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Association between Plasma Homocysteine Level and Atherogenic Index of Plasma among Hypothyroid Patients - A Case-Control Study

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Abstract **Original Research Article**

Introduction: Hypothyroidism is a common metabolic disorder in general population. Hypothyroidism is a commonly encountered health problem in Bangladesh and morbidity and mortality toll due to cardiovascular disease resulting from hypothyroidism is quite high. Hypothyroidism, dyslipidaemia and hyperhomocysteinemia are recognized risk factor for atherosclerosis and cardiovascular disease. ***Aim of the Study*:** The aim of this study was to evaluate the association between plasma Homocysteine level and atherogenic Index of plasma in patients with hypothyroidism. ***Methods*:** This was a case-control study and conducted in the Department of Biochemistry in cooperation with Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period from January, 2012 to December, 2013. In our study, we included 60 newly diagnosed hypothyroid individuals as case and 60 euthyroid individuals as control. ***Result*:** In this study, most of the participants were female (62%) compared to male (38%) and we found the mean age of the case and control group was 34.31 ± 11.77 years and 32.42 ± 12.51 years. Mean serum homocysteine was found significantly higher in case group (19.00 ± 7.58 µmol/L) than control group (9.59 ± 1.91µmol/L).Mean AIP was found significantly higher in case (0.75 ± 0.27) than control (0.35 ± 0.20). We found 49 (81.67%) cases were within increased risk group of atherogenesis where as in control group it was 28 (46.67%).In present study, mild hyperhomocysteinemia was found in 80% cases and moderate hyperhomocysteinemia in 13.3% cases where as in control group it was 10% & 0% respectively. ***Conclusion*:** In this study, we found that total plasma homocysteine level was significantly increased in recently diagnosed hypothyroidism and was normal in control groups. We also found that hypothyroidism is associated with high atherogenic index and hyperhomocysteinemia which causes premature atherosclerosis.

Keywords: Hypothyroidism, Homocysteine level, Atherogenic Index of Plasma.

INTRODUCTION

Thyroid diseases are common worldwide. Thyroid diseases are more prevalent and the most common among all the endocrine diseases [1]. In India 11% of the population are affected from hypothyroidism. Women were three times more prone for hypothyroidism than men [2]. According to the 6-year duration National Health and Nutrition Examination Survey (NHANES III) Study, the prevalence of hypothyroidism was 4.6% (0.3% clinical and 4.3% subclinical) in population aged at least 12years, showing an age and sex dependence [3]. Hypothyroidism occurs in 0.4% women and 0.1 % men [4]. Thyroid failure is more common in women and its prevalence rises with age [5].

Hypothyroidism is defined as a deficiency of thyroid activity, which results from reduced secretion of both T3 and T4 irrespective of the cause [6]. Hypothyroidism may be due to primary disease of the thyroid gland itself or lack of pituitary TSH [7]. Biochemically decrease in T4 and T3 concentrations lead to hypersecretion of pituitary TSH and an amplified increase in serum TSH levels [8]. The incidence of hypothyroidism varies, depending on geographical and the environmental factors such as dietary iodide, goitrogen intake, the genetic characteristic of the population and the age distribution of the population. Hypothyroidism affects the cardiovascular, pulmonary, renal, neuromuscular, nervous and the reproductive system [9].

Hypothyroidism is associated with high cholesterol and lipoprotein levels, which are normalized after thyroid hor- mone replacement [10-12]. The atherogenic lipid profile in particular, but also other abnormalities have been suggested to be responsible for

the increased cardiovascular morbidity in hypothyroid patients.[10-15] Total homocysteine (tHcy) in plasma has recently been proposed as an independent risk factor for occlusive cardio- vascular disease [16, 17]. The plasma level is affected by several life-style and physiological factors and is elevated under conditions of impaired folate and cobalamin status and in renal failure [16]. We recently reported that plasma tHcy is influenced by thyroid status. Hypothyroid patients had higher plasma tHcy levels than healthy controls and hyperthyroid patients, but a tendency toward low tHcy in hyperthyroidism did not reach statistical significance [18]. Homocysteine is a sulphur containing amino acid which is formed as an intermediate in the methionine metabolism and methionine is the only source of homocysteine in the human body. Hyperhomocysteinemia is defined as the levels of homocysteine> 10 µmol/L. There are various causes for hyperhomocysteinemia. Hypothyroidism is one of the treatable cause for hyperhomocysteinemia. For each 1 µmol/L increase in homocysteine concentration there is a 1% increase in risk to develop cardiovascular events or death [19]. Hyperhomocysteinemia is an important and independent risk factor for atherosclerosis. 60% of the patients affected by cardiovascular disease have hyperhomocysteinemia [20]. Many studies have reported mild hyperhomocysteinemia as an independent risk factor for venous and arterial occlusive disease. [21] For each 5 µmol/L increase in homocysteine there is a 33% risk of developing atherosclerosis [22]. Hypothyroidism decreases the enzyme involved in the remethylation pathway of homocysteine and thus leads to hyperhomocysteinemia [23]. Thyroid hormones stimulate flavokinase involved in the synthesis of flavin adenine mononucleotide and flavin adenine dinucleotide [24, 25].

OBJECTIVE OF THE STUDY

The main objective of the study was to evaluate the association between plasma Homocysteine level and atherogenic Index of plasma in patients with hypothyroidism.

METHODOLOGY & MATERIALS

This was a case-control study and was conducted in the Department of Biochemistry in cooperation with Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period from January, 2012 to December, 2013. In our study we included 60 newly diagnosed hypothyroid individuals as case and 60 euthyroid individuals as control.

These are the following criteria to be eligible for enrollment as our study participants:

a) Patients aged between 21 to 50 years;
b) Patients diagnosed with hypothyroidism;
c) Patients with TSH value > 4mIU/L;
d) Patients with FT4 value < 0.9ng/dl;
e) Patients who were willing to participate were included in the study and
a) Patients with uncontrolled DM,
b) Patients with hypertension;
c) Patients with thyroid hormone medication;
d) Patients with hyperthyroidism;
e) Patients with any history acute illness (e.g., renal failure, pancreatic diseases, etc.) were excluded from our study.

Operational Definitions:

1) Hypothyroid-When TSH value >4mIU/L, FT4 value < 0.9 ng/dl is called Hypothyroid [26]
2) Atherogenic Index: Atherogenic index of plasma (AIP) is defined as log of TG to HDL-C ratio.
   AIP = Log (TG / HDL-C) [27]
   AIP<0.11-low risk
   AIP< (0.11-0.21)-intermediate risk
   AIP>0.21- increased risk.
3) Hyperhomocysteinemia: When serum Homocysteine level > 15 µmol/L [28]

Sample Collection & Preservation

With full aseptic precaution 5ml venous blood from each of the 120 study patients was collected after an overnight fast of at least 12 hours in a disposable syringe and was delivered immediately into a clean dry heparinized tube. Then plasma was separated after centrifuging at 3000 rpm for 5 minutes and stored in an ultra-freezer at -25°C until analytical measurements of plasma homocysteine, plasma triglyceride & HDL-C were done.

Statistical Analysis

All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS 15 (Statistical Package for Social Sciences) for windows version 10. Probability value <0.05 was considered as level of significance. The study was approved by Ethical Review Committee of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

RESULTS

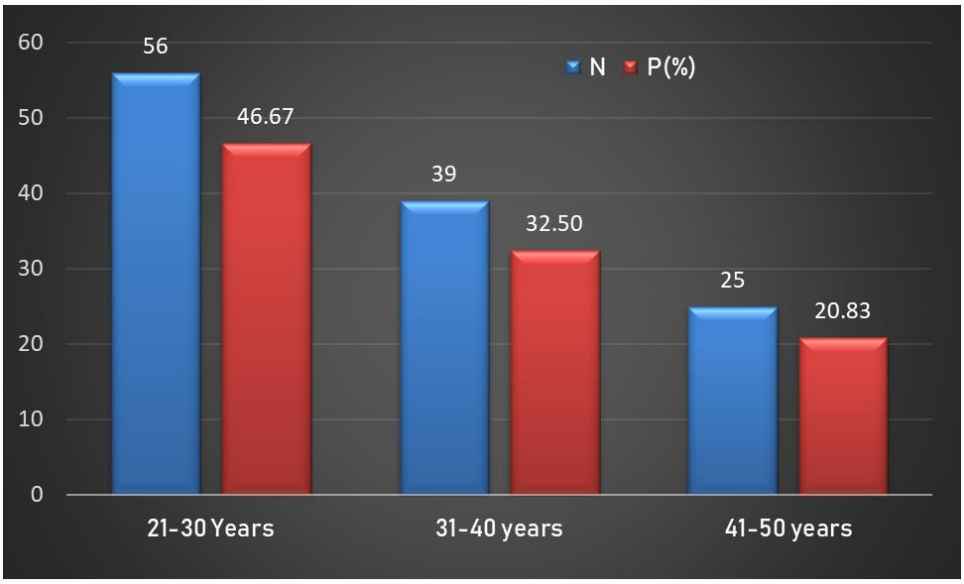

Figure 1: Age distribution of our study patients

Figure 1 shows that majority (46.67%) of participants belonged to the age group 21-30 years, followed by 32.50%of participants were 31-40 years and 20.83% belonged to the age group 41-50 years.

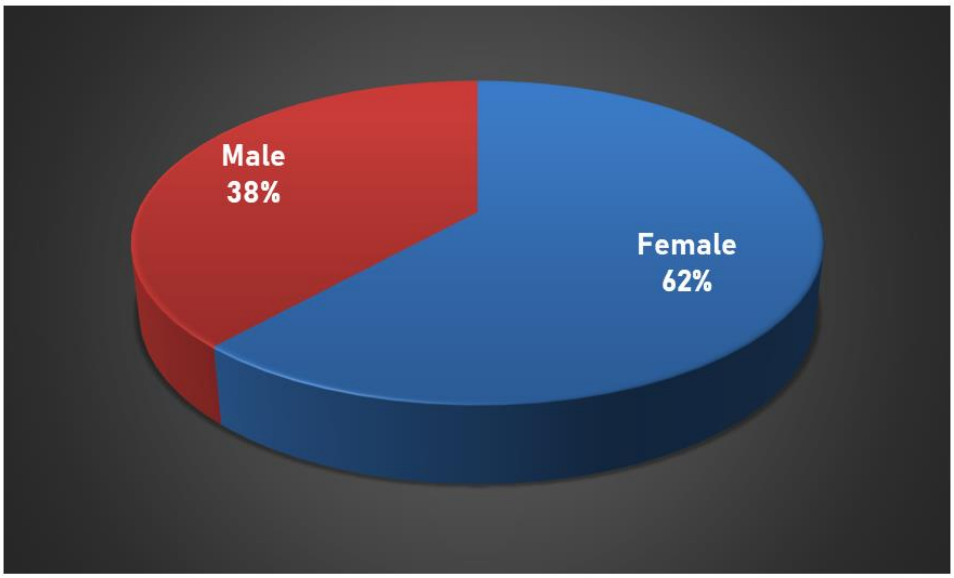

Figure 2: Gender distribution of our study patients

Figure 2 shows that most of the participants were female (62%) compared to male (38%).

Table 1: Baseline characteristics of our study patients

Baseline	**N**	**P (%)**
Mean age (years)	35.69 ± 13.83	
Education		
Illiterate	18	15.00
Primary education	36	30.00
Secondary education	35	29.17
Higher above	49	40.83
Height (cm)	154.97±15.107	
Weight (kg)	61.05±14.24	
BMI (kg/m^2)	28.67±6.24	

Heart Rate (per minute)	86 ± 17
Systolic blood pressure (mm Hg)	135.24 ± 20.78
Diastolic blood pressure (mm Hg)	83.94 ± 10.69

In table 1 we found the mean age 35.69 ± 12.83 years. Majority (40.83%) of our patients were doing higher studies. The mean BMI was 28.67±4.24 kg/m^2. The mean SBP & DBP was 135.24 ± 20.78 & 83.94 ± 10.69 mmHg respectively.

Table 2: Distribution of our study subjects by the clinical characteristics & biochemical parameters

Clinical characteristics	Case		Control		P-value
	N=60	P(%)	N=60	P(%)	
TSH (mIU/L)	9.98 ±4.31		1.52± 2.14		
FT4 (ng/dl)	0.18 ±0.61		1.18 ±0.87		
Tg (mg/dl)	274.43± 87.32		165.03± 90.27		
HDL (mg/dl)	41.83 ±10.56		39.43 ±12.74		
Biochemical parameters					
Homocysteine (µmol/L)	19.00 ± 7.58		9.59 ± 1.91		0.001
Atherogenic index of plasma	0.75 ± 0.27		0.35 ± 0.20		0.001
Homocysteine level					
Normal	4	6.67	54	90.00	0.001
Mild	48	80.00	6	10.00	
Moderate	8	13.33	0	0.00	
Level of AIP					
AIP < 0.21	11	18.33	32	53.33	0.001
AIP ≥ 0.21	49	81.67	28	46.67	

Table 2 shows the clinical characteristics & biochemical parameters of our study subjects. There are significant differences in mean TSH & Tg level while no significant difference was found in HDL level. Mean homocysteine was 19.00 ± 7.58 µmol/L in case group and 9.59 ± 1.91µmol/L in control group. Mean AIP level was 0.75 ± 0.27 in case group and 0.35 ± 0.20 in control group. In the case out of 60 hypothyroid patients, 6.67% represent normal t-Hcy level, 80% mild & 13.3% moderate hyperhomocysteinemia level. In control group 90% & 10% represent normal & mild t-Hcy level respectively and the difference was statistically significant. We found 49 (81.67%) cases were within increased risk group of atherogenesis where as in control group it was 28 (46.67%) which was statistically significant.

DISCUSSION

In this study female subjects are more in both case (40) and control (34) group than male subjects because females are more prone to develop hypothyroidism than male. Aryal *et al*., found female are more vulnerable to thyroid dysfunction, typically overt and sub-clinical hypothyroidism in Karve area of Nepal [29]. Overall prevalence of hypothyroidism was 4.8% in men and 12.8% in women in an iodine sufficient area of Iran was found by Aminorroya *et al*., [30].

In our study we found the mean age of the case and control group was 34.31 ± 11.77 years and 32.42 ± 12.51 years respectively ranging from 21-50 years. In a similar study conducted by Ellatif *et al*., found the mean ages of case and control groups were 44.7 ± 9.5 years and 43.2 ± 6.0 years respectively ranging from 35-53 years [31]. In another study conducted by Sunanda *et al*., the age range was 20-60 years [32]. Study done by Saini *et al*., where age range is 20-50 years [33].

In this study mean serum homocysteine was significantly higher in case group than control group. Mean serum homocysteine was 19.00 ± 7.58 µmol/L in case where as 9.59 ± 1.91 µmol/L in control group. In a similar study conducted by Ellatif *et al*., found a significant higher total plasma homocysteine concentration in hypothyroid patients 15.4 ± 7.5 µmol/L than in control group 7.9 ± 2.8 µmol/L (P <0.01) [31]. Nedrebo *et al*., showed that, mean t-Hcy level was higher (16.3) than the control subject (10.5) [24]. Orzechowska-Pawilojc *et al*., found mean homocysteine level in case were 12.73 ± 5.58 µmol/L while that in control was 11.15 ± 9.50 µmol/L. The homocysteine was significantly higher (P=0.001) in hypothyroids as compared to control [34]. In present study, mild hyperhomocysteinemia was found in 80% cases and moderate hyperhomocysteinemia in 13.3% cases where as in control group it was 10% & 0% respectively.

In the current study, we found mean AIP level was 0.75 ± 0.27 in case group and 0.35 ± 0.20 in control group which indicates among both group case was the highest with AIP level. In a study conducted by Rajab *et al*., showed that, mean atherogenic index was higher in hypothyroid individual (0.20 ± 0.03) compared to euthyroid (0.11 ± 0.02) with (p < 0.05). Here

Atherogenic index was calculated by using AIP= log (TG/HDL-C) formula [35]. Shivakrishna *et al*., also found that atherogenic index was higher in hypothyroid than euthyroid subjects. In their study, the atherogenic index was 0.27± 0.20 in overt hypothyroid case, 0.17± 0.10 in subclinical hypothyroid case and 0.07± 0.10 in euthyroid control subject [36].

Recent studies have indicates that TG/HDL-C ratio transformed logarithmically can estimate the atherogenic risk better than all others. TG and HDL-C perfectly reflects the balance between atherogenic lipoproteins and protective lipoproteins. Clinical studies revealed that atherogenic index of plasma can estimate the cardiovascular risk. This index is also sensitive to pharmacological treatment, being a barometer of therapeutic success. The reduced risk of cardiovascular events is associated with low AIP level (<0.11); range from 0.11 to 0.21 indicates intermediate risk of CV disease and values > 0.21 shows a high cardiovascular risk [27]. In the current study, we found 49 (81.67%) cases out of 60 were within increased risk group of atherogenesis where as in control group it was 28 (46.67%) out of 60 which was statistically significant.

Limitations of the Study

Our study was a single centre study. We took a small sample size due to our short study period. After evaluating once those patients we did not follow-up them for a long term and have not known other possible interference that may happen in the long term with these patients.

CONCLUSION AND RECOMMENDATIONS

In this study, we found that total plasma homocysteine level was significantly increased in recently diagnosed hypothyroidism and was normal in control groups. We also found that hypothyroidism is associated with high atherogenic index and hyperhomocysteinemia which causes premature atherosclerosis.

So, further study with a prospective and longitudinal study design including larger sample size needs to be done to know more about cardiovascular risk factors and to avoid complications in hypothyroidism individuals.

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