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Original Research Article

Clinical profile and lipid abnormalities in subclinical and overt primary hypothyroidism

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ABSTRACT

Background: Overt and subclinical hypothyroidism, affects metabolism of lipids particularly that of cholesterol, low density lipoprotein and triglyceride. Hypercholesterolemia predisposes to atherosclerosis and thereby increases cardiovascular risks.
Methods: Hundred patients of primary hypothyroidism of age more than 15 yrs were included. Five milliliters of venous blood was drawn in fasting state and serum obtained; thyroid function test (TFT) and fasting lipid profile were performed. Based on the TFT, patients were categorized as sub clinical or overt hypothyroidism. Clinical data, thyroid and lipid profiles obtained were analyzed and compared using statistical methods.
Results: Seventy patients were females and thirty were males in the ratio of 2.3:1. Most common age group was 51-60years followed by 41-50years. Most common symptom was generalised weakness followed by weight gain, cold intolerance, constipation, hair loss, paraesthesia's. Most common signs were myxoedema, delayed ankle reflex relaxation, dry and coarse skin, bradycardia, non-pitting peripheral edema, madarosis, pallor, goiter. Patients with Overt hypothyroidism had significantly higher serum levels of total cholesterol(249.1±31.7 mg/dl), Triglycerides (191.5±68.5 mg/dl) and LDL cholesterol(167.7±31 mg/dl) than the Subclinical hypothyroidism with total cholesterol(202±19.8),triglycerides(155.6±35) and LDL cholesterol(129±21.1) but HDL cholesterol level remains normal in both overt (44.0±4.7) and subclinical (43.1±4.4)hypothyroidism respectively.
Conclusions: Patients with Overt hypothyroidism had significantly higher levels of Total cholesterol, Triglycerides (TG) and LDL cholesterol than the Subclinical hypothyroidism but HDL cholesterol level remains normal in both. So, concomitant estimation of lipid profile in hypothyroidism patients is needed for early intervention and prevention of cardiovascular morbidity and mortality.

Keywords: Cholesterol, Hypothyroidism, Lipid profile, TSH

INTRODUCTION

As per United States National Health and Nutrition Examination Survey (NHANES III), the prevalence of overt hypothyroidism was found to be 0.3%, prevalence of subclinical hypothyroidism was found to be 4.3% in USA, the prevalence of hypothyroidism was 9.5% in UK, the incidence of hypothyroidism was found to be 3.5 per 1000 in women and 0.6 per 1000 in men.[1-3] In India registry of hypothyroidism is not available like many

other diseases however some studies like Unnikrishnan et al. in Kerala the prevalence of hypothyroidism and sub-clinical hypothyroidism were 3.9% and 9.4% respectively.[4] The prevalence was 11.4% in women as compared to 6.2% in men.[4]

Recently, hypothyroidism like other non- infectious diseases is getting attention in developing countries like us. Hypothyroidism is found to have a link with cardiovascular morbidity and mortality by inducing abnormalities in lipid metabolism. Both overt and subclinical forms can give rise to abnormal lipid metabolism predisposing the patient to cardiovascular risk. Thyroid hormones regulate the activity of many key transport proteins and enzymes involved in lipid metabolism and include Cholesterol Ester Transfer Protein (CETP), Lipoprotein lipase (LL), Hepatic lipase (HL), 3-Hydroxy-3-Methyl-Glutaryl-CoA Reductase (HMG CoA), therefore can alter the lipoprotein levels in hypothyroidism favouring various lipid abnormalities.

Different studies have found different patterns of lipid abnormalities. This study was therefore taken up to find the pattern of dyslipidemia and compare between overt and subclinical hypothyroidism, clinical profile was also studied as a secondary objective.

METHODS

This observational study was conducted on patients attending to the inpatient and outpatient department of internal medicine of Veer Surendra Sai Institute of Medical Sciences and Research **(**VIMSAR), Burla. One hundred (100) patients satisfying inclusion and exclusion criteria of primary hypothyroidism were included in the study between a period from November 2016- November 2018. Cases suspected clinically and confirmed by hormonal studies above the age of 15 years were included. Age below 15 years and patients with history of coronary heart disease, pregnancy, renal failure, chronic liver disease, diabetes and chronic pancreatitis were excluded as well as cases on thyroxine therapy and with lipid lowering drugs by relevant history, physical examination and investigations.

Clinically suspected patients were subjected to estimations of thyroid stimulating hormone (TSH), Free thyroxine (Free T4), Free tri-iodothyronine (FreeT3) for making a diagnosis. After obtaining a written informed consent 5 ml venous blood was drawn and serum obtained; thyroid function test (TFT) and fasting lipid profile were performed. Based on the TFT, patients were categorised into sub clinical and overt hypothyroidism. Along with the clinical data, thyroid and lipid profiles of subjects were entered in the proforma. Electrocardiogram (ECG), echocardiography, urine βhcg test, liver function tests, fasting blood sugar, post prandial blood sugar, serum urea, creatinine and ultrasonogram of abdomen to exclude coronary artery disease, pregnancy, chronic liver disease, diabetes, chronic kidney disease respectively**.**

Definition of terms

Subclinical hypothyroidism

It was serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with a serum free thyroxine (T4) within the reference range.

Overt hypothyroidism

It was considered in whom the serum thyroid stimulating hormone (TSH) concentration is elevated and serum FT4 (free thyroxine) and/FT3 (free triiodothyronine) were below the reference range.

Thyroid function tests

Thyroid function tests were done by chemical electro-chemi-luminescence immune assay analyser, Elecsys-2010 (Roche laboratories) USA. Free T3 and free T4 levels were estimated by competitive principle and TSH by sandwich principle. The normal reference ranges of TFT are: Free T3: 0.8-2.0 ng/ml, Free T4: 4.8-12.7 mcg/dl and, TSH: 0.27-4.5 mIU/L.

Lipid profile

The samples were centrifuged within 1 h at 3000 rpm for 5 min. These were processed to obtain serum for the estimation of fasting lipid profile (Triglycerides, Cholesterol, and HDL) and the test was carried out on a fully automated Cobas Integra 400 plus clinical chemistry analyzer. LDL value was derived by Friedwald's formula: {LDL=Total cholesterol-[HDL+(Triglyceride/5)]}. Normal reference ranges of lipids are: total cholesterol (TC): 150-200 mg/dl, LDL cholesterol (LDL-C): 80-130 mg/dl, triglyceride cholesterol (TG): 40-150 mg/dl, HDL cholesterol (HDL-C): >40 mg/dl.

Statistical analysis

Data was entered and analysed using SPSS version 21 software. The biochemical parameters were expressed as mean plus standard deviation (SD) values. Independent 't' test was done to evaluate the association between lipid profile and hypothyroidism; P value <0.05 was considered significant.

Informed consent was obtained in each case, this study was approved by institutional ethical committee.

RESULTS

In the present study of 100 patients with primary hypothyroidism 70 were females (70%), 30 patients were males constituting (30%). Sixty two patients had overt and 38 patients had subclinical hypothyroidism with number of females were more than males (Figure 1),

and the majority of hypothyroid patients belonged to age group of 51- 60 years (Figure 2).

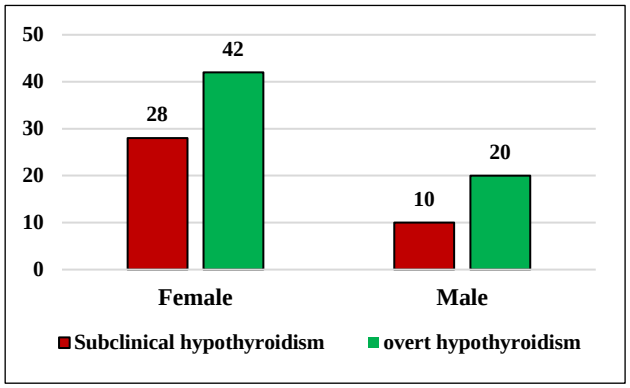

Figure 1: Sex wise distribution among subclinical and over hypothyroidism patients.

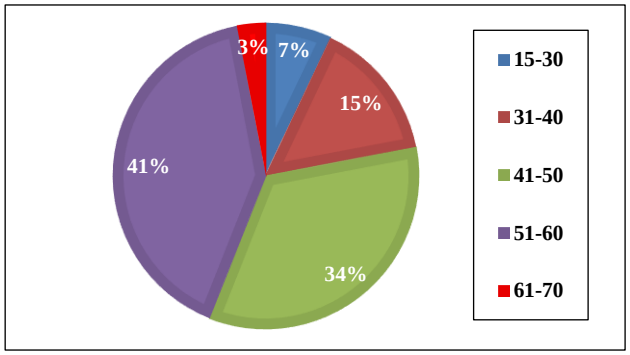

Figure 2: Age distribution among study subjects of hypothyroidism (n=100).

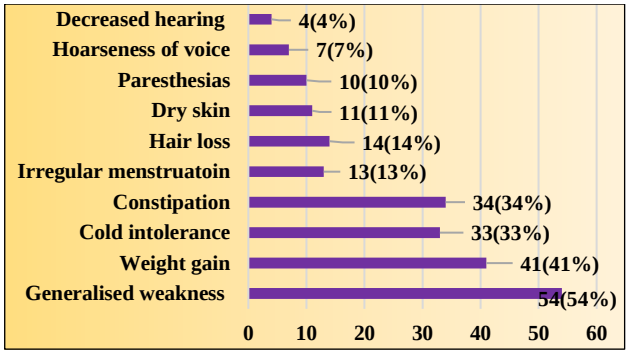

Figure 3: Common symptoms in hypothyroidism patients (n=100).

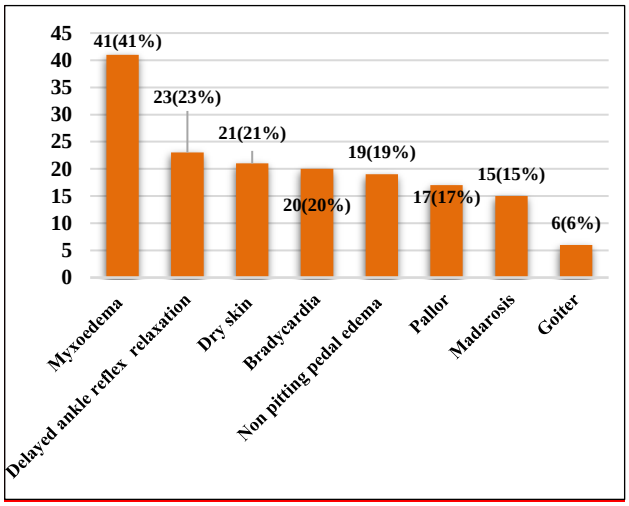

Figure 4: common signs in hypothyroidism patients (n=100).

Table 1: Thyroid test results and lipid parameters in subclinical and overt hypothyroidism(n=100).

Parameters	Subclinical hypothyroids (38) Mean±SD	Overt hypothyroids (62) Mean±SD	P value
TSH levels (mIU/l)	13.4±9.4	31.4±4.2	<0.001
Free T3 (ng/ml)	1.3±0.6	0.9±0.4	<0.001
Free T4 (mcg/dl)	6.6±1.5	1.6±1	<0.001
Total Cholesterol (mg/dl)	202.8±19.8	249.1±31.7	<0.001
Triglycerides (mg/dl)	155.6±35	191.5±68.5	<0.05
HDL (mg/dl)	43.1±4.4	44.0±4.7	>0.05
LDL (mg/dl)	129±21.1	167.7±31	<0.001

Common symptoms in hypothyroidism were generalised weakness followed by weight gain, cold intolerance, constipation, hair loss, paresthesias in 54%, 41%, 33%, 34%, 14%, 9% patients respectively (Figure 3). Menstrual irregularities were found in 13 (18%) out of 70 females with hypothyroidism of them 10 patients had oligomenorrhea and three had menorrhagia. Common signs were myxoedema, delayed ankle reflex relaxation, dry and coarse skin, bradycardia, non-pitting peripheral edema, madarosis, pallor, goiter in 41%, 23%, 21%, 20%, 19%, 15%, 17% ,6% patients respectively (Figure 4). The mean values of serum TSH, Free T4, Free T3 in subclinical hypothyroidism were 13.4±9.4 (mIU/L), 6.6±1.5 (mcg/dl), 1.3±0.6 (ng/ml) respectively versus 31.4±4.2 (mIU/L), 1.6±1 (mcg/dl), 0.9±0.4 (ng/ml) respectively in overt hypothyroidism (Table 1).

The mean values for serum Total cholesterol (TC), TG, HDL, and LDL cholesterol in subclinical hypothyroidism were 202.8±19.8 mg/dl, 155.6±35 mg/dl, 43.1±4.4 mg/dl and 129±21.1 (mg/dl) respectively. In overt hypothyroidism TC, TG,HDL and LDL means were 249.1±31.7 mg/dl, 191.5±68.5 mg/dl, 44±4.7 mg/dl, and 167.7±31 mg/dl respectively (Table 1).

A significant difference was observed in the mean values of total cholesterol, triglycerides and LDL levels between clinical and subclinical hypothyroidism.

The associated difference was statistically significant. No significant relation established for HDL in both overt and subclinical hypothyroid patients.

DISCUSSION

Age and sex distribution

In the present study 100 patients of hypothyroidism were enrolled which included 62 patients of overt and 38 patients of subclinical hypothyroidism; the majority of hypothyroid patients belonged to age group of 51-60 years (Figure 2). Similar observations were found in studies done by Unnikrishnan et al, MPJ Vanderpump et al, (Wickham survey), Hollowel et al (NHANES III), Teixeira et al and Raj Kumar Yadav et al. However, in the colorado thyroid disease prevalence study, the most common age group was more than 74 years.[4,5,1,6,2]

In our study the majority of patients were females. Out of 100 patients, 70 were females (70%), 30 patients were males(30%). Similarly, females represented more often in each of subclinical and overt hypothyroidism (Figure 1). The higher prevalence of hypothyroidism in women suggests possible role of estrogen in pathophysiology of thyroid function. Estradiol has antagonistic action against the hormones T3 and T4, the reason being estradiol competes with T3 and T4 for binding sites on receptor proteins (Vasudevan N et al).[8]

Clinical profile of hypothyroidism

Cold intolerance was found in one third (33%) of study subjects. Similar to M Bahemuka et al.[9] However, study by Ali Jabbari et al, the reported higher incidence of 62.7% and 95% respectively, possibly because of higher number of study subjects.[10] Of the total of male subjects 8 (26.6%) had cold intolerance and 25 (35.71%) females had cold intolerance amongst the total female cases in our study (Figure 3).

In our study the incidence of constipation was 34 (34%). Which is less than the studies carried out by Ali Jabbari et al, and Zulewski et al, with incidence of 76% and 52% respectively.[10,11] Fourteen (46.66%) of male and 20 (28.51%) of total females showed incidence of constipation (Figure 3).

Fifty four patient (54%) presented with complaints of generalised weakness in our study. In study done by, Dogra and Dua (2005) found (lethargy) generalised weakness in (65.62%) as prominent symptoms and Samanta BB found fatigue and lethargy in 46.61% as prominent symptom.[12,13] Of the total male cases, 16 (53.33%) complained of fatigue and of the total female subjects 38 (54.28%) complained of fatigue (Figure 3).

Fourty one (41%) presented with complaints of weight gain while it was 56.3% in the study done by Ashok Kumar et al, (56.3 %) and 84% in the study by Ali Jabbari et al.[14,10] In the latter group higher incidence could be due to larger number of patients included. Of the total male subjects, 15 (50%) males complained of weight gain and of the total female subjects, 26 (37.17%) complained of weight gain (Figure 3).

Menstrual irregularities in the form of oligomenorrhea (14.28%) and menorrhagia (4.28%) was found in present study. Ali Jabbari et al, though reported higher incidence with 92.85 % females were having irregular menses; among them 14 (14.4%) had menorrhagia and 35 (36.1%) had oligimenorrhoea.[10]

Paraesthesia was present in total 10% of patients. It had a sensitivity of 47.3% and specificity of 37.8%. Zulweski et al, reported a sensitivity of 52% and specificity of 82.5%.[11]

Myxoedema was present in 41% of study subjects similar to study by Sampath, Singh CP et al, (37.5%), who reported myxoedema as the commonest sign during presentation to hospital.[15] Of the total male cases, eleven (33.33%) males had myxoedema and 30 (42.85%) females had myxoedema from the total female cases (Figure 4).

Twenty (20%) patients were having bradycardia nearly similar to findings by Kumar A et al, and Ali Jabbari et al, (29.4%) and 16% respectively.[14,10] However, study done by Zulewski et al, reported a higher incidence of bradycardia (70%). Of the total of male subjects, 8 (26.6%) had bradycardia and 12 (17.14%) females had bradycardia from the total female cases in our study (Figure 4).[11]

Dry coarse thick skin was observed in nearly one fifth of cases (21%) in present study in contrast to studies by Dogra and Dua (56%), Samanta BB (40%) and Raju D et al, (69.23%). Of total of male cases, 5 (16.6%) and 16 (22.85%) females had dry skin from the total female cases in our study (Figure 4).[12,13,16]

Madarosis was found in 15 (15%) in present study similar to the study done by Haritha S et al, who cited an incidence of 20% in hypothyroidism.[17] Of the total of males, 5 (16.6%) had madarosis and 10 (14.28%) females had madarosis of the total female cases in our study (Figure 4).

Hoarseness of voice was observed in 7 (7%) patients out of whom one was male and six were females. Zulweski et al, cited the higher incidence of hoarse voice 74% possibly large study group (Figure 3).[11]

Thyroid function tests and lipid profile

There was elevation of serum total cholesterol and triglyceride level in both subclinical and overt hypothyroid compared to normal value, but the elevation was statistically significant in overt hypothyroid patients (P=<0.001) as compared to subclinical hypothyroid patients (Table 1). Study also showed statistically significant elevation of LDL in overt hypothyroid compared to subclinical hypothyroid patients (P=<0.001) (Table 1). However, HDL level did not show any significant change in both overt and subclinical hypothyroid patients (Table 1).

The primary mechanism for hypercholesterolemia in hypothyroidism is accumulation of LDL cholesterol due to reduction in number of cell surface receptors for LDL, resulting in decreased catabolism of LDL.[17] The promoter of LDL receptor gene contains thyroid responsive gene which allows the tri-iodothyronine to up regulate the gene expression of LDL receptor.[16]

Furthermore, decreased thyroid function not only increases the number of lipid particles but also promotes LDL oxidization. Hypertriglyceridemia associated with increased levels VLDL is attributable to decreased activity of lipoprotein lipase (LL) which results in a decreased clearance of triglyceride rich lipoproteins. Thus, hypothyroidism is major risk factor for hyperlipidemia.[16]

Prakash et al, compared lipid profile with varying levels of serum TSH.[18] They found increased serum levels of LDL, TC and decreased level of HDL in patients with increased levels of serum TSH. In the present study TG was significantly elevated and HDL was normal in hypothyroid patients.

Tagami et al, studied lipid profile in Hashimoto's thyroditis and the effects of thyroxine on lipid profile.[19] TC, TG and LDL were elevated in hypothyroid patients which was statistically significant. In this study also TC, LDL and TG was significantly elevated in hypothyroid patients.

Saini et al, studied lipid profile in patients with hypothyroidism which showed increased levels of TC, LDL and TG compared to control group.[20] In their study they also found out that HDL did not show any significant difference between hypothyroid group and control group. In this study TC, TG and LDL were elevated in overt hypothyroid patients which is statistically significant. TC and TG are also elevated in subclinical hypothyroid patients. HDL did not show any significant change in both overt and subclinical hypothyroid patients.

The Colorado thyroid disease prevalence study, compared lipid profiles between different levels of TSH, which showed increased levels of TC and TG with increased levels of TSH.[2] HDL did not show any change. This is similar to our study where TG were significantly elevated in overt hypothyroid patients compared to subclinical hypothyroid patients.

A Regmiet al in their study compared lipid profile between hypothyroid and normal subjects.[21] They found increased levels of TC, LDL and TG. HDL was elevated in hypothyroid patients compared to controls. In our study also TC and TG was elevated, HDL was not elevated in hypothyroid.

Limitation of the study is, small sample size and effect of levothyroxine therapy on lipid profile not done in this study need further study.

CONCLUSION

Patients with Overt hypothyroidism had significantly higher levels of Total cholesterol (TC), Triglycerides (TG) and LDL cholesterol than the Subclinical hypothyroidism but HDL cholesterol level remains normal in both. So, concomitant estimation of lipid profile must be done in hypothyroid patients for early intervention and prevention of cardiovascular morbidity and mortality. Conversely those found to have lipid abnormalities may be screened for hypothyroidism to detect them early.

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