114	78	96	2	N
25	6099/08	New	Sudha	22	F	163	57	2.657	21.5	1.34	7.63	27.8	74	175	50	45	10	120	110	74	71	1	N
26	2185/05	Clinical	Nirmala	31	F	152	55	2.31	23.8	0.21	1.52	99.61	76	275	75	48	15	212	114	78	90	1	N
27	4912/07	Clinical	Kanagavalli	28	F	156	40	2.434	16.4	0.21	0.2	150	69	160	54	37	10.8	112.2	110	70	89	1	N
28	9600/07	Clinical	Kanmani	24	F	148	45	2.19	20.5	0.69	3.91	17.32	70	152	111	41	22.2	88.8	112	72	98	1	N
29	4564/07	Clinical	Sarasvathi	37	F	147	70	2.161	32.4	0.21	1.1	100	88	200	97	48	19.4	132.6	134	90	110	4	Y
30	7893/06	Clinical	Nagamma	36	F	155	55	2.403	22.9	1.19	6.6	11.94	71	284	78	63	15.6	205.4	112	74	96	0	N

31	5036/08	New	sumathy	27	F	155	66	2.403	27.5	0.56	91	13.2	79	218	228	46	45.6	126.4	120	80	119	3	N
32	4493/03	Subclinica	Pappa	43	F	157	90	2.465	36.5	0.54	8.2	4.8	102	252	191	42	38.2	171.8	142	94	85	4	Y
33	10195/07	Subclinica	Rukmani	43	F	152	65	2.31	28.1	1.38	4.35	5.65	90	184	131	41	26.2	116.8	140	90	130	4	Y
34	6736/08	New	Chithra	21	F	145	76	2.103	36.1	0.45	94	9.59	98	231	341	35	68.2	127.8	110	72	161	4	Y
35	1077/07	Subclinica	Zeenath	33	F	155	79	2.403	32.9	1.6	1.98	9.07	93	174	332	35	66.4	72.6	124	78	144	4	Y
36	4825/05	Subclinica	Lakshmi	42	F	154	80	2.372	33.7	1.83	8.05	5.5	94	250	351	38	70.2	141.8	136	90	111	5	Y
37	4921/07	Subclinica	Valli	50	F	153	55	2.341	23.5	0.8	7.12	5.17	81	169	222	40	44.4	84.6	134	88	118	5	Y
38	6765/05	Subclinica	Shanthi	46	F	150	76	2.25	33.8	0.62	4.3	9.66	97	258	237	38	47.4	172.6	130	86	182	5	Y
39	1862/06	Subclinica	Shanthi	40	F	155	65	2.403	27.1	1.06	7.74	6.78	88	205	155	40	31	134	126	78	93	3	Y
40	1088/07	Subclinica	Nagalakshmi	27	F	157	85	2.465	34.5	0.91	4.08	5.78	99	302	80	40	16	246	120	72	189	3	Y
41	1112/07	Subclinica	Vijaya	31	F	141	45	1.988	22.6	0.72	3.25	8.99	70	178	147	52	29.4	96.6	120	78	112	1	N
42	2720/08	New	Datchayani	32	F	152	41	2.31	17.7	0.56	72	8.7	62	126	154	82	30.8	13.2	122	78	89	1	N
43	1055/03	Subclinica	Vanathy	30	F	148	50	2.19	22.8	1.79	4.85	5.04	78	170	83	49	16.6	104.4	120	76	106	2	N
44	6643/08	New	Sakunthala	30	F	148	58	2.19	26.5	1.41	152	9.17	79	160	237	33	47.4	79.6	124	80	90	2	N
45	4331/03	Subclinica	Karpagam	46	F	148	60	2.19	27.4	0.69	7.1	6.93	78	289	115	42	23	224	124	80	111	2	N
46	786/06	Subclinica	Jayanthi	37	F	148	58	2.19	26.5	0.58	7.05	5.32	77	190	108	49	21.6	119.4	114	76	91	1	N
47	6721/08	New	Ammani	37	F	148	40	2.19	18.3	0.46	121	6.47	69	186	84	42	16.8	127.2	130	86	94	2	N
48	4555/04	Subclinica	Mythili	33	F	150	60	2.25	26.7	0.89	5.36	7.85	85	180	127	41	25.4	113.6	120	78	93	2	N
49	2821/08	New	Lakshmi	34	F	146	40	2.132	18.8	1.13	5.6	6.71	58	118	87	33	17.4	67.6	116	80	80	1	N
50	7583/08	New	Thulasi	29	F	146	51	2.132	23.9	1.37	6.3	7.55	74	154	182	45	36.4	72.6	100	72	93	2	N
51	5099/06	Subclinica	Sasireka	34	F	155	60	2.403	25	0.52	4.4	6.17	77	253	327	46	65.4	141.6	120	80	99	2	N
52	6529/02	Subclinica	Selvi	24	F	143	50	2.045	24.5	0.58	15.19	9.29	74	203	176	48	35.2	119.8	120	70	112	3	N
53	6852/08	New	Rathinamathi	33	F	147	60	2.161	27.8	0.55	91	9.87	83	290	200	50	40	200	122	80	95	2	N
54	4607/05	Subclinica	Rajamani	43	F	152	58	2.31	25.1	1.75	3.84	8.48	78	220	163	35	32.6	152.4	134	88	101	4	N
55	7068/08	New	sulpha	45	F	155	62	2.403	25.8	0.98	38.5	5.02	79	168	134	41	26.8	100.2	128	78	101	2	N