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# The correlation between serum homocysteine levels and hypothyroidism: A 1-year case control study

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## ABSTRACT

### Background

Thyroid hormones have significant effects on lipid metabolism and homocysteine levels. Decrease in thyroid hormone levels may alter the homeostasis of lipid metabolism and homocysteine levels.

### Objectives

To study the incidence of hyperhomocysteinemia and hypercholesterolemia in patients with hypothyroidism, and to find out the correlation of homocysteine with cholesterol levels, thyroid hormones and thyroid-stimulating hormone (TSH) in newly detected hypothyroid patients.

### Methods

In this prospective case-control study, 30 hypothyroid patients (case group) and 30 euthyroid controls were included. Patients with a TSH level >4.78 mIU/mL were considered in the case group and those with TSH level <4.78 mIU/mL were included in the control group. Cases and controls were matched on the basis of age, sex, and body mass index. Levels of TSH, free T3 andT4, fasting serum homocysteine, and total cholesterol were investigated in both case and control groups. The data were statistically analysed with Independent t-test and Pearson's correlation method by SPSS 20.0.

### Results

Compared to controls, significant increase in serum homocysteine levels was observed in in hypothyroid group ($P$ = 0.0064). Serum total cholesterol levels were significantly higher in hypothyroid group when compared with control ($P$ = 0.0066). Correlation of serum homocysteine levels with the levels of TSH, free T3 and T4, and serum cholesterol levels were statistically not significant in both hypothyroid group.

### Conclusion

We observed a significant increase in levels of homocysteine and total cholesterol levels in hypothyroid group when compared with control. Hyperhomocysteinemia and increased cholesterol levels can contribute to cardiovascular risks. We recommend screening of serum homocysteine levels in hypothyroid patients to detect atherosclerosis and cardiovascular diseases.

**Keywords:** Hypothyroidism, Hyperhomocysteinemia, Cardiovascular Disease.

## INTRODUCTION

Thyroid hormones play an important role in regulating metabolism, and normal growth and development. In hypothyroidism, the thyroid gland fails to produce adequate thyroid hormones to meet the metabolic demand of the body. Patients with thyroid dysfunction have increased risk of cardiovascular diseases [1].

Homocysteine is a sulfur-containing amino acid formed as an intermediate during the metabolism of methionine. Hypothyroidism-associated reduction in hepatic enzyme functions and concurrent changes in the renal system, especially in glomerular filtration rate, lead to increased serum homocysteine levels [2, 3]. Elevated homocysteine level is an independent risk factor for cardiovascular-related complications and mortality [4].

Hyperhomocysteinemia and hypothyroidism together contribute to unfavorable modifications in the coronary artery and lipid metabolism. Elevated homocysteine levels may affect endothelial function and trigger coagulation cascade in the coronary artery [5]. It can also induce oxidative stress, smooth muscle hypertrophy, and oxidation of low-density lipoprotein (LDL) cholesterol. A remarkable reduction of hydroxymethylglutaryl-CoA (HMG-CoA) reductase can be observed in the cases of hypothyroidism. This can lead to increased levels of total cholesterol and LDL cholesterol. Also, the levels of triglyceride increases due to impaired clearance of triglyceride-rich lipoproteins [6]. Higher C-reactive protein and interleukin-6 levels are also observed in hypothyroid cases [7]. Hypothyroidism and hyperhomocysteinemia can promote atherosclerosis leading to severe coronary artery diseases. Physiological and pathological changes during hypothyroidism and hyperhomocysteinemia may adversely influence the normal lipid profile and coronary functions [8-11].

All these facts, focusing the significance of establishing the association between levels of thyroid hormones, homocysteine and lipid profile in our population. Thus, we conducted this study to compare the levels of thyroid hormones, homocysteine and total cholesterol in hypothyroid patients and euthyroid control group.

## MATERIALS AND METHODS

This was a 1-year case-control study conducted at the Department of Medicine, KLE's Dr. Prabhakar Kore Hospital and Medical Research Center, Belagavi from January to December 2015. A total of 30 newly detected hypothyroid patients and 30 matched controls were enrolled in the study. Consent was obtained from the patients before the commencement of the study. Patients with TSH level >4.78 mIU/mL were included in the case group and those with a TSH level <4.78 mIU/mL were included in the control group. Cases and controls were matched on the basis of age, sex, and body mass index. Patients with hemorrhagic, ischemic strokes, cardioembolic strokes, renal failure, and patients with history of coronary events or any cardiac interventions, hypertension, type 2 diabetes mellitus, and deep vein thrombosis were excluded from the study.

Ethical clearance were obtained from the Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi. After collecting informed consent, levels of TSH, free T3 and T4, fasting serum homocysteine and total cholesterol were investigated in both case and control groups.

SPSS 20.0 was used to perform statistical analysis. The data were compared by independent t-test. Correlation of serum homocysteine with the measured parameters (levels of TSH, free T3 and T4, and total cholesterol) in hypothyroid and control group were performed by Pearson's correlation method. $P$ <0.05 was considered as statistically significant.

## RESULTS

Majority of the patients were women and men-to-women ratio was 3:7. The most prevalent age-group was ≤30 years. The mean ages of hypothyroid and control group were 40.60±15.58 and 41.40±14.90 years, respectively. TSH, free T3 T4, serum homocysteine, and serum total cholesterol levels of hypothyroid and control group are shown in Table 1. Significant differences were observed in TSH levels between hypothyroid group and control group. Mean TSH levels observed in hypothyroid group and control group were 46.95±57.67 and was 2.27±1.08 mIU/mL, respectively ($P$ = 0.0001). No significant difference was observed in free T3 and T4 levels of

hypothyroid group and the control group. Observed mean free T3 levels in hypothyroid group and control group were 1.41±0.91 and 1.80±0.98 pg/mL, respectively whereas, mean free T4 levels of hypothyroid group and control group were 4.69 ±3.73 and 5.75±3.60 ng/dL, respectively.

Significant elevation of serum homocysteine levels was observed in hypothyroid group when compared with the control group. Mean serum homocysteine levels in the hypothyroid group and control group were 25.02±14.31 and 16.65±7.54 µmol/L, respectively ($P$ = 0.0064).

Hypothyroid group showed increased levels of total cholesterol when compared with control group. Mean serum total cholesterol levels in hypothyroid group and control group were 193.03±34.89 and 165.90±39.55 mg/dL, respectively ($P$ = 0.0066).

Correlation of serum homocysteine levels with TSH, free T3 and T4, and serum cholesterol levels were statistically not significant in hypothyroid group (Table 2). We observed a negative correlation of serum homocysteine with levels of TSH in case group (r = -0.0595). No significant correlation was observed in serum homocysteine with levels of total cholesterol in hypothyroidism cases (r = 0.0395).

**Table 1**. Age, sex, TSH, free T3 and T4, serum homocysteine, and serum total cholesterol levels of hypothyroid and control group

| **Parameters** | **Hypothyroidism n = 30 (mean ± SD)** | **Control n = 30 (mean ± SD)** | ***P*-value** |
|---|---|---|---|
| Age (Years) | 40.60±15.58 | 41.40±14.90 | 0.840 |
| TSH (mIU/mL) | 46.95±57.67 | 2.27±1.08 | <0.001 |
| Free T3 (pg/mL) | 1.41±0.91 | 1.80±0.98 | 0.115 |
| free T4 (ng/dL) | 4.69±3.73 | 5.75±3.60 | 0.268 |
| Serum Homocysteine (µmol/L) | 25.02±14.31 | 16.65±7.54 | 0.006 |
| Serum Total Cholesterol (mg/dl) | 193.03±34.89 | 165.90±39.55 | 0.006 |

**Table 2**. Correlation of serum homocysteine with the measured parameters in hypothyroid group.

| **Measured parameter** | **Homocysteine** | |
|---|---|---|
| | *r*-value | *p*-value |
| TSH level | −0.0595 | 0.755 |
| Free T3 level | −0.1284 | 0.499 |
| Free T4 level | 0.1111 | 0.559 |
| Total cholesterol level | 0.0395 | 0.836 |

## DISCUSSION

In the present study, most of our patients were women under the age group ≤30 years. This may be because, women are more susceptible to hormonal leaps and highly sensitive to hormonal changes. Significantly elevated levels of serum homocysteine was observed in hypothyroid patients in comparison with control. Elevated serum homocysteine levels could be due to the decreased vitamin B levels from dietary sources or impaired metabolism and clearance of homocysteine due to hypothyroidism [12]. Anorexia induced by hypothyroidism might lead to malnutrition and poor vitamin levels in the body. Reduced activity of hepatic enzymes involved in the remethylation pathway of homocysteine and decrease in glomerular filtration rate lead to hyperhomocysteinemia [13]. Similar results were observed in the studies conducted by Al-Habori et al [14] and Bamashmoos et al [2] Various other clinical studies have demonstrated strong evidence for elevated homocysteine levels in hypothyroid patients [3, 10, 15, 16].

Also, a significantly higher serum total cholesterol level was observed in hypothyroid group when compared with the control group. This observation was consistent with the reports of Rahbani-Nobar et al [11] and Turhan et al [10] Hypothyroidism can significantly affect lipoprotein metabolism and might lead to abnormalities in the lipid profile. Changes in lipid profile can further lead to atherosclerosis and coronary artery complications [17-19]. Activation of lipoprotein lipase, cholesterol ester transfer protein, and hepatic lipase by thyroid hormone help in regulating the lipid metabolism [6]. Reduction in thyroid hormone levels disrupts the normal lipid metabolism and clearance. This enhances the levels of LDL and triglyceride-rich lipoproteins. Study have reported reduction in total and LDL cholesterol levels when patients with mild thyroid failure are treated with thyroid hormones [4]. This shows a positive correlation between hypercholesterolemia and hypothyroidism. Hypercholesterolemia can induce unfavorable modifications such as endothelial injury, increased oxidative stress, and altered coagulation cascade in the coronary artery. Moreover, hypothyroidism leads to increased levels of β-carotene and C-reactive protein, thus increasing oxidative stress and inflammation [20].

Increased homocysteine levels observed in hypothyroid patients is an additional risk factor for cardiac diseases along with hypothyroidism [21, 22]. Homocysteine adversely affects the endothelial cells and bioavailability of nitric oxide [6, 23]. Nitric oxide modulate vascular dilator tone and protect the blood vessels from injurious consequences of platelets. Thus, reduction of nitric oxide can increase proatherogenic mechanism and increase intracellular oxidative stress leading to thrombotic events.

Correlation of serum homocysteine levels with TSH, free T3 and T4, and serum cholesterol levels were statistically not significant in hypothyroid group due to smaller sample size. Previous studies have shown a well-established correlation between serum homocysteine levels with TSH, free T3 and T4, and serum cholesterol levels [10, 11, 14].

## CONCLUSION

The present study has shown a significant increase in levels of homocysteine and total cholesterol levels in hypothyroid group when compared with control. Hyperhomocysteinemia and increased cholesterol levels can contribute to cardiovascular risks. We recommend screening of serum homocysteine levels in hypothyroid patients to detect atherosclerosis and cardiovascular diseases.

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None
Conflict of Interest: None

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