“A CASE CONTROL STUDY OF SERUM LIPID LEVEL ALTERATIONS IN SUBCLINICAL HYPOTHYROID PATIENTS”

REG NO. BG0110009

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

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ENDORSEMENT

This is to certify that the dissertation entitled **"A CASE CONTROL STUDY OF SERUM LIPID LEVEL ALTERATIONS IN SUBCLINICAL HYPOTHYROID PATIENTS"** is a bonafide research work done by **THE CANDIDATE REGISTER NUMBER BG0110009**.

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LIST OF ABBREVIATIONS USED

%	– Percentage
µg/l	– Microgram per litre
µIU/mL	– Micro International units per mililitre
AntiTPO	– Anti thyroid peroxidase antibodies
Apo A	– Apolipoprotein A1
Apo B	– Apolipoprotein B
BMI	– Body mass index
BMR	– Basal metabolic rate
BP	– Blood pressure
CAD	– Coronary Artery Disease
CETP	– Cholesterol ester transfer protein
CHD	– Coronary heart disease
Cms	– Centimeters
CVD	– Cardiovascular Disease
DF	– Degree of freedom
dL	– Deci Litre
DM	– Diabetes Mellitus
FBS	– Fasting blood glucose
fT3	– Free triiodothyronin
fT4	– Free thyroxine
HDL	– High density Lipoprotein
HDL-C	– High density Lipoprotein Cholesterol
HTN	– Hypertension
kg/m^2	– Kilograms per square metre
LDL	– Low density lipoprotein

LDL-C – Low density lipoprotein Cholesterol

LT4 – Levothyroxine

LVDD – Left ventricular diastolic dysfunction

LVET – Left ventricular ejection time

mg – milligrams

mg/dL – Milligrams per deciliter

MI – Myocardial Infarction

mm Hg – Millimeters of mercury

mmol/l – Milli mol per litre

ng – Nano gram

PEP – Pre ejection period

pg – Pico gram

SCH – Sub clinical hypothyroidism

SD – standard deviation

T3 – Total triiodothyronin

T4 – Total thyroxine

TC – Total cholesterol

TG – Triglycerides

TRH – Thyrotropin releasing hormone

TSH – Thyrotropin stimulating hormone

UK – United Kingdom

VLDL – Very low density lipoprotein

WHO – World Health Organization

µg/min – Microgram per minute

µU/L – Microunit per litre

ABSTRACT

Background and objectives

Subclinical hypothyroidism may be associated with increased risk of CAD, PVD and various biochemical abnormalities including increased LDL-C levels, increased total cholesterol and serum triglyceride values. The present study was aimed to determine lipid abnormalities in patients with subclinical hypothyroidism and its interpretation.

Methodology

This case control study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011. A total of 50 patients (25 cases with subclinical hypothyroidism and 25 euthyroid controls) were studied. The thyroid profile was assessed by estimating TSH, FT3 and FT4. A fully automated immunoflorescence immunoassay analyser was used to estimate TSH, FT3 and FT4.

Results

In the present study among cases 96% were females when compared to 64% in controls (p=0.013). It was observed that 80% of the cases were below 45 years of age as compared to 56% in controls (p=0.262). Overall, the mean age of cases was 37.25 years and in controls was 20.46 years (p=<0.001). Among the cases, 20% had high cholesterol, 40% had high triglycerides and 44% had high LDL. The lower HDL was recorded in 24% of cases.

Conclusion and interpretation

Overall, the present study showed significantly higher levels of triglycerides and low density lipoprotein levels in patients with sub-clinical hypothyroidism. The quantitative analysis of serum cholesterol showed significant raised serum cholesterol levels. No statistically significant relation was found between high density lipoprotein and subclinical hypothyroidism.

Keywords

Apolipoprotein; High density lipoprotein; Lipid abnormalities; Low density lipoprotein; Serum cholesterol; Subclinical hypothyroidism; Triglycerides;

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Chapter 1

Introduction

INTRODUCTION

Hypothyroidism is defined as a deficiency of thyroid activity. It results from reduced secretion of total thyroxine (T4) and triiodothyronine (T3). Biochemical decrease in T4 and T3 lead to hyper secretion of pituitary thyroid stimulating hormone (TSH) and an amplified increase in serum TSH levels.

Subclinical hypothyroidism (SCH) can be best defined as a high serum thyroid stimulating hormone (TSH) and normal serum total/free thyroxine (T4), triiodothyronine (T3) concentrations associated with few or no symptoms/signs of hypothyroidism. It is referred to as a state of mild thyroid failure and is essentially a laboratory diagnosis.[1,2] Subclinical hypothyroidism is much more common than overt hypothyroidism.[3,4] Therefore, early diagnosis and treatment may prevent the onset of overt hypothyroidism and its associated effects.

In population-based studies, the prevalence of subclinical hypothyroidism ranges from 4 to 15%.[5,6] In the United States National Health and Examination Survey (NHANES III), which excluded subjects with known thyroid disease, 4.3% of 16,533 people had subclinical hypothyroidism.[7] The prevalence rises with age, is higher in females than males, and is lower in blacks than in white.[7,8] 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 India 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.[9] Recent population-based study reported prevalence of hypothyroidism

as 3.9%. and prevalence of subclinical hypothyroidism was also high (9.4%). In women, the prevalence was higher 11.4%, when compared with men, in whom the prevalence was 6.2%.[10] The prevalence of subclinical hypothyroidism increased with age.[9]

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 remains the cornerstone of management.[9]

Thyroid hormones have significant effects on the synthesis, mobilization and metabolism of lipids. They affect serum cholesterol mainly by altering lipoprotein metabolism. Overt hypothyroidism is associated with significant increases in circulating concentration of total and low density lipoprotein cholesterol (LDL).[11] Hypercholesterolemia is favored due to the hormone deficit and to the decreased activity of the lipoprotein lipase.[12] A relationship between dyslipidemia and atherosclerosis is well established in overt hypothyroidism.

Similarly, subclinical hypothyroidism may be associated with increased risk of coronary artery disease (CAD), peripheral vascular disease, and various biochemical abnormalities including increased LDL-C levels, increased total cholesterol and serum triglyceride values.[13] It is uncertain whether subclinical hypothyroidism (increased serum TSH, normal serum T4 and T3) is also associated with hyperlipidemia. Some case-control studies, have reported increased concentration of serum total cholesterol and LDL cholesterol in subjects with subclinical hypothyroidism compared with euthyroid controls.[14]

Several large cross-sectional studies found no significant difference in total cholesterol or LDL-C between subjects with subclinical hypothyroidism and euthyroidism.[8,15,16]

However, the results of lipid profile alterations in subclinical hypothyroidism are controversial in different studies; some of those showing positive correlation and prompt reversal of changes following treatment[17,18] and while other refuting any correlation between the two.[19] Further, there are very few Indian studies about lipid profile changes in subclinical hypothyroidism.

Hence the present study was planned to determine lipid abnormalities in patients with subclinical hypothyroidism and its interpretation.

Chapter 2

Objectives

OBJECTIVES

The objective of the study was to assess the serum lipid abnormalities in patients diagnosed to have subclinical hypothyroidism.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

While screening patients for thyroid disease, physicians often find increased thyrotropin-stimulating hormone (TSH) levels in patients whose free thyroxine (FT4) levels are not below normal. This state, termed "subclinical hypothyroidism," is most commonly an early stage of hypothyroidism. Although the condition may resolve or remain unchanged within few years in some patients, overt hypothyroidism develops, with low free T4 levels as well as a raised TSH level. The likelihood that this will happen increases with greater TSH elevations and detectable antithyroid antibodies. Because patients with subclinical hypothyroidism sometimes have subtle hypothyroid symptoms and may have mild abnormalities of serum lipoproteins and cardiac function, patients with definite and persistent TSH elevation should be considered for thyroid treatment. Levothyroxine, in a dosage that maintains serum TSH levels within the normal range, is the preferred therapy in these patients.[20]

Thyroid disease is common and may present to a wide range of doctors. With the advent of serum thyrotropin (TSH) radioimmunoassay in the 1970s, the entity of mildly elevated TSH and normal serum thyroid hormones levels was recognised, the introduction of the second and third generation sensitive TSH in the 1980s identified the entity of subclinical hyperthyroidism in which serum TSH is suppressed and serum thyroxine T4 and triiodothyronine T3 levels are normal.[21] Controversy exists on whether early treatment or close follow-up is warranted in apparently healthy persons in whom the only indication of a thyroid disorder is an abnormal test result.[22]

There is controversy in the definition, clinical importance, and necessity for prompt diagnosis and treatment of subclinical thyroid disease. Subclinical hypothyroidism, also called mild hypothyroidism, is a term used for a condition in which there are small elevations in thyroid-stimulating hormone, yet normal circulating levels of thyroid hormones. This condition is more common in the elderly and is found twice as often in women as in men.[4,23] While it is uncommon in younger persons, by the age of 65 years, the overall prevalence of the disorder is about 17% in women and seven percent in men.[1]

American College of Physicians recognizes that screening women older than 50 years for hypothyroidism may have some value, they specifically note that the benefit of treating patients with subclinical hypothyroidism has not been evaluated.[24] The decision about whether to screen patients for this disorder is clouded by inconsistent evidence of any benefit from early treatment. A few trials have found that persons with subclinical hypothyroidism who are given L-thyroxine experience some improvements in their energy level and feelings of well-being.[25-27] Perhaps the most ambitious attempt to address the contentious issues of subclinical thyroid disease in a non-biased and systematic way was undertaken recently by The (American) Endocrine Society, the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE). These societies co-sponsored a Consensus Development Conference in 2002 and contracted an independent consulting firm to review and summarize existing published evidence.[28] The planning committee posed a series of clinically relevant questions related to the diagnosis and management

of subclinical thyroid disease. Of those questions raised by committee five questions are mentioned here.

- What is the definition of subclinical thyroid disease?
- What is the epidemiology of subclinical thyroid disease?
- What are the consequences of untreated subclinical thyroid disease, and how should it be evaluated?
- What are the risks and benefits of treatment for subclinical thyroid disease?
- Is screening for subclinical thyroid disease warranted?

  Subclinical hypothyroidism is a more common entity than subclinical hyperthyroidism.

Despite recognition of this condition and the observation that as small percentage of these patients advance to overt hypothyroidism each year, controversy continues over whether elderly individuals should be screened for subclinical hypothyroidism.[29-31] Whereas the American Thyroid Association[32] has endorsed screening for this disorder, others, such as the US Preventive Services Task Force[33] have advised against routine screening.

Epidemiology

Prevalence

Worldwide

Recent studies have clearly linked epidemiology by the TSH range used to define the problem. Certain different studies utilized different ranges. The

prevalence of subclinical hypothyroidism in the United States adult population is 4.0 to 8.5%,[7,34,35] although this figure increases with age, may differ among ethnic groups and less consistent data is available among men.[21] The progression to overt hypothyroidism is approximately two to five percent per year. The rate of progression is proportional to baseline TSH concentration and is higher in individuals with antithyroid antibodies.[28]

Indian scenario

In India too, there is a significant burden of thyroid diseases. 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.[9] Among adult population 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%.[10] The prevalence of subclinical hypothyroidism was also high in this study,[10] the value being 9.4%. In women, the prevalence was 11.4%, when compared with men, in whom the prevalence was 6.2%. The prevalence of subclinical hypothyroidism increased with age.[9] About 53% of subjects with subclinical hypothyroidism were positive for anti-TPO antibodies. This was a population-based study, which used cluster sampling strategy.[9] In this study,[9] Urinary Iodine Status was studied in 954 subjects from the same population sampled, and the median value was 211 μg/l; this suggested that this population was iodine sufficient.

Prevalence and Natural history

Large population studies have suggested that the prevalence of subclinical hypothyroidism is much higher in women than men and increases with age. In the Whickham survey, TSH levels above 6mIU/l were approximately three times more common in females (7.5%) than in males (2.8%) and occurred more frequently in females over 45 years of age. TSH levels also showed a progressive increase with age in women but not in men.[36] The prevalence of subclinical hypothyroidism varies from 4.3-9%.[7,35] The local prevalence is estimated at 6.5% in a study on 75 subjects admitted to a geriatric ward in a restructured hospital.[37]

There is also a strong association between positive antithyroid antibodies and elevated TSH. Generally the prevalence of elevated TSH levels parallels that of antibody positivity.[36] A high prevalence of antibodies was found in a UK study where antibodies were present in 81% of those with TSH concentration over 10 mU/l, 46% of those with TSH over 5 mU/l and less than or equal to 10 mU/l and only in 5.7% of those whose TSH concentration was less than 0.5 mU/l.[6]

After 20 years of follow-up of subjects in the Whickham Survey, the risk of overt hypothyroidism was found to be 4.3% per year in women with elevated TSH and antithyroid antibodies at baseline. This is 38 times increased risk over normal women moreover, an isolated elevation in TSH or presence of antithyroid antibodies alone at baseline also conferred an increased risk of overt hypothyroidism (2.6% per year and 2.1% per year respectively).[38] Progression to hypothyroidism was noted to be more common in those with initial TSH value greater than 10 mU/l and in those with positive antithyroid antibodies.[40] Authors

found that basal TSH, thyroid reserve (increase in T3 after TRH stimulation) and the presence of antimicrosomal antibody are important prognostic factors for the development of overt hypothyroidism. Interestingly, antibodies against thyroglobulin did not have a predictive value.[39]

Causes

Subclinical hypothyroidism is caused by the same disorders of the thyroid gland those cause overt hypothyroidism. Chief among these is chronic autoimmune thyroiditis (Hashimoto's disease), which is commonly associated with increased titers of antithyroid antibodies, such as antithyroid microsomal antibodies (antithyroid peroxidase) and antithyroglobulin antibodies.[40] This disorder is suspected when thyroid enlargement is observed, but antithyroid antibodies may also be associated with atrophy of the thyroid and hypothyroidism.[20]

Another common cause of hypothyroidism is the treatment of Graves' disease. Thyroid failure is most common after radioactive iodine treatment, but hypothyroidism may eventually occur in five to 25% of patients treated with surgery or antithyroid drugs.[41] Less common causes of hypothyroidism include use of medications such as lithium and amiodarone. Pituitary failure is a cause of secondary hypothyroidism but since, in this circumstance, the TSH level is low rather than high (and thus the direct cause of the thyroid failure), this condition cannot be diagnosed with certainty until thyroid hormone levels fall below normal, and subclinical hypothyroidism as usually defined would not be detected.[20]

Causes of Hypothyroidism[20]

- Chronic autoimmune thyroiditis
- Treated Graves disease
    - Radioactive iodine therapy
    - Subtotal thyroidectomy
    - Antithyroid drugs
- Head and neck surgery
- Radiation therapy to the head, neck or chest area
- Iodine deficiency
- Medications: lithium, iodine, amiodarone (Cordarone)
- Secondary hypothyroidism (hypopituitarism)
- Idiopathic
- Congenital

Course

What happens to patients who are found to have an elevated TSH level without other findings? In some cases, the TSH level will be normal if measured again several months later; they would then attribute the initial elevation to laboratory error or to an episode of silent thyroiditis with a transient hypothyroid phase. In other cases, the subclinical hypothyroidism remains unchanged. The third possibility, progression to overt hypothyroidism, occurs at a rate of about five percent per year in patients with raised TSH levels and detectable antithyroid antibodies.[42] In selected cases (elderly patients with high titers of antithyroid antibodies), the risk of progression to overt disease may be closer to 20% per

year. Consideration of these possible outcomes affects the decision about whether to treat or to observe without treatment.[20]

Manifestations

Symptoms

The clinical signs and symptoms of hypothyroidism will manifest when the disease is fully developed. But even in the earliest (subclinical stage), one or more of these findings may occur. In one study,[25] symptoms in 33 patients with subclinical hypothyroidism were compared with symptoms in 20 euthyroid patients in the same thyroid clinic. Dry skin, cold intolerance and easy fatigability were significantly more common in the patients with raised TSH levels, and these symptoms improved after treatment with thyroid hormone. In another study 11 of 69 female patients with subclinical hypothyroidism, a clinical index based on symptoms and physical signs was shown to be more abnormal in patients with higher TSH levels, even though all patients had normal serum levels of total T4 and free T4. These studies suggest that some patients with subclinical hypothyroidism do indeed have clinical manifestations of mild thyroid failure.

Signs and Symptoms of Hypothyroidism[20]

- Weakness, lethargy, fatigue
- Dry skin
- Coarse hair
- Cold intolerance
- Constipation

- Weight gain
- Muscle cramps
- Edema of eyelids, face, legs (nonpitting)
- Hoarseness
- Hearing loss
- Menorrhagia
- Slowing of return phase of reflexes (e.g., knee jerk)
- Bradycardia

Serum Lipids

In patients with full-blown hypothyroidism, serum levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol are elevated. In patients with subclinical hypothyroidism, not surprisingly, the same changes are present but are less marked and less consistent. This pattern of lipid abnormalities, of course, is important because it is a risk factor for atherosclerotic cardiovascular disease. Some studies,[43,44] but not others,[25] have shown a decrease in LDL cholesterol and total cholesterol levels after treatment with levothyroxine (Levoxyl, Levothroid, Synthroid).

Clinical implications

The potential benefits and risks of therapy for subclinical hypothyroidism have been debated for two decades. The possible advantages of treating subclinical hypothyroidism generally include, firstly, preventing the progression to overt hypothyroidism.[45]

Secondly, thyroxine therapy may improve the serum lipid profile and there by potentially decrease the risk of death from cardiovascular causes. Finally, treatment may reverse the symptoms of mild hypothyroidism, including psychiatric and cognitive abnormalities.[45]

Cardiac effects

In several studies, a sensitive measure of myocardial contractility, the ratio of pre-ejection period to left ventricular ejection time (PEP:LVET) was shown to improve significantly in patients with subclinical hypothyroidism who were treated with levothyroxine, compared with patients who were treated with placebo.[25,26]

Cardiac changes are evident in subclinical hypothyroidism. These include impairment of left ventricular diastolic function at rest (affecting the relaxation of the left ventricle and hence ventricular filling), reduced LV systolic function, prolongation of pre-ejection time and lastly impaired intrinsic myocardial contractility.[46-49]

There is evidence that these abnormalities improve with L-T4 treatment, demonstrating that adequate thyroid replacement improves cardiac output accompanied by substantial decrease in systemic vascular resistance, a reversal of diastolic dysfunction, and importantly an improvement in left ventricular ejection fraction during exercise.[46-48,50]

It has been demonstrated in the Rotterdam Study that subclinical hypothyroidism is a strong indicator risk for atherosclerosis and myocardial infarction.[51]

Inadequately treated hypothyroidism has also been demonstrated to have angiographic evidence of coronary atherosclerosis progression.[52]

Impairment of endothelium-dependent vasodilatation, a harbinger of atherosclerosis, has also been detected in patients with subclinical hypothyroidism[53] which can be reversed by levothyroxine supplementation.[54]

In view of clear structural and biological cardiovascular risks associated with the presence of subclinical hypothyroidism, treatment of this condition would be expected to provide protection against the development of cardiovascular disease, although there have been no long term outcome studies published to date.

Somatic and neuromuscular effects

Patients with subclinical hypothyroidism can have subtle clinical manifestations and non-specific symptomatology such as dry skin, cold intolerance, constipation, and easy fatigability.[55]

In addition, patients with muscular symptoms have mitochondrial oxidative dysfunction with significant lactate increment during exercise.[56]

A study also demonstrated the presence of subclinical polyneuropathy of probable axonal origin in patients with subclinical hypothyroidism.[57]

Subclinical hypothyroid subjects reported significantly more total symptoms than euthyroid individual in the Colarado study[35] and these symptoms do improve with L-T4 therapy. The greatest improvement seen is of patients with baseline TSH of >12 mU/l.[58]

A study observed no improvement in symptoms score after trial of thyroxine for six months in patients with TSH level between 5 and 10 mU/l.[59] Prospective studies suggest that patients with mild thyroid failure have a higher prevalence of somatic symptoms, mood disorders, cognitive dysfunction, and atypical responses to standard psychiatric therapeutic interventions.[1]

The lifetime frequency of depression is significantly higher in patients with subclinical hypothyroidism compared with patients with normal thyroid function, suggesting that subclinical hypothyroidism lowers the threshold for depression.[53]

Effects on serum lipid levels

Anatomically thyroid gland is located at front section of the neck. The thyroid hormones thyroxin (T4) and triidothyronine (T3) interfere with the body metabolism as whole. The over activity, under activity of the thyroid gland are defined as hyperthyroidism and hypothyroidism, respectively.[60]

In hypothyroidism, the thyroid gland produces less amount of thyroid hormone, such subjects eventually will lead to have lower metabolic rate and clinical manifestation such as over weight, fatigue, hypotension and depression. The symptoms of either hyperthyroidism or hypothyroidism can put the patient

life at risk, therefore the diagnosis and management of thyroid abnormalities is a curtail task for the clinicians as well as medical diagnostic laboratories world-wide. Laboratory measurements of Thyroid Stimulating Hormone (TSH) and thyroxin (T4) and tri-idothyronine (T3) are the key hormones in helping the clinicians to diagnose the thyroid patient abnormality. In general TSH and T4 play an even bigger role in the diagnosis of either hyperthyroidism or hypothyroidism. On condition of low TSH, high T4 and high TSH, low T4 the diagnosis can be either overt hyperthyroidism or hypothyroidism respectively.[60]

The other clinically mainly undiagnosed thyroid abnormalities are either sub-clinical hyperthyroidism or sub-clinical hypothyroidism which usually can be diagnosed on the basis of laboratory blood test results. The sub-clinical hyperthyroidism and sub-clinical hypothyroidism are diagnosed when the T4, T3, serum concentrations are at normal range with low and high TSH serum levels respectively. Whether sub-clinical thyroid dysfunction, accompanied with any metabolic disorders, it still remain to be answered and it is not fully understood. Thyroid disorder can be correlated with other metabolic abnormalities, among all are dyslipidemia, cardiovascular, liver diseases and anemia.[60]

Hypothyroidism and serum lipid alteration

It is universally accepted that there is a correlation of lipid profile alteration among hypothyroidism patients and since half century ago, there were documented studies, that the dyslipidemia in hypothyroidism may finally lead to cardiovascular diseases.[60]

In the middle of 20th century when the thyroid hormone assessment was not as easy as lipid measurement, the serum lipid profile and in particular serum cholesterol level was the major point for diagnosing thyroid hormone insufficiency. It is also important that on considering thyroid hormonal status the reference intervals in each particular region should be separately estimated to avoid the misdiagnosis,. The normal range of thyroid hormones should also have to be assessed at different condition of an individual to avoid the miss-conduct of thyroid hormones interpretations. There are many reports of metabolic disorders among pregnant women, such as nausea and vomiting in early pregnancy, which is due to the thyroid hormone alteration and perhaps the excessive requirements of thyroid hormone during pregnancy, the author of this review and his colleagues conducted a study to follow the pattern of changes of thyroid hormonal level during pregnancy and it was found that it is of great importance to assess carefully the reference ranges of normal for this phase of life.[61]

On the basis of latter studies it can be argued that during pregnancy the women should have been cared for lipid disorders to prevent the possible adverse effects of lipid alterations. One other matter which should be evaluated before going into a dramatic series of test among hypothyroid patients is the urinary iodine concentration measurements. In various studies they have carried out a survey of urinary iodine concentration and found that about 15.7% of the sample population were iodine deficient and should be assessed for goiter prevalence, such population might have been checked for dyslipidemia,[62] because there are various reports indicating the dyslipidemia among subjects with hypothyroidism. There are reports of lipid disorder among sub-clinical hypothyroidism as well as

overt hypothyroidism, the main dyslipidemia is hypercholesterolemia. In this scenario, hypercholesterolemia, mainly elevated by increased level of low density lipoprotein.[60]

Lipid peroxidation in the serum of hypothyroid patients were studied and it has been found that hypothyroidism enhance lipid peroxidation with subsequent free radical production, which lead to tissue damages. As it was mentioned above in hypothyroidism serum lipid levels are elevated and therefore the precursor for production of free radicals are available, a matter which should have been taken seriously.[63]

Hypothyroid patients may also exhibit elevated levels of HDL mainly due to increased concentration of HDL2 particles. Indeed, due to a reduction of hepatic lipase activity a decrease in HDL2 catabolism is observed. Moreover, decreased activity of the CETP results in reduced transfer of cholesteryl esters from HDL to VLDL, thus increasing HDL levels.[64]

Hypothyroid patients have increased Apolipoprotein A levels, which are associated with increased CVD risk. A study documented that HDL metabolism was altered in thyroid dysfunction, and the effect of thyroid hormone on HDL was mediated mainly via its effect on hepatic lipase activity.[64]

Sub-clinical hypothyroidism

Sub clinical hypothyroidism which is called mild hypothyroidism is a condition where the thyroid gland produce normal amount of thyroxin and tri iodothyronine, but thyroid stimulating hormone is slightly elevated, above the

upper limit of normal range (7-10 uIU/mL). This status of thyroid hormone usually presented at older age and is more common among women.[62] This type of thyroid disorders, usually are not observed among younger subjects.[60]

This type of thyroid disorder although is not commonly occurred, but its incidence higher than hyperthyroidism. Sub-clinical hypothyroidism case finding is easy task compared to the sub-clinical hyperthyroidism. As it is imply from the definition of sub-clinical hypothyroidism, subjects with such thyroid disorder do not show particularly symptom of overt hypothyroidism and the patient specifically do not show a clinical picture representing thyroid hormone deficiency.[60]

This form of hypothyroidism usually is diagnosed on the thyroid function test in the medical diagnostic laboratories. The sub-clinical patients inhibit elevated serum Thyroid Stimulating Hormone (TSH), while at the same time thyroxin (T4) and triiodothyronine (T3) may remain within normal range.[60]

The upper limit of TSH concentration varies according to some studies and therefore the level at which laboratory introduces a subject with sub-clinical hypothyroidism may differ by different definition of upper limit of reference intervals for TSH serum concentration. In some studies subjects with TSH concentration up to 10 mu L^{-1} and normal thyroid hormone of T4 and T3 considered to be sub-clinically hypothyroidism.[60]

In other study,[8] the TSH upper limit for the definition of sub-clinical hypothyroidism was considered about 7 mu L^{-1}. It seems very important to finalize the cut-off point for the definition of elevated TSH before considering a

patient for sub-clinical hypothyroidism disorder, because, in this type of thyroid disorder it is the laboratory thyroid hormone results which can be a base for the clinician to follow up the patient for thyroid disorder.[60]

The upper limit of TSH has conflicting results. one study even suggested that the patients with TSH level of more than 2 mu L^{-1} was to be considered a risk factor for subsequent hypothyroidism, although the upper limit of reference intervals should be kept about 0.4-5 mu L^{-1}.[65]

Although there are not a universally agreed border line at what upper limit of TSH reference range, a subject has to be considered as sub-clinically hypothyroidism, but on the bases of many articles existed in the literature, when the TSH concentration elevated to more than upper limit of normal range with subsequent dyslipidemia, at that point the individual can be further considered for sub-clinical hypothyroidism. Therefore as mentioned above, the TSH more than its upper limit can be considered as base line for identifying the sub-clinical hypothyroidism patient and due to this definition, the degree of sub-clinically hypothyroidism can be varied in various parts of the world due to the definition of reference range intervals and upper limit of normal in one society and the laboratory kit manufacturer of TSH. It depends to the TSH upper limit border line which an individual can be diagnosed as sub-clinically hypothyroidism. Age, gender and ethnicity are other factors which are related to the higher incidence of sub-clinical hypothyroidism. The other risk factor involved in prevalence of subclinical hypothyroidism is the thyroid autoimmunity.[60]

Lipid profile in sub-clinical hypothyroidism

It is universally accepted that overt hypothyroidism is associated with elevation of serum total cholesterol, Particularly low density lipoprotein-cholesterol.[58,66-68] The reason why sub-clinical hypothyroidism should be a matter for further investigation, is due to dyslipidemia which is associated with this type of thyroid disorder, but still there are a lot of controversial arguments about whether sub-clinical hypothyroidism constantly and universally associated with lipid disorder. Some report[19] argued, that the sub-clinical hypothyroidism associated with dyslipidemia of increased concentration of total cholesterol and particularly LDL-cholesterol,[14] but there are other studies,[68] which do not support the latter findings.

Few studies which concentrated on large cross-sectional investigation, reported that there was no significant differences among total cholesterol or LDL-cholesterol between individuals with sub-clinical hypothyroidism and healthy subjects, on the other hand some cross-sectional studies reported elevation of total cholesterol and low density lipoprotein cholesterol (LDL-c) among sub-clinical hypothyroid patient compared to healthy subjects.[60] There are also studies, that reported even total cholesterol of female subjects with sub-clinical hypothyroidism was even lower than euthyroid women,[69] but this type of report is very rare and cannot be taken seriously and the author of this review article[60] already reported that the lipid profile in women with sub-clinical hypothyroid, compared to euthyroid females[62] are elevated.

There are also some reports indicating in addition to total cholesterol and LDL-cholesterol, Apolipoprotein A concentration is also increased.[70]

Other study on the state of lipoprotein reported Apolipoprotein (B) and Apolipoprotein (A) increased in sub-clinical hypothyroid subjects with no significant alteration of triglycerides and high density lipoprotein cholesterol but with significant increase of total cholesterol and low density lipoprotein.[71]

A study[72] performed on the state of lipid profile alterations in sub-clinical hypothyroidism, concludes that in sub-clinical hypothyroidism, serum cholesterol and triglycerides concentration were increased, also the patients with this type of thyroid disorder inhibited the higher ratios of total cholesterol/HDL and LDL/HDL, this latter study indicated that Apolipoprotein B is also increased in the same patients.

Although overt hypothyroidism is frequently related with lipid disorder and it is universally agreed and it is well documented in the literatures, but dyslipidemia among sub-clinical hypothyroidism are not fully and comprehensively agreed on, literatures reviews on this present study indicates that in particular state of sub-clinical hypothyroidism, when the TSH level exceed about (7-10 mU L^{-1}) significant elevation in total cholesterol and low density lipoprotein cholesterol were occurred, some other studies even suggested that patients with elevated cholesterol should be examined further for thyroid function assessments.[73]

Adverse consequences of dyslipidemia in sub-clinical hypothyroidism

Overt hypothyroidism believed to play an important role in the development of atherosclerosis, which is enhanced by the presence of hypercholesterolemia, which is the consequence of thyroid hormone deficiency with ultimate reduction in the activity of lipoprotein lipase.[67]

It is not absolutely indicated whether, the sub-clinical hypothyroidism is also correlated with cardiovascular disease. There are some reports indicating that the intensity of sub-clinical hypothyroidism at some point enhance the cardiovascular abnormality with subsequent atherosclerosis due to dyslipidmia.[74]

It is not also clearly well documented whether levothyroxine therapy has shown to have some effect for the treatment of atherosclerosis and dyslipidemia in sub-clinical hypothyroid subjects. The studies in this area are contradictory. There are some report in favor of thyroxin administration to treat dyslipidemia with consequence of cardiovascular disease prevention.[1,14] But on the other hand various studies concluded that hormone therapy does not lead to overall improvement of dyslipidemia and its related risk factor in sub-clinical hypothyroid subjects. It is uncertain what would be the consequence of untreated subjects. There are arguments in favor of treating the sub-clinically hypothyroid patients with ultimate improvement in dyslipidemia,[35] but on the other hand studies are not supporting the latter findings and arguing that thyroxin therapy do not improve the patient conditions.[60]

The relationship between mild thyroid failure and reversible elevation in serum lipid levels has been widely investigated, but the findings remain

controversial. Several cross-sectional studies[70,75] suggest that serum cholesterol concentrations are elevated in individuals with mild thyroid failure when compared with euthyroid controls. In other similar studies,[76,77] however, the observed differences between euthyroid and mild hypothyroid individuals have not been significant. The Colorado study[35] which screened 25,862 subjects, found that mean total cholesterol and low density lipoprotein cholesterol progressively increased with increasing serum TSH levels. A reanalysis[78] in 1996 found that subclinical hypothyroidism was two to three times more frequent in people with elevated total plasma cholesterol.

Thyroid substitution therapy restoring the TSH levels to normal decreased total cholesterol by 0.2 to 0.4 mmol/l and mean LDL cholesterol by 0.26mmol/l and increased in HDL cholesterol by 0.08 mmol/l while triglycerides, and Apolipoprotein AI levels remained unchanged.[22]

In another study, total cholesterol and LDL cholesterol levels decreased only in pretreatment TSH values greater than 10 mU/l.[14]

The decrease in total cholesterol and LDL levels with pretreatment TSH values greater than 40 mU/l was greater than in those levels between 10 and 40 mU/l.[22]

Thyroid hormone has multiple effects on the regulation of lipid synthesis, absorption, and metabolism. Studies consistently demonstrate elevated levels of serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), Apolipoprotein B, and possibly triglycerides in individuals with overt hypothyroidism, all of which are reversible with levothyroxine therapy. Although

it is estimated that one to 11% of all patients with dyslipidemia have subclinical hypothyroidism, the effects of subclinical hypothyroidism on serum lipid values are less clear. Apolipoprotein B levels may be increased in patients with subclinical hypothyroidism. Although some studies have demonstrated that total cholesterol and LDL-C levels were elevated in patients with subclinical hypothyroidism, others have not shown any effect of subclinical hypothyroidism on these lipid measurements. Serum triglycerides, lipid subparticle size and LDL-C oxidizability may be altered in subclinical hypothyroidism, but these studies have also been inconsistent. The preponderance of evidence suggests that HDL-C and Apolipoprotein A levels are not altered in subclinically hypothyroid patients. Smoking and insulin resistance may modify the effects of subclinical hypothyroidism on serum lipid values. Clinical trials to date have not consistently shown a beneficial effect of levothyroxine treatment on serum lipid levels in subclinically hypothyroid patients.[79]

The nature and degree of dyslipidemia in overt hypothyroidism has been demonstrated in many studies and there is no doubt about the beneficial effects of thyroid substitution on serum lipids and on the risk for CAD. However, the possible effects of subtle alterations of thyroid function on lipid profile and atherogenesis remain unclear. There is, infact, doubt as to whether SCH should be treated.[71]

The evidence provided by different authors is controversial and concerns different aspects of this condition. There is growing evidence, however, that SCH is an indicator of increased risk for atherosclerosis and myocardial infarction in elderly women.[51]

In a substantial number of studies, TC and/or LDL-C seem to be elevated in SCH compared with controls.[70] However, there are studies that do not confirm this observation.[4,6] In this respect, in a cohort, subjects with SCH had significantly higher levels of TC, LDL-C, Apo B and Apo A, thus displaying a more atherogenic lipid profile when compared with healthy individuals. The lipid response to L-thyroxine substitution is another, yet clinically very important matter. The results of previous studies have been inconsistent.[71]

A number of studies[60] suggest a decrease of TC and LDL-C after L-thyroxine-substitution, whereas others report no significant changes. It appears that the degree of change depends on two parameters: the initial levels of cholesterol and the degree of thyroid dysfunction. Indeed, in the subgroups of patients with 'more severe' hypothyroidism (namely TSH 10 mU=ml) or high baseline levels of TC (240 mg/dl), there was a significant response of TC and LDL-C to treatment.

Even more contradictory results have been presented on HDL-C levels. They are reported as either lower,[70] or comparable[60,80,81] with control groups. Furthermore, the response of HDL-C levels to thyroid substitution remains obscure. A few studies have shown an increase in HDL-C levels,[82] whereas others showed either no change or decrease.[44]

A meta-analysis[3] including 13 studies showed no effect of L-thyroxine therapy on HDL-C and TG concentrations. In studies, a significant decrease in HDL-C levels was observed after initiation of L-thyroxine therapy both in the treated group as a whole and in the subgroup with higher initial TSH levels. Only

a few studies have shown a post-treatment decrease in HDL levels.[83] It is well known that hepatic lipase activity is low in hypothyroid patients and increases with thyroid substitution therapy, leading to an increased catabolism of HDL2 and lower HDL-C plasma concentrations.[84]

Although decreased hepatic lipase activity has not been shown in SCH, their finding could be attributed to an increase of hepatic lipase activity triggered by L-thyroxine. The percentage of the TC and LDL-C decreases after treatment found in a group of patients is comparable with previous observations.[79]

Apolipoprotein A is an independent risk factor for atherosclerosis.[85] There is limited information with regard to the effect of SCH on Apo A levels. Apolipoprotein A levels and their response to treatment in SCH have been evaluated in five previous studies.[86]

SCH was associated with raised serum Apo A levels. However, Apo A did not change after treatment with L-thyroxine. This suggests the predominance of genetic factors in Apo A metabolism, at least in SCH, although thyroid hormones are proposed to play a role in Apo A metabolism.[87] As stated before, changes in Apo A are more prominent in the transition from a hyper to a euthyroid state, where possibly the catabolism of Apo A through the LDL receptor plays a more important role than its production.[88]

Thyroid disorders are known to alter the lipid metabolism. Hypothyroidism results in a rise in circulating total cholesterol and LDL cholesterol levels. The elevated LDL cholesterol level in hypothyroidism may occur as a result of increased cholesterol synthesis and absorption, decreased

hepatic lipase and lipoprotein lipase activities and defect in the receptor mediated catabolism of LDL cholesterol. The elevation in LDL cholesterol levels may be accompanied by increased formation of oxidized LDL cholesterol contributing to enhanced risk of atherosclerosis.[89]

Cardiovascular system is very sensitive to minimal defects of circulating thyroid hormone and cardiovascular diseases are associated with overt hypothyroidism. The abnormalities in myocardial contractility and the changes of lipoprotein profile are frequently documented in hypothyroid patients. Therefore SCH may be considered a true risk factor for the development of coronary heart disease. At a younger age, SCH has more severe pathophysiolgical effects resulting in accelerated vascular disease through dyslipidemia, endothelial dysfunction or a direct effect on myocardium. With advancing age subjects that are relatively resistant to the adverse vascular effect of SCH may survive, leading to an attenuation of this effect in old age.[89]

In a metaanalysis,[90] the majority of studies that determined the prevalence of lipid abnormalities in subclinical hypothyroidism and studies that evaluated the effects of thyroxine replacement on lipids were small, uncontrolled, and varied in inclusion criteria. Six randomized, placebo-controlled trials were identified which evaluated the effect of levothyroxine on lipids in subclinically hypothyroid patients. The study concluded that, subclinical hypothyroidism can potentially contribute to a pro-atherogenic lipid profile, with effects being greater at higher thyroid-stimulating hormone levels. Thyroxine replacement reduces total cholesterol and low-density lipoprotein cholesterol, with no effect on triglycerides.

In another study[91] data of serum lipid profile such as total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very low density lipoprotein cholesterol and triglyceride from 100 patients in the age range of 15-65 years of both sex having subclinical hypothyroidism were compared with euthyroid controls, to observe that whether subclinical hypothyroidism is associated with abnormal lipid levels or not. It was a population-based sample from Northern Indians study. A significant increase in triglycerides and very low density lipoprotein cholesterol levels were observed in patients of subclinical hypothyroidism with respect to euthyroid controls while a nominal increase in serum cholesterol, low-density lipoprotein and high-density lipoprotein levels were recorded. However, there was no statistical difference found in any of the lipid fraction levels with change in the severity of subclinical hypothyroidism. All these observation suggested that subclinical hypothyroidism did not have a marked impact on any of the fraction of lipids.

In another study,[70] the authors evaluated alterations in the lipid profile in a group of patients with subclinical hypothyroidism. Fifty-two patients with subclinical hypothyroidism were compared with 98 healthy controls matched by body mass index, age, and sex. A third-generation thyroid-stimulating hormone assay and serum lipid levels-total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-c), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), Apolipoprotein A, Apolipoprotein B, TC/HDL, and LDL/HDL ratio-were measured. Subclinical hypothyroid patients had higher TC, LDL-c, TG, Apo B levels, TC/HDL and LDL/HDL ratio compared with the control group. There were no differences in relation to HDL-c, Apolipoprotein A . There was an

association between subclinical hypothyroidism and TC >200 and TG >200 mg/dL; 55.7% of the patients had hypercholesterolemia as compared with 34.6% in the control group (P = 0.01) and 17.3% of patients had hypertriglyceridemia compared with 5.1% in the control group (P = 0.01). The authors concluded that subclinical hypothyroidism is associated with elevated cholesterol and triglyceride levels and high total cholesterol/HDL and LDL/HDL ratios.

Another study[89] aimed to estimate the prevalence of subclinical hypothyroidism and to assess its association with dyslipidemia enrolled 1157 subjects attending the NRI Hospital, Guntur, India for routine check up. The patients were not under any medication. TSH and lipid profile were determined for all the subjects. The thyroid screening was done on Centaur CP and lipid profile on Dade Behring autoanalyzer. FT4 was estimated in subjects with TSH level 5.5 to 10μIU/ml to confirm SCH. Results showed that, the prevalence of Subclinical Hypothyroidism was 8.29% and the SCH was associated with increased dyslipidemia. Total cholesterol, triglyceride, LDL were raised up to 317 mg/dl, 575mg/dl and 201mg/dl respectively. TSH level significantly correlated with total cholesterol and LDL cholesterol.

Whickham survey[24] defined that younger women with a mildly TSH level (6-9mU/L) had a lower risk for progression. The risk of progression was not evenly distributed throughout the follow up period. In patients with SCH and elevated total cholesterol level, L-thyroxine treatment may reduce serum cholesterol and thereby decrease the incidence of coronary artery disease, stroke, and peripheral vascular disease.

Treatment[20]

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 they 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 μIu/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 μIU per mL (5 to 10 mU per L) range.

Factors Favoring Levothyroxine Therapy in Patients With a Thyroid-Stimulating Hormone (TSH) Level of 5 to 10 mIU/L

- Pregnancy or intention of pregnancy

- Goiter
- Therapeutic trial for possible hypothyroid symptoms
- Patient preference
- Childhood and adolescence
- 2 TSH levels >8 mIU/L
- Bipolar disorder, depression
- Infertility
- Presence of antithyroid antibodies
- Progressive TSH increase
- Ovulatory dysfunction
- Young age of the patient

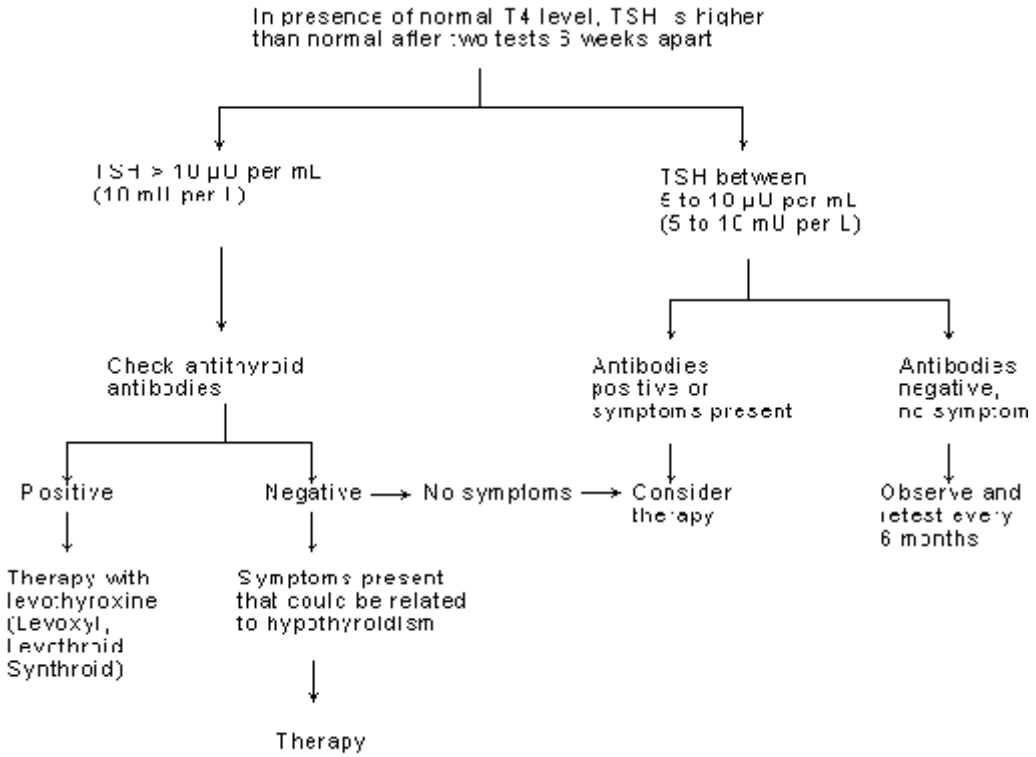


Figure 1. Algorithm for the management of subclinical hypothyroidism.

(T4 = thyroxine; TSH = thyrotropin-stimulating hormone)

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.

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.

Screening

The community should be screened for SCH in high risk group to identify the patients and treat them. Treatment of SCH in pregnant women is mandatory to decrease the risk for pregnancy complication and impaired cognitive development in offspring. Children with SCH should be treated to prevent growth retardation. Studies have reported psychiatric problems such as panic disorder, anxiety and depression disorders are more common in SCH. Recommendations about thyroid screening, however, have been inconsistent. American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every five years thereafter particularly in women.[89]

Individuals with symptoms and signs potentially attributable to thyroid dysfunction and those with risk factors for its development may require more frequent serum thyrotropin testing.[92]

According to American College of Physicians, and American Academy of Family Physicians, there is insufficient evidence to recommend routine screening.

The U.S. Preventive Services Task Force concludes the evidence is insufficient to recommend for or against routine screening for thyroid disease in adults. And some authors have recommended testing in women more than 40 years of age and in geriatric patients. Danese and co-workers24 demonstrated through a decision model that TSH screening every five years, starting at age 35, was cost effective because progression to overt hypothyroidism was prevented, serum cholesterol levels were reduced and symptoms were relieved with early treatment of hypothyroidism.[92]

The American Thyroid Association recommends that adults be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every five years thereafter 25 years.[92]

Chapter 4

Methodology

METHODOLOGY

This study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was case control study.

Study period and duration

The present case control study was conducted during the period of January 2011 to December 2011.

Place

This study was conducted at Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients with subclinical hypothyroidism attending both OPD and IPD of Department of General Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

A total of 50 that is, 25 cases of subclinical hypothyroidism and 25 euthyroid controls were selected for the study.

Sampling procedure

The prevalence of lipid abnormalities in subclinical hypothyroidism is contradictory in the literature. Hence arbitrarily a sample size of 25 cases and 25 euthyroid controls was planned.

Selection criteria

Inclusion Criteria

- Patients with;
    - Elevated TSH levels (> 5.00 µIU/mL)
    - Normal Free T3 (FT3) levels that is, FT3 from 1.45 to 3.48 pg/mL.
    - Normal Free T4 (FT4) levels that is, FT4 from 0.7 to 1.85 ng/mL.
- Patients aged above 18 years.

Exclusion Criteria

- Patients with overt hypothyroidism and on treatment with thyroxine and antithyroid drugs.
- Patients with;
    - End stage renal disease.
    - Post myocardial infarction.
    - Congestive cardiac failure.
    - Type 2 diabetes mellitus.
- Patients on antilipidemic drugs.
- Pregnant women and those on oral contraceptives.

- Patients with acute medical illness.
- Patients with familial hypercholesteremia.

Ethical clearance

Before the commencement of the study Ethical Clearance was obtained from the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients fulfilling selection criteria were explained about the purpose of study and a written informed consent was obtained before enrollment (Annexure I).

Method of collection of data

Demographic data such as age and sex were recorded. A thorough physical examination such as anthropometry, vitals and systemic examination was conducted. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Body mass index

Body mass index was calculated based on formula;

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

Body mass index was classified according to Overweight and obesity by BMI in adult Asians as below.[93]

Classification	BMI (Kg/m^2)	Risk of co-morbidities
Underweight	< 18.5	Low (But increased risk of other clinical problems)
Normal range	18.5 to 22.9	Average
Overweight	≥ 23	
At risk	23.0 to 24.9	Increased
Obese I	25.0 to 29.9	Moderate
Obese II	≥ 30.0	Severe

Investigations

Investigations such as haemogram, fasting blood sugar, fasting lipid profile (total cholesterol, triglycerides, HDL, LDL), Apolipoprotein A and B were done.

Lipid profile

Based on NCEP (National Cholesterol Education Program) guidelines[94] normal values of lipid parameters were;

- Low density lipoprotein < 100 mg/dL.
- High density lipoprotein;
    - Female > 50 mg/dL.
    - Males > 40 mg/dL.
- Total Cholesterol < 200 mg/dL.

- Triglycerides < 150 mg/dL.

Apolipoprotein

Estimation of apolipoprotein A and B was done using 4010 Semiautoanalyser (Make Erba Trans Asia) and the results were interpreted[95] as below;

Apolipoprotein A

- Males – 94 to 178 mg/dL
- Females – 101 to 199 mg/dL

Apolipoprotein B

- Males – 55 to 140 mg/dL
- Females – 55 to 125 mg/dL

Thyroid profile

The thyroid profile was assessed by withdrawing venous blood under aseptic precautions and estimation of TSH, FT3 and FT4 was done using a fully automated immunoflorescence immunoassay analyser (Make: Abott Axsym) was used to estimate TSH, FT3 and FT4. The results obtained were interpreted as below;[96,97]

Thyroid stimulating hormone

- Normal range – 0.49 to 4.67 µIU/mL.
- Abnormal - < 0.49 or > 4.67 µIU/mL.

Free Triiodothyronine

- Normal range – 1.45 to 3.48 pg/mL.
- Abnormal - < 1.45 or > 3.48 pg/mL.

Free thyroxine

- Normal range – 0.70 to 1.85 ng/dL.
- Abnormal - < 0.7 or > 1.85 ng/dL.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical data was expressed as rates, ratios and proportions and chi-square test was used to compare the data. The continous data was expressed as mean ± standard deviation (SD) and the comparison was done using unpaired 't' test. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

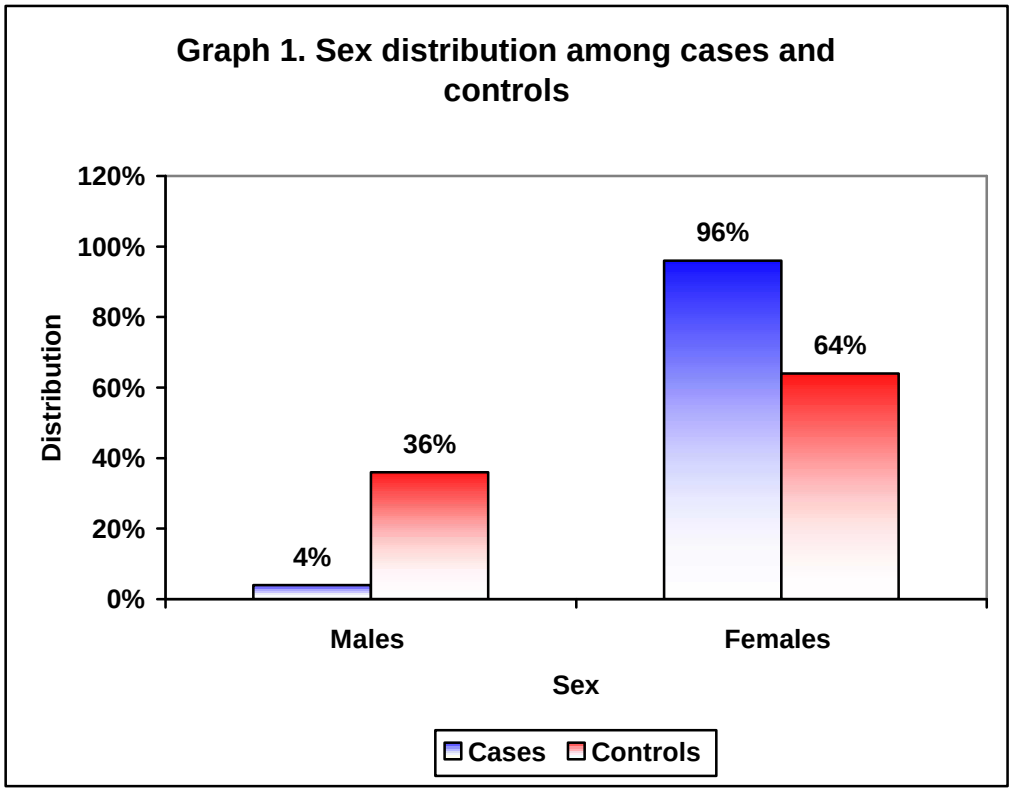
The present case control study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011. A total of 50 patients (25 cases with subclinical hypothyroidism and 25 euthyroid controls) were studied. The thyroid profile was assessed by estimating TSH, FT3 and FT4 and fasting lipid profile was done in both cases and controls. A fully automated immunoflorescence immunoassay analyser was used to estimate TSH, FT3 and FT4.

The data obtained was coded and entered into Microsoft Excel Worksheet. The data was analysed and the final observations and results were tabulated as below.

Table 1. Sex distribution among cases and controls

Sex	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Male	1	4	9	36
Female	24	96	16	64
Total	**25**	**100.00**	**25**	**100.00**

x^2_{yc} = 6.125 **p = 0.013**

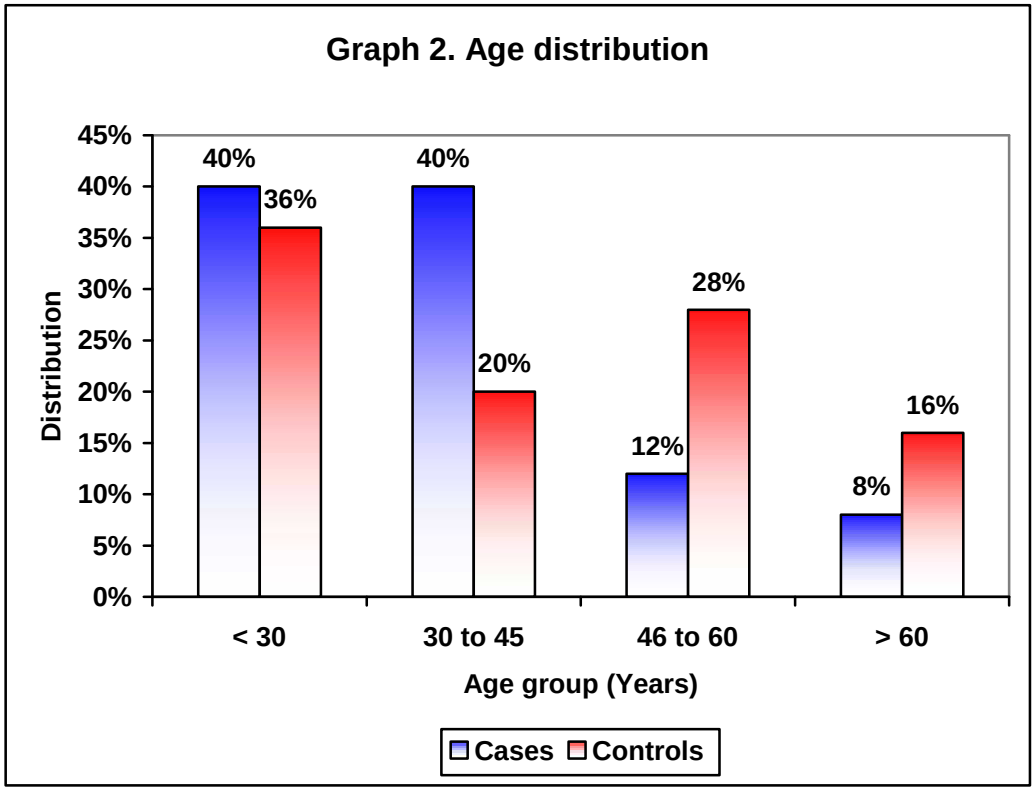


In our study it was observed that among cases 96% were females when compared to 64% in controls.(p=0.013)

Table 2. Age distribution

Age group (Years)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
< 30	10	40	9	36
30 to 45	10	40	5	20
46 to 60	3	12	7	28
> 60	2	8	4	16
Total	**25**	**100.00**	**25**	**100.00**

x^2_3 **= 3.985** **p = 0.262**



In our study it was observed that 80% of the cases were below 45 years of age as compared to 56% in controls. However the difference between cases and controls was not statistically significant (p=0.262)

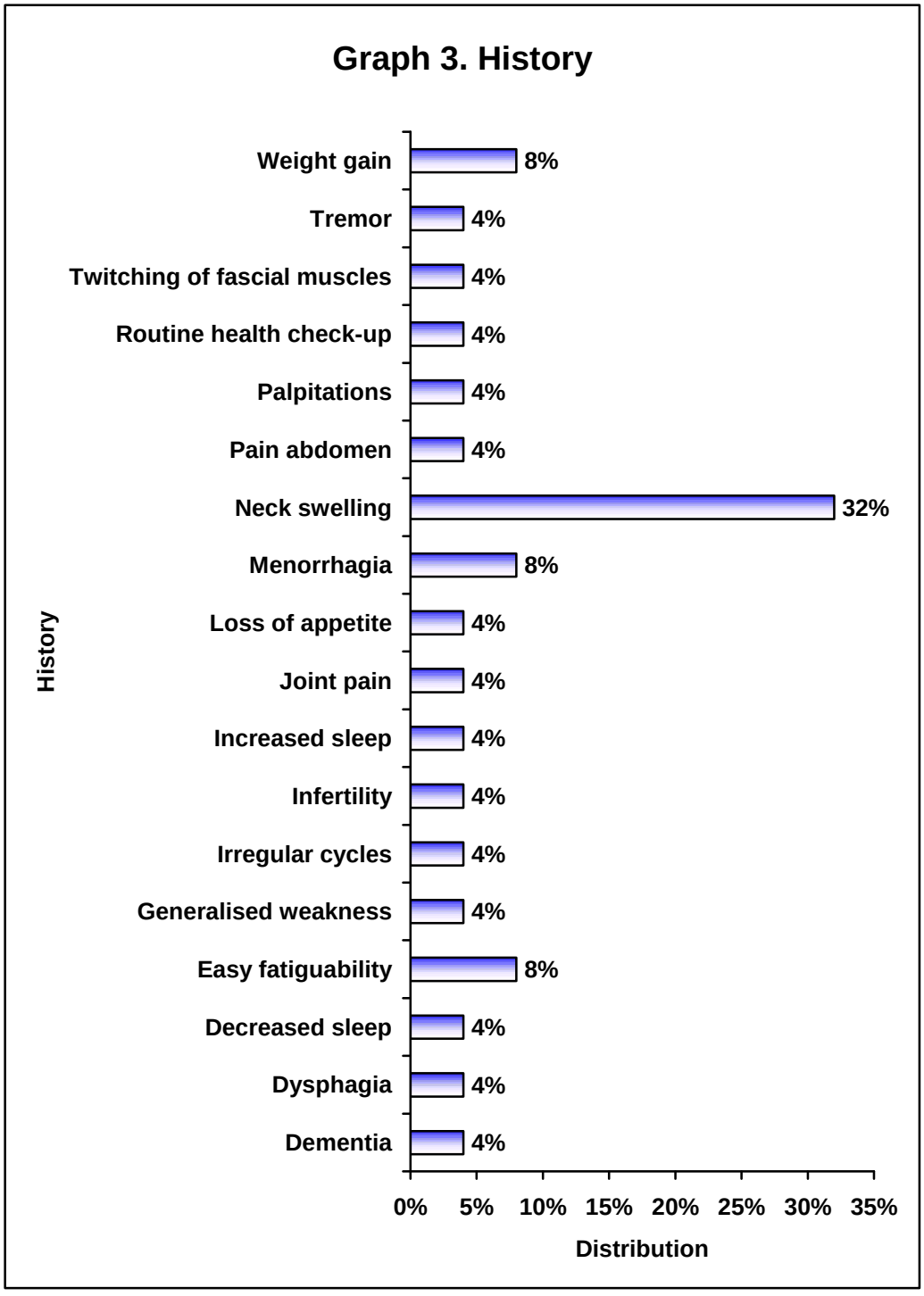
Table 3. Mean age

Age (Years)	Cases (n=25)	Controls (n=25)
Mean	37.25	20.46
SD	13.73	1.68
Median	35.5	20.59
Minimum	20	17.85
Maximum	66	23.62
t = 6.069		**p <0.001**

In our study the mean age of cases was 37.25 years and in controls was 20.46 years ($p<0.001$).

Table 4. History

History	Cases (n=25)	
	Number	**Percent**
Dementia	1	4
Dysphagia	1	4
Decreased sleep	1	4
Easy fatiguability	2	8
Generalised weakness	1	4
Irregular cycles	1	4
Infertility	1	4
Increased sleep	1	4
Joint pain	1	4
Loss of appetite	1	4
Menorrhagia	2	8
Neck swelling	8	32
Pain abdomen	1	4
Palpitations	1	4
Routine health check-up	1	4
Twitching of fascial muscles	1	4
Tremor	1	4
Weight gain	2	8

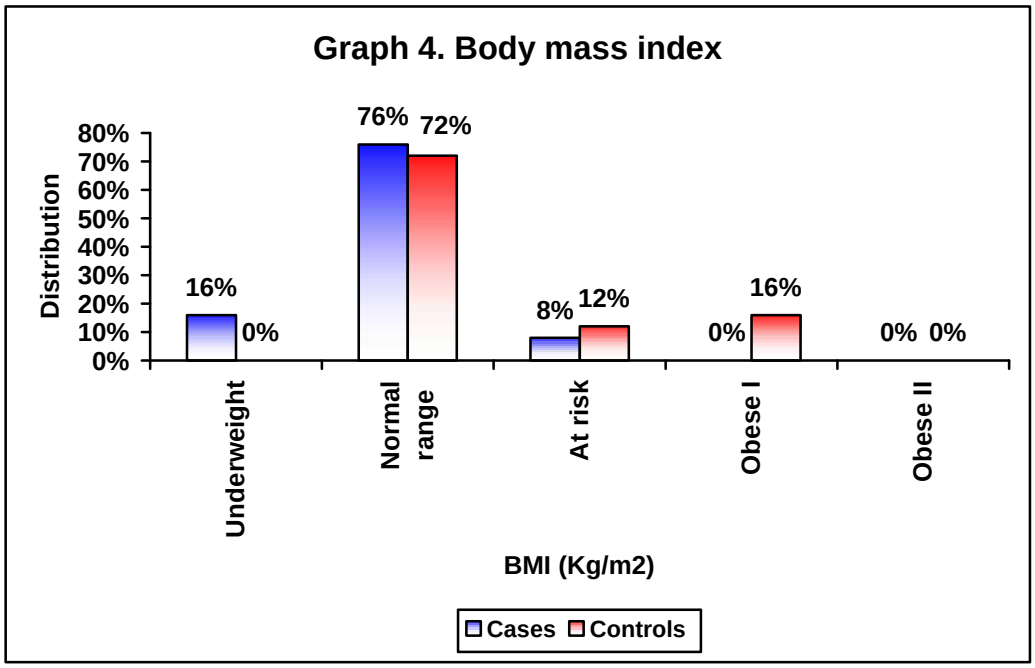


In our study 32 % of the cases had significant history of neck swelling. The next common symptoms in our study population were easy fatiguability (8%)weight gain(8%) and menorrhagia (8% of cases)

Table 5. Body mass index

BMI (Kg/m^2)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Underweight	4	16	0	0
Normal range	19	76	18	72
At risk	2	8	3	12
Obese I	0	0	4	16
Obese II	0	0	0	0
Total	**25**	**100.00**	**25**	**100.00**

x^2_2 = 6.804 **p=0.033**



In our study 76% of the cases belonged to normal range of body mass index compared to 72% in controls.

Table 6. Mean Body mass index

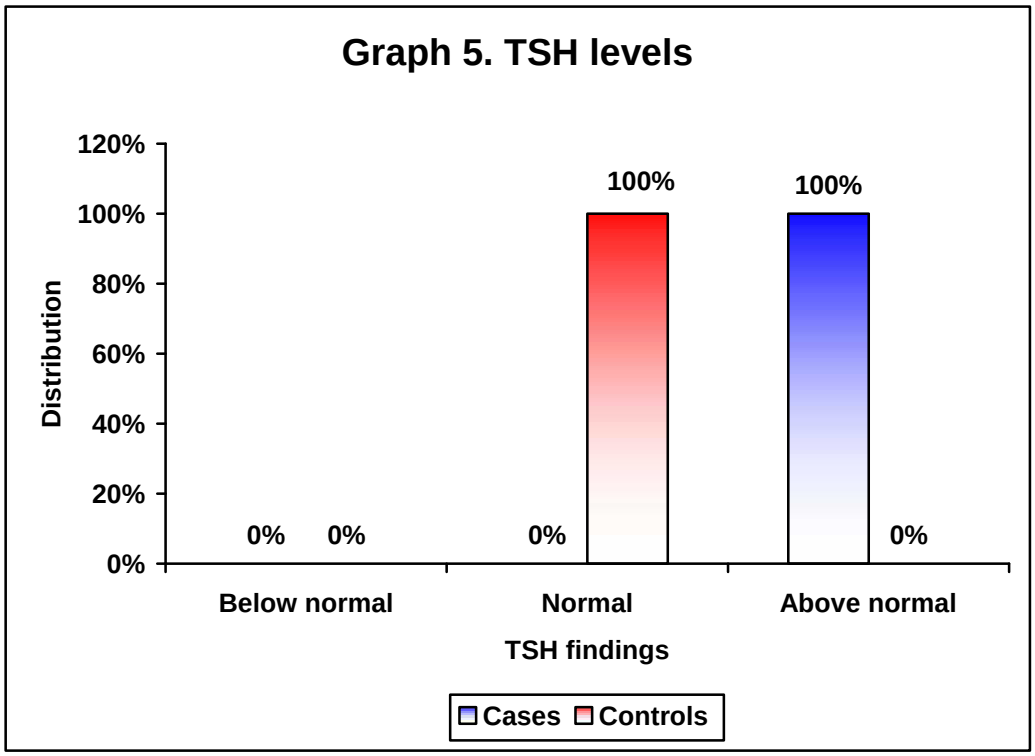
BMI (kg/m^2)	**Cases (n=25)**	**Controls (n=25)**
Mean	20.46	21.58
SD	1.68	2.8
Median	20.59	21.41
Minimum	17.85	18.53
Maximum	23.62	28.97
t = 1.715		**p = 0.099**

The mean BMI in cases in our study was 20.46 ± 1.68 Kg/m^2 when compared to 21.58 ± 2.8 Kg/m^2 in controls.

Table 7. TSH levels

TSH findings	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Below normal	0	0	0	0
Normal	0	0	25	100
Above normal	25	100	0	0
Total	**25**	**100.00**	**25**	**100.00**

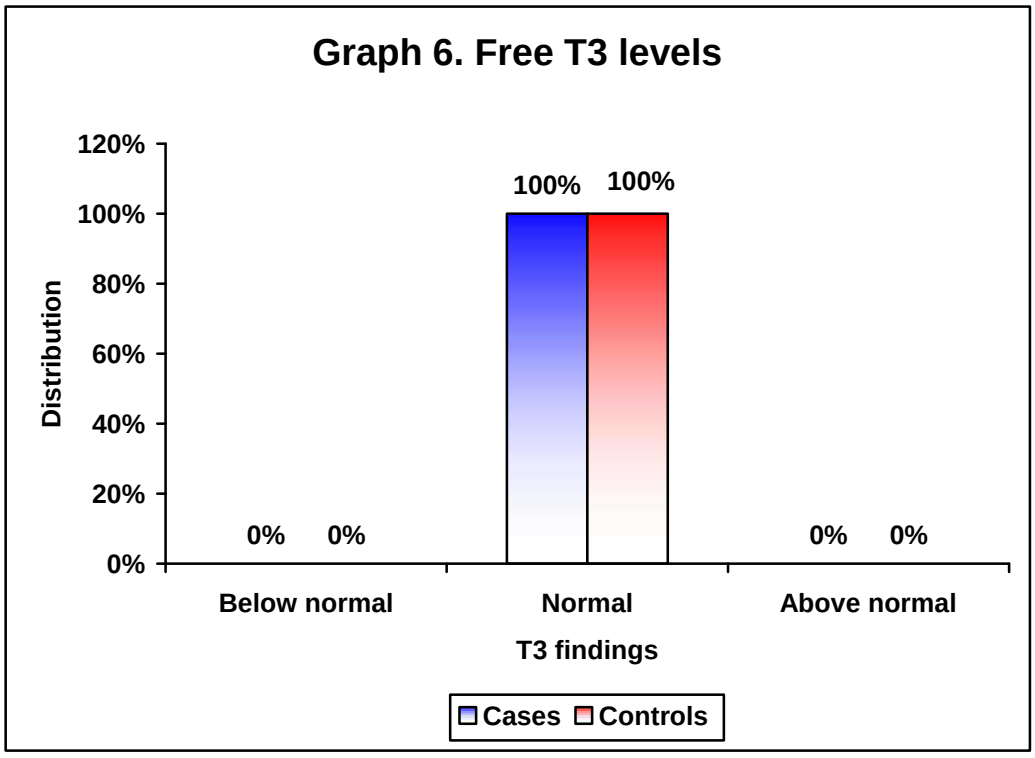
p<0.001 (Fisher exact)



In our study all the cases had TSH levels more than 5 µIU/ml as defined by inclusion criteria.

Table 8. FreeT3 levels

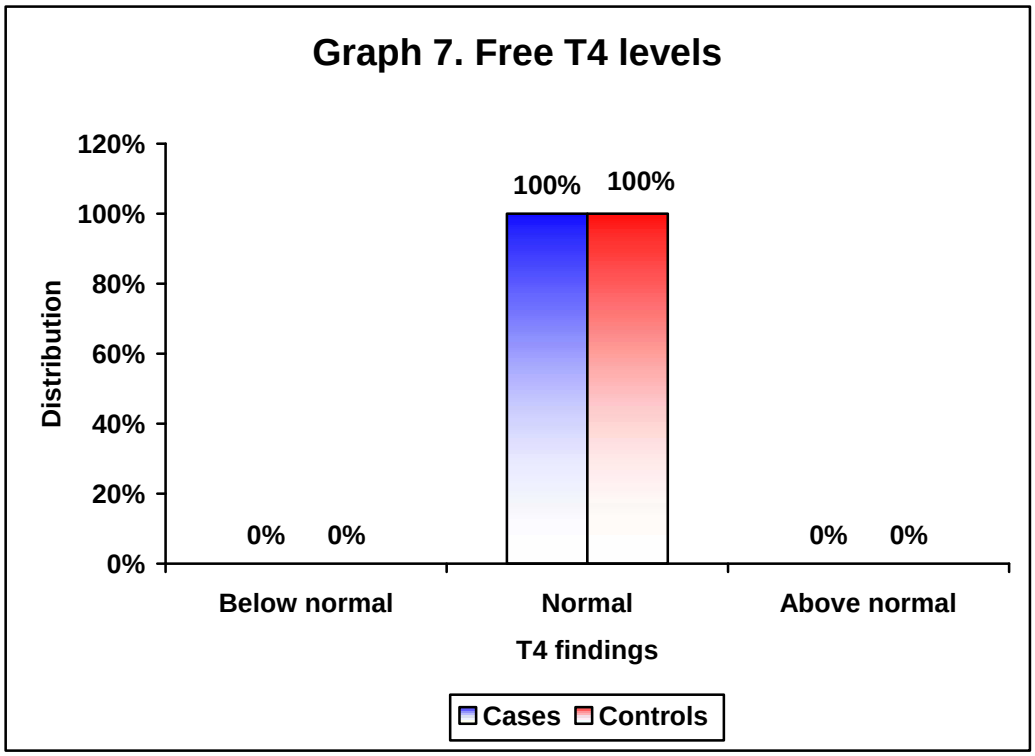
Free FT3 findings	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Below normal	0	0	0	0
Normal	25	100	25	100
Above normal	0	0	0	0
Total	**25**	**100.00**	**25**	**100.00**



In our study all the cases and controls had normal FT3 levels as defined by inclusion criteria.

Table 9. Free T4 levels

FeeeT4 findings	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Below normal	0	0	0	0
Normal	25	100	25	100
Above normal	0	0	0	0
Total	**25**	**100.00**	**25**	**100.00**

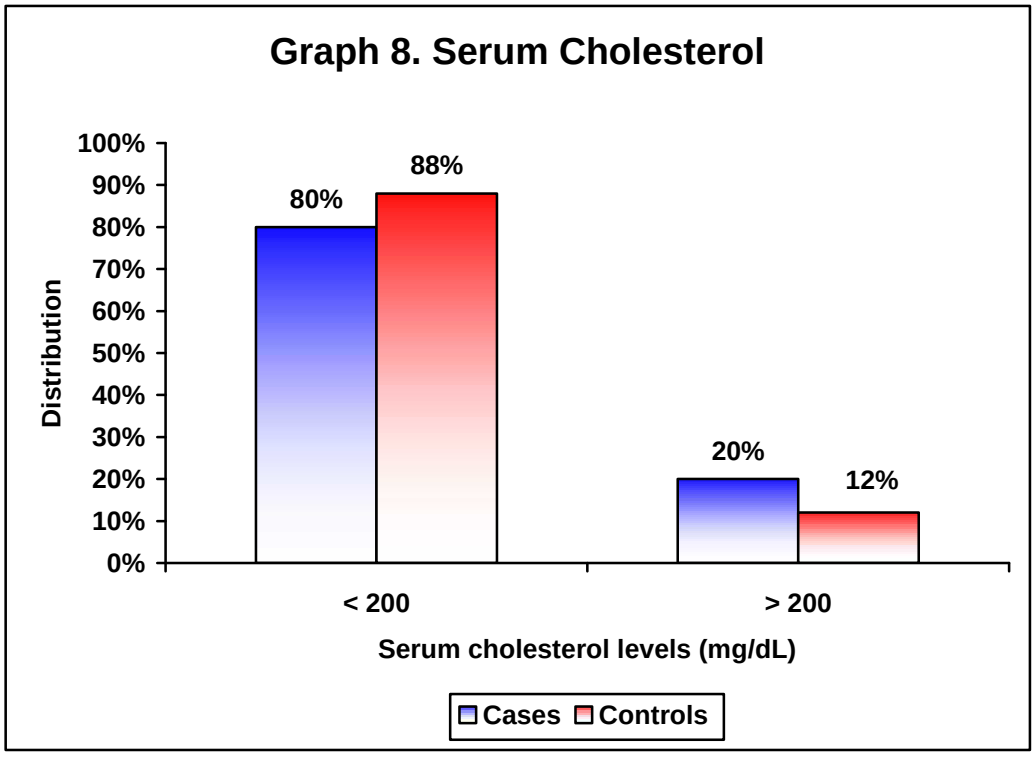


In our study all the cases and controls had normal FT4 levels as defined by inclusion criteria

Table 10. Serum Cholesterol

Serum cholesterol levels (mg/dL)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
< 200	20	80	22	88
> 200	5	20	3	12
Total	**25**	**100.00**	**25**	**100.00**

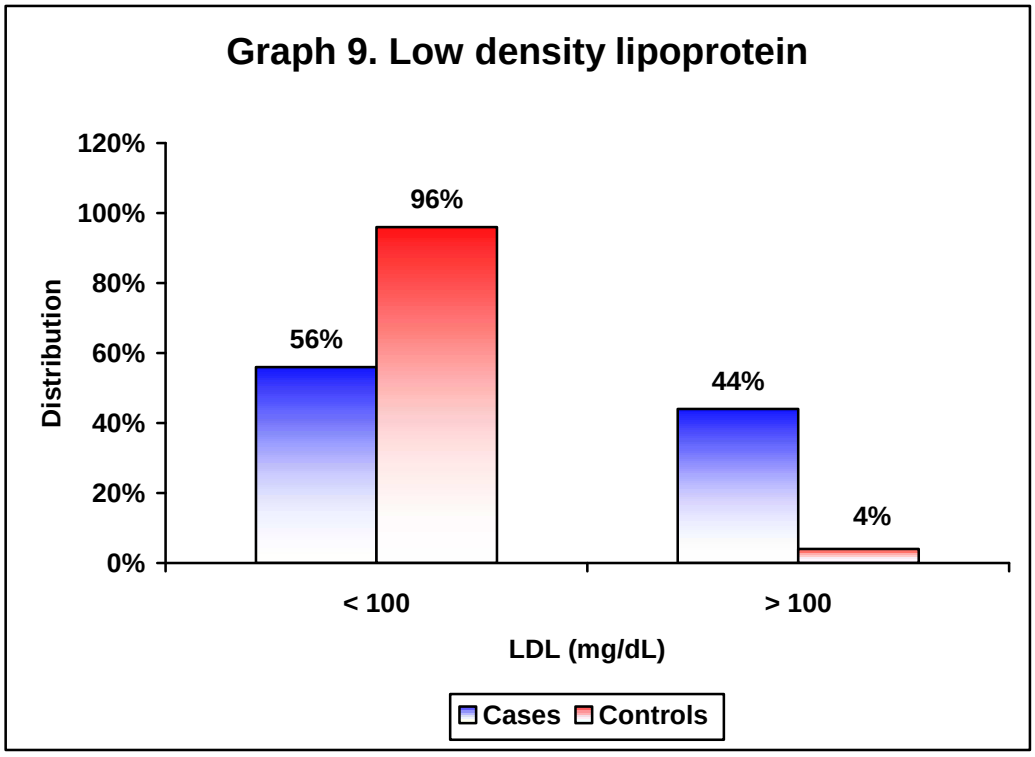
x^2_{yc}=0.148 **p=0.699**



In our study it was observed that 20% of the cases had high cholesterol (>200 mg/dl) compared to 12% in controls. However this difference was not statistically significant (p=0.699).

Table 11. Low density lipoprotein

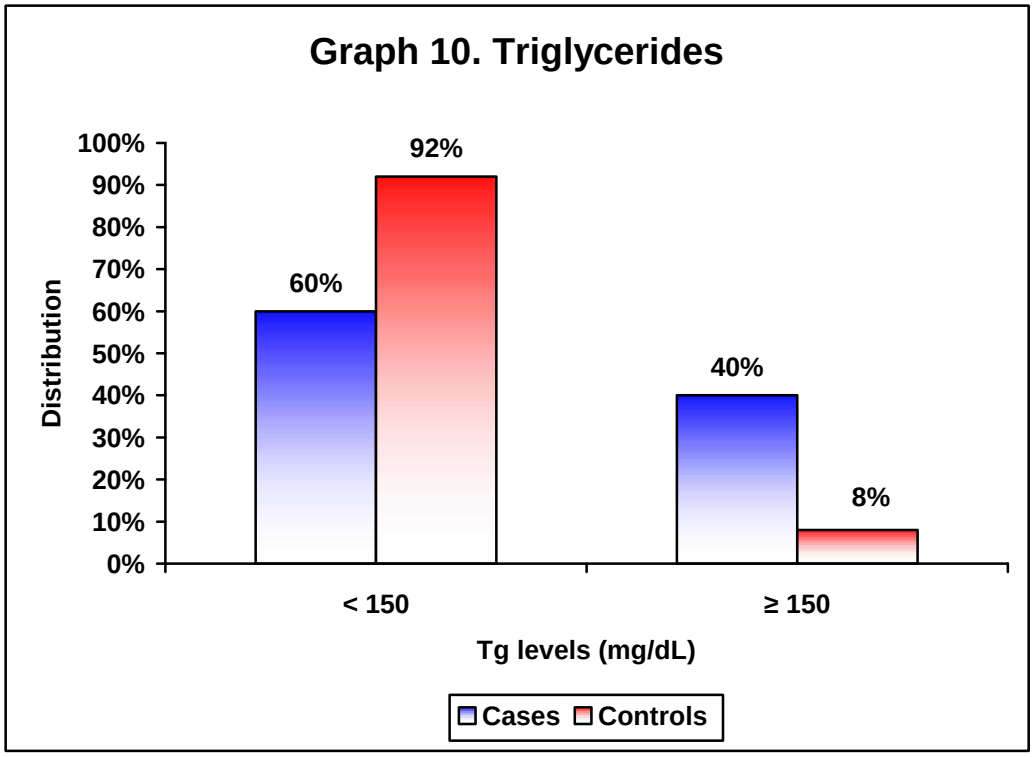
Low density lipoprotein (mg/dL)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
< 100	14	56	24	96
> 100	11	44	1	4
Total	**25**	**100.00**	**25**	**100.00**
x^2_{yc}=8.881			**p=0.003**	



In our study it was observed that 44% of the cases had high low density lipoprotein (>100mg/dl) compared to 4% in controls and this difference was statistically significant (p=0.003).

Table 12. Triglycerides

Triglyceride levels (mg/dL)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
< 150	15	60	23	92
≥ 150	10	40	2	8
Total	**25**	**100.00**	**25**	**100.00**
x^2_{yc}=5.372			p=0.020	

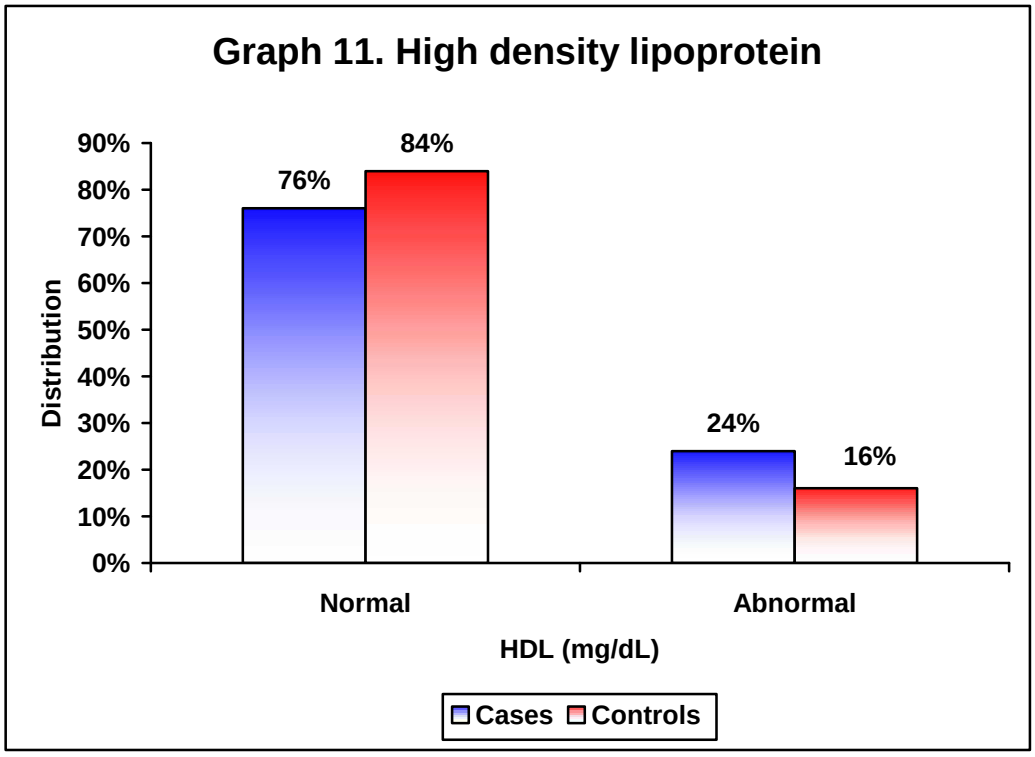


In our study it was observed that 40% of the cases had high triglycerides (>150mg/dl) compared to 8% in controls and this difference was statistically significant (p=0.020).

Table 13. High density lipoprotein

HDL Levels (mg/dL)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Normal	19	76	21	84
Abnormal	6	24	4	16
Total	**25**	**100.00**	**25**	**100.00**

x^2_{yc}=0.125 **p=0.723**

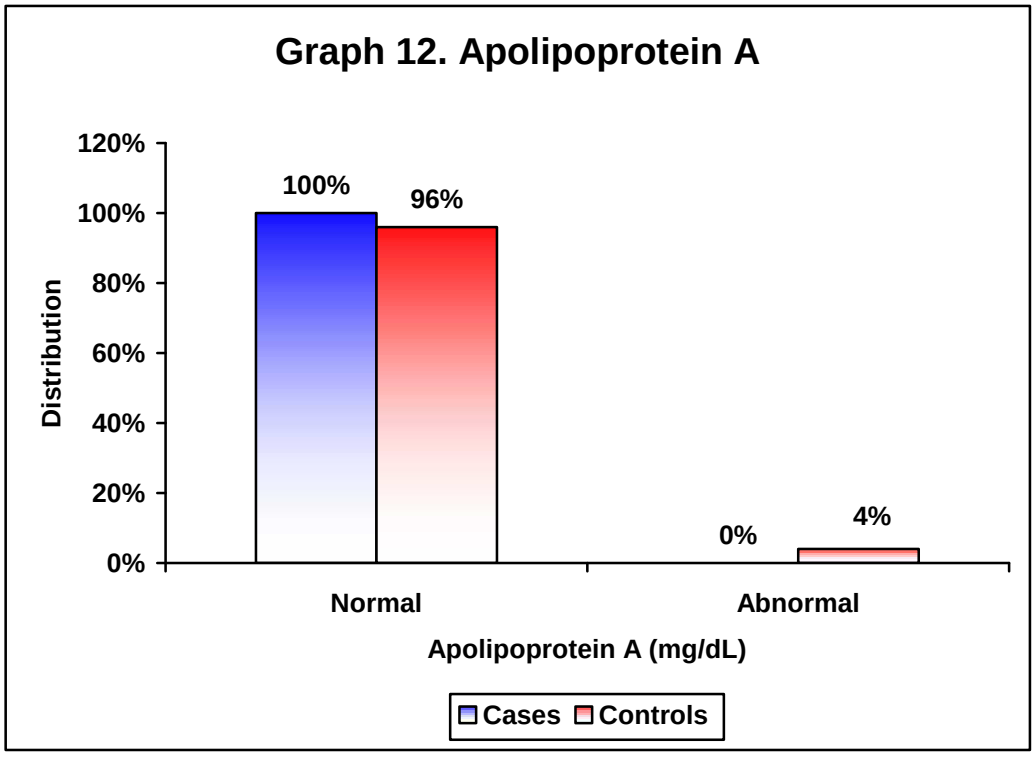


In our study it was observed that 24% of the cases had low HDL (Less than 40 mg/dL in male and less than 50 mg/dL in female) compared to 16% in controls. However this difference was statistically not significant (p=0.723).

Table 14. Apolipoprotein A

Apolipoprotein A (mg/dL)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Normal	25	100	24	96
Abnormal	0	0	1	4
Total	**25**	**100.00**	**25**	**100.00**

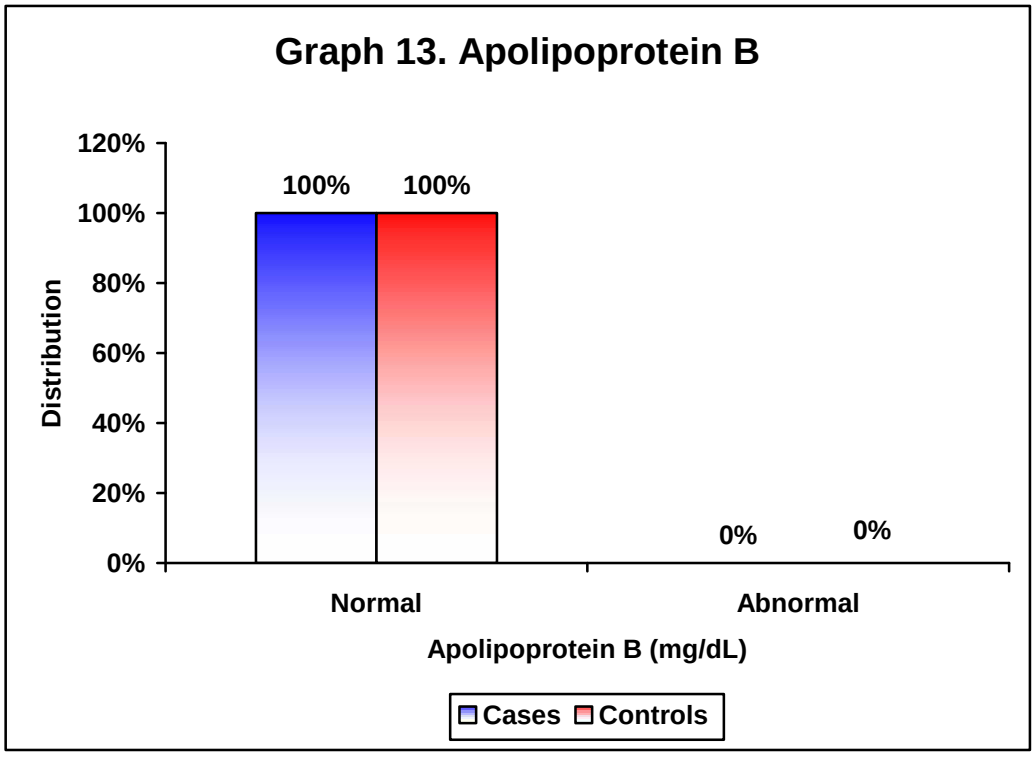
p=1 (Fisher exact)



In our study it was observed that none of the cases had abnormal Apolipoprotein A values as compared to 4% of controls having abnormal values.

Table 15. Apolipoprotein B

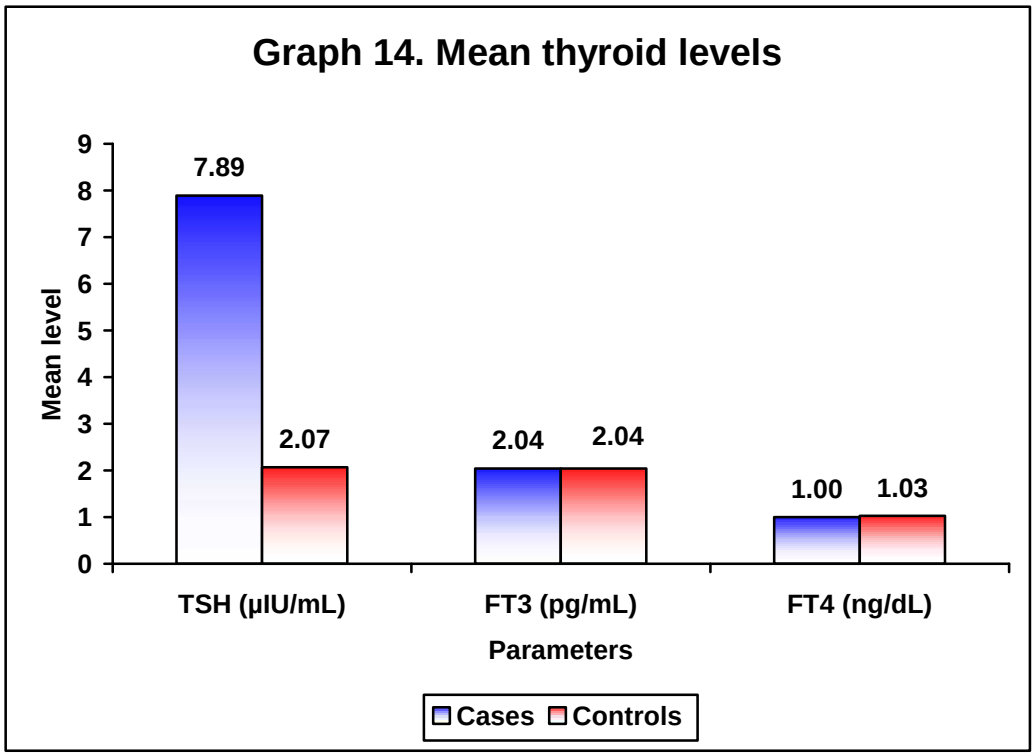
Apolipoprotein B (mg/dL)	Cases (n=25)		Controls (n=25)	
	Number	**Percent**	**Number**	**Percent**
Normal	25	100	25	100
Abnormal	0	0	0	0
Total	**25**	**100.00**	**25**	**100.00**



In our study it was observed that none of the cases and controls had abnormal Apolipoprotein B values.

Table 16. Mean thyroid levels

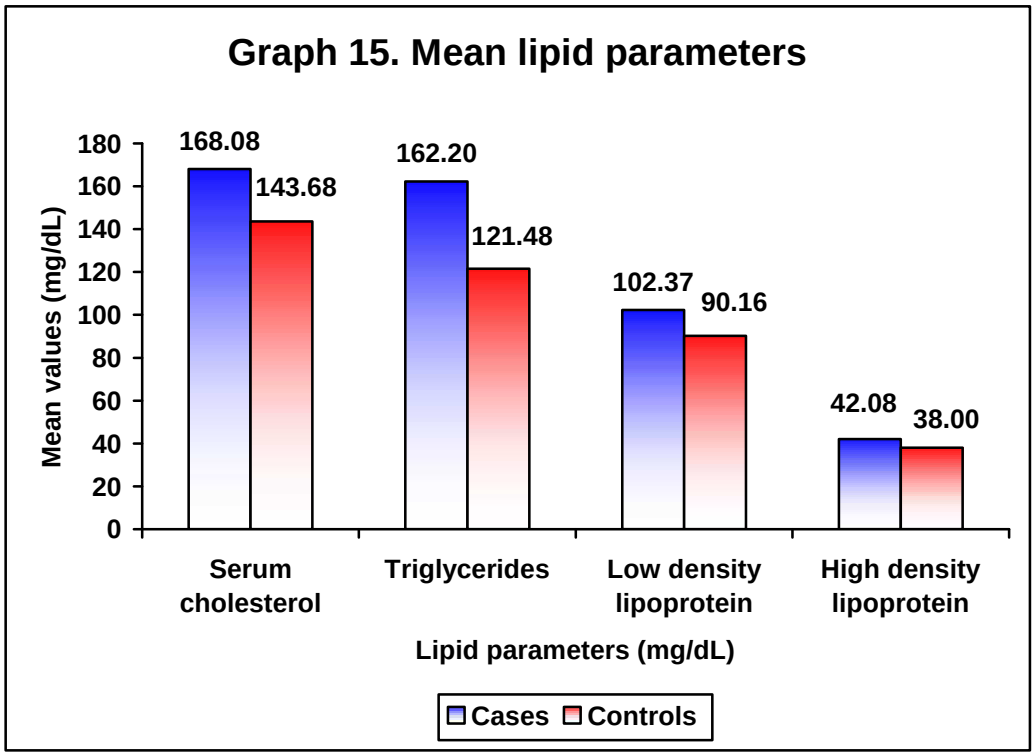
Parameters	Cases (n=25)		Controls (n=25)		t	DF	p
	Mean	SD	Mean	SD			
TSH (µIU/mL)	7.89	2.51	2.07	1.01	15.19	48	<0.001
fT3 (pg/mL)	2.04	0.39	2.04	0.52	0.00	48	1.000
fT4 (ng/dL)	1.00	0.29	1.03	0.33	0.48	48	0.631



In the present study it was observed that among the cases the mean TSH level was significantly high (7.89 ± 2.51 vs. 2.07 ± 1.01 µIU/ml; p<0.001). However no significant difference was noted among cases and controls when fT3 and fT4 were compared.

Table 17. Mean lipid parameters

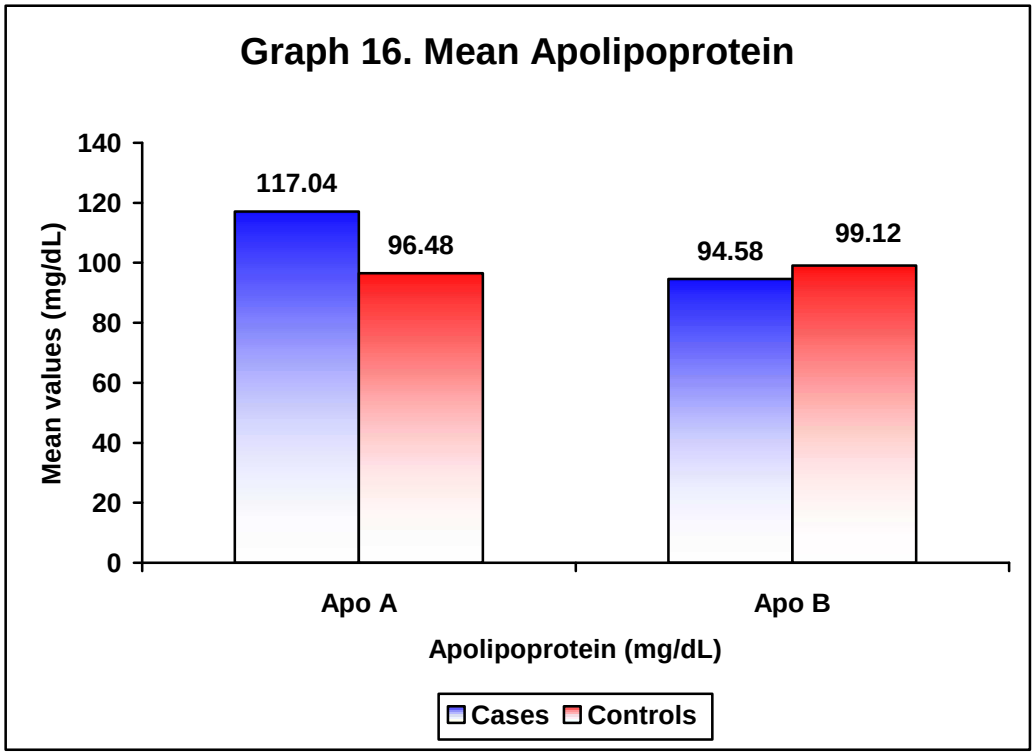
Lipid parameters(mg/dL)	Cases (n=25)		Controls (n=25)		t	p
	Mean	SD	Mean	SD		
Serum cholesterol	168.08	39.35	143.68	38.15	2.226	0.031
Triglycerides	162.2	71.87	121.48	34.42	2.555	0.017
Low density lipoprotein	102.37	41.18	90.16	20.43	1.328	0.197
High density lipoprotein	42.08	9.80	38.00	5.86	1.787	0.087



In this study significant rise was noted in cases with regard to serum cholesterol (168.08 ± 39.35 mg/dL vs. 143.68 ± 38.15 mg/dL; p=0.031) and triglycerides (162.02 ± 71.87 mg/dL vs 121.48 ± 34.42 mg/dL; p<0.001). However, there was no difference between cases and controls when mean HDL and LDL were compared.

Table 18. Mean Apolipoprotein

Apolipoprotein (mg/dL)	Cases (n=25)		Controls (n=25)		t	p
	Mean	SD	Mean	SD		
Apo A	117.04	19.27	96.48	7.38	7.982	<0.001
Apo B	94.58	15.2	99.12	9.22	1.387	0.175



In the present study it was observed that mean apolipoprotein A levels were significantly high in cases (117.04 ± 19.27 mg/dL vs 96.48 ± 7.38 mg/dL; $p<0.001$) whereas no statistically significant difference was observed between both the groups with regard to apolipoprotein B.

Chapter 6

Discussion

DISCUSSION

Thyroid disorders are the most common endocrinal disorders. Thyroid diseases are among the common endocrinal disorders worldwide. The symptoms of subclinical hypothyroidism are vague and non specific. It is diagnosed by normal free thyroxine (FT4) and normal free triiodothyronine (FT3) and an elevated TSH level.

SCH has emerged as an independent risk factor for aortic atherosclerosis and myocardial infarction. However, the results of lipid profile alterations in subclinical hypothyroidism are controversial in different studies; some have showed positive correlation and prompt reversal of changes following treatment, [17,18] while others have not shown any correlation between the two.[19] Further, there are very few Indian studies on lipid profile changes in subclinical hypothyroidism. The present study was aimed to determine lipid abnormalities in patients with subclinical hypothyroidism.

This study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2011 to December 2011. A total of 50 patients (25 cases and 25 euthyroid controls) were studied.

In the present study, among cases, 24 (96%) were females when compared to 16 (64%) in controls (p=0.013). This study showed female predominance which was similar to study done at Calcutta,[98] where females constituted 78% of study populations. Another studies done in Punjab[91] and New Delhi[99] where females was 88% & 80.22% of the study population respectively.

80% of the cases were below 45 years of age as compared to 56% in controls. However this difference was statistically not significant (p=0.262). The mean age of cases was 37.25 years which was similar to a study done at Calcutta[98] where it was 38.56 years and 31.55± 2.1 years in another study done in New Delhi[99] and in controls mean age was 20.46 years (p<0.001).

In our study 32% of the cases had significant history of neck swelling followed by easy fatiguability (8%), weight gain (8%) and menorrhagia (8%). 76% of the cases had normal body mass index compared to 72% in controls. The mean BMI in cases was 20.46±1.68 Kg/m^2 while in controls it was 21.58 ± 2.8 Kg/m^2. This finding was in sharp contrast to a study[59] where mean BMI was 25.5kg/ $m^{2.}$

In this study all the cases had raised TSH levels (>5 µIU/ml) and normal FT3 and FT4 levels as defined by inclusion criteria which is similar to a study done in Punjab[91] and New Delhi,[99] where the cut off limit for TSH was > 5.0 µIU/ml and 6.1 µIU/ml respectively.

In the present study, we observed that 20% of the cases had high cholesterol (>200 mg/dl) compared to 12% in controls. 24% of the cases had low HDL (< 40 mg/dL in male and < 50 mg/dL in female) compared to 16% in controls. However this difference was statistically not significant (p> 0.05).These findings are similar to a study done in Punjab[91] where no significant changes were seen in levels of cholesterol and HDL.

In this study, the low density lipoprotein was high in 44% of the cases (>100mg/dl) compared to four percent in controls. This finding is similar to a study done in Gorgan[60] where LDL was (169.0 ± 45.02mg/dl).

Hypertriglyceridemia is a well known risk factor for cardiovascular diseases like atherosclerosis. 40% of the cases had high triglycerides (>150 mg/dL) compared to eight percent in controls. This difference was statistically significant ($p<0.05$). These findings are similar to a study done in Punjab[91] where mean triglycerides levels were 174.78 ±32.92 mg/dL.

In the present study, it was observed that the Apolipoprotein A values were normal in cases whereas it was raised in 4% of the controls and Apolipoprotein B values were normal in both cases and controls.

In the present study, it was observed that mean TSH level was significantly high in cases compared to controls (7.89±2.51 vs. 2.07±1.01 µIU/mL; $p<0.001$). This finding was similar to a study done in New Delhi[99] where mean TSH was 7.615±0.11 µIU/mL.

No significant difference was noted when FT3 and FT4 levels were compared among cases and controls.

Free T3 levels between cases and controls were similar. This is an expected finding because peripheral deiodination of T4 to T3 is unaffected in subclinical hypothyroidism. A study from Italy[100] yielded similar results.

In this study mean serum cholesterol was significantly high in cases compared to controls (168.08 ± 39.35 mg/dL vs. 143.68 ± 38.15 mg/dL; $p=0.031$)

This result was in accordance with the study conducted in Punjab[91] (181.58 ±35.16 mg/dL) However many other studies have reported higher mean total cholesterol as compared to present study like a study done in New Delhi[99] shows a mean cholesterol levels of 236.724 ± 9.472 mg/dL, similarly a study done at Gorgan[60] shows a mean cholesterol of 262.66 ± 67.94 mg/dL.

In this study, mean serum triglycerides was higher in cases as compared to controls which was statistically significant (162.02 ± 71.87 mg/dL vs 121.48 ± 34.42 mg/dL; $p<0.001$). This observation was similar to a study done at New Delhi[99] where the values were 166.48 ± 7.481mg/dl. However, there was no difference between cases and controls when mean HDL and LDL were compared.

In the present study, it was observed that, mean Apolipoprotein A levels were significantly high in cases (117.04 ± 19.27 mg/dL vs 96.48 ± 7.38 mg/dL; $p<0.001$) compared to controls whereas no statistically significant difference was observed between both the groups with regard to Apolipoprotein B levels.

Chapter 7

Conclusion

CONCLUSION

The present study showed significantly higher levels of triglycerides and low density lipoprotein levels in patients with sub-clinical hypothyroidism. The quantitative analysis showed significantly raised serum cholesterol levels among patients with subclinical hypothyroidism. No statistically significant relation was found between high density lipoprotein and subclinical hypothyroidism.

The mean Apo A levels were significantly higher in patients with subclinical hypothyroidism but there was no statistically significant difference in Apo B levels.

It seems necessary that subjects with laboratory report of hypercholesterolemia and hypertriglyceridemia should be also further examined and tested for serum thyroid hormones measurements and particularly the evaluation of thyroid stimulating hormone (TSH) should be reassessed carefully.

Chapter 8

Summary

SUMMARY

Subclinical hypothyroidism may be associated with increased risk of CAD, PVD and various biochemical abnormalities including increased LDL-C levels, increased total cholesterol and serum triglyceride values. It is uncertain whether subclinical hypothyroidism (increased serum TSH, normal serum T4 and T3) is also associated with hyperlipidemia. The present study was aimed to determine lipid abnormalities in patients with subclinical hypothyroidism and its interpretation.

This case control study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011. A total of 50 patients (25 cases with subclinical hypothyroidism and 25 euthyroid controls) were studied. The thyroid profile was assessed by estimating TSH, FT3 and FT4. A fully automated immunoflorescence immunoassay analyser was used to estimate TSH, FT3 and FT4.

In the present study among cases 96% were females when compared to 64% in controls (p=0.013). It was observed that 80% of the cases were below 45 years of age as compared to 56% in controls (p=0.262). Overall, the mean age of cases was 37.25 years and in controls was 20.46 years (p=<0.001). Among the cases, 20% had high cholesterol, 40% had high triglycerides and 44% had high LDL. The lower HDL was recorded in 24% of cases.

Overall, the present study showed significantly higher levels of triglycerides and low density lipoprotein levels in patients with sub-clinical

hypothyroidism. The quantitative analysis of serum cholesterol showed significantly raised serum cholesterol levels. No statistically significant relation was found between high density lipoprotein and subclinical hypothyroidism.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

A CASE CONTROL STUDY OF SERUM LIPID LEVEL ALTERATIONS IN SUBCLINICAL HYPOTHYROID PATIENTS

Objective and purpose of the study

This research is intended to assess serum lipid levels alterations in sub-clinical hypothyroid patients. The Principal Investigator of the study is Dr. ***** ****** under the Guidance of Dr. **** ******. My cooperation will be of great help to patients with subclinical hypothyroidism and dyslipidemia and also predict their complications in the future.

Procedure

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood samples for the necessary investigations.

Risk and Benefits

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part, you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research.

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your rights as a participant, you may call Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number **** ******.

In case of the queries during study or in future you may contact following persons.

Principal investigator : Dr. ****** ******

Guide : Dr. ****** ******

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant: _____Signature / Thumb print _____

Name of the Witness _____Signature / Thumb print _____

Investigator Name: _____Signature / Thumb print _____

Date: Place:

Annexures

Annexure II

ANNEXURE II – PROFORMA

Serial Number :

In Patient Number :

Name :

Age :

Sex :

Occupation :

Religion :

Address :

History

Duration of onset of symptoms:

History of easy fatiguability:

Dry skin, skin changes:

Weight gain, loss of appetite, bowel disturbances

Dyspnoea, dysphagia, hoarseness of voice

Menstrual irregularities: Menorrhagia, oligomenorrhoea amenorrhoea, infertility

Thyroid swelling;

Paresthesia, numbness, tremors, impaired hearing

Past history: Previous significant medical illness: History of diabetes, hypertension, tuberculosis, ischemic heart disease, neck irradiation, thyroid surgery.

Family history: History of thyroid disease in the family, diabetes, hypertension, tuberculosis, ischemic heart disease

Drug history: History of ingestion of drugs that are likely to intervene in the thyroid metabolism. e.g., amiodarone, lithium, PAS, sulfonamides, glucocorticoids, rifampicin, catecholamine etc.

Personal history

Diet: Appetite:

Sleep: Bowel and bladder:

Examination

Height (Cms): Weight (Kgs):

Body mass index (Kg/m^2):

Pallor / cyanosis, lymphadenopathy, edema

Pulse (bpm)

Blood pressure (mm Hg)

Temperature

Thyroid swelling

Skin changes

Tremors

Systemic examination

Central nervous system

Higher mental functions

Cranial nerves

Motor symptoms

Cerebellar system

Cardiovascular system

Apex: S1, S2

Cardiomegaly Murmurs

Per abdomen

Respiratory system

Diagnosis:

Investigations

Complete blood count

Fasting blood sugar

Thyroid profile

Fasting lipid profile

Additional investigations if required

Treatment received

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

µg/l	– Microgram per litre
µIU/mL	– Micro International units per mililitre
BC	– Backache
BV	– Blurring vision
Cms	– Centimeters
DM	– Dementia
DP	– Dysphagia
DS	– Decreased sleep
EF	– Easy fatiguability
F	– Female
FHPT	– Family history of hypothyroidism
GW	– Generalised weakness
gm	– Gram
HD	– Headache
HDL	– High density Lipoprotein
IC	– Irregular cycles
IG	– Imbalance gait
INF	– Infertility
IS	– Increased sleep

JP – Joint pain

kg/m^2 – Kilograms per square metre

LA – Loss of appetite

LDL – Low density lipoprotein

M – Male

m – Months

MG – Menorrhagia

mg/dL – Milligrams per deciliter

mmol/l – Milli mol per litre

NB – Numbness

ng – Nano gram

NS – Neck swelling

OL – Oligomenorrhia

PA – Pain abdomen

pg – Pico gram

PP – Palpitations

RHC – Routine health check-up

SC – Syncope

SM – Skin mottling

SS – Slurring of speech

SVT – Supraventricular tachycardia

T3 – Total triiodothyronine

T4 – Total thyroxine

TFM – Twitching of fascial muscles

TG – Triglycerides

TR – Tremor

TSH – Thyrotropin stimulating hormone

UH – Umbilical hernia

WG – Weight gain

WL – Weight loss

Y – Years