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INCIDENCE OF DYSLIPIDEMIA IN PATIENTS OF SUBCLINICAL HYPOTHYROIDISM IN A TERTIARY CARE CENTRE OF UTTARAKHAND

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ABSTRACT

INTRODUCTION : Subclinical hypothyroidism may be associated with an increased risk of coronary artery disease, peripheral vascular disease and various biochemical abnormalities including increased LDL –C levels, increased total cholesterol levels and increased triglyceride levels. Dyslipidemia is common in subclinical hypothyroidism.

SUMMARY: In the above study the overall incidence of dyslipidemia in patients of subclinical hypothyroidism was found to be 92%. The most common subtype was hypertriglyceridemia which was found in 86% of patients. Hypercholesterolaemia was found in 62% was the next common finding. 22% of patients had deranged LDL – C levels. 19% of patients had deranged VLDL – C levels and 11.2% patients had abnormalities in HDL-C. Overall, the author would like to conclude that since a very high incidence of dylipidemia is found in subclinical hypothyroidism, patients with mild thyroid failure should be adequately treated.

KEYWORDS

INTRODUCTION :

The term subclinical hypothyroidism was introduced in early 1970s co incident with the introduction of serum TSH measurements. This term eventually replaced terminologies like preclinical myxoedema, compensated euthyroidism, preclinical hypothyroidism and decreased thyroid reserve.[1] Large epidemiological studies indicate that subclinical hypothyroidism is the most prevalent thyroid disease in the community.[2]

Subclinical hypothyroidism, also called as mild thyroid failure is diagnosed when peripheral thyroid hormone levels are within normal reference laboratory range but serum thyroid stimulating hormone(TSH) levels are mildly elevated.[3]

Subclinical hypothyroidism is defined as a serum thyroid stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine[3]. Serum TSH has a log – linear relationship with circulating thyroid hormone levels(a two – fold change in free thyroxine will produce a 100 – fold change in TSH). Thus, serum TSH measurement is the necessary test for diagnosis of mild thyroid failure when peripheral thyroid hormone levels are within normal laboratory range[3]. The individual range for peripheral thyroid hormones is narrower than the population reference laboratory range therefore, a slight reduction within the normal range will result in elevation of serum TSH above the normal range.

Subclinical hypothyroidism is a common problem with a prevalence of 3% to 8% in the population without known thyroid disease.[4,5] Its prevalence increases with age and is substantially higher in women.[4] After the sixth decade of life, the prevalence in men almost approaches that of women, with a combined prevalence of 10%.[4]Antithyroid antibodies can be detected in 80% of patients with subclinical hypothyroidism with 80% of patients of subclinical hypothyroidism having a serum TSH of less than 10 μIU/l.[4]

The overall progression rate from subclinical to overt hypothyroidism is very high, the incidence ranges from 33 to 55% in prospective studies withnearly 10–20 years of follow up.[6,7,8] This progression rate is considered to bearound 2.6–4.3% each year. [6] The importance of studying subclinical hypothyroidism is that it is much more common than overt hypothyroidism[2] and hence an early diagnosis and prompt treatment may prevent onset of overt hypothyroidism and its associated effects. Subclinical hypothyroidism may be associated with an increased risk of coronary artery disease, peripheral vascular disease and various biochemical abnormalities including increased LDL –C levels, increased total cholesterol levels and increased triglyceride levels.

SUBCLINICAL HYPOTHYROIDISM AND CHOLESTEROL METABOLISM

A cross sectional study revealed individuals with serum TSH between 5.1 and 10μIU/L had significantly higher mean cholesterol concentrations compared with euthyroid individuals.[9] There are studies revealing a link between elevated TSH and increased total cholesterol and LDL – cholesterol.[10] Another trial revealed that PCOS females with subclinical hypothyroidism have higher levels of low density lipoprotein (LDL) cholesterol while all other parameters of lipid profile and phenotypic manifestations are not altered by subclinical hypothyroidism.[11]

HYPOTHYROIDISM AND EFFECT ON LIPID METABOLISM

Elevated levels of total cholesterol, LDL cholesterol, andapolipoprotein B are well documented features of overthypothyroidism[12]. Early studies in humans with hypothyroidism, using isotopically labelled LDL, demonstrated aprolonged half-life of LDL cholesterol because of decreasedcatabolism, an effect that was reversible with T4therapy[13].

Additional data in human fibroblasts verified that the T3-inducedincrease in LDL degradation was mediated through an increase inLDL receptor number, without any change in the affinity of LDLfor its receptor. A specific effect of thyroid hormone on the LDLreceptor was suggested by a lack of T3effect on LDLconcentration in cultured cells without LDL receptors[14]. Thesefindings were supported by an *in vivo* study in a hypothyroidwoman whose receptor mediated LDL catabolism was reduced, compared with euthyroid controls, with significant improvementafter T4replacement therapy[15].

Studies have also shown that hypothyroidism causes qualitativechanges in circulating lipoproteins that increase theiratherogenicity. Two studies have shown that LDL is moresusceptible to oxidation in patients with hypothyroidism, withnormalisation after restoration of the euthyroidstate[16,17].

Increased levels of lipoprotein(a) [Lp(a)], a particularly otheratherogenicLDL variant in which apo-lipoprotein(a) and apo-lipoprotein B(Apo B) are covalently bound, have also been reported inhypothyroidism, compared with euthyroid controls. Severalstudies have shown decreases in the Lp(a) concentration after T4treatment of hypothyroid patients[18]. However, otherreports have not confirmed this relationship[19].

Ito *et al*studied the effect of T4therapy on lipid profiles of patients withovert and subclinical hypothyroidism, including their non-HDL-C(a measure of total cholesterol minus HDL-C)[20]. They showedthat After T4replacement, the serum concentrations of alllipoproteins, except Lp(a), were significantly decreased in patientswith overt hypothyroidism.

However, the reduction in the non-HDL-C levels did not correlatewith the reduction in the HDL-C, Lp(a), and apo-lipoprotein A-Ilevels. These results suggest that altered serum concentrations ofnon-HDL-C in hypothyroidism may be related to the disturbedmetabolism of low-density lipoprotein, remnant lipoprotein, andApo B[21].

Additional potentially atherogenic effects of hypothyroidism onlipid metabolism include a reversible reduction in clearance ofchylomicron remnants[21]; reduced activity of cholesteryl estertransfer protein, which is involved in reverse cholesterol transport pathway[22]; and decreased activity of hepatic lipase andlipoprotein lipase[23].

Several studies have demonstrated elevated homocysteine levels inhypothyroidism[24], with improvement after T4replacement[25]. This is likely to be caused by impaired renalhomocysteine clearance, although an effect of thyroid hormone onenzymes involved in folate metabolism has also beenproposed[26]. The magnitude of decline in homocysteinelevels after T4 treatment is sufficient to lower cardiovascular risk, with a decrease of 2–5 mol/L when hypothyroid patients weretreated with T4to a level suppressing the serum TSHconcentration[26].

MATERIAL AND METHOD :

The present study was carried out in the Dept. of Medicine, Government Medical College and associated Dr.SusheelaTiwari Government Hospital, Haldwani, Dist, Nainital, Uttarakhand.

A total of 100 patients were included in this study who fell in the inclusion criteria:

INCLUSION CRITERIA :

1) All patients (>16 years of age) attending Medicine OPD/ WARD and Gynaecology OPD / WARD from September 2014 to September 2016 fulfilling the criteria of subclinical hypothyroidism were included.

2) Serum T3, T4 and TSH estimation in this study was done by immunosorbent assay method in the Dept. of Biochemistry, GMC, Haldwani

METHODS AND DIAGNOSTIC CRITERIA :

Informed consent from all the patients was taken. A detailed history and clinical examination was done. Subclinical hypothyroid patients whose TSH was between 7 - 10μIU/ml. lipid profile of all these patients were compiled and analysed.

Table 1 : Reference range for thyroid profile[27]

SERUM TSH	0.5 - 5μIU/ ml
SERUM T3	70 – 190 ng/dl
SERUM T4	5 – 12 μg/dl

1) Total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol was estimated by cholesterol oxidase/peroxidase method. Biosystems kit was used.[28,29]

Table 2 : Reference range for lipid profile[30]

Total cholesterol	50 – 200 mg/dl
Triglycerides	40 – 128 mg/dl
HDL – C	35 – 65 mg/dl
LDL – C	50 – 150 mg/dl
VLDL – C	10 – 30 mg/dl

STATISTICAL ANALYSIS:

Chi square test was used to find the significance of study characteristics.[31] Student t test was used to find the significance of study parameters. Effect size was computed to get conclusions on the clinical and etiological factors of subclinical and overt hypothyroidism.

STATISTICAL SOFTWARE :

The statistical software[32] namely SPSS 11.0, Strata 8.0, Systat 11.0, Medcalc 9.0.1 and Effect size calculator were used for the analysis of the data and Microsoft Word and Microsoft Excel were used to generate the graphs, tables and charts.

OBSERVATION AND RESULTS :

1) LIPID PROFILE :

- **TOTAL CHOLESTEROL :** The mean total cholesterol levels in patients with subclinical hypothyroidism was 218.35 mg/dl. Patients with overt hypothyroidism had a mean total cholesterol of 238.2 mg/dl.

- **SERUM TRIGLYCERIDES** : The mean triglyceride levels in patients with subclinical hypothyroidism was 171.71 mg/dl. Patients with overt hypothyroidism had a mean triglyceride value of 179.05 mg/dl.

- **LDL CHOLESTEROL :**The mean LDL cholesterol levels in patients with subclinical hypothyroidism was 124.63 mg/dl. Patients with overt hypothyroidism had a mean LDL cholesterol value of 122.6 mg/dl.

- **HDL CHOLESTEROL :** The mean HDL cholesterol levels in patients with subclinical hypothyroidism was 36.83 mg/dl. Patients with overt hypothyroidism had a mean HDL cholesterol value of 37.85 mg/dl.

- **VLDL CHOLESTEROL :** The mean VLDL cholesterol levels in patients with subclinical hypothyroidism was 26.35 mg/dl. Patients with overt hypothyroidism had a mean VLDL cholesterol value of 50.44 mg/dl.

Table 19: Lipid profile (Mean±SD) - Present study

TC	218.35±39.90
TGL	171.71±25.07
LDL	124.63±16.34
HDL	38.838±5.21
VLDL	26.354±1.09

Comparison in lipid profile between present study and other studies.

Lipid profile (mg/dl)	Present study	Asrana *et al.*[33]	Vierhapper *et al.*[34]	Bell *et al.*[34]	Hueston *et al.*[35]

TC	218.35	173.72	219	221	217
TG	171.71	32.98	125.7	168	178.1
LDL	124.63	106.07	137.5	139.2	140
VLDL	38.83	32.98	36.9	35.2	37.2
HDL	26.35	38.63	56.4	58.6	5.1

DISCUSSION :

1) LIPID PROFILE :

- **TOTAL CHOLESTEROL :** The mean total cholesterol levels in patients with subclinical hypothyroidism was 218.35mg/dl. Patients with overt hypothyroidism had a mean total cholesterol of 238.2mg/dl. Efstathiadou et al[36] found a mean cholesterol value of 222mg/dl. William J Hueston[37] et al demonstrated total cholesterol of 217 mg/dl.

- **SERUM TRIGLYCERIDES :** The mean triglyceride levels in patients with subclinical hypothyroidism was 171.71mg/dl. Patients with overt hypothyroidism had a mean triglyceride value of 179.05mg/dl. Kong et al[38] have reported a mean value of 159 mg/dl. William J Hueston et al[37] had shown a mean triglyceride value of 178.1 mg/dl in their study.

- **LDL CHOLESTEROL :** The mean LDL cholesterol levels in patients with subclinical hypothyroidism was 124.63mg/dl. Patients with overt hypothyroidism had a mean LDL cholesterol value of 122.6 mg/dl. Rajan et al[39] have shown mean LDL value of 134 mg/dl. Tromsostudy[40] also demonstrated elevated LDL – cholesterol levels which came down after treatment.

- **HDL CHOLESTEROL :** The mean HDL cholesterol levels in patients with subclinical hypothyroidism was 36.83mg/dl. Patients with overt hypothyroidism had a mean HDL cholesterol value of 37.85mg/dl. Kong et al[41] had shown mean HDL- cholesterol value of 39 mg/dl. Rajan et al[39] had shown HDL value of 41.5 mg/dl.

- **VLDL CHOLESTEROL :** The mean VLDL cholesterol levels in patients with subclinical hypothyroidism was 26.35mg/dl. Patients with overt hypothyroidism had a mean VLDL cholesterol value of 50.44 mg/dl.

Dyslipidemia is common in subclinical hypothyroidism. The present study concludes that all patients with non-specific symptoms in specific age groups having dyslipidemia should be screened with thyroid function tests.[42]

CONCLUSION:

In the above study the overall incidence of dyslipidemia in patients of subclinical hypothyroidism was found to be 92%. The most common subtype was hypertriglyceridemia which was found in 86% of patients. Hypercholesterolaemia was found in 62% was the next common finding. 22% of patients had deranged LDL – C levels. 19% of patients had deranged VLDL – C levels and 11.2% patients had abnormalities in HDL-C. Overall, the author would like to conclude that since a very high incidence of dylipidemia is found in subclinical hypothyroidism, patients with mild thyroid failure should be adequately treated.

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