# A STUDY ON THE PREVALENCE OF ELEVATED HIGH SENSITIVITY C-REACTIVE PROTEIN IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

***Dissertation Submitted to***

**THE TAMILNADU DR. M.G.R. MEDICAL UNIVERISTY**

**CHENNAI – 600 032**

***In partial fulfillment of the regulations***

***For the Award of the Degree of***

**M.D. (GENERAL MEDICINE)**

**BRANCH -1**


**MADRAS MEDICAL COLLEGE**
**RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL**
**CHENNAI- 600 003**
**APRIL 2012**

# CERTIFICATE

This is to certify that the dissertation entitled **"A study on the prevalence of elevated High Sensitivity C-Reactive Protein in patients with subclinical hypothyroidism"**is a bonafide original work of **Dr. ALIEM.N.M,** in partial fulfillment of the requirements for M.D. Branch– I (General Medicine) Examination of the Tamil Nadu Dr. M.G.R Medical University to be held in APRIL 2012 under my guidance and supervision during the period of May 2011-November 2011.

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# DECLARATION

I hereby solemnly declare that this dissertation entitled "**A study on the prevalence of elevated High Sensitivity C-Reactive Protein in patients with subclinical hypothyroidism**" was done by me at Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 during May 2011-November 2011 under the guidance and supervision of Prof. G. ELANGOVAN, M.D. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of requirement for the award of M.D. Degree Branch I (General Medicine).

Place: **SIGNATURE OF THE CANDIDATE**

Date:

# ACKNOWLEDGEMENT

I express my heartful gratitude to the Dean, **Dr.V.KANAGASABAI.,M.D**., Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 for permitting me to do this study.

I am deeply indebted to **Prof. C. RAJENDIRAN, M.D**., Director & Professor, Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital for his support and guidance.

I am very grateful to **Prof. G. ELANGOVAN M.D.,** Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital who guided and trimmed my work throughout the period of my study.

I am very grateful to **Prof. A. RADHAKRISHNAN M.D.,** Endocrinology, Madras Medical College & Rajiv Gandhi Government General Hospital for guiding and helping me throughout my study.

I am very much thankful for the help rendered by Assistant Professor **Dr. M. SHARMILA M.D.,** for her constant help and encouragement.

I also thank all the patients who were part of the study and my Professional colleagues for their support and criticisms.

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# ABBREVIATIONS

| | | |
|---|---|---|
| ALP | - | Alkaline Phosphatase |
| BMI | - | Body Mass Index |
| CRP | - | C- Reactive Protein |
| DBP | - | Diastolic Blood Pressure |
| FT3 | - | Free T3 |
| FT4 | - | Free T4 |
| HDL | - | High Density Lipoprotein |
| HSCRP | - | High Sensitivity C- Reactive Protein |
| LDL | - | Low Density Lipoprotein |
| SBP | - | Systolic Blood Pressure |
| SCH | - | SubClinical Hypothyroidism |
| SGOT | - | Serum glutamate oxaloacetate transaminase |
| SGPT | - | Serum glutamate pyruvate transaminase |
| TC | - | Total Cholesterol |
| TGL | - | Triglycerides |

| | | |
|---|---|---|
| Tg | - | Thyroglobulin |
| TSH | - | Thyroid Stimulating Hormone |
| W/H RATIO | - | Waist/Hip Ratio |

# INTRODUCTION

Thyroid diseases are, arguably, among the commonest endocrine disorders worldwide. India too, is no exception. According to a projection from various studies on thyroid disease, it has been estimated that about 42 million people in India suffer from thyroid diseases[1]. Thyroid diseases are different from other diseases in terms of their ease of diagnosis, accessibility of medical treatment, and the relative visibility that even a small swelling of the thyroid offers to the treating physician. Early diagnosis and treatment remain the cornerstone of management.

By definition, subclinical hypothyroidism refers to patients who have an elevated TSH level and a normal free $T_4$ level [2]. Patients with subclinical thyroid disease have few or no symptoms or signs of thyroid dysfunction and thus, by its very nature, subclinical thyroid disease is a laboratory diagnosis. The prevalence of subclinical hypothyroidism in the United States adult population is 4–8.5%, although this figure increases with age, may differ among ethnic groups and less consistent data is available among men. The progression to overt hypothyroidism is approximately 2–5% per year[2]. The rate of progression is proportional to baseline TSH concentration and is higher in individuals with antithyroid antibodies. In India, the prevalence of subclinical hypothyroidism has

been estimated to be 9.4%[1]. In the past decade, a number of review articles addressing subclinical thyroid disease have been published. They have in turn focused on evolving issues regarding definition, diagnosis and management of this common condition. It is important to note that the literature in this area is still inadequate[3].

There is substantial evidence that overt hypothyroidism alters several of the traditional risk factors for cardiovascular disease. The studies in this regard support a biologically plausible role for hypothyroidism increasing the risk of atherosclerotic cardiovascular diseases, via increases in circulating levels of highly atherogenic low-density lipoprotein (LDL) cholesterol particles, induction of diastolic hypertension, altered coagulability, and direct effects on vascular smooth muscle. Furthermore, some evidence suggests that hypothyroidism may exacerbate the cardiovascular risks associated with cigarette smoking and insulin resistance[4].

The association between subclinical hypothyroidism and coronary artery disease is not clear. The popular Whickham Survey[5], which evaluated vascular events over 20 years in community-dwelling subjects stratified by thyroid function and thyroid autoantibody status, found no association between ischemic heart disease (IHD) and a composite

autoimmune thyroid disease group, comprising individuals with subclinical hypothyroidism (SCH), with positive thyroid antibodies or those using levothyroxine. This result appears to be at odds with the findings of other cohort studies. Reanalysis of the Whickham Survey shows an association of subclinical hypothyroidism and heart disease. This study, done by Razvi et al. suggests that there is an increased risk of cardiac disease and death in those with subclinical hypothyroidism[6].

CRP is an acute-phase reactant synthesized mainly in the liver. Emerging evidence suggests that elevated plasma levels of CRP have become one of the strongest independent predictors of CHD[7]. Standard clinical assays for CRP typically have a lower detection limit of 3 to 8 mg/L. Thus, these assays lack sensitivity within the low-normal range and cannot be used effectively for vascular risk prediction.

In recognition of this limitation, initial epidemiological studies used research-based assays designed to determine CRP levels with excellent fidelity and reproducibility across the normal range. Several such “high-sensitivity” or “ultra-sensitive” assays for CRP are now commercially available, and formal standardization programs have been undertaken to ensure comparability across hs-CRP assays[8].

In our study, we attempted to find out the prevalence of elevated levels of high sensitivity CRP in individuals with subclinical hypothyroidism, and thereby assessing the risk of developing coronary vascular events in future.

## AIMS AND OBJECTIVES

1. To determine the concentration of high sensitivity C-reactive protein and to estimate the prevalence of elevated high sensitivity C-reactive protein in individuals with subclinical hypothyroidism and control group.
2. To correlate the level of hs-CRP with serum TSH, Lipid profile and anthropometric parameters.
3. To risk-categorize the patients for cardiovascular disorders based on hs-CRP levels.

# REVIEW OF LITERATURE

## (A) ANATOMY AND HISTOLOGY OF THE THYROID GLAND[9]

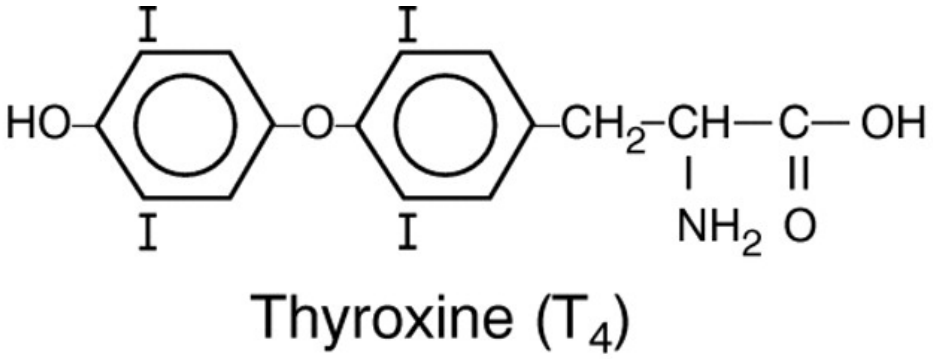
The thyroid is one of the largest of the endocrine organs, weighing approximately 15 to 20 g. The normal thyroid is made up of two lobes joined by a thin band of tissue, the isthmus. Two pairs of vessels constitute the major arterial blood supply, the superior thyroid artery, arising from the external carotid artery, and the inferior thyroid artery, arising from the subclavian artery. Estimates of thyroid blood flow range from 4 to 6 mL/min/g, well in excess of the blood flow to the kidney (3 mL/min/g). In diffuse toxic goiter due to Graves' disease, blood flow may exceed 1 L/min and be associated with an audible bruit or even a palpable thrill.

The gland is composed of closely packed spherical units termed *follicles,* which are invested with a rich capillary network. The interior of the follicle is filled with the clear proteinaceous colloid that normally is the major constituent of the total thyroid mass. On cross section, thyroid tissue appears as closely packed ring-shaped structures consisting of a single layer of thyroid cells surrounding a lumen. The follicular cells vary in height with the degree of glandular stimulation, becoming columnar when active and cuboidal when inactive. The epithelium rests on a

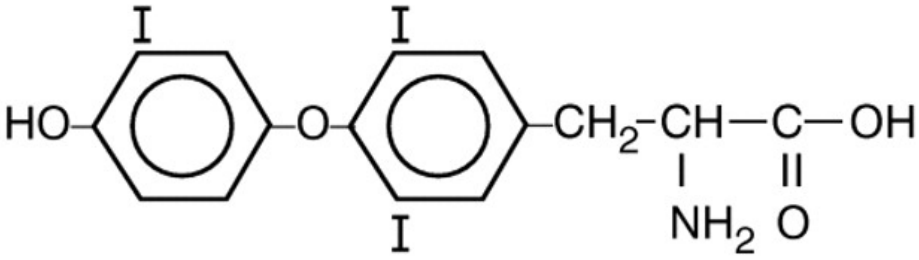
basement membrane that is rich with glycoproteins separating the follicular cells from the surrounding capillaries. From 20 to 40 follicles are demarcated by connective tissue septa to form a lobule supplied by a single artery. The function of a given lobule may differ from that of its neighbours.

On electron microscopy, the thyroid follicular epithelium has many features in common with other secretory cells and some peculiar to the thyroid. From the apex of the follicular cell, numerous microvilli extend into the colloid. It is at or near this surface of the cell that iodination, exocytosis, and the initial phase of hormone secretion, namely colloid resorption, occur.[10] The nucleus has no distinctive features and the cytoplasm contains an extensive endoplasmic reticulum laden with microsomes. The endoplasmic reticulum is composed of a network of wide irregular tubules that contain the precursor of Tg. The carbohydrate component of Tg is added to this precursor in the Golgi apparatus which is located apically. Lysosomes and mitochondria are scattered throughout the cytoplasm. Stimulation by TSH results in enlargement of the Golgi apparatus, formation of pseudopodia at the apical surface, and the appearance in the apical portion of the cell of many droplets that contain colloid taken up from the follicular lumen.

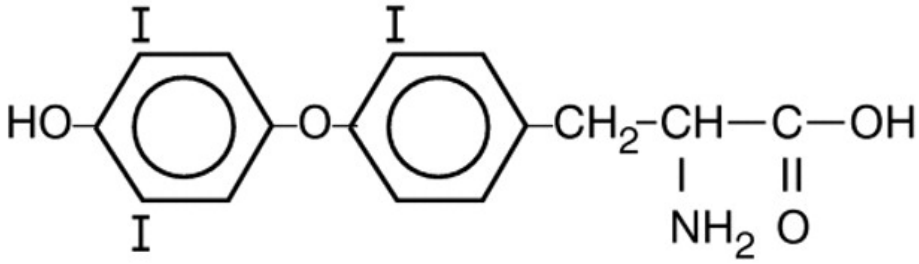
**(B) Chemical structure of thyroid hormones**




Thyroxine ($T_4$)




3, 5, 3'-Triiodothyronine ($T_3$)




3, 3', 5'-Triiodothyronine (reverse $T_3$, $rT_3$)

**Figure 1. Chemical structure of thyroid hormones**

## (C)SYNTHESIS AND SECRETION OF THE THYROID HORMONES[11]

About 93 per cent of the metabolically active hormones secreted by the thyroid gland is *thyroxine*, and 7 per cent *triiodothyronine*. However, almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so that both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.

*Iodine Is Required for Formation of Thyroxine*

To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required each year, or about 1 mg/week. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.

Iodides ingested orally are absorbed from the Gastrointestinal tract into the blood. Normally, most of the iodides are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones. *Iodide Pump (Iodide Trapping),* the first stage in the formation of thyroid

hormones, is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is called iodide trapping. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH, which stimulates the activity of the iodide pump in thyroid cells. The thyroid cells are typical protein-secreting glandular cells. The endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called thyroglobulin. Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form within the thyroglobulin molecule. That is, the thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid.

*Oxidation of the Iodide Ion.* The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an oxidized form of iodine, that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme ***peroxidase*** and its

accompanying hydrogen peroxide, which provide a potent system capable of oxidizing iodides.

The peroxidase is either located in the apical membrane of the cell or attached to it, thus providing the oxidized iodine at exactly the point in the cell where the thyroglobulin molecule issues forth from the Golgi apparatus and through the cell membrane into the stored thyroid gland colloid. When the peroxidase system is blocked or when it is hereditarily absent from the cells, the rate of formation of thyroid hormones falls to zero.

*Organification of Thyroglobulin.* The binding of iodine with the thyroglobulin molecule is called organification of the thyroglobulin. Oxidized iodine even in the molecular form will bind directly but very slowly with the amino acid tyrosine. In the thyroid cells, however, the oxidized iodine is associated with an *iodinase* enzyme that causes the process to occur within seconds or minutes. Tyrosine is first iodized to monoiodotyrosine and then to diiodotyrosine. Then, during the next few minutes, hours, and even days, more and more of the iodotyrosine residues become coupled with one another.

The major hormonal product of the coupling reaction is the molecule thyroxine that remains part of the thyroglobulin molecule. Or one molecule of monoiodotyrosine couples with one molecule of diiodotyrosine to form *triiodothyronine,* which represents about one fifteenth of the final hormones.

*Storage of Thyroglobulin.* After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months.

*Release of Thyroxine and Triiodothyronine from the Thyroid Gland.*

To get released into circulation, thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule. This process occurs as follows: The apical surface of the thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form *pinocytic vesicles* that enter the apex of the thyroid cell. Then *lysosomes* in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles containing digestive enzymes from the lysosomes mixed with the colloid. Multiple *proteases* among the enzymes digest the thyroglobulin molecules and release thyroxine and triiodothyronine in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus, the thyroid hormones are released into the blood.

About three quarters of the iodinated tyrosine in the thyroglobulin never becomes thyroid hormones but remains monoiodotyrosine and diiodotyrosine.

During the digestion of the thyroglobulin molecule to cause release of thyroxine and triiodothyronine, these iodinated tyrosines also are freed from the thyroglobulin molecules. However, they are not secreted into the blood. Instead, their iodine is cleaved from them by a *deiodinase enzyme* that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. In the congenital absence of this deiodinase enzyme, many persons become iodine-deficient because of failure of this recycling process.

*Daily Rate of Secretion of Thyroxine and Triiodothyronine.*

About 93 per cent of the thyroid hormone released from the thyroid gland is normally thyroxine and only 7 per cent is triiodothyronine. However, during the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine. Therefore, the hormone finally delivered to and used by the tissues is mainly triiodothyronine.

*Transport of Thyroxine and Triiodothyronine to Tissues.*

Thyroxine and Triiodothyronine Are Bound to Plasma Proteins. On entering the blood, over 99 per cent of the thyroxine and triiodothyronine combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with thyroxine-binding globulin and much less so with thyroxine-binding prealbumin and albumin. Thyroxine and Triiodothyronine Are Released Slowly to Tissue Cells. Because of high

affinity of the plasma- binding proteins for the thyroid hormones, these substances—in particular, thyroxine—are released to the tissue cells slowly.

**(D) MECHANISM OF ACTION**[12]

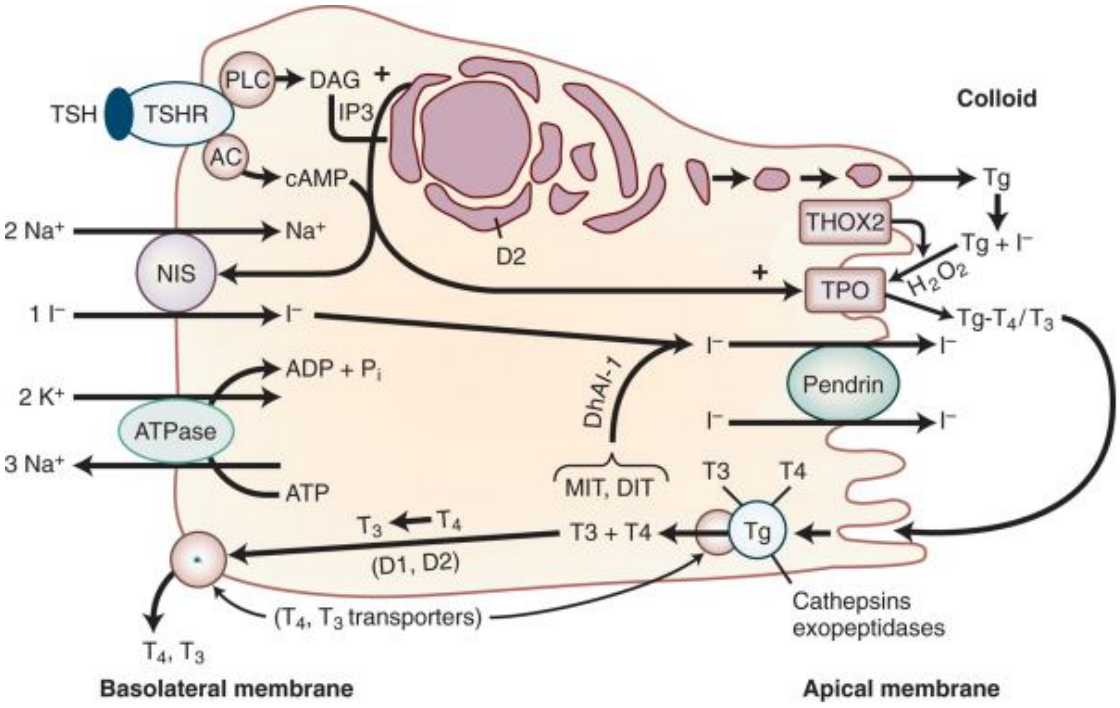



Figure 2. Schematic illustration of a follicular cell showing the key aspects of thyroid iodine transport and thyroid hormone synthesis. *NIS*, Sodium-iodide symporter; $T_3$, triiodothyronine; $T_4$, thyroxine; *Tg*, thyroglobulin; *TPO*, thyroid peroxidase *TSHR*, thyrotropin receptor[13].

Thyroid hormones enter cells and T3 binds to thyroid receptors (TR) in the nuclei. T4 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 proteins that regulate cell function. Thus, the nuclear receptors for thyroid hormones are members of the superfamily of hormonesensitive nuclear transcription factors. There are two human TR genes: an receptor gene on chromosome 17 and a receptor gene on chromosome 3. By alternative splicing, each forms at least two different mRNAs and therefore two different receptor proteins. TR 2 is found only in the brain, but TR 1, TR 2, and TR 1 are widely distributed. TR 2 differs from the other three in that it does not bind T3 and its function is not yet fully established. TRs bind to DNA as monomers, homodimers, and heterodimers with other nuclear receptors, particularly the retinoid X receptor (RXR). The TR/RXR heterodimer does not bind 9-cis retinoic acid, the usual ligand for RXR, but TR binding to DNA is greatly enhanced in response to thyroid hormones when the receptor is in the form of this heterodimer. There are also coactivator and corepressor proteins that affect the actions of TRs. Presumably, this complexity underlies the ability of thyroid hormones to produce many different effects in the body. In most of its actions, T3 acts more rapidly and is three to five times more potent than T4. This is because T3 is less tightly bound to plasma proteins than is T4, but binds more avidly to thyroid hormone receptors. RT3 is inert.

## (E) PHYSIOLOGIC FUNCTIONS OF THE THYROID HORMONES [12]

Some of the widespread effects of thyroid hormones in the body are secondary to stimulation of O2 consumption (calorigenic action), although the hormones also affect growth and development in mammals, help regulate lipid metabolism, and increase the absorption of carbohydrates from the intestine . They also increase the dissociation of oxygen from hemoglobin by increasing red cell 2,3-diphosphoglycerate (DPG).

### 1. CALORIGENIC ACTION

T4 and T3 increase the O2 consumption of almost all metabolically active tissues. The exceptions are the adult brain, testes, uterus, lymph nodes, spleen, and anterior pituitary. T4 actually depresses the O2 consumption of the anterior pituitary, presumably because it inhibits TSH secretion. The increase in metabolic rate produced by a single dose of T4 becomes measurable after a latent period of several hours and lasts 6 days or more. Some of the calorigenic effect of thyroid hormones is due to metabolism of the fatty acids they mobilize. In addition, thyroid hormones increase the activity of the membrane-bound Na, K ATPase in many tissues.

### EFFECTS SECONDARY TO CALORIGENESIS

When the metabolic rate is increased by T4 and T3 in adults, nitrogen excretion is increased; if food intake is not increased, endogenous protein and

fat stores are catabolized and weight is lost. In hypothyroid children, small doses of thyroid hormones cause a positive nitrogen balance because they stimulate growth, but large doses cause protein catabolism similar to that produced in the adult. The potassium liberated during protein catabolism appears in the urine, and there is also an increase in urinary hexosamine and uric acid excretion.

When the metabolic rate is increased, the need for all vitamins is increased and vitamin deficiency syndromes may be precipitated. Thyroid hormones are necessary for hepatic conversion of carotene to vitamin A, and the accumulation of carotene in the bloodstream (carotenemia) in hypothyroidism is responsible for the yellowish tint of the skin. Carotenemia can be distinguished from jaundice because in the former condition the scleras are not yellow.

The skin normally contains a variety of proteins combined with polysaccharides, hyaluronic acid, and chondroitin sulfuric acid. In hypothyroidism, these complexes accumulate, promoting water retention and the characteristic puffiness of the skin (myxedema). When thyroid hormones are administered, the proteins are metabolized, and diuresis continues until the myxedema is cleared.

Milk secretion is decreased in hypothyroidism and stimulated by thyroid hormones, a fact sometimes put to practical use in the dairy industry. Thyroid

hormones do not stimulate the metabolism of the uterus but are essential for normal menstrual cycles and fertility.

## 2. EFFECTS ON THE NERVOUS SYSTEM

In hypothyroidism, mentation is slow and the cerebrospinal fluid (CSF) protein level elevated. Thyroid hormones reverse these changes, and large doses cause rapid mentation, irritability, and restlessness. Overall, cerebral blood flow and glucose and O2 consumption by the brain are normal in adult hypo- and hyperthyroidism. However, thyroid hormones enter the brain in adults and are found in gray matter in numerous different locations. In addition, astrocytes in the brain convert T4 to T3, and there is a sharp increase in brain D2 activity

after thyroidectomy that is reversed within 4 h by a single intravenous dose of T3. Some of the effects of thyroid hormones on the brain are probably secondary to increased responsiveness to catecholamines, with consequent

increased activation of the reticular activating system. In addition, thyroid hormones have marked effects on brain development. The parts of the central nervous system (CNS) most affected are the cerebral cortex and the basal ganglia. In addition, the cochlea is also affected. Consequently, thyroid hormone deficiency during development causes mental retardation, motor rigidity, and deaf–mutism. Deficiencies in thyroid hormone synthesis secondary

to a failure of thyrocytes to transport iodide presumably also contribute to deafness in Pendred syndrome, discussed above.

Thyroid hormones also exert effects on reflexes. The reaction time of stretch reflexes is shortened in hyperthyroidism and prolonged in hypothyroidism. Measurement of the reaction time of the ankle jerk (Achilles reflex) has attracted attention as a clinical test for evaluating thyroid function, but this reaction time is also affected by other diseases and thus is not a specific assessment of thyroid activity.

## 3. RELATION TO CATECHOLAMINES

The actions of thyroid hormones and the catecholamines norepinephrine and epinephrine are intimately interrelated. Epinephrine increases the metabolic rate, stimulates the nervous system, and produces cardiovascular effects similar to those of thyroid hormones, although the duration of these actions is brief.

Norepinephrine has generally similar actions. The toxicity of the catecholamines is markedly increased in rats treated with T4 . Although plasma catecholamine levels are normal in hyperthyroidism, the cardiovascular

effects, tremulousness, and sweating produced by thyroid hormones can be reduced or abolished by sympathectomy. They can also be reduced by drugs such as propranolol that block -adrenergic receptors. Indeed, propranolol and other blockers are used extensively in the treatment of thyrotoxicosis and in the

treatment of the severe exacerbations of hyperthyroidism called thyroid storms. However, even though blockers are weak inhibitors of extrathyroidal conversion of T4 to T3, and consequently may produce a small fall in plasma T3, they have little effect on the other actions of thyroid hormones. Presumably, the functional synergism observed between catecholamines and thyroid hormones, particularly in pathological settings, arises from their overlapping biological functions as well as the ability of thyroid hormones to increase expression of catecholamine receptors and the signaling effectors to which they are linked.

## 4. EFFECTS ON SKELETAL MUSCLE

Muscle weakness occurs in most patients with hyperthyroidism (thyrotoxic myopathy), and when the hyperthyroidism is severe and prolonged, the myopathy may be severe. The muscle weakness may be due in part to increased protein catabolism. Thyroid hormones affect the expression of the MHC genes in skeletal as well as cardiac muscle. However, the effects produced are complex and their relation to the myopathy is not established. Hypothyroidism is also associated with muscle weakness, cramps, and stiffness.

## 5. EFFECTS ON CARBOHYDRATE METABOLISM

Thyroid hormones increase the rate of absorption of carbohydrates from the gastrointestinal tract, an action that is probably independent of their calorigenic action. In hyperthyroidism, therefore, the plasma glucose level rises

rapidly after a carbohydrate meal, sometimes exceeding the renal threshold. However, it falls again at a rapid rate.

## 6. EFFECTS ON GROWTH

Thyroid hormones are essential for normal growth and skeletal maturation . In hypothyroid children, bone growth is slowed and epiphysial closure delayed. In the absence of thyroid hormones, growth hormone secretion is also depressed. This further impairs growth and development, since thyroid hormones normally potentiate the effect of growth hormone on tissues.

## 7. EFFECTS ON THE CARDIOVASCULAR SYSTEM

Large doses of thyroid hormones cause enough extra heat production to lead to a slight rise in body temperatures, which in turn activates heat-dissipating mechanisms. Peripheral resistance decreases because of cutaneous vasodilation, and this increases levels of renal Na+ and water absorption, expanding blood volume. Cardiac output is increased by the direct action of thyroid hormones, as well as that of catecholamines, on the heart, so that pulse pressure and cardiac rate are increased and circulation time is shortened.

T3 is not formed from T4 in myocytes to any degree, but circulatory T3 enters the myocytes, combines with its receptors, and enters the nucleus, where it promotes the expression of some genes and inhibits the expression of others. Those that are enhanced include the genes for -myosin heavy chain,

sarcoplasmic reticulum Ca2+ ATPase, -adrenergic receptors, G proteins, Na, K ATPase, and certain K+ channels. Those that are inhibited include the genes for -myosin heavy chain, phospholamban, two types of adenylyl cyclase, T3 nuclear receptors, and NCX, the Na+–Ca2+ exchanger. The net result is increased heart rate and force of contraction.

8. EFFECTS ON CHOLESTEROL METABOLISM

Thyroid hormones lower circulating cholesterol levels. The plasma cholesterol level drops before the metabolic rate rises, which indicates that this action is independent of the stimulation of O2 consumption. The decrease in plasma cholesterol concentration is due to increased formation of low-density lipoprotein (LDL) receptors in the liver, resulting in increased hepatic removal of cholesterol from the circulation. Despite considerable effort, however, it has not been possible to produce a clinically useful thyroid hormone analog that lowers plasma cholesterol without increasing metabolism.

## (F) HYPOTHYROIDISM

Many structural or functional abnormalities can impair the production of thyroid hormones and cause the clinical state termed *hypothyroidism*. The causes can be divided into six main categories[9]:

1. Hypothyroidism with compensatory thyroid enlargement due to transient

or progressive impairment of hormone biosynthesis (goitrous hypothyroidism).

2. Permanent loss or atrophy of thyroid tissue (atrophic hypothyroidism).
3. Transient hypothyroidism.
4. Consumptive hypothyroidism.
5. Central hypothyroidism, that is, hypothyroidism due to insufficient stimulation of a normal gland as a result of hypothalamic or pituitary disease or defects in the thyroid-stimulating hormone (TSH) molecule itself.
6. Resistance to thyroid hormone (RTH).

**Epidemiology**

Global Prevalence:

Primary hypothyroidism accounts for approximately 99% of cases, with fewer than 1% being due to TSH deficiency. Comparison of studies of the prevalence and incidence of hypothyroidism is hampered by differing definitions and population samples. Using a uniform set of diagnostic criteria, the prevalence of previously undiagnosed, spontaneous, overt hypothyroidism in community-based studies has been estimated between 2-4/1000 total population world-wide. If all cases of previously diagnosed hypothyroidism,

previous thyroid surgery and radioiodine treatment are included, this prevalence rises to approximately 10/1000, and if subclinical cases are included, then the prevalence is probably over 50/1000 total population. The annual incidence of overt hypothyroidism is between 1-2/1000 for female and around 2/10,000 for males, with individuals having previously elevated TSH and positive circulating thyroid autoantibodies, being particularly at risk[14].

Prevalence in India :

Among adult people in India, the prevalence of hypothyroidism has been recently studied. In this population-based study done in Cochin on 971 adult subjects, the prevalence of hypothyroidism was 3.9%[1]. The prevalence of subclinical hypothyroidism was also high in this study, the value being 9.4%. In women, the prevalence was higher, at 11.4%, when compared with men, in whom the prevalence was 6.2%. The prevalence of subclinical hypothyroidism increased with age. About 53% of subjects with subclinical hypothyroidism were positive for anti-TPO antibodies

**Clinical Features[15]**

Signs and Symptoms of Hypothyroidism (Descending Order of Frequency)

**Symptoms**

- 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

## SUBCLINICAL HYPOTHYROIDISM

### (a)Definition[3]

Subclinical hypothyroidism is defined as “a serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxine (T4) within the reference range”.

Other terms for this condition are *mild hypothyroidism*, *preclinical hypothyroidism, biochemical hypothyroidism*, and *decreased thyroid reserve*. The TSH elevation in such patients is modest, with values typically between 5 and 15 mU/L[9]. This syndrome is most often seen in patients with early Hashimoto's disease and is a common phenomenon, occurring in 7% to 10% of older women.

### (b) Epidemiology

In population-based studies, the prevalence of subclinical hypothyroidism ranges from 4 to 15 percent [17-21]. In the United States National Health and Examination Survey (NHANES III), which excluded subjects with known thyroid disease, 4.3 percent of 16,533 people had subclinical hypothyroidism. The prevalence rises with age, is higher in females than males, and is lower in blacks than in whites . However, the prevalence is determined by the upper limit of normal for serum TSH. If the upper limit of normal rises with age, as appears

to be the case, then the prevalence may not be as high as has been previously thought.

In Europe, where iodine intake is variable, subclinical hypothyroidism is more prevalent in areas of iodine sufficiency. In one study, the prevalence of subclinical hypothyroidism ranged from 4.2 percent in iodine-deficient areas to 23.9 percent in an area of abundant iodine intake, despite a similar prevalence of patients with high serum concentrations of anti-thyroid peroxidase antibodies [22].

In India, the prevalence of subclinical hypothyroidism has been estimated to be 9.4%[1]. In a study conducted by Gayatri et al[23], the prevalence of subclinical hypothyroidism in asymptomatic pregnant women attending outpatient department, was 2.8% which corroborated with that of western literature.

**(c) Causes[16]**

**1.** Chronic autoimmune thyroiditis

2. Persistent TSH increase in

a.subacute thyroiditis

b. postpartum thyroiditis

c. painless thyroiditis

3. Thyroid injury

a. partial thyroidectomy or other neck surgery,

b. radioactive iodine therapy

c. external radiotherapy of the head and neck

4. Drugs impairing thyroid function:

a.iodine and iodine-containing medications (amiodarone, radiographic contrast agents)

b. lithium carbonate

c. cytokines (especially interferon)

d. aminoglutetimide,

e. ethionamide

f. sulfonamides

g. sulfonylureas

5. Inadequate replacement therapy for overt hypothyroidism

6. Thyroid infiltration

a. Amyloidosis

b. Sarcoidosis

c. Hemochromatosis

d. Riedel's thyroiditis

e. Cystinosis

f. AIDS

g. primary thyroid lymphoma

7. Central hypothyroidism with impaired TSH bioactivity

8. Toxic substances, industrial and environmental agents

9. TSH receptor gene mutations

**(d) Diagnosis**

Patients with subclinical thyroid disease have few or no symptoms or signs of thyroid dysfunction and thus by its very nature, subclinical thyroid disease is a laboratory diagnosis[3]. The reference normal range for TSH, Free T4 and Free T3 taken for this study is as follows(1):

| | | |
|---|---|---|
| TSH | : | 0.34–4.25 mIU/L |
| Free T4 | : | 0.7–1.24 ng/dL |
| Free T3 | : | 2.4–4.2 pg/mL |

**(e) Potential Complications**

1. **Progression to Overt Hypothyroidism**.

In the experience of most clinicians, that process of progression from early thyroid failure to overt hypothyroidism has been slow. This general pattern has prompted most experts to recommend monitoring of the serum TSH concentration at intervals of 6 to 12 months.[24,25] Several longitudinal studies have examined the factors associated with progression.[26] In a recent study, 82

women with subclinical hypothyroidism underwent follow-up for a mean of 9.2 years.[27] Patients were classified into 3 groups on the basis of their initial TSH values—4 to 6, 6 to 12, and greater than 12 µIU/mL—and the 10-year incidence of hypothyroidism was 0%, 42.8%, and 76.9%, respectively, in those 3 groups. The rate of progression to overt hypothyroidism was significantly faster in those women with a higher baseline serum TSH concentration. The presence of anti-TPO antibodies also correlated with a significantly increased incidence of progression to overt hypothyroidism. The influence of the magnitude of the antibody elevation has not been specifically studied. On the basis of these criteria, our patient had a likelihood of progression to overt hypothyroidism of approximately 5% per year.

2. **Association with Dyslipoproteinemia and Atherosclerosis**

A relationship between dyslipidemia and atherosclerosis is well established in overt hypothyroidism [28]. Early clinical and autopsy studies have suggested an association between subclinical hypothyroidism and coronary heart disease [29,30]. Furthermore, in a recent population-based survey, subclinical hypothyroidism emerged as an independent risk factor for aortic atherosclerosis and myocardial infarction [31]. However, the association of SCH with changes in serum lipid levels and the effect of l-T4 replacement on these changes are still open questions, despite the fact that several clinical trials have addressed the issue. In some large epidemiological studies, no association could

be detected between SCH and serum TC or LDLc levels.Tzotzas et al. [31] recently reported that none of the commonly measured lipoproteins differed between SCH patients and controls, nor did the lipoprotein profile change significantly in SCH patients upon achieving euthyroidism. In contrast, Caron et al.[32] reported lower HDLc levels in SCH patients than in a control group and demonstrated a significant increase in ApoA and HDLc levels after l-T4 therapy,with normalization of the TC/HDLc ratio. Arem and Patsch [33], on the other hand, reported a reduction in LDLc, ApoB,and the TC/HDL ratio after l-T4 replacement in a group of SCH patients with a mean TSH level of 16.6 mIU/liter. Recently, a double-blind, placebo-controlled trial [34] demonstrated the effectiveness of l-T4 replacement therapy in both reducing LDL cholesterol levels and improving clinical symptoms of hypothyroidism in SCH patients. Moreover, LDLc decrease was more pronounced in SCH patients with high TSH values (12 mIU/liter) or elevated pretreatment LDLc levels (4.0mmol/liter). These rather disparate results may depend on differences in patient selection (e.g. cause and duration of thyroid dysfunction, range of TSH values, smoking status) as well as time of evaluation after restoration of euthyroidism[35].

## Atherosclerosis

The relationship between subclinical hypothyroidism and the later development of atherosclerosis is unclear.[36,37,38] The Whickham survey found no relationship between initial TSH levels and the subsequent development of ischemic heart disease over 20 years of followup.[38]

A widely publicized population-based study of 1,149 women aged 55 or older from Rotterdam came to a different conclusion.[37] The main analysis in the paper was cross-sectional. In that analysis, after adjustment for age, body mass index, cholesterol level, blood pressure, and smoking status, a serum TSH greater than 4.0 mU/L was associated with a history of myocardial infarction (OR, 2.3; CI, 1.3-4.2) and with atherosclerosis of the abdominal aorta, which was diagnosed by blinded review of a lateral radiograph of the lumbar spine (OR, 1.9; CI, 1.2-3.1). An analysis of incident myocardial infarction over 3 to 6 years of followup found a statistically non-significant increased risk in women with a serum TSH greater than 4.0 mU/L (adjusted relative risk, 2.5; CI, 0.7-9.1).

The strengths of the Rotterdam study are the relatively large sample size, adjustment for some potential confounders, and validated, blinded assessment of outcomes. Because the study was primarily cross-sectional, however, the findings do not prove that an elevated TSH precedes the development of

atherosclerosis. The prospective part of the study adds little because, at baseline, the women who had an elevated TSH had a higher prevalence of atherosclerotic disease; they would be expected to have a higher incidence of myocardial infarction over 3 to 6 years, in any case. The prospective analysis would have been more consequential if patients who had atherosclerosis at baseline had been excluded.

In the Rotterdam study, women with subclinical hypothyroidism had lower lipid levels than euthyroid women; this might be an artifact of higher use of diet or other lipid-lowering therapy in women with known cardiovascular risk factors, but it also might suggest that atherosclerosis developed by another mechanism. One hypothesis is that elevations in both homocysteine and cholesterol may contribute to the elevated risk for atherosclerosis in overt hypothyroidism. In cross-sectional studies, including an analysis of the Second National Health and Nutrition Examination Survey (NHANES-II) sample, patients with overt hypothyroidism had higher homocysteine levels than euthyroid patients.[39,40] The association of elevated homocysteine and overt hypothyroidism appears to persist after controlling for serum folate levels, which are decreased in overt hypothyroidism.[41,42,43] However, in the only study concerning patients who had subclinical hypothyroidism, there was no association.[44]

**3. Symptoms, mood, and quality of life.**

In its 1998 review and guideline, the American College of Physicians concluded that, in the general population, it was not clear if the prevalence and severity of symptoms and quality of life differs for individuals who have mildly elevated TSH levels[45,46]. Since then, 2 cross-sectional studies in volunteers have addressed this question, with mixed results. A cross-sectional interview survey of 825 Medicare enrollees in New Mexico found no differences in the age-adjusted frequency of self-reported symptoms between participants with serum TSH elevations from 4.7 to 10 mU/L and those with normal TSH concentrations.[47] A larger survey from Colorado (n = 25,862) is less pertinent because it included subjects who took levothyroxine in the analysis of symptoms. It also found no difference between euthyroid subjects and those with subclinical hypothyroidism in current symptoms, but found a higher percentage of "changed symptoms" in the subclinical hypothyroid group (13.4% vs 15.4%).[48]

Patients who have subclinical hypothyroidism and a history of antithyroid treatment for Graves' disease or nodular thyroid disease have a higher prevalence of symptoms than healthy controls.[49,50] It is likely that this observation is valid, but an important limitation of the evidence should be noted: the appropriate comparison group is not healthy volunteers, but patients who have a normal TSH and a history of antithyroid treatment. The reason is

that euthyroid patients who have a history of treatment for hyperthyroidism also have a higher prevalence of anxiety, depression, and psychosocial dysfunction than healthy controls.[51]

**4. Pregnancy complications.**

Three recent reports from a cohort study of pregnant women have linked TSH levels in pregnancy to poor obstetric outcomes and to poor cognitive development in children. In the first report, among 9,403 women with singleton pregnancies, serum TSH measurements were 6 mU/l or greater in 209 women (2.2%).[52] The rate of fetal death was significantly higher in those pregnancies (3.8%) than in the women with serum TSH less than 6 mU/l (0.9%, OR, 4.4; 95% CI, 1.9–9.5). In the second report, the children of women who had a high serum TSH (mean 13.2 ± 0.3 mU/L) in the first trimester of pregnancy had lower IQ scores than matched controls (mean serum TSH 1.4 ± 0.2 mU/L) when they were 7 to 9 years of age.[53] The average difference in IQ was 7 points; 19% of the children of hypothyroid mothers had IQ scores of 85 or less. Although no statistical adjustment for baseline differences was done, at baseline, age, socioeconomic status, and other risk factors for low IQ were similar in the 2 groups. Results for the subgroup who had subclinical hypothyroidism were not broken out, but most of the women fell into this

category (that is, they had normal T4 levels).The third report from these authors analyzed TSH levels by outcomes. Fifty percent of the children of 20 mothers who had a TSH equal to or higher than the 99.85 percentile had IQ scores greater than 1 standard deviation (SD) below the control mean. Fifteen percent of the children of controls, and 21 percent of the children of women who had a TSH between the 98 and 99.85 percentile, had IQ scores this low.

### (f) Management of Subclinical hypothyroidism[54]

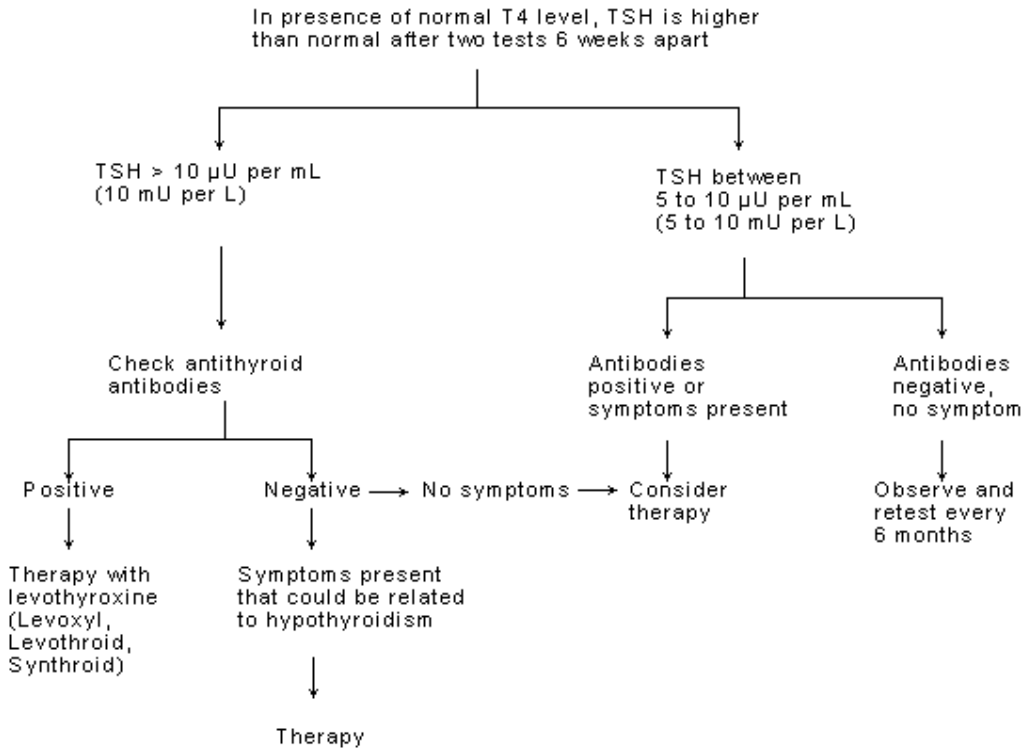



**Figure 3.** Algorithm for the management of subclinical hypothyroidism. (T4 = thyroxine; TSH = thyrotropin-stimulating hormone)

Indications for treatment in subclinical hypothyroidism are not established, but general guidelines can be offered. Greater magnitude and duration of TSH elevation and higher titers of antithyroid antibodies increase the probability that the condition will progress to overt hypothyroidism and, therefore, increase the potential benefit of treatment with levothyroxine. The presence of symptoms that might be related to mild hypothyroidism also increases the potential benefit of treatment. Risk of harm to the patient, against which this potential benefit must be balanced, is quite small, since the use of the sensitive TSH assay provides assurance that we are not raising the blood thyroid hormone levels too much as long as TSH levels do not fall below the normal range. In patients with coronary artery disease and minimal elevations of TSH, however, it may be advisable to follow the TSH level rather than subject the patient to the small risk of levothyroxine therapy.

In short, it seems reasonable to treat patients who have a TSH level that is consistently elevated above 10 μU per mL (10 mU per L), especially if titers of antithyroid antibodies are increased. Also, patients who complain of fatigue, dry skin, constipation, muscle cramps or other common symptoms of hypothyroidism may possibly benefit from treatment even if their TSH level is elevated only into the 5 to 10 μU per mL (5 to 10 mU per L) range. An algorithm summarizing this approach is presented in Figure 3.

Management in Pregnancy[55]

There is only fair evidence to support an association between subclinical hypothyroidism and adverse outcomes in pregnancy. However, the consensus panel[56]. recommends screening serum TSH levels in patients who are pregnant or who are planning to become pregnant when there is a family or personal history of thyroid disease, evidence of goiter, symptoms of hypothyroidism, type 1 diabetes, or a personal history of autoimmune disorder.

Although there are few data, the panel recommends treatment with levothyroxine during pregnancy to maintain serum TSH levels within the reference range, with repeat testing every six to eight weeks. Physiologic requirements of levothyroxine often increase during pregnancy; therefore, women who were receiving therapeutic replacement dosages before becoming pregnant should have their serum TSH level monitored every six to eight weeks during pregnancy.[56]

Treatment

Treatment is similar to that recommended in patients with overt hypothyroidism. Levothyroxine is the agent of choice, rather than a preparation containing tri-iodothyronine (T3), since T3 has a short half-life and requires multiple daily doses to maintain blood levels in the normal range. Levothyroxine, however, has a long half-life (approximately seven days) and is

partially converted to T3 in the body, resulting in a constant physiologic blood level of both T4 and T3 with a single daily dose.[57]

In patients with overt hypothyroidism, the average daily replacement dosage of levothyroxine is 75 to 125 μg, or 50 to 100 μg in the elderly, or about 1.6 μg per kg per day. Treatment is commonly initiated with 25 to 50 μg daily and raised by increments of 25 to 50 μg, according to TSH measurements at six- to eight-week intervals. In patients who are elderly or debilitated, or who have heart disease, lower starting dosages and slower increases are advisable.

Patients with subclinical hypothyroidism, because of the minimal extent of the thyroid hormone deficiency, may be controlled with total daily dosages of levothyroxine as low as 25 to 50 μg. This initial dosage should be maintained for six to eight weeks before a TSH measurement is repeated to guide adjustment of the levothyroxine dosage. The goal is to maintain the TSH level within normal limits; the dosage of levothyroxine should be increased if the TSH level remains above normal and should be decreased if the TSH level falls below normal. Once the correct dosage of thyroxine is established, the frequency of TSH measurement may be decreased to every six to 12 months.

A common error is the failure to decrease the levothyroxine dosage if the TSH level is suppressed below the normal range, which may occur without the free T4 level rising above normal. This state is considered to represent

"subclinical hyperthyroidism," and although formerly it was thought to be harmless, it is now believed to be associated with undesired effects on bone density (osteoporosis) and cardiac function, and to be a possible cause of neuropsychologic symptoms and other mild manifestations of hyperthyroidism.[58,59]

## C-REACTIVE PROTEIN

**C-reactive protein** (**CRP**) is a protein found in the blood, the levels of which rise in response to inflammation (i.e. C-reactive protein is an acute-phase protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex.[60]

CRP is synthesized by the liver[61] in response to factors released by fat cells (adipocytes).[62] It is a member of the pentraxin family of proteins. It is not related to C-peptide or protein C. C-reactive protein was the first pattern recognition receptor (PRR) to be identified.[63]

History and nomenclature

CRP was so named because it was first discovered as a substance in the serum of patients with acute inflammation that reacted with the C- (capsular) polysaccharide of pneumococcus.

Discovered by Tillett and Francis in 1930 [64], it was initially thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer, however, discovery of hepatic synthesis demonstrated that it is a native protein.[65]

Molecular Structure

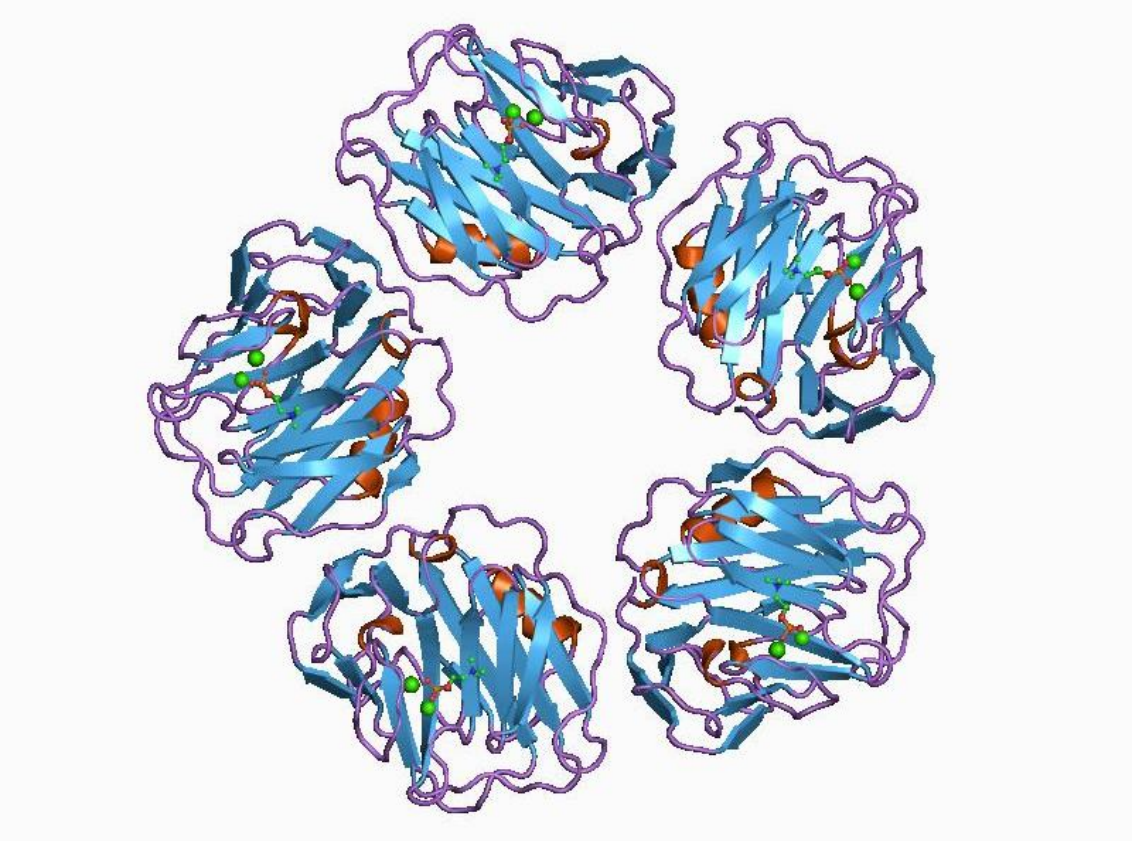


**Figure 4. Molecular structure of C-Reactive Protein**

The human *crp* gene is located on chromosome 1q23[66], and consists of two exons and one intron.[67] CRP is synthesized as a 206 amino acid polypeptide and secreted by hepatocytes as an approximately 23 κDa, non-glycosylated monomer, which non-covalently associates to form the homopentameric ring structure characteristic of pentraxin family members. CRP molecule folds to form a flattened jellyroll structure, which then assembles into a radially symmetrical pentamer. (Figure 4).

## ASSOCIATIONS OF CRP WITH ATHEROSCLEROSIS

Our understanding of atherosclerosis has evolved beyond the view that these lesions consist of a lifeless collection of lipid debris. Current evidence supports a central role for inflammation in all phases of the atherosclerotic process. Substantial biological data implicate inflammatory pathways in early atherogenesis, in the progression of lesions, and finally in the thrombotic complications of this disease. Clinical studies affirm correlation of circulating markers of inflammation with propensity to develop ischemic events and with prognosis after ACS[68].

## CRP: A NOVEL, PROATHEROGENIC INFLAMMATORY ADIPOKINE

Adipokines are mediators of endothelial injury And atherosclerosis.

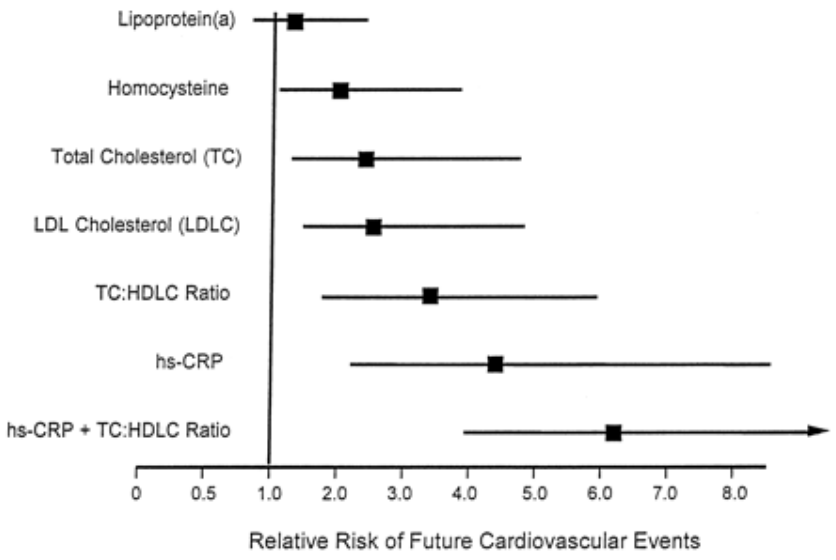
CRP is not merely an inflammatory marker but directly participates in the process of atherogenesis by modulating endothelial function [69]. CRP, at concentrations known to predict cardiovascular events, induces the expression of VCAM-1, ICAM-1, selectins, and MCP-1 in cultured endothelial cells via increased secretion of ET-1, a potent endogenous vasoconstrictor, and IL-6 . CRP attenuates basal and stimulated endothelial NO production by downregulating endothelial NO synthase mRNA and protein expression[70]. The diminished NO activity may in turn inhibit angiogenesis, an important compensatory response in chronic ischemia. Furthermore, in vascular smooth muscle cells, CRP upregulates angiotensin type 1 receptor ($AT_1$-R) mRNA and protein levels and increased $AT_1$-R expression on the cell surface . The $AT_1$-R is a key atherosclerotic switch that facilitates ANG II-induced reactive oxygen species production, vascular smooth muscle cell migration and proliferation, and vascular remodeling [71]. Interestingly, the effect of CRP on endothelial dysfunction is potentiated by hyperglycemia, and these effects are attenuated by rosiglitazone, an insulin-sensitizing thiazolidinedione (TZD) antidiabetic drug .

Direct Comparisons of HSCRP With Other Novel Markers of Vascular Risk [72]

Testing for homocysteine and lipoprotein(a), both of which are involved in atherothrombosis, have been recommended for certain high-risk groups. For example, homocysteine evaluation is recommended among those with impaired methionine metabolism due to renal failure or hypothyroidism, whereas

lipoprotein(a) assessment has been recommended for those with premature atherosclerosis in the absence of other risk factors.

Three large-scale prospective studies have compared directly the relative efficacy of homocysteine screening to HSCRP evaluation. In each study, magnitude of risk prediction associated with HSCRP levels in the top quintile was greater than that associated with similar elevations of homocysteine.




**High Sensitivity C-Reactive Protein**

Standard clinical assays for CRP typically have a lower detection limit of 3 to 8 mg/L. Thus, these assays lack sensitivity within the low-normal range and cannot be used effectively for vascular risk prediction. In recognition of this limitation, initial epidemiological studies used research-based assays designed to determine CRP levels with excellent fidelity and reproducibility across the normal range. Several such “high-sensitivity” or “ultra-sensitive” assays for

CRP are now commercially available, and formal standardization programs have been undertaken to ensure comparability across hs-CRP assays.

Reference Range for hs-CRP

- Less than 1.0 mg/L = Low Risk for CVD
- 1.0 – 2.9 mg/L = Intermediate Risk for CVD
- Greater than 3.0 mg/L High Risk for CVD

Other conditions in which hs-CRP is elevated

hs-CRP is non specific, and is elevated in a number of other conditions like,

- Malignancy
- Connective tissue disease
- Infection
- Inflammatory bowel disease (IBD)
- SLE
- Pneumococcal pneumonia
- Rheumatoid arthritis
- Acute Rheumatic fever
- Tuberculosis

# MATERIALS & METHODS

## (a) SUBJECTS

Case Group: Patients with subclinical hypothyroidism attending Endocrinology Outpatient Department and those who are inpatients in Rajiv Gandhi Government General Hospital, Chennai.

Control Group: Patients who are Euthyroid and matched with cases in terms of age, sex and height, and not having any of the exclusion criteria.

## (b) PERIOD OF STUDY

6 months

## (c) DESIGN OF STUDY

Cross-sectional study

## (d) CONSENT

Informed consent from all patients

## (e) ELIGIBILITY CRITERIA

CASES : Patients with subclinical hypothyroidism based on serum TSH and free T4 levels, attending Endocrinology OPD and those who are inpatients in Government General Hospital, Chennai.

CONTROLS : Patients who are euthyroid, based on serum TSH and free T4 levels, attending Endocrinology OPD or those admitted for diseases other than those listed in exclusion criteria, with normal thyroid profile.

## (f) EXCLUSION CRITERIA

- Patients who are already on thyroxine replacement therapy.
- Patients with coexisting Diabetes mellitus and Hypertension.
- Patients with rheumatological disorders.
- Patients who have fever of any cause.
- Patients taking any medication that can raise hs-CRP levels (NSAIDs/Statins/HRT).
- Patients who have undergone any surgery in the recent past.
- Patients with recent trauma.
- Patients who are smokers.

- Patients who already have Coronary Artery Disease.

**(g) METHODOLOGY**

Patients with subclinical hypothyroidism based on serum TSH and free T4 levels were carefully selected, based on the inclusion and exclusion criteria. Complete and relevant history was elicited and a thorough general and systemic examination was done as per proforma. Blood samples were collected after overnight fast, and analysed for the required parameters. The same protocol was followed for controls.

**(h) Investigation details**

Complete history and examination was done. Blood / Serum samples were collected after overnight fast for Complete Blood Count, Fasting Blood Sugar, Renal Function Tests, Liver Function Tests, Lipid Profile (Total cholesterol, Triglycerides and HDL), High Sensitivity C-Reactive Protein (by turbidometry), ECG and Echocardiogram if necessary.

**(i) Data Collection And Methods**

Collection of data as per proforma with consent from Cases and Controls in Medicine wards and OP department.

Analysis : Data analyzed using statistical Package-SPSS software

Conflict of interest : Nil.

Financial data : Nil

**(h) Normal Values of parameters Assessed[15]**

TSH : 0.34–4.25 mIU/L

Free T4 : 0.7–1.24 ng/dL

Free T3 : 2.4–4.2 pg/mL

Fasting Plasma Glucose : 75-100 mg/dl

Total Cholesterol : Less than 200 mg/dl

Triglycerides : 30-200 mg/dl

HDL Cholesterol : 40-60 mg/dl

High Sensitivity C-Reactive Protein (based on the risk for atherosclerosis):

Low Risk : Less than 1 mg/l

Intermediate Risk : 1-2.9 mg/l

High Risk : More than or equal to 3 mg/l

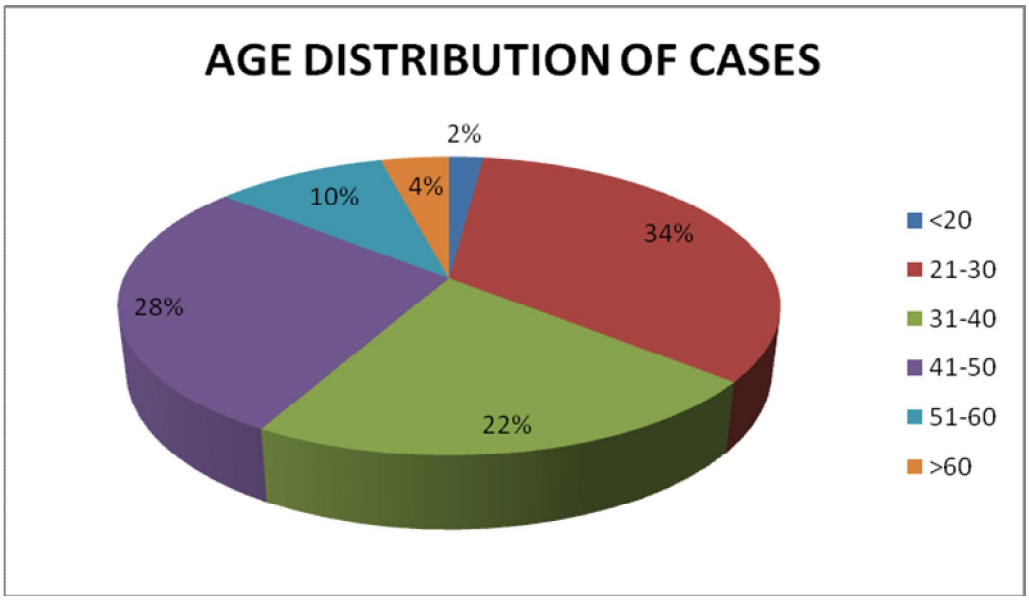
# OBSERVATIONS

## (1) AGE DISTRIBUTION

### (A) CASES

**Table 1. showing age distribution among cases**

| AGE | NUMBER |
|---|---|
| **<20** | 1 |
| **21-30** | 17 |
| **31-40** | 11 |
| **41-50** | 14 |
| **51-60** | 5 |
| **>60** | 2 |
| **TOTAL** | **50** |

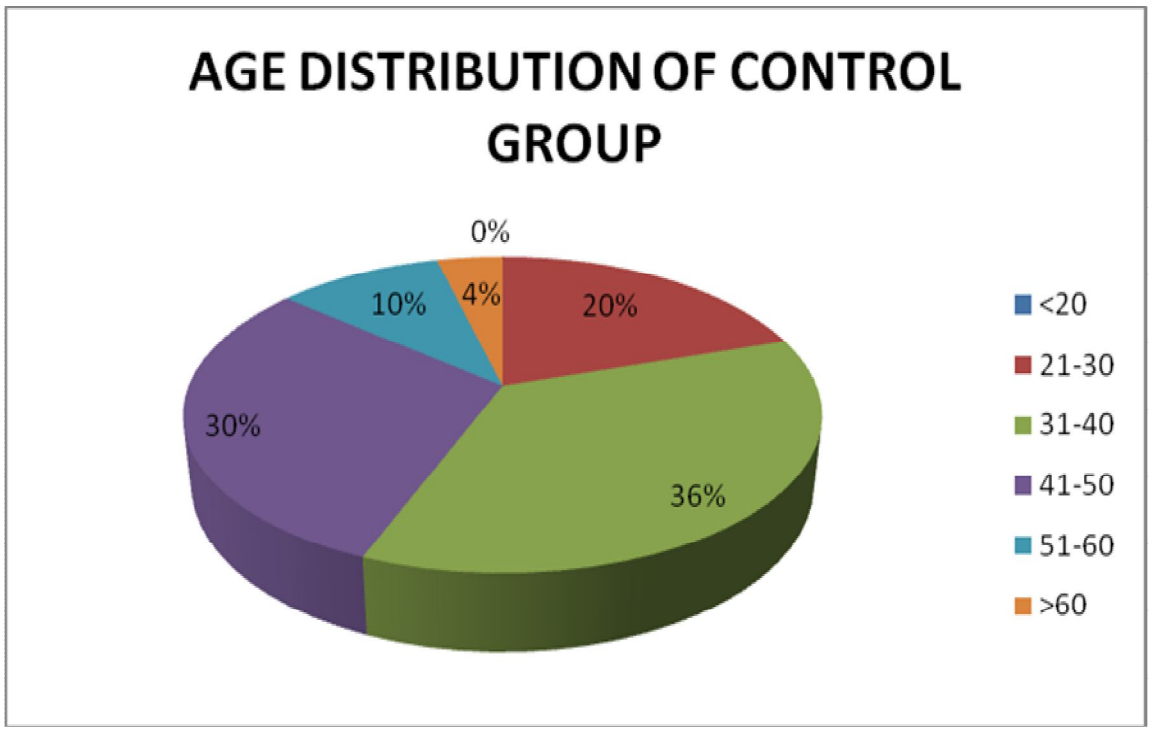



Among cases, most were aged between 21 to 30 years (34%), and the least number of cases were found in extremes of age, i.e. less than 20 (2%) and more than 60 years (4%) of age. In a broader sense, the bulk of the cases were constituted by 21 to 50 years of age.

**(B) CONTROL GROUP**

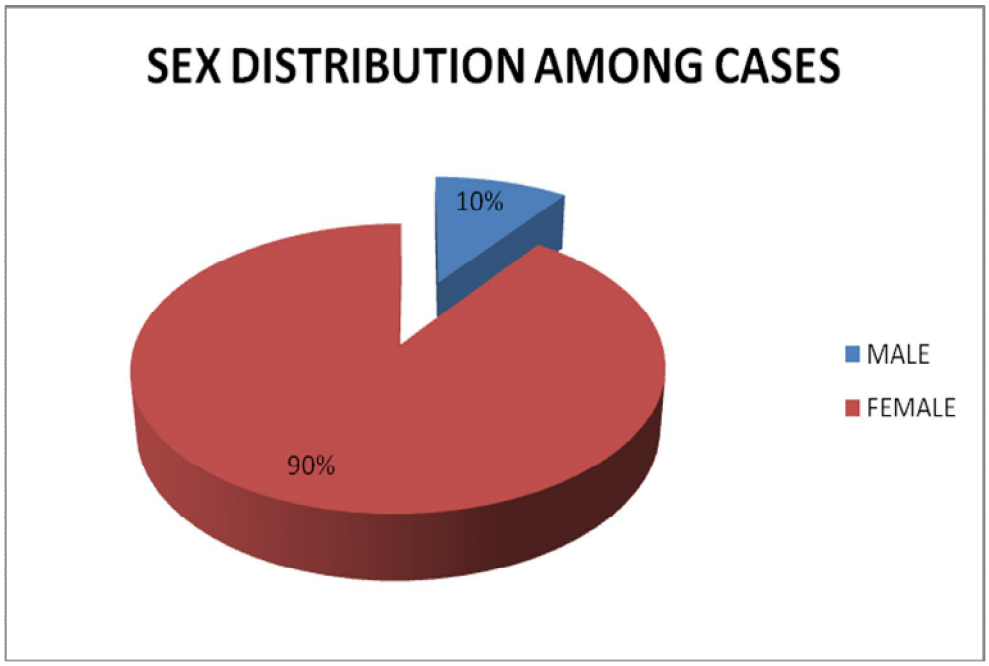
**Table 2. showing age distribution among controls**

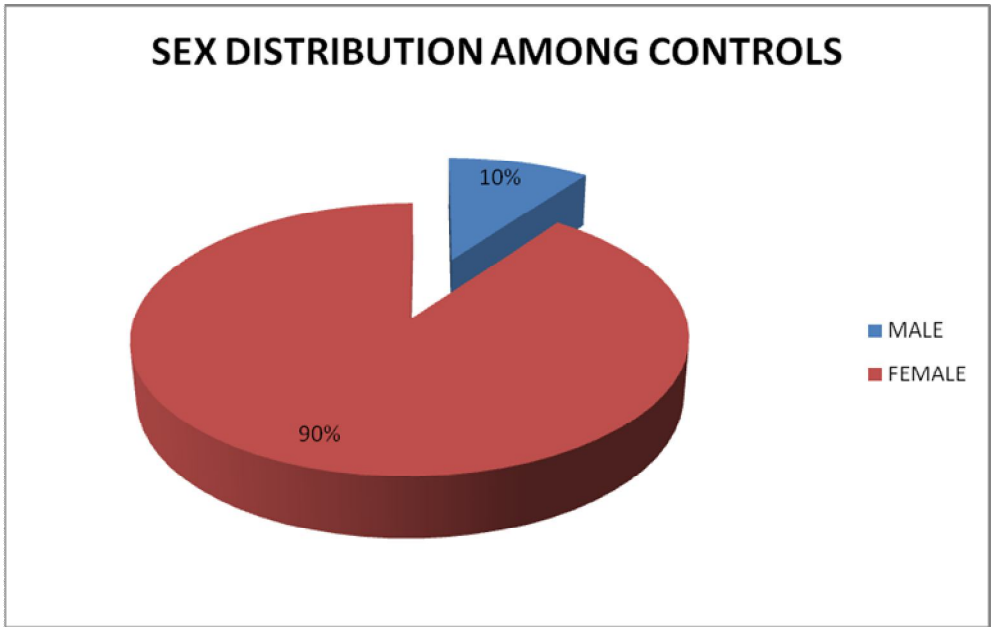
| **AGE** | **NUMBER** |
|---|---|
| **<20** | 0 |
| **21-30** | 10 |
| **31-40** | 18 |
| **41-50** | 15 |
| **51-60** | 5 |
| **>60** | 2 |
| **TOTAL** | 50 |




Among controls, most were aged between 31 to 40 years (36%), and the least number of cases were found in extremes of age, i.e. less than 20 (0%) and more than 60 years (4%) of age. Like cases, in a broader sense, the bulk of the cases were constituted by 21 to 50 years of age.

## (2) SEX DISTRIBUTION



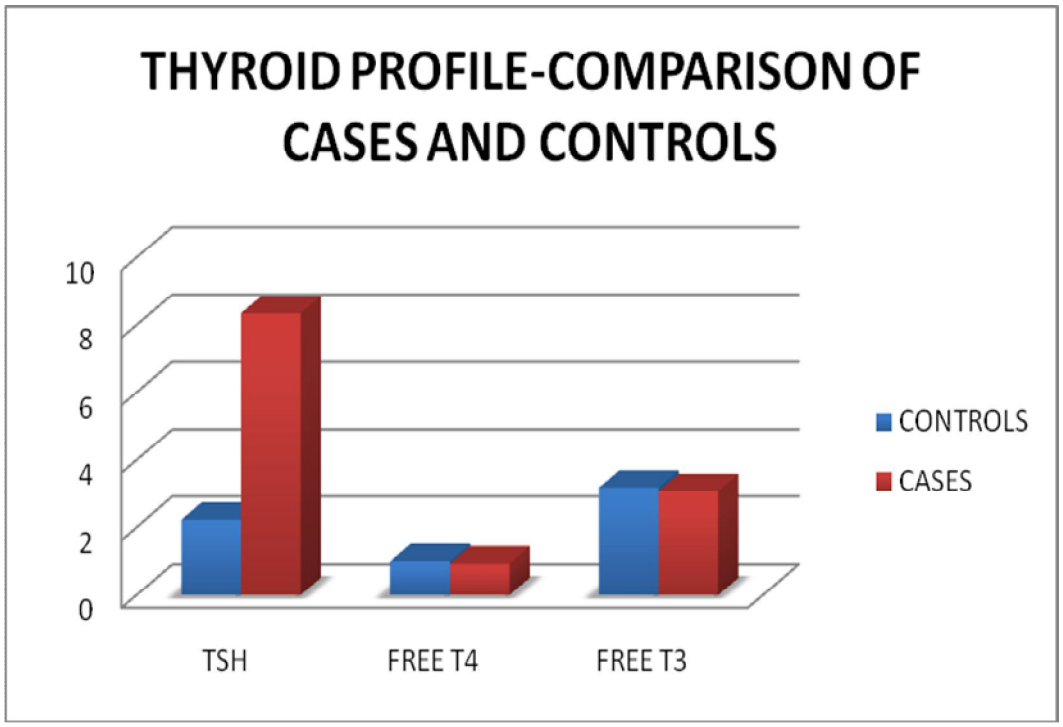



Among cases, females predominated, constituting 90% of total cases. Since we chose controls matched with cases for sex also, the sex distribution of controls is exactly the same as cases, i.e 90% females and 10% males.

**3) THYROID PROFILE**

**Table 3. Comparing mean levels of TSH, T4 and T3 among cases and controls**

| | **CONTROLS** | **CASES** |
|---|---|---|
| **TSH** | 2.22 | 8.35 |
| **FREE T4** | 0.99 | 0.92 |
| **FREE T3** | 3.17 | 3.07 |

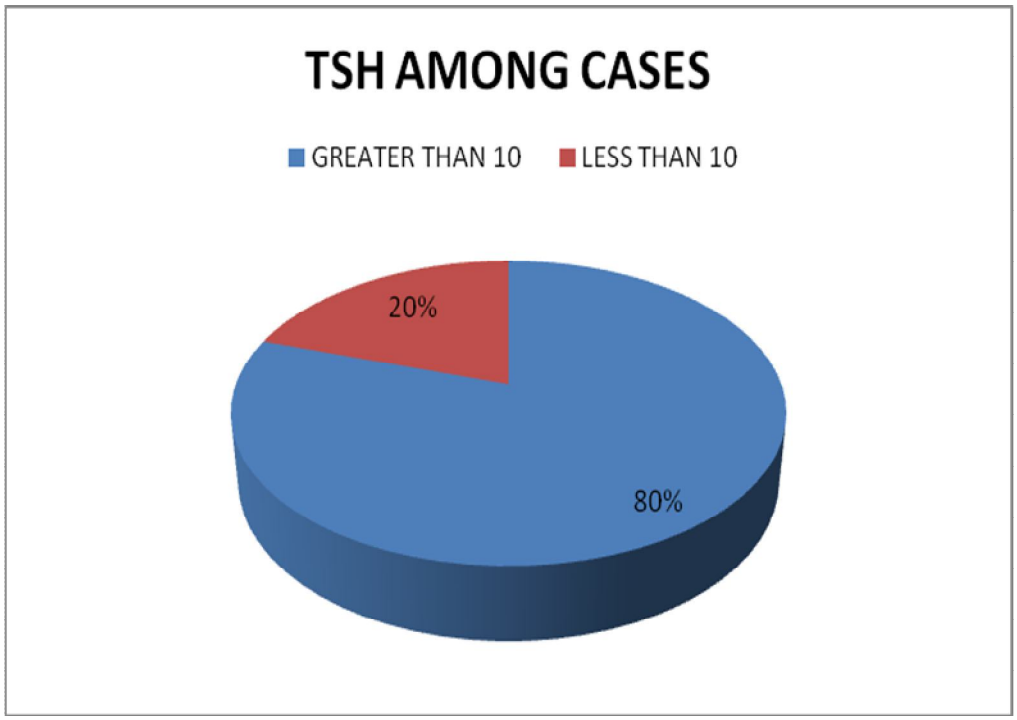



From the above table and diagram, it is inferred that the levels of TSH are above normal in cases and within normal limits in controls. Levels of Free T4 and Free T3 are within normal limits in both cases and controls, but the mean levels of both are slightly on the lower side in cases, when compared to controls.

## TSH LEVELS IN CASES

**Table 4. showing TSH levels among cases, taking 10 as the cut-off**

| | |
|---|---|
| GREATER THAN 10 | 40 |
| LESS THAN 10 | 10 |

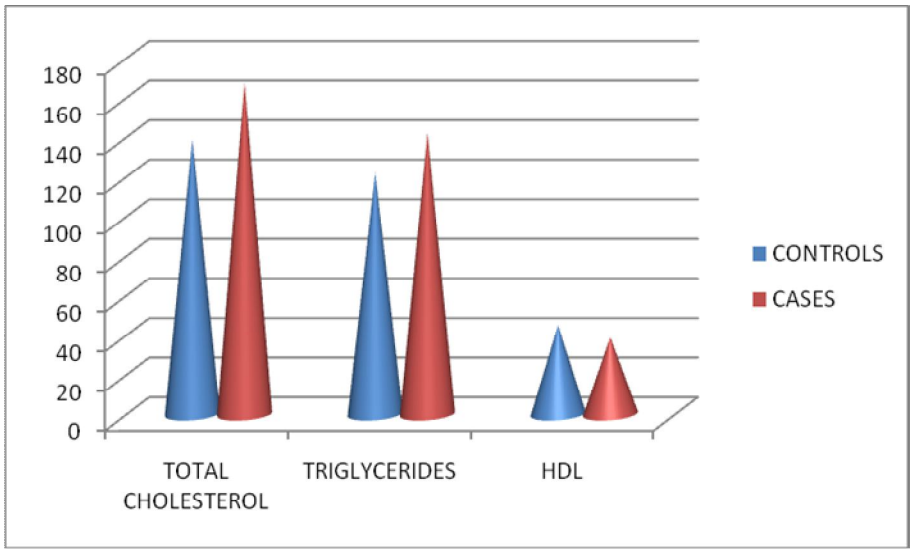



Levels of TSH among cases below 10 mIU/ml constituted the maximum, with 40 out of 50 cases in this range (80%).

## (5) COMPARISON OF LIPID PROFILE OF CASES AND CONTROL

**Table 5. showing mean levels of Total cholesterol, Triglycerides and HDL among controls and cases**

| | CONTROLS | CASES |
|---|---|---|
| **TOTAL CHOLESTEROL** | 138.98 | 167.56 |
| **TRIGLYCERIDES** | 122.02 | 142.06 |
| **HDL** | 44.88 | 38.8 |

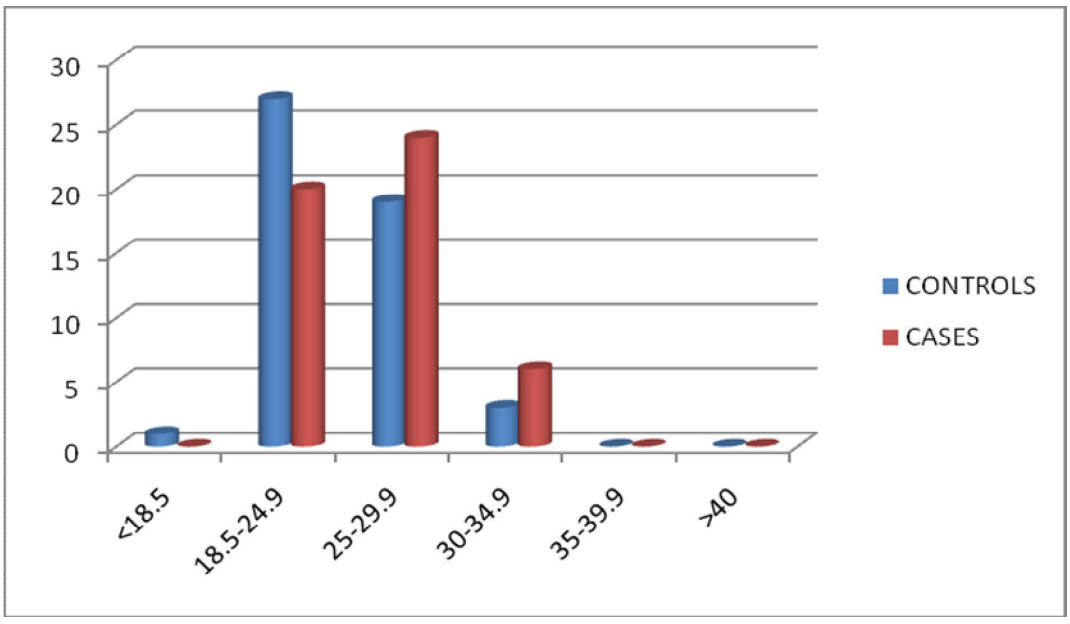



From the above table and diagram, it is inferred that mean values of Total cholesterol and Triglycerides are higher among cases than controls. Mean value of HDL was lower among cases.

## 6) RISK STRATFICATION OF CASES AND CONTROLS BASED ON BMI

**Table 6. comparing the cases and controls by Body Mass Index, stratified into classes of obesity**

| CLASS | BMI | CONTROLS | CASES |
|---|---|---|---|
| **UNDERWEIGHT** | **<18.5** | 1 | 0 |
| **HEALTHY WEIGHT** | **18.5-24.9** | 27 | 20 |
| **OVERWEIGHT** | **25-29.9** | 19 | 24 |
| **OBESITY CLASS I** | **30-34.9** | 3 | 6 |
| **OBESITY CLASS II** | **35-39.9** | 0 | 0 |
| **OBESITY CLASS III** | **>40** | 0 | 0 |
| | **TOTAL** | 50 | 50 |



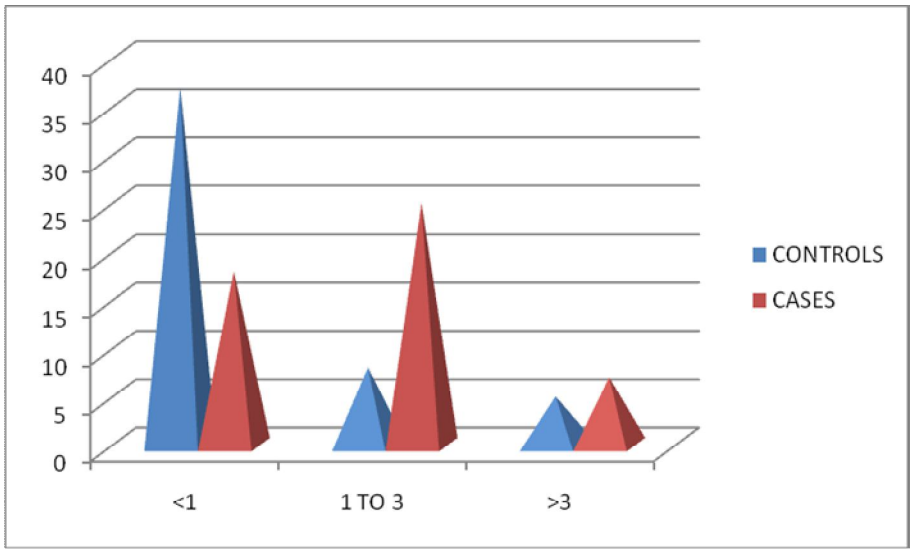
From the above table and diagram, it is inferred that in both case and control group, most of the individuals are clustered in the 'healthy weight' and 'overweight' category, as far as BMI is concerned. A few of them are in the category of Class I obesity. One person in the control group is underweight. None among the cases or controls are in Class II or III obesity.

It is also inferred that the proportion of individuals in the 'healthy weight' group is lower among cases when compared to controls. Also, the proportion of individuals in the 'over weight' and class I obesity are higher among cases when compared to controls.

## 7) hs-CRP LEVELS OF VARYING SEVERITY AMONG CASES AND CONTROLS

**Table 7. Comparison of cases and controls by hs-CRP, stratified into risk groups**

| **hs-CRP** | **CONTROLS** | **CASES** |
|---|---|---|
| **<1** | 37 | 18 |
| **1 TO 3** | 8 | 25 |
| **>3** | 5 | 7 |
| **TOTAL** | 50 | 50 |




From the above table and diagram, it is inferred that the number of cases with levels of hs-CRP in the intermediate and High risk range, is obiously higher among than controls. In the low risk range, control group have more number than cases.

## STATISTICAL ANALYSIS

### (A) Analysis of cases and controls in terms of age:

**TABLE 8.**

| | CONTROLS | | CASES | | P VALUE |
|---|---|---|---|---|---|
| | MEAN | S.D. | MEAN | S.D. | |
| AGE | 39.44 | 10.5 | 39.04 | 11.31 | 0.855 |

From the above table, it is inferred that there is no statistically significant association between cases and controls in terms of age as the p value is >0.05.

**(B) Analysis of cases and controls in terms of height, weight and BMI**

**TABLE 9.**

| | **CONTROLS** | | **CASES** | | **P VALUE** |
|---|---|---|---|---|---|
| | **MEAN** | **S.D.** | **MEAN** | **S.D.** | |
| **HEIGHT** | 1.59 | 0.07 | 1.59 | 0.07 | 0.566 |
| **WEIGHT** | 61.96 | 8.91 | 66.14 | 10.16 | .031 |
| **BMI** | 25.09 | 3.47 | 25.02 | 3.41 | 0.036 |

From the above table, it is inferred that there is no statistically significant association between cases and controls in terms of height as the p value is >.05. But there is statistically significant association in terms of weight and BMI as the p value is <0.05.

**(C) Analysis of cases and controls in terms of Waist Hip Ratio**

**TABLE 10.**

| | CONTROLS | | CASES | | P VALUE |
|---|---|---|---|---|---|
| | **MEAN** | **S.D.** | **MEAN** | **S.D.** | |
| **WAIST CIRCUMFERENCE** | 82.74 | 10.1 | 83.76 | 11.35 | 0.636 |
| **HIP CIRCUMFERENCE** | 91.96 | 9.25 | 91.64 | 11.49 | 0.88 |
| **WAIST HIP RATIO** | 0.9 | 0.09 | 0.91 | 0.1 | 0.509 |

From the above table, it is inferred that there is no statistically significant association between cases and controls in terms of Waist and Hip circumference and waist/hip ratio as the p value is >0.05.

**(D) Analysis of cases and controls in terms of Blood Pressure**

**TABLE 11.**

| **BLOOD PRESSURE** | **CONTROLS** | | **CASES** | | **P VALUE** |
|---|---|---|---|---|---|
| | **MEAN** | **S.D.** | **MEAN** | **S.D.** | |
| **SYSTOLIC BP** | 114.12 | 4.36 | 115.08 | 6.44 | 0.385 |
| **DIASTOLIC BP** | 75.2 | 4.99 | 75.48 | 5.1 | 0.782 |

From the above table, it is inferred that there is no statistically significant association between cases and controls in terms of Blood pressure, as the p value is >0.05.

**(E) Analysis of cases and controls in terms of Lipid Profile**

**TABLE 12.**

| **LIPID PROFILE** | **CONTROLS** | | **CASES** | | **P VALUE** |
|---|---|---|---|---|---|
| | **MEAN** | **S.D.** | **MEAN** | **S.D.** | |
| **TOTAL CHOLESTEROL** | 138.98 | 53.54 | 167.56 | 42.41 | 0.004 |
| **HDL CHOLESTEROL** | 44.88 | 7.33 | 38.8 | 8.32 | 0.000 |
| **TRIGLYCERIDE** | 122.02 | 28.7 | 142.06 | 50.51 | 0.017 |

From the above table, it is inferred that there is statistically significant association between cases and controls in terms of Total cholesterol, HDL cholesterol and Triglycerides, as the p value is <0.05.

**(F) Analysis of cases and controls in terms of Thyroid Profile**

**TABLE 13.**

| THYROID FUNCTION TESTS | CONTROLS | | CASES | | P VALUE |
|---|---|---|---|---|---|
| | MEAN | S.D. | MEAN | S.D. | |
| TSH | 2.22 | 1.02 | 8.35 | 2.26 | 0.000 |
| FREE T4 | 0.99 | 0.17 | 0.92 | 0.16 | 0.036 |
| FREE T3 | 3.17 | 0.61 | 3.07 | 0.53 | 0.431 |

From the above table, it is inferred that there is statistically significant association between cases and controls in terms of TSH, as the p value is <0.05.There is no statistically significant association between cases and controls in terms of Free T4 and Free T3, as the p value is >0.05.

**(G) Analysis of cases and controls in terms of hs-CRP**

**TABLE 14.**

| | CONTROLS | | CASES | | P VALUE |
|---|---|---|---|---|---|
| | MEAN | S.D. | MEAN | S.D. | |
| hsCRP | 1.15 | 1.2 | 1.93 | 1.49 | 0.005 |

From the above table, it is inferred that there is statistically significant association between cases and controls in terms of hs-CRP, as the p value is <0.05.

**ANALYSIS OF CORRELATION OF VARIABLES STUDIED WITH HS CRP**

**Table 15.**

| S.NO | COMPARED PARAMETERS | F VALUE | P VALUE |
|---|---|---|---|
| **1** | AGE AND hs-CRP | 0.825 | 0.682 |
| **2** | TSH AND hs-CRP | 58.35 | 0.00 |
| **3** | FT4 AND hs-CRP | 1.24 | 0.41 |
| **4** | FT3 AND hs-CRP | 1.06 | 0.51 |
| **5** | TOTAL CHOLESTEROL AND hs-CRP | 0.65 | 0.81 |
| **6** | TRIGLYCERIDES AND hs-CRP | 1.29 | 0.38 |
| **7** | HDL AND hs-CRP | 0.78 | 0.71 |
| **8** | BMI AND hs-CRP | 0.57 | 0.87 |
| **9** | W/H RATIO AND hs-CRP | 1.16 | 0.45 |

From the above table, it is inferred that there is statistically significant correlation between TSH levels and hs-CRP, as the p value is <0.05. The other variables, like age, Free T4, Free T3, Total cholesterol, Triglycerides, HDL, Body Mass Index and Waist/Hip ration did not show any correlation with HS-CRP, as the p value is >0.05.

**Table 16.**

| | **Statistical parameter** | **TSH** | **HS-CRP** |
|---|---|---|---|
| **TSH** | **Pearson Correlation** | 1 | 0.856 |
| | **N** | 50 | 50 |
| | **Significance (2 tailed)** | 0.000 | 0.000 |
| **HSCRP** | **Pearson Correlation** | 0.856 | 1 |
| | **N** | 50 | 50 |
| | **Significance (2 tailed)** | 0.000 | 0.000 |

Tests for the association between TSH and hs-CRP also showed that there is a strong association between the two, as the p value is <0.05.

# DISCUSSION

A case group consisting of 62 patients of biochemically evident subclinical hypothyroidism defined by serum TSH and Free T4 levels were considered for the study. Of these, 12 patients were excluded from the study as they had other comorbid illnesses, or were already taking Levo thyroxine. The remaining 50 patients were labelled as Cases.

Control group for the study consists of carefully chosen euthyroid subjects who are matched with the cases for age, sex and height. They were also included in the study after carefully evaluating for the presence or absence of any of the exclusion criteria.

Both the cases and controls were subjected to complete relevant history and physical examination, including anthropometry. Fasting samples of blood and serum were collected for the analysis of Complete Blood Count, Renal Function Tests, Liver Function Tests, Lipid Profile, Fasting Blood Sugar and High Sensitivity CRP assay. The parameters were tabulated and analyzed.

A similar study has been conducted by Alpaslan et al[77]. in Turkey, where they have analyzed the levels of hs-CRP in patients with subclinical hypothyroidism. In the study, they have included plasma insulin levels, HOMA-IR index and serum prolactin levels. Due to limited financial resources, we could not include these in our study.

## (1) POPULATION CHARACTERISTICS

There have been suggestions that age [73] and gender[74] may have an impact on IHD risk in people with SCH, but no quantitative analysis has been performed to investigate this. The prevalence increases with age, and in women older than 60 years, subclinical hypothyroidism is present in up to 20%.[75]The data are less consistent in men; in those older than 65 years, the prevalence increases and approaches that of women in some, but not all, studies.[76]

In our study, the age distribution of subclinical hypothyroidism shows a characteristic pattern, with most cases occurring in the age range of 21 to 30 years. This was closely followed by 41-50 years of age. 80% of cases were woman, which is consistent with the prevalence of Subclinical hypothyroidism in most of the studies. The mean ages for cases and controls, respectively in our study are 39.04$\pm$11.3 and 39.44$\pm$10.5. This is slightly higher than the mean ages of study and control population of the study conducted by Alpaslan et al[77].

## (2) THYROID PROFILE

Mean levels of TSH, for controls and cases in our study, respectively, are 2.22$\pm$2.26 and 8.3$\pm$1.02 uIU/ml. This pattern resembles the same in the study

conducted by Alpaslan et al. [77], in which the mean values are 1.5 and 7.4, respectively.

Though by definition, Subclinical hypothyroidism is characterised by elevated TSH and normal free T4 levels, most studies indicate that values of TSH are less than 10 mIU/l in most cases. In a study conducted by Toft et al., approximately 75% had values lower than 10 mIU/L(4).Our study also reflects this pattern of TSH, with 80% of cases having less than 10 mIU/l.

Most studies on subclinical hypothyroidism indicate that although Free T3 and T4 are normal in this condition by definition, they are on the lower normal range. This is also shown in our study with lower level of mean values of both hormones in cases when compared to controls. In the study conducted by Alpaslan et al., the mean values of Free T4 in cases and controls, respectively, are 1.18$\pm$0.22 and 1.38$\pm$0.26, and in our study, they are 0.99$\pm$0.17 and 0.92$\pm$0.16.

**(3) SERUM hs-CRP LEVELS**

Number of cases with Mean levels of hs-CRP in the intermediate and High risk range, was obiously higher among than controls. In the low risk range, control group had more number than cases. This obviously shows that persons in the case group have a high prevalence of hs-CRP when compared to case. This is consistent with the study conducted by Alpaslan et al. [77]

The mean values of hs-CRP among controls is 1.93±1.49, which is similar to the value in the same study. But the mean value of hs-CRP in cases in our study (1.93) is lower than the same in that study (4.2).

**(4) LIPID PROFILE**

Mean value of Total cholesterol (cases – 167.5±42.4controls-138.9±53.5) and Triglycerides (cases – 142.06±52.5,controls-122.02±28.7) was found to be higher among cases than controls. Mean value of HDL (cases – 38.8±8.32,controls-44.8±7.3) was lower among cases.

In the study conducted by Alpaslan et al[77] ., significant association was found only in Total and LDL cholesterol level. In our study, significant association was found for Total cholesterol, LDL cholesterol and HDL cholesterol between cases and controls, with the later lower in cases than controls.

The mean values of Triglycerides and HDL are similar to those in the study conducted by Alpaslan et al., but the mean value of Total cholesterol in our study, both in cases and controls are notably lower than those in the said study.

**(5) CORRELATION BETWEEN hs-CRP AND OTHER VARIABLES**

Analysis of correlation between hs-CRP and other variables was done. The parameters compared with hs-CRP for correlation are : age, sex, Total

cholesterol, Triglycerides, HDL cholesterol, BMI and Waist Hip ratio.It was found that there was statistically significant positive correlation and association between TSH and hs-CRP levels. This is consistent with the study conducted by Alpaslan et al. [77],which also showed a positive association between the same. The other parameters did not show a significant association with hs-CRP.

## SUMMARY AND CONCLUSION

It is concluded that

1. Subclinical hypothyroidism has a predilection to affect females much more commonly than males.

2. Though the definition of subclinical hypothyroidism includes high TSH and normal free T4, most patients with this condition have a TSH value of less than 10 mIU/l and both free T4 and free T3 in the low normal range.

3. Prevalence of Elevated levels of High Sensitivity C-Reactive Protein is more among individuals with Subclinical hypothyroidism. The prevalence of those in the high risk for Cardiovascular Disease is also alarmingly high.

4. Prevalence of overweight and Class I obesity is more in Subclinical hypothyroidism.

5. Mean levels of Total Cholesterol and Triglycerides are high, and HDL levels are low in patients with Subclinical hypothyroidism.

6. There is a positive correlation between serum TSH levels and hs-CRP levels.

From conclusions 3,4,5 and 6, it is clear that patients with subclinical hypothyroidism are more prone for Atherosclerotic Cardiovascular diseases. Hence, it is prudent to screen for this condition among those with other risk factors for coronary artery disease. Also, in patients with established Subclinical

hypothyroidism, estimation of High Sensitivity C-Reactive Protein provides a cost effective method of screening patients at increased risk for Atherosclerotic Coronary Artery disease. Early institution of Thyroxine replacement may prevent or delay the onset of the same.

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**INSTITUTE OF INTERNAL MEDICINE**

**MMC & RGGGH, CHENNAI-3**

**"A STUDY ON THE PREVALENCE OF ELEVATED HIGH SENSITIVITY C-REACTIVE PROTEIN IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM" - PROFORMA**

**NAME :** **ADDRESS :**

**AGE/SEX :**

**OCCUPATION :** **PHONE NO.**

**SYMPTOMS**

Poor appetite : Y / N

Constipation : Y / N

Cold intolerance : Y / N

Weight gain : Y / N

Chest pain : Y / N

Breathlessness : Y / N

Palpitation : Y / N

Swelling of legs : Y / N

Syncope : Y / N

Fever : Y / N

**PAST HISTORY**

Diabetes : Systemic Hypertension: CAD :

Stroke/TIA: CKD : TB:

Surgery: Rheumatological disorder: Trauma:

**PERSONAL HISTORY**

Smoker : Alcoholic :

**DRUG HISTORY:**

whether on L- thyroxine replacement: Y / N NSAIDs: Y / N

Statins: Y / N Others: Y / N

**MENSTRUAL HISTORY:**

## GENERAL EXAMINATION

PULSE : BP :

WEIGHT: HEIGHT : BMI :

WAIST CIRCUMFERENCE: HIP CIRCUMFERENCE:

WAIST/HIP :

FEATURES OF HYPOTHYROIDISM:

Dry skin: Hoarse Voice: cool peripheral extremities:

Carpal tunnel syndrome:

NECK: Goitre: Surgical scar:

**SYSTEMS:**

**CVS :**

**RS :**

**ABDOMEN :**

**CNS** : Delayed tendon reflex relaxation

## INVESTIGATIONS:

### 1. COMPLETE BLOOD COUNT

Total count

Differential count : P L E M B

Haemoglobin: gms%

ESR:

Platelets:

### 2. RENAL FUNCTION TESTS

Blood urea:

Fasting blood sugar:

Serum creatinine:

Serum sodium:

Serum potassium:

3. **LIVER FUNCTION TESTS**

Total bilirubin: Direct bilirubin:

SGOT: SGPT:

Alkaline phosphatase:

Total protein: Albumin:

4. **THYROID PROFILE:**

TSH :

FREE T4 : FREE T3 :

5. **BLOOD SUGAR :**

FASTING : POST PRANDIAL :

6. **FASTING LIPID PROFILE :**

TOTAL CHOLESTEROL: TG:

HDL: LDL:

7. **High Sensitive C-Reactive Protein:**

Value :

Risk category :

8. **ECG in all leads :**

9. **Echocardiogram :**

**FINAL IMPRESSION:**

MASTER CHART CASES

| MASTER CHART (CASES) | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **S.NO** | **AGE** | **SEX** | **TSH (mIU/L)** | **FREE T4 (ng/dL)** | **FREE T3 ( pg/mL)** | **HS CRP (mg/l)** | **TOTAL CHOLESTEROL (mg/dl)** | **TRIGLYCERIDES (mg/dl)** | **HDL (mg/dl)** | **HEIGHT (cm)** | **WEIGHT (kg)** | **BMI** | **WAIST CIRCUMFERENCE (cm)** | **HIP CIRCUMFERENCE (cm)** | **WAIST/HIP RATIO** | **SYSTOLIC BP** | **DIASTOLIC BP** |
| 1 | 27 | F | 6.4 | 1.14 | 2.5 | 0.45 | 148 | 268 | 42 | 1.78 | 86 | 27.1 | 100.8 | 105.6 | 0.95 | 120 | 80 |
| 2 | 25 | F | 5.72 | 1.13 | 3.05 | 0.2 | 185 | 90 | 38 | 1.5 | 73 | 32.4 | 88.9 | 96.5 | 0.92 | 108 | 76 |
| 3 | 27 | F | 7.25 | 1.21 | 2.68 | 0.9 | 173 | 167 | 49 | 1.52 | 71 | 30.7 | 83.6 | 94.4 | 0.89 | 120 | 80 |
| 4 | 55 | F | 6.4 | 1.22 | 2.8 | 0.5 | 148 | 137 | 42 | 1.52 | 55 | 23.8 | 83.7 | 105.6 | 0.79 | 104 | 70 |
| 5 | 45 | F | 8.58 | 0.8 | 2.93 | 2.4 | 165 | 162 | 45 | 1.6 | 72 | 28.1 | 97.7 | 102.5 | 0.95 | 116 | 68 |
| 6 | 42 | M | 7.31 | 0.89 | 2.87 | 1.3 | 266 | 177 | 34 | 1.57 | 71 | 28.8 | 94.6 | 102.8 | 0.92 | 120 | 80 |
| 7 | 30 | F | 10.61 | 0.72 | 3.21 | 2.84 | 184 | 260 | 35 | 1.65 | 77 | 28.3 | 90.6 | 96.5 | 0.94 | 118 | 68 |
| 8 | 50 | F | 9.56 | 0.78 | 3.1 | 2.95 | 168 | 124 | 49 | 1.75 | 70 | 22.9 | 98.1 | 99.3 | 0.99 | 102 | 76 |
| 9 | 30 | F | 7.84 | 1.14 | 2.52 | 2.2 | 165 | 82 | 45 | 1.61 | 64 | 24.7 | 84 | 94 | 0.89 | 112 | 80 |
| 10 | 37 | F | 14.4 | 0.98 | 2.75 | 2.49 | 91 | 160 | 38 | 1.57 | 71 | 28.8 | 103.1 | 117.1 | 0.88 | 110 | 70 |
| 11 | 46 | F | 11.85 | 1.17 | 2.9 | 4.65 | 192 | 86 | 42 | 1.55 | 66 | 27.5 | 99.1 | 109.2 | 0.77 | 116 | 68 |
| 12 | 29 | F | 9.83 | 0.95 | 2.59 | 3.9 | 61 | 208 | 40 | 1.58 | 60 | 24 | 85.6 | 101.4 | 0.84 | 124 | 80 |
| 13 | 47 | M | 5.07 | 0.83 | 3 | 0.03 | 195 | 79 | 47 | 1.54 | 68 | 28.7 | 81.3 | 88.2 | 0.92 | 120 | 80 |
| 14 | 30 | F | 6.71 | 1.12 | 2.86 | 0.8 | 144 | 159 | 36 | 1.74 | 72 | 23.8 | 74.8 | 83.4 | 0.9 | 118 | 78 |
| 15 | 30 | F | 7.6 | 0.8 | 3.05 | 1.57 | 148 | 96 | 51 | 1.62 | 73 | 27.8 | 92.4 | 101.1 | 0.91 | 110 | 80 |
| 16 | 37 | F | 8.44 | 1.12 | 3.25 | 2.4 | 87 | 136 | 22 | 1.53 | 54 | 23.1 | 68.4 | 79.5 | 0.86 | 118 | 68 |
| 17 | 22 | F | 9.1 | 1.09 | 4.11 | 2.7 | 149 | 149 | 43 | 1.48 | 59 | 26.9 | 71.1 | 76.2 | 0.93 | 120 | 80 |

MASTER CHART CASES

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18 | 63 | F | 9 | 0.86 | 3.9 | 2.6 | 148 | 132 | 37 | 1.68 | 68 | 24.1 | 96.5 | 112.9 | 0.85 | 108 | 78 |
| 19 | 59 | F | 11.29 | 0.85 | 4.1 | 1.55 | 181 | 195 | 38 | 1.48 | 57 | 26 | 68 | 73.6 | 0.92 | 122 | 76 |
| 20 | 36 | F | 12.57 | 1.21 | 3.73 | 5.4 | 207 | 215 | 20 | 1.59 | 68 | 26.9 | 70.5 | 86.5 | 0.82 | 120 | 80 |
| 21 | 38 | F | 13.75 | 0.72 | 2.45 | 5.7 | 149 | 106 | 42 | 1.58 | 52 | 20.8 | 71.1 | 81.2 | 0.88 | 120 | 80 |
| 22 | 42 | F | 8.1 | 0.84 | 2.91 | 2.27 | 196 | 142 | 48 | 1.63 | 59 | 22.2 | 86.6 | 105.3 | 0.82 | 110 | 70 |
| 23 | 47 | F | 12.06 | 0.76 | 2.54 | 4.96 | 148 | 144 | 27 | 1.56 | 46 | 18.9 | 66.4 | 84.1 | 0.79 | 124 | 78 |
| 24 | 56 | F | 5.7 | 1.23 | 3.72 | 0.2 | 256 | 158 | 22 | 1.57 | 60 | 24.3 | 68.9 | 87.6 | 0.79 | 100 | 68 |
| 25 | 30 | F | 6.4 | 1.2 | 2.72 | 0.57 | 177 | 126 | 40 | 1.63 | 81 | 30.5 | 98.1 | 83.8 | 1.17 | 118 | 80 |
| 26 | 40 | F | 7.68 | 0.81 | 2.5 | 1.9 | 246 | 136 | 39 | 1.57 | 52 | 21.1 | 78 | 90 | 0.87 | 118 | 76 |
| 27 | 24 | F | 9.7 | 0.7 | 2.54 | 2.97 | 120 | 104 | 40 | 1.59 | 66 | 26.1 | 70.3 | 79.9 | 0.88 | 100 | 70 |
| 28 | 28 | M | 6.08 | 0.75 | 3.8 | 0.4 | 162 | 131 | 38 | 1.62 | 71 | 27.1 | 88.6 | 90.7 | 0.98 | 120 | 76 |
| 29 | 48 | F | 7.55 | 0.71 | 2.93 | 1.5 | 175 | 83 | 41 | 1.76 | 94 | 30.4 | 102.6 | 104.3 | 0.98 | 116 | 70 |
| 30 | 28 | F | 8.65 | 0.78 | 4 | 2.4 | 73 | 167 | 24 | 1.71 | 55 | 18.8 | 68.7 | 86.9 | 0.79 | 110 | 70 |
| 31 | 35 | F | 9.06 | 0.77 | 3.6 | 2.7 | 140 | 86 | 37 | 1.55 | 62 | 25.8 | 71.9 | 80.4 | 0.89 | 120 | 80 |
| 32 | 39 | F | 9.46 | 0.85 | 2.96 | 2.89 | 188 | 156 | 36 | 1.67 | 58 | 20.8 | 77.9 | 91.1 | 0.86 | 110 | 70 |
| 33 | 46 | F | 9.89 | 0.75 | 2.61 | 2.16 | 163 | 67 | 44 | 1.48 | 68 | 31 | 83.8 | 87.6 | 0.96 | 120 | 80 |
| 34 | 23 | F | 5.15 | 0.92 | 2.46 | 0.06 | 92 | 115 | 20 | 1.47 | 63 | 29.2 | 71.1 | 76.2 | 0.93 | 120 | 80 |
| 35 | 52 | M | 7.04 | 0.99 | 4.13 | 0.7 | 157 | 97 | 42 | 1.55 | 77 | 32.1 | 91.3 | 75.5 | 1.21 | 112 | 70 |
| 36 | 49 | F | 5.75 | 1.11 | 3.24 | 0.21 | 144 | 152 | 43 | 1.61 | 74 | 28.6 | 83.6 | 97.8 | 0.85 | 116 | 70 |
| 37 | 65 | M | 10.53 | 0.97 | 2.42 | 4.2 | 221 | 130 | 38 | 1.51 | 62 | 27.2 | 89.3 | 91.4 | 0.98 | 120 | 80 |
| 38 | 55 | F | 7.3 | 0.76 | 2.68 | 0.99 | 183 | 64 | 42 | 1.69 | 72 | 25.2 | 73.5 | 83 | 0.89 | 116 | 70 |
| 39 | 46 | F | 6.01 | 0.94 | 2.72 | 0.3 | 180 | 142 | 48 | 1.63 | 76 | 28.6 | 89.5 | 71.2 | 1.26 | 120 | 80 |
| 40 | 38 | F | 7.42 | 0.88 | 4.04 | 1.4 | 198 | 178 | 31 | 1.62 | 65 | 24.8 | 67.8 | 83.3 | 0.81 | 110 | 80 |
| 41 | 34 | F | 6.78 | 0.74 | 2.67 | 0.62 | 178 | 140 | 44 | 1.47 | 55 | 25.5 | 85 | 83 | 1.02 | 100 | 70 |
| 42 | 40 | F | 5.79 | 1.1 | 3.1 | 0.22 | 184 | 108 | 47 | 1.56 | 72 | 29.6 | 90.4 | 73.8 | 1.22 | 116 | 86 |
| 43 | 28 | F | 7.6 | 0.73 | 3.44 | 1.8 | 168 | 240 | 43 | 1.44 | 39 | 18.8 | 71.1 | 83.8 | 0.85 | 104 | 68 |
| 44 | 29 | F | 5.89 | 0.78 | 2.51 | 0.33 | 212 | 62 | 58 | 1.57 | 59 | 23.9 | 69.4 | 88.1 | 0.79 | 120 | 80 |
| 45 | 49 | F | 8.07 | 0.88 | 2.99 | 2.7 | 180 | 147 | 28 | 1.64 | 66 | 24.5 | 89.4 | 105.2 | 0.85 | 116 | 78 |
| 46 | 20 | F | 10.8 | 0.91 | 2.63 | 4.6 | 169 | 106 | 40 | 1.71 | 82 | 28 | 93.9 | 95.9 | 0.98 | 118 | 78 |
| 47 | 26 | F | 11.85 | 0.78 | 3.9 | 1.74 | 203 | 221 | 48 | 1.6 | 70 | 27.3 | 93.2 | 94 | 0.99 | 120 | 70 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 48 | 42 | F | 8.39 | 0.92 | 3.47 | 2.35 | 234 | 189 | 28 | 1.61 | 75 | 28.9 | 96.2 | 104.6 | 0.92 | 118 | 70 |
| 49 | 49 | F | 7.35 | 0.91 | 3.79 | 1.3 | 131 | 94 | 36 | 1.63 | 57 | 21.5 | 70.4 | 84.3 | 0.84 | 116 | 80 |
| 50 | 39 | F | 6.55 | 0.96 | 2.59 | 0.57 | 146 | 230 | 33 | 1.65 | 64 | 23.5 | 97.2 | 112 | 0.87 | 120 | 80 |

MASTER CHART ( CONTROLS)

| S.NO | AGE | SEX | TSH (mIU/L) | FREE T4 (ng/dL) | FREE T3 ( pg/mL) | HS CRP (mg/l) | TOTAL CHOLESTEROL (mg/dl) | TRIGLYCERIDES (mg/dl) | HDL (mg/dl) | HEIGHT (cm) | WEIGHT (kg) | BMI | WAIST CIRCUMFERENCE (cm) | HIP CIRCUMFERENCE (cm) | WAIST/HIP RATIO | SYSTOLIC BP | DIASTOLIC BP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 43 | F | 2.25 | 1.2 | 3.51 | 0.73 | 110 | 80 | 42 | 1.48 | 40 | 18.3 | 71.7 | 84.8 | 0.85 | 110 | 70 |
| 2 | 32 | F | 4.04 | 1.16 | 2.62 | 0.99 | 97 | 75 | 45 | 1.54 | 56 | 23.6 | 72.6 | 79.4 | 0.91 | 110 | 80 |
| 3 | 38 | F | 1.15 | 0.95 | 4.19 | 0.26 | 90 | 140 | 57 | 1.5 | 59 | 26.2 | 67.8 | 73.3 | 0.92 | 116 | 70 |
| 4 | 42 | F | 2.78 | 1.09 | 2.56 | 2.2 | 244 | 118 | 49 | 1.62 | 59 | 22.5 | 83 | 95 | 0.87 | 118 | 76 |
| 5 | 31 | F | 3.27 | 1.1 | 2.44 | 0.8 | 257 | 126 | 52 | 1.55 | 61 | 25.4 | 86.6 | 89.3 | 0.97 | 118 | 70 |
| 6 | 42 | F | 3.98 | 1.08 | 2.7 | 0.6 | 159 | 137 | 54 | 1.49 | 56 | 25.2 | 72.6 | 80.8 | 0.9 | 116 | 70 |
| 7 | 43 | M | 1.89 | 0.72 | 2.86 | 0.54 | 121 | 167 | 30 | 1.52 | 55 | 23.8 | 84.6 | 93.4 | 0.91 | 116 | 68 |
| 8 | 45 | F | 0.55 | 0.93 | 4.13 | 0.62 | 139 | 139 | 40 | 1.61 | 54 | 20.8 | 76.8 | 91.3 | 0.84 | 110 | 70 |
| 9 | 33 | F | 3.12 | 0.72 | 2.5 | 0.79 | 74 | 101 | 54 | 1.68 | 60 | 21.3 | 89.8 | 104 | 0.86 | 110 | 80 |
| 10 | 64 | F | 3.49 | 0.8 | 2.47 | 3.7 | 186 | 172 | 43 | 1.51 | 61 | 26.8 | 84.8 | 95.4 | 0.89 | 120 | 70 |
| 11 | 28 | F | 1.36 | 0.82 | 2.52 | 0.93 | 160 | 146 | 46 | 1.55 | 54 | 22.5 | 75.1 | 81.2 | 0.92 | 110 | 70 |
| 12 | 32 | F | 0.87 | 0.91 | 2.96 | 0.89 | 73 | 132 | 47 | 1.57 | 55 | 22.3 | 70.5 | 85.3 | 0.83 | 116 | 70 |
| 13 | 54 | M | 1.06 | 1.18 | 2.57 | 0.75 | 162 | 159 | 28 | 1.71 | 71 | 24.3 | 99.5 | 83.9 | 1.19 | 110 | 80 |
| 14 | 48 | F | 0.76 | 1.24 | 2.68 | 3.3 | 114 | 92 | 46 | 1.52 | 57 | 24.7 | 90.7 | 106 | 0.86 | 120 | 80 |
| 15 | 58 | F | 1.55 | 0.78 | 2.83 | 0.4 | 88 | 141 | 49 | 1.65 | 68 | 25 | 95.8 | 103 | 0.93 | 110 | 80 |
| 16 | 33 | F | 2.24 | 1.05 | 4.09 | 0.69 | 148 | 150 | 57 | 1.56 | 64 | 26.3 | 82.6 | 94.4 | 0.88 | 120 | 80 |
| 17 | 37 | F | 3.63 | 0.75 | 3.93 | 0.5 | 168 | 116 | 54 | 1.78 | 69 | 21.8 | 94.5 | 96.6 | 0.98 | 118 | 76 |
| 18 | 35 | F | 4.09 | 1.18 | 3.61 | 0.74 | 149 | 208 | 55 | 1.52 | 57 | 24.7 | 75.9 | 85.4 | 0.89 | 110 | 70 |
| 19 | 52 | F | 1.18 | 1.24 | 2.47 | 0.3 | 156 | 115 | 47 | 1.54 | 54 | 22.8 | 69.7 | 87.8 | 0.79 | 120 | 80 |
| 20 | 64 | F | 2.61 | 1.11 | 3.94 | 1.4 | 138 | 94 | 58 | 1.59 | 54 | 21.4 | 71.7 | 78.5 | 0.91 | 110 | 80 |

MASTER CHART ( CONTROLS)

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | 37 | F | 1.46 | 0.72 | 4.18 | 0.42 | 75 | 126 | 48 | 1.62 | 66 | 25.2 | 90.7 | 107 | 0.85 | 120 | 80 |
| 22 | 30 | M | 2.97 | 0.94 | 2.71 | 1.2 | 286 | 132 | 43 | 1.57 | 75 | 30.4 | 93.4 | 98.8 | 0.95 | 110 | 70 |
| 23 | 32 | F | 1.98 | 1.09 | 2.44 | 0.1 | 140 | 107 | 50 | 1.73 | 86 | 28.7 | 101 | 105 | 0.97 | 120 | 80 |
| 24 | 29 | F | 2.83 | 0.81 | 3.47 | 0.44 | 82 | 113 | 45 | 1.6 | 65 | 25.4 | 94.4 | 103 | 0.92 | 120 | 80 |
| 25 | 46 | F | 1.5 | 1.03 | 2.52 | 0.21 | 111 | 141 | 54 | 1.65 | 60 | 22 | 69.4 | 84 | 0.83 | 116 | 70 |
| 26 | 48 | F | 3.54 | 0.94 | 4.15 | 2.5 | 148 | 95 | 49 | 1.53 | 61 | 26.1 | 86.1 | 102 | 0.84 | 110 | 70 |
| 27 | 34 | F | 2.65 | 1.12 | 2.75 | 0.36 | 107 | 86 | 46 | 1.62 | 83 | 31.6 | 99.7 | 84.3 | 1.18 | 110 | 80 |
| 28 | 25 | F | 2.46 | 0.87 | 2.43 | 0.88 | 90 | 103 | 48 | 1.58 | 63 | 25.2 | 97.5 | 106 | 0.92 | 116 | 70 |
| 29 | 42 | F | 3.96 | 1.14 | 3.86 | 4.6 | 82 | 154 | 48 | 1.62 | 59 | 22.5 | 72.9 | 87.7 | 0.83 | 110 | 80 |
| 30 | 25 | F | 1.69 | 0.89 | 2.84 | 0.38 | 300 | 118 | 45 | 1.6 | 73 | 28.5 | 89.4 | 93.2 | 0.96 | 120 | 80 |
| 31 | 59 | F | 3.2 | 0.77 | 2.41 | 1.9 | 163 | 147 | 25 | 1.7 | 55 | 19 | 69.3 | 89.7 | 0.77 | 110 | 70 |
| 32 | 35 | F | 1.55 | 1.22 | 2.66 | 1.5 | 99 | 97 | 46 | 1.53 | 61 | 26.1 | 87.4 | 90.5 | 0.97 | 110 | 80 |
| 33 | 40 | F | 2.84 | 0.8 | 4 | 0.5 | 159 | 117 | 35 | 1.51 | 61 | 26.8 | 75.5 | 89 | 0.85 | 110 | 80 |
| 34 | 27 | F | 0.86 | 0.89 | 2.56 | 0.23 | 116 | 187 | 42 | 1.55 | 46 | 19.2 | 69.1 | 87.3 | 0.79 | 120 | 80 |
| 35 | 22 | F | 2.21 | 0.92 | 2.91 | 0.33 | 149 | 86 | 35 | 1.7 | 60 | 20.8 | 73.2 | 83 | 0.88 | 110 | 70 |
| 36 | 47 | M | 3.44 | 0.75 | 2.76 | 2.9 | 213 | 98 | 47 | 1.63 | 76 | 28.6 | 84.7 | 99.9 | 0.85 | 110 | 80 |
| 37 | 34 | F | 3.38 | 1.04 | 2.6 | 0.92 | 96 | 116 | 45 | 1.49 | 57 | 25.7 | 72.8 | 86.4 | 0.84 | 116 | 70 |
| 38 | 39 | F | 0.83 | 1.12 | 3.88 | 0.23 | 150 | 159 | 32 | 1.52 | 67 | 29 | 94.2 | 79.3 | 1.19 | 120 | 80 |
| 39 | 24 | M | 1.98 | 0.76 | 4.03 | 0.87 | 162 | 86 | 38 | 1.55 | 60 | 25 | 72.7 | 86.8 | 0.84 | 110 | 80 |
| 40 | 42 | F | 1.4 | 0.9 | 3.69 | 5.3 | 120 | 124 | 39 | 1.57 | 54 | 21.9 | 69.4 | 88.5 | 0.78 | 118 | 80 |
| 41 | 33 | F | 2.75 | 1.24 | 3.56 | 0.15 | 215 | 129 | 45 | 1.66 | 72 | 26.1 | 95.2 | 103 | 0.93 | 110 | 70 |
| 42 | 29 | F | 1.04 | 0.84 | 2.92 | 0.77 | 139 | 114 | 47 | 1.7 | 72 | 24.9 | 74.1 | 86 | 0.86 | 120 | 80 |
| 43 | 26 | F | 1.65 | 1.19 | 3.12 | 0.99 | 87 | 95 | 45 | 1.57 | 75 | 30.4 | 89.3 | 99.9 | 0.89 | 110 | 80 |
| 44 | 44 | F | 2.43 | 1.2 | 3.24 | 0.5 | 168 | 109 | 49 | 1.6 | 59 | 23.1 | 85.1 | 105 | 0.81 | 116 | 70 |
| 45 | 47 | F | 1.71 | 1.02 | 4.07 | 0.65 | 94 | 128 | 36 | 1.57 | 56 | 22.7 | 86.2 | 106 | 0.82 | 110 | 70 |
| 46 | 60 | F | 0.56 | 1.12 | 3.43 | 4.2 | 73 | 137 | 42 | 1.5 | 51 | 22.7 | 70.6 | 76.3 | 0.93 | 120 | 80 |
| 47 | 40 | F | 2.81 | 1.21 | 3.39 | 0.73 | 80 | 102 | 45 | 1.67 | 66 | 23.7 | 89.2 | 106 | 0.84 | 116 | 70 |
| 48 | 41 | F | 1.81 | 0.91 | 2.93 | 0.72 | 133 | 100 | 43 | 1.63 | 76 | 28.6 | 90.5 | 99.3 | 0.91 | 110 | 80 |
| 49 | 35 | F | 2.98 | 1.04 | 3.53 | 0.39 | 152 | 85 | 39 | 1.58 | 62 | 24.8 | 88.9 | 94.1 | 0.94 | 110 | 70 |
| 50 | 46 | F | 0.94 | 1.23 | 3.91 | 1.6 | 127 | 102 | 40 | 1.46 | 57 | 26.7 | 88.7 | 84 | 1.06 | 110 | 70 |

# PATIENT CONSENT FORM

Study detail: "A STUDY ON THE PREVALENCE OF ELEVATED HIGH SENSITIVITY C-REACTIVE PROTEIN IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM"

Study centre : Rajiv Gandhi Government general hospital, Chennai.

Patients Name :

Patients Age :

Identification Number :

Patient may check ( ✓) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐ ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my ☐

permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patients Name and Address: Place Date

Signature of investigator :

Study investigator's Name : Place Date