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Original Research Article

Study of Lipid Profile in Subclinical Hypothyroidism

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Abstract

Background: Subclinical hypothyroidism (SCH) is defined as an elevated serum Thyroid StimulatingHormone (TSH) level associated with serum free thyroxine (fT4) and free tri-iodothyronine (fT3) concentrations within the reference range with few or no symptoms of hypothyroidism. There are studies which report changes in lipid profile levels in patients with subclinical hypothyroidism.

Materials & Methods: 50 cases and 50 controls were included into the study. Patients with subclinicalhypothyroidism, age and sex matched with normal individuals in Adichunchanagiri Hospital and Research Center with respect to parameters such as FT3, FT4, TSH, LDL,HDL, VLDL TC and TGL levels were assessed. The mean levels amongst the cases and controls were compared. Statistical analysis was done by descriptive statistics andstudent "t" test.

Results: The majority of the patients were females. We found an increased TSH, LDL, VLDL, TC and TGL levels, while there was a drop in the HDL levels. The mean ± SD level of TSH in controls and cases was found to be 2.31 ± 0.81μIU/ml and 7.07 ± 1.56 μIU/ml respectively with FT3 & FT4 levels within the normal range which confirmed the diagnosisof subclinical hypothyroidism amongst the cases. Comparison between the mean levels of TSH, LDL, HDL, VLDL TC and TGL were found to be statistically significant ($p<0.05$).

Conclusion: We found an increase in the TSH, LDL, VLDL, TC, TGL levels except HDL levels,which were statistically significant. The results showed that there exists a definite relationship between subclinical hypothyroidism and dyslipidemias.

Keywords: Subclinical hypothyroidism; Triglycerides, Cholesterol, Lipoproteins.

Introduction

Thyroid gland plays an important role in the growth as well as regulations of body functions. It is imperative to say that it plays a major role in the day to-day life of an individual. Thyroid gland regulates itself with TSH concentration, normal serum total (T4)/free thyroxine (fT4), triiodothyronine (T3) concentrations with the positive- negative feedback mechanism.[1] A decrease in the thyroid levels is termed as hypothyroidism and has a direct impact on the functions as well as the quality of life of an individual. Hypothyroidism is one of the common forms of hormonal dysfunction resulting from the deficiency of thyroid hormone or its impaired activity.[2] Among the 42 million people suffering from thyroid

diseases in India, hypothyroidism is the commonest.[3,4]

Subclinical hypothyroidism (SCH) is defined as an elevated serum Thyroid Stimulating Hormone (TSH) level associated with serum free thyroxin (fT4) and free triiodothyronine (fT3) concentrations within the reference range with few or no symptoms of hypothyroidism.[5]

Subclinical hypothyroidism is more commonly found affecting women (10 times greater than men) and also have a high risk potency of getting converted to true hypothyroidism. Hence early diagnosis and treatment of the same has been found to be an important aspect due to its hideous nature.[6]

Subclinical hypothyroidism is more of a laboratory diagnosis rather than a clinical diagnosis as it shows few/no symptoms of hypothyroidism with high serum TSH concentration and normal serum total/free thyroxine (fT4), free triiodothyronine (fT3) concentrations. Nevertheless, there still exists some controversy wherein some researchers who believe that only patients without any classical signs/symptoms of hypothyroidism should be categorized as subclinical hypothyroidism.[7]

The prominence of understanding subclinical hypothyroidism is not uncommon than overt hypothyroidism. It is believed that early diagnosis & treatment might preclude the inception of overt hypothyroidism and its effects. However, overt hypothyroidism is defined as low T4 levels and elevated serum TSH with evident clinical features.[2]

Patients with subclinical hypothyroidism have been found to have increased risk of coronary artery disease, peripheral vascular disease and various biochemical abnormalities, including increased LDL-C levels, increased total cholesterol as well as serum triglyceride levels.[8] The correlation between overt hypothyroidism and lipid profile changes is well established over the years. However, it has been found that early treatment of subclinical hypothyroidism leads to reversal of changes.[8] Recently, levothyroxine therapy for persons with serum TSH of more than 10 µIU/ml and the therapy is individualized for patients with a TSH value of less than 10µIU/ml.[6]

Further during diagnosis, antithyroid antibodies are found to be positive in 80% of patients with SCH. Also radioiodine therapy, external neck and head irradiation could be the reason for mild form of thyroid dysfunction.[6] Further studies have suggested that SCH to cause complications during pregnancy and brain development of fetus. Hence, screening of pregnant women for subclinical hypothyroidism is suggested.[6] Hence, the present study is undertaken to understand the relationship between serum lipid profile with subclinical hypothyroidism

Materials and Methods

This study was done as an observational case control study will be conducted at Adichunchanagiri Hospital and Research Center, B G Nagara for a period of 18 months (December 2019- June 2021) in department of Medicine, Adichunchanagiri Hospital and Research Center, B G Nagara in patients with subclinical hypothyroidism with age and sex matched with normal individuals in Adichunchanagiri Hospital and Research Center with respect to lipid profile. 50 patients were included in control group and 50 patients with subclinical hypothyroidism.

Information will be collected through a pre-tested and structured proforma for the subject. In all the selected subjects detailed history and physical examination will be noted. Every patient will be subjected to relevant investigations after taking informed consent.

In our study both males and females. With age > 18yrs, patients with subclinical hypothyroidism i.e with normal free T3, normal free T4 and raised TSH levels [both

diagnosed cases of subclinical hypothyroidism and newly detected subclinical hypothyroidism cases] with age and sex matched with the control group.

While patients with pregnancy, prior thyroid illness., febrile illness, on drugs like phenytoin, PAS, lithium, amiodarone, radioactive iodine therapy and patients with dyslipidemia associated with diabetes mellitus, chronic kidney disease and familial dyslipidemia were excluded.

Data will be analyzed using descriptive statistics and t test. Suitable statistical software will be utilized for analysis.

Results

In our study most of the patients were in 31-40 years age group, Out of the total 50 subjects in the study group, 29 subjects were females and 21 were males. In the control group as well as the study group, subjects had FT3 levels within the normal range that is 2.23 – 6.43 pmol/l.

In the control group as well as the study group, subjects had FT4 levels within the normal range that is 10 – 23.81 pmol/l., while in the control group, all the subjects had TSH levels of 0.45 – 4.1 µIU/ml and in the study group, all the 50 subjects had TSH levels of 4.1 - <10 µIU/ml.

Lipid Profile

In the control group, all the subjects had cholesterol levels within the normal range. In the study group, 37 subjects had normal and 9 subjects had borderline and 4 subjects had high cholesterol levels. In the control group, all the subjects had LDL-C levels within the normal range. In the study group, 37 subjects had normal and 9 subjects had borderline and 4 subjects had high LDL-C levels.

In the control group, all the subjects had triglyceride levels within the normal range. In the study group, 35 subjects had normal and 10 subjects had borderline and 5 subjects had high triglyceride levels.

In the control group, all the subjects had HDL levels within the normal range. In the study group, 45 subjects had normal and 5 subjects had abnormal HDL levels. In the control group, all the subjects had VLDL levels within the normal range. In the study group, 42 subjects had normal and 8 subjects had abnormal VLDL levels.

Table 1: Comparison between controls and cases

Thyroid and lipid parameters	Controls	Cases	P- Value
FT3	4.46 ±1.02	4.36 ± 1.120	0.330977
FT4	15.88 ± 3.10	16.02 ± 3.15	0.410422
TSH	2.31 ± 0.81	7.07 ± 1.56	<0 .00001
TC	130.82 ± 20.05	189.1 ± 27.23	<0 .00001
LDL	90.82 ± 14.74	126.8 ± 16.11	<0 .00001
HDL	68.14 ± 11.37	57.78 ± 6.95	<0 .00001
VLDL	22.55 ± 3.60	26.12 ± 9.23	0.006249
Triglyceride	110.22 ± 15.96	146 ± 33.42	<0 .00001

The mean ± SD level of FT3 in controls and cases was found to be 4.46 ± 1.02 pmol/l and 4.36 ± 1.120 pmol/l respectively. There was no statistically significance noted. The mean ± SD level of FT4 in controls and cases was found to be 15.88 ± 3.10pmol/l and 16.02 ± 3.15 pmol/l respectively. There was no statistically significance noted. The mean ± SD level of TSH in controls and cases was found to be 2.31 ± 0.81µIU/ml and 7.07 ± 1.56 µIU/ml respectively. There was statistical significance noted.

The mean ± SD level of TC in controls and cases was found to be 130.82 ± 20.05 mg/dl and 189.1 ±27.23 mg/dl respectively. There was statistical significance noted. The mean ± SD level of LDL-C in controls and cases

was found to be 90.82 ± 14.74 mg/dl and 126.8 ±16.11mg/dl respectively. There was statistical significance noted. The mean ± SD level of HDL-C in controls and cases was found to be 68.14 ± 11.37mg/dl and 57.75 ±6.95mg/dl respectively. There was statistical significance noted. The mean ± SD level of VLDL-C in controls and cases was found to be 22.55 ± 3.6mg/dl and 26.12 ± 9.23 mg/dl respectively. There was statistical significance noted. The mean ± SD level of Triglyceride in controls and cases was found to be 110.22 ± 15.96mg/dl and 146 ± 33.42mg/dl respectively. There was statistical significance noted.

Discussion

Subclinical hypothyroidism is not an uncommon disorder affecting individuals with a global prevalence of 2.8% - 4.4% in men and 7.5% - 8.5% in women.[9] Subclinical hypothyroidism is defined as an elevated TSH concentration in presence of normal serum free thyroxine (FT4) and free triiodothyronine (FT3).[10]

Thyroid hormones play an essential role in initiation, regulation and maintenance of many functions of the body. Similarly lipid metabolism has been affected as thyroid hormones play a vital role in the production, utilization and metabolism of lipids.

In our study we assessed the lipid profile of patients who were suffering from subclinical hypothyroidism. Even though it has been proven that overt hypothyroidism is associated with lipid abnormalities there is minimal evidence that subclinical hypothyroidism, which is a predecessor of overt hypothyroidism also shows alteration in lipid profiles.

The diagnosis of subclinical hypothyroidism is more of a laboratory based diagnosis rather than a clinical diagnosis as the fT3 & fT4 levels in the body appear to be within the normal range and there is only mild derangements in TSH levels. As the changes are miniscule in nature to be observed it is difficult to identify the disease process clinically and is more of an incidental finding as we see it. Hence, for this reason it is classified as a mild form of hypothyroidism.[11]

In present study, the maximum no of patients in the study group belonged to the 31-40 yrs age group, followed by the 51-60 yrs age group, 61-70 yrs age group, 41 – 50 yrs age group, 21 – 30 yrs age group, 71 – 80 yrs and 81 – 90 yrs age group category.In a similar study done by Laway BA *et al* they found the mean age group of the patients to be 36.5 ± 10.1 years.[11] In another similar study done by Nabil A. El-Kafrawy *et al* the mean age was found to be 34.3 ± 9.2 years in SCH group.[12]

In present study, out of the total 50 subjects in the study group, 29 subjects were females and 21 were males. The predominance of females being affected by thyroid disease is not something new and has been established since a long time. In a similar study done by Nabil A. El-Kafrawy *et al*., they found that 65% of the subjects were females.[12] Singh and Prasad I *et al*., they found that 70% of the patients to be women in their study.[13] It is postulated that estrogen might be a causative factor in the pathophysiology of thyroid dysfunction. The antagonistic role of estradiol on the T3 and T4 hormones supports the hypothesis. Estradiol has an affinity towards the T3 and T4 for binding sites on the receptor proteins which is found to be the reason for hypothyroidism.

The FT3 as well as the FT4 levels in the study group were found to be within the normal range. The mean ± SD level of FT3 in controls and cases was found to be 4.46 ± 1.02 pmol/l and 4.36 ± 1.120 pmol/l respectively, which was found to be statistically insignificant. In case of subclinical hypothyroidism the FT3 as well as the FT4 levels remain within the normal range but the TSH levels appear to be raised. However in some cases we may also see an increase in the T4 levels along with increased TSH levels which is a clear sign of overt hypothyroidism. It is noteworthy that subclinical hypothyroidism is a

predecessor of overt hypothyroidism and should be considered before formulation of a diagnosis.

The mean ± SD level of FT4 in controls and cases was found to be 15.88 ± 3.10 pmol/l and 16.02 ± 3.15 pmol/l respectively, which was found to be statistically insignificant. The variation in the levels of FT4, which was very minimal as the value was 16.02pmol/l against the normal range of 15.88 pmol/l and can be attributed to many other confounding factors. Our next hypothesis would be if they are the patients at risk for hypothyroidism without any early signs of the disease process as seen in subclinical hypothyroidism.

All the 50 subjects in present study group had TSH levels between 4.1 and <10 µIU/ml. The mean ± SD level of TSH in controls and cases was found to be 2.31 ± 0.81 µIU/ml and 7.07 ± 1.56 µIU/ml which was found to be statistically significant. There was a mild increase in the TSH levels in the study group patients which is a clear indicator of subclinical hypothyroidism. The association of the increased TSH levels with normal fT3 and fT4 levels in the study group patient acts as the diagnostic test of choice to detect subclinical hypothyroidism. In a study done by Kumar R *et al*., the mean TSH levels (15.77 ± 9.9µIU/ml) of cases were high compared to controls (3.7 ± 0.98µIU/ml)[14]

The total cholesterol levels of the study group in the normal range, borderline and high levels was found to be 74%, 18% and 8% respectively and in the control group, the total cholesterol levels in all the subjects were within the normal range. In our study, the mean ± SD level of TC in controls and cases was found to be 130.82 ± 20.05 mg/dl and 189.1 ± 27.23 mg/dl respectively, which was found to be statistically significant. In a study done by Nabil A. El-Kafrawy *et al*., the mean TC value was 165.4 ±25.9 mg/dl in control and 232.1±38.5 mg/dl in cases.[12] In a study done by Laway BA *et al*., the mean serum TC in subjects was 182.91 ± 41.01 mg/dl - versus 170.19 ± 34.36 mg/dl in controls (P value = 0.03).[11]

The level of LDL was expected to remain within the normal limits as we know that T3 influences the LDL-cholesterol levels, as the agent of the LDL receptor gene has a thyroid hormone receptive element (TRE) modulating the gene expression of the LDL-receptor. This has a direct effect wherein a higher T3 level means lower levels of LDL-cholesterol and vice versa.[15]

In the study group, subjects with LDL levels in the normal range, borderline and high levels was found to be 74%, 18% and 8% respectively with the mean ± SD level of LDL in controls and study group found to be 90.82 ± 14.74 mg/dl and 126.8 ± 16.11 mg/dl respectively, which was found to be statistically significant. In a study done by Kumar R *et al*., the mean LDL value in cases was 146.14±34.12 mg/dl and 133.05±32.14 mg/dl in the control group.[14] In another study done by Rajan *et al*, they found a mean LDL level of 134 mg/dl with statistical significance recorded, which was comparatively higher than that found in our study.[16]

It is hypothesized that hypothyroidism brings the thyroid hormone levels down, which in turn increases the production of LDL-cholesterol attributable to increased cholesterol production as well as absorption. There is also a decrease in the HDL receptors on the hepatocytes noted.

In the study group, subjects with triglyceride levels in the normal range, borderline and high levels was found to be 70%, 20% and 10% respectively with the triglyceride levels of all the patients in the control group being within the normal range. The mean ± SD level of triglyceride in controls and study group was found to be 110.22 ± 15.96 mg/dl and 146.0 ± 33.42 mg/dl respectively, which was statistically significant. In a study done by Laway BA *et al*, mean serum TG in subjects were 173.79 ± 99 mg/dl versus 138.67 ± 57.40 mg/dl in controls (P value = 0.00).11 In a

study done by Nabil A. El-Kafrawy *et al*.,the mean TG level was found to be 129.9± 10.1 mg/dl control group and 169.1± 19.8 mg/dl in the study group.[12]

It is known that, higher serum triglycerides may be observed in overtly hypothyroid individuals because of their lower lipoprotein lipase activity. So, we can hypothesize that higher level of serum triglycerides can be considered as early indicators of subclinical hypothyroidism. To further support our hypothesis, a few studies showing similar results are enumerated below

In a study done by Kong *et al*., 80 have reported a mean triglyceride value of 159mg/dl, which was comparatively higher than in comparison with patients of our study group.[17] In another study done by William L Hueston *et al*., reported a mean triglyceride level of 178.1mg/dl was recorded.[18]

In present study, 90% of the subjects in the study group were found to be in the normal range and 10% of the subjects in the abnormal range for HDL cholesterol. The mean ± SD level of HDL in controls and cases was found to be 68.14 ± 11.37mg/dl and 57.78 ± 6.95 mg/dl respectively, which was statistically significant. In a study done by Kong *et al*, the mean HDL cholesterol level was found to be 39 mg/dl.17 In a similar study done by Sridevi A *et al*.,the high density lipoprotein cholesterol (44.23±4.65 mg/dl vs 42.26±3.20 mg/dl, p=0.0507) levels were found to be lower in cases.[19]

In the control group, subjects with VLDL levels in the normal range were found to be 100%.In the study group, subject with VLDL levels in the normal range and abnormal range were found to be 84% and 16% respectively. The mean ± SD level of VLDL in controls and cases was found to be 22.55 ± 3.6 mg/dl and 26.12 ± 9.23mg/dl respectively, which was statistically significant. Our study showed increased levels of VLDL in the study group against the control group. In a study done by Laway BA *et al*., the mean serum VLDL in subjects was found to be 34.83 ± 19.75 mg/dl versus 28.12 ± 11.36 mg/dl in controls (P value = 0.00). [11]

In our study, we assessed the lipid profile of all patients with subclinical hypothyroidism and found that most of the parameters assessed were altered indicative of the disease process, but the severity could not be established as subclinical hypothyroidism is more of a laboratory diagnosis rather than a clinical diagnosis.

Our study also showed the effect of subclinical hypothyroidism on the lipid parameters wherein there was an increase in the total cholesterol, LDL, VLDL as well as triglyceride levels, indicative of its capability to be a causative factor of cardiovascular diseases. However, we need more evidence to establish a concrete evidence to reach conclusive evidence.

Conclusion

Subclinical hypothyroidism is more of a laboratory diagnosis than a clinical diagnosis, as patients will show minimal or no clinical symptoms or signs, with the laboratory parameters showing normal FT3 and FT4 levels except TSH which appears to be raised above the normal but less than 10 μIU/ml. In present study, the majority of the patients were found to be females and also there was a significant increase in the TSH, LDL, VLDL, TC, TGL levels except HDL levels, which were statistically significant. The results showed that there exists a definite relationship between subclinical hypothyroidism and dyslipidemias. Early detection, follow up of the cases and management helps in further progression of the disease process.

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