ORIGINAL ARTICLE

# Levels of Homocysteine and Lipid Profile in Subclinical Hypothyroidism

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**ABSTRACT**

**Objective:** To measure the serum levels of homocysteine and lipid profile in patients of subclinical hypothyroidism.

**Study Design:** A case control observational study.

**Place and Duration of Study:** The Study was conducted in Biochemistry Department of Islamic International Medical College, Rawalpindi during a period of one year from March 2016 to February 2017.

**Materials and Methods:** A total of 128 subjects were selected for the study from the medical outpatient department using convenient non probability sampling technique. Selection criterion was age group of 20 to 55 years and exclusion criteria were history of diabetes, hypertension, cardiovascular or renal disease. Selected patients were divided into two groups. In group I (selected as control) were sixty four healthy volunteers who presented for routine annual medical and physical examination. In group II (patient's group) were 64 patients diagnosed as subclinical hypothyroidism based upon thyroid stimulating hormone (TSH) levels >4.12 mU/mL and normal free T3 (FT3) and T4 (FT4) levels on two consecutive measurements.Lipid profile and homocysteine levels in the serum of the subjects of both groups were estimated. The collected data was entered in SPSS version 21 for analysis. Descriptive data were given as mean ± standard deviation (SD). Independent t test was used and p values less than 0.05 were considered statistically significant.

**Results:** Group I (control) consisted of 82.81% females and 17.18% males. In group II (sub clinical hypothyroid patients) were 87.5% females and 12.5% males. The mean ages of controls and subclinical hypothyroid patients were 33.65±5.98 and 35.20±7.55 years respectively. There was a significant increase in mean tHcy in subclinical hypothyroid patients than in control group (Mean ± SD, 12.67±2.35 µmol /l vs 3.76±1.59 µmol/l). Serum total cholesterol in subclinical hypothyroid patients was significantly increased than the control group (Mean ± SD, 195.25 ± 10.63 mg/dl vs 162.05 ± 17.39 mg/dl). There was a significant decrease in mean HDL-Cholesterol in subclinical hypothyroid patients than in control group (Mean ± SD, 48.11 ± 4.62 mg/dl vs 53.85 ± 6.55 mg/dl). There was a decrease in mean serum triglyceride in hypothyroid patients than in control group which was not statistically significant (Mean ± SD, 111.25 ± 18.82 mg/dl vs 140.29 ± 17.69 mg/dl).

**Conclusion:** It was found in our study that the serum levels of homocysteine and lipid profile are increased in subclinical hypothyroidism.

**Key Words:** *Atherosclerosis, Homocysteine, Lipid Profile, Subclinical Hypothyroidism.*

## Introduction

In developed, as well as developing countries cardiovascular disease namely the coronary heart disease remains the leading cause of mortality and morbidity.[1] In Pakistan it is estimated that 410 out of 10,000 people die every year due to ischemic heart disease.[2] Atherosclerosis is an important risk factor in cardiovascular disease which is caused by dyslipidemia.[3] Dyslipidemia is increase of plasma cholesterol and triglycerides (TGs) and a low HDL-Cholesterol level which contributes to the progress of atherosclerosis. Dyslipidemia is diagnosed by measuring plasma levels of total cholesterol, TGs, and individual lipoproteins and these are collectively termed as lipid profile.

In addition to the increase in levels of cholesterol and LDL-Cholesterol investigators have found serum homocysteine to be an independent risk factor for atherosclerosis.[4] Hcy increases the possibility of cardiovascular disease by various mechanisms including endothelial dysfunction, oxidative stress, endoplasmic reticulum stress, smooth muscle cell proliferation and platelet aggregation.

Thyroid disease, namely hypothyroidism and

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hyperthyroidism, constitutes one of the most common endocrine abnormalities. Among the thyroid diseases, hypothyroidism is a disorder in which thyroid activity is reduced and does not produce enough thyroid hormones. It leads to hyper secretion of pituitary thyroid stimulating hormone (TSH) and an increase in the serum level of TSH.[2] Its prevalence worldwide is estimated to be 4-15 %.[5] In Pakistan it is 4.1%[6] mainly due to deficiency of iodine. Thyroid hormones, Thyroxine (T4), and Triiodothyronine (T3) play an important role in all major metabolic pathways by regulating protein, carbohydrate, and lipid metabolism; including synthesis, mobilization, and degradation.

Hypothyroidism is an endocrine disorder which presents with varied degree of thyroid dysfunction and metabolic effects.[7] It is a proven fact that patients with hypothyroidism are prone to develop cardiovascular disease. This is based upon autopsy findings revealing that coronary artery atherosclerosis is two times common in a hypothyroid patient as compared to the control.[1] This increased incidence of cardiovascular disease in hypothyroid patients has been attributed to increase in the levels of low-density lipoprotein and total cholesterol.[8] Subclinical hypothyroidism is the earliest stage of thyroid dysfunction and is defined as increased serum thyroid stimulating hormone (TSH) concentrations with normal thyroid hormone levels and absence of clinical symptoms and signs of hypothyroidism.[9] It is yet to be proven that subclinical hypothyroid disease is prone to atherosclerosis[10,11] and we aimed to find it out in our study. In this study we measured serum lipid profile and plasma Hcy concentrations of subclinical hypothyroid patients and compared them to control group to find any predisposition toward atherosclerosis.

## Materials and Methods

This was a case control observational study conducted at biochemistry department of Islamic International Medical College Rawalpindi with the collaboration of department of medicine, Pakistan Railways Hospital during a period of one year from March 2016 to February 2017. Approval from the ethical review committee of the institute was attained before the commencement of the study. An informed verbal and written consent from the patients was taken to participate in the study. A total of 128 subjects were selected for the study from the medical outpatient department using convenient non probability sampling technique. Selection criterion was age group of 20 to 55 years and exclusion criteria were history of diabetes, hypertension, cardiovascular or renal disease. Selected patients were divided into two groups. In group I (selected as control) were sixty four healthy volunteers who presented for routine annual medical and physical examination. In group II (patient's group) were 64 patients diagnosed as subclinical hypothyroidism based upon thyroid stimulating hormone (TSH) levels >4.12 mU/mL and normal free T3 (FT3) and T4 (FT4) levels on two consecutive measurements. After overnight fasting of 12 hours, 5 ml of blood was collected from the median cubital vein of each control and patient. Sample of plain tube was left to clot for 30 minutes then centrifuged at 3500 × g for 5 minutes; the separated serum was divided into several aliquots and stored at −70°C until the estimation of total homocysteine and lipid profile.

Plasma homocysteine were measured using an ELISA kit from Cusabio according to the manufacturer's instructions in the biochemistry laboratory of Islamic international medical college. Serum levels of total cholesterol, HDL-Cholesterol, LDL-Cholesterol and triglycerides were determined using a Cobas Dimension RXL Autoanalyzer (Germany) in the Pakistan railways hospital laboratory. The desirable levels for lipid profile parameters were total cholesterol (< 200 mg/dl), triglycerides (< 150mg/dl), HDL-Cholesterol (30-60 mg/dl) and LDL-Cholesterol (< 100 mg/dl).

The collected data was entered into SPSS version 21 for analysis. Gender was expressed as percentages. Descriptive data were given as mean ± standard deviation (SD).Independent t test was used and p values less than 0.05 were considered statistically significant.

## Results

Group I (control) consisted of 82.81% females and 17.18% males. In group II (subclinical hypothyroid patients) were 87.5% females and 12.5% males. (Table I) The mean ages of controls and subclinical hypothyroid patients were 33.65±5.98 and 35.20±7.55 years respectively. There was a

significant increase in mean values of Hcy levels in subclinical hypothyroid patients than in control group (Mean ± SD, 12.67 ± 2.35 µmol /l vs 3.76 ± 1.59 µmol/ l; 95% Confidence Interval, respectively; p=0.002) (Table II). The mean tHcy of subclinical hypothyroid patients was 8.91µmol/l higher than of control group.

There was a significant increase in mean serum total cholesterol in subclinical hypothyroid patients than in control group (Mean ± SD, 195.25 ± 10.63 mg/dl vs 162.05 ± 17.39 mg/dl; 95% Confidence Interval, respectively; p=0.000) (Table II). The mean serum total cholesterol of subclinical hypothyroid patients was 33.2 mg/dl higher than of control group.

There was a significant decrease in mean values of HDL-Cholesterol in subclinical hypothyroid patients than in control group (Mean ± SD, 48.11 ± 4.62 mg/dl vs 53.85 ± 6.55 mg/dl; 95% Confidence Interval, respectively; p=0.000) (Table II). The mean values of HDL-Cholesterol of hypothyroid patients were 5.74 mg/dl lower than of control group.

There was a significant increase in mean serum LDL-Cholesterol in subclinical hypothyroid patients than in control group (Mean ± SD, 126.79 ± 22.24 mg/dl vs 93.70 ± 14.58 mg/dl; 95% Confidence Interval, respectively; p=0.000) (Table II). The mean Serum LDL-Cholesterol of subclinical hypothyroid patients was 33.09 mg/dl higher than of control group.

There was a decrease in mean serum triglyceride in hypothyroid patients than in control group which was not significant (Mean ± SD, 111.25 ± 18.82 mg/dl vs 140.29 ± 17.69 mg/dl; 95% Confidence Interval, respectively; p=0.010) (Table II).

**Table I: Demographic Characteristic of Control and Subclinical Hypothyroid Patients**

| | Gender | Mean age in years ± SD | Gender Distribution |
|---|---|---|---|
| Group I Control (n=64) | Male | 32.12 ± 7.98 | 17.18% |
| | Female | 35.45 ± 8.23 | 82.81% |
| Group II Subclinical Hypothyroid (n=64) | Male | 34.65 ± 9.76 | 12.5% |
| | Female | 36.23 ± 9.44 | 87.5% |

## Discussion

In our study we found serum total cholesterol (TC) and LDL-Cholesterol (LDL) was significantly increased in subclinical hypothyroidism patients as compared to control. These findings are consistent with results of Duntas LH[12], Bandi A et al[13]and Díez JJ.[14] It is postulated that in hypothyroidism there is reduced activity of HMG CoA reductase which might lead to decrease in total cholesterol but our findings are on the contrary. The elevation of serum cholesterol might be because of rise in the levels of serum low density lipoproteins and intermediate density lipoprotein. Furthermore the plasma concentration of cholesterol might also be increased due to decrease in the rate of cholesterol secretion in the bile and resulting reduced excretion in the feces. This happens due to decrease in number of low density lipoprotein(LDL) receptors on liver cells leading to decreased in activity of LDL receptors and decreased receptor-mediated catabolism of low density lipoproteins (LDL) and Intermediate density lipoproteins.

**Table II:Comparison of Lipid Profile and Homocysteine Levels between Control and Subclinical Hypothyroid Patients**

| Parameter | Group I Control (n=64) Mean ± SD | Group II Subclinical Hypothyroid patients (n=-64) Mean ± SD | P value |
|---|---|---|---|
| Homocysteine(µmol/l) | 3.76 ± 1.59 | 12.67 ± 12.35 | 0.002 |
| Totalcholesterl (mg/dl) | 162.05 ± 17.39 | 195.25 ± 30.63 | 0.000 |
| HDL-Cholesterol (mg/dl) | 53.85 ± 6.55 | 48.11 ± 4.62 | 0.000 |
| Triglycerides(mg/dl) | 111.25 ± 18.82 | 140.29 ± 47.69 | 0.010 |
| LDL-Cholesterol (mg/dl) | 93.70 ± 14.58 | 126.79 ± 22.24 | 0.000 |

HDL-Cholesterol (HDL) levels are elevated in hypothyroidism. It occurs due to the decreased activity of the cholesterol ester transfer protein (CETP) resulting in reduced transfer of cholesteryl esters from HDL to very LDL-Cholesterol (LDL). But our findings were on the contrary. In our study we found that serum HDL levels were significantly decreased in subclinical hypothyroid patients compared to the control. These findings are in consistent with the results of Pandian BG[15]and Al-Hakeim HK[16] who also reported decreased HDL levels in hypothyroid patients.

In our study serum triglycerides (TG) levels were found increased in patients of subclinical hypothyroidism. This finding is consistent with the reports of Ali A[17] and Saleh AA[18]who also reported high TG levels in hypothyroidism. The reason being, lipoprotein lipase activity is decreased in hypothyroidism which decreases the clearance of Triglyceride rich lipoproteins. In our study we observed that Hcy was significantly elevated in patients of subclinical hypothyroidism as compared to the control group. This finding is contrary to the report of AldasouqiSetal[19] but is in accordance to reports by Saleh AA[18]and Al-Habori MA.[20] There are two postulated mechanisms of increase in homocysteine levels in hypothyroidism. Either there is a rise in homocysteine formation due to direct effect of thyroid hormone on homocysteine metabolism in the liver or there is decreased in homocysteine clearance from the kidneys. Decreased serum levels of thyroid hormone affect the Hepatic activity of flavoproteinmethy lenetetrahyd rofolate reductase (MTHFR) enzymes vital for remethylation of homocysteine to methionine. Furthermore the conversion of riboflavin to the active coenzyme flavin-adeninedinucleotide becomes faulty leading to poor activity of MTHFR and hence increased Hcy levels.

There were few limitations of this study, which include small sample size and it should have been a cohort study. Despite this we believe that our study may prove helpful in further research related to homocysteine and lipid profile parameters in subclinical hypothyroidism.

## Conclusion

It was found in our study that the serum levels of homocysteine and lipid profile are increased in subclinical hypothyroidism. As these they are prone to atherosclerosis, therefore early screening and regular monitoring of these factors are recommended in subclinical hypothyroid patients.

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