Original Article

Pattern of dyslipidemia among patients with subclinical hypothyroidism and its relation with thyroid stimulating hormone

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ABSTRACT

Background: *The relationship between subclinical hypothyroidism (SCH) and dyslipidemia is still debatable about whether SCH is constantly associated with lipid disorder. The aim of this study was to assess the lipid abnormalities in patients with SCH and to evaluate the relation between thyroid stimulating hormone (TSH) and lipid profile.*

Methods: *This cross-sectional observational study was conducted in outpatient department (OPD) of the Hormone and Diabetes Clinic at MARKS Medical College & Hospital in Dhaka, Bangladesh from May 2018 to October 2019. A total of 308 subjects (age 30 - 60 years) were included in this study using covenience sampling. Among them, 156 were diagnosed case of SCH, while 152 were euthyroid healthy individuals in control group (matched for age, gender and weight). Laboratory test included serum TSH and free thyroxine (FT4) and fasting lipid profile. Data were analyzed using SPSS version 18 statistical software.*

Results: *In this study, dyslipidemia was more prevalent in patients with SCH compared to control group [p<0.001]. SCH group showed altered lipid profile i.e. significantly higher serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TGs) and lower high density lipoprotein cholesterol (HDL-C) when compared with the euthyroid subjects [p < 0.05 for each]. Pearson's correlation coefficient for the relationships between serum TSH and lipid level showed that TSH levels were positively correlated with TC, LDL-C, TG and negatively correlated with HDL-C in patients with SCH [p < 0.05 for each].*

Conclusions*: Dyslipidemia is a common feature in SCH compared to euthyroid controls. The study showed that TSH level was positively correlated with TC, LDL-C, TG and negatively correlated with HDL-C. SCH should be a matter for further investigation because dyslipidemia is associated with this thyroid disorder.*

Key words: *Subclinical hypothyroid, lipid profile, thyroid stimulating hormone.*

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INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine (FT4).[1] It is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease [2] and the incidence is more common in women, almost twice than men.[3] Patients of SCH are mostly asymptomatic or have minimal symptoms. Thus, SCH is solely a laboratory diagnosis.[4]

Thyroid hormones are of vital importance in maintaining the initial level of phospholipids in cell membranes and fatty acid composition of the lipids.[5] Though lipid abnormalities in overt hypothyroidism include elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) has been proven by some studies,[6] however, debate still persists regarding the lipid levels in SCH and its clinical significance.[7]

The pathophysiology of the lipid alterations of overt and SCH includes elevations in serum total cholesterol

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due to changes in the synthesis, metabolism and mobilization of lipids in liver and adipose tissue. High TSH level induces the hepatic expression of hydroxy methyl glutaryl coenzyme A reductase, which results in increased cholesterol synthesis.[8]

In recent studies, SCH appeared as an independent risk factor for aortic atherosclerosis and myocardial infarction.[9] But still the association between SCH and dyslipidemia is disputed, alterations in lipid profile in these patients have been observed in several studies.[10, 11] Many studies have reported significant increase in TC, LDL-C and TG in patients with SCH.[8, 12] Moreover, there is growing evidence that treatment with thyroxin lowers serum lipid in SCH that is why it is important to treat cases of SCH with dyslipidemia. Additionally, small reductions in levels of lipid profiles result in significant reduction in cardiovascular morbidity.[13]

The present study aimed to determine the pattern of lipid abnormalities in patients with SCH and to find out the relation between TSH and dyslipidemia.

METHODS

Operational Definitions

Subclinical hypothyroidism

SCH is defined biochemically as normal free T4 in the presence of an elevated TSH. [14] The study included subjects as case of SCH who have elevated TSH (>5.0 - <10.0 μIU/mL) and free T4 is within normal reference value (0.71-1.85 ng/dL) repeated twice at least 6 weeks apart.

Dyslipidemia

Dyslipidemia means levels of lipid are too high or low in the bloodstream. The most common types of dyslipidemia are: high levels of LDL cholesterol, low levels of HDL cholesterol and high levels of TG. [15] Based on AACE guidelines[16] the lipid concentration was considered to be altered when the TC was ≥200 mg/dl, the TG were ≥150 mg/dl, HDL cholesterol was < 40 mg/dl in males and <50 mg/dl in females and LDL cholesterol was ≥130 mg/dl.

Study design and patient population

It was an cross-sectional observational study which was conducted in outpatient department (OPD) of the Hormone and Diabetes clinic at MARKS Medical College & Hospital in Dhaka, Bangladesh. The study was carried out during May 2018 to October 2019 after taking permission from the ethical review committee of the institute. A total of 308 subjects age ranging from 30 - 60 years were included in this study using convenience sampling. Most of them were referred from the outpatient departments of different hospitals and clinics for the evaluation of their thyroid function. Subjects with age < 30 years and > 60 years were excluded from the study. Among the study population, 156 patients were diagnosed as case of SCH, while 152 patients were euthyroid healthy individuals in control group (matched for age, gender and weight). A written informed consent was taken from every patient after full explanation of the study.

Eligibility criteria

Inclusion criteria

The study included subjects with newly diagnosed and untreated cases of SCH as case who have TSH more than 5.0 μIU/mL but below 10.0 μIU/mL and free T4 is within normal reference range (0.71-1.85 ng/dL) repeated twice at least 6 weeks apart. Age, sex and weight matched euthyroid subjects who have normal serum TSH level (0.47-5.0 μIU/mL), and normal Free T4 (0.71-1.85 ng/dL) levels.

Exclusion criteria

Patients were on lipid lowering agents or under treatment with thyroxine or anti-thyroid drugs; and older than 60 years were excluded from the study. While exclusion criteria include any factors altering thyroid function test (TFT) [17] including: pregnancy; drugs like estrogen-containing oral contraceptives, amiodarone, phenytoin and steroids; subjects having acute or chronic illnesses such as coronary heart disease, diabetes mellitus, renal failure, pancreatitis, liver or renal disorders or patient had history of recent surgery; previous thyroid disorders or family history of thyroid diseases; obesity , malnutrition, smoking, alcoholism etc .[18,19]

The detailed history of all such patients was taken and, physical and relevant clinical examination was performed. A pre-designed structured questionnaire was used to obtain information from participants.

Anthropometric measurements

Height and weight were measured by a reliable height scale and weighing scale, respectively. According to

the Body Mass Index (BMI) for Asian population: weight in kilograms/square of height in meters (kg/m^2), the patients were categorized as underweight (≤18.5 kg/ m^2), normal weight (BMI: 18.5–22.9 kg/m^2), overweight (BMI: 23–24.9 kg/m^2) and obese (BMI: ≥25 kg/m^2). [20] Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg[21].The blood pressure was measured by a manual sphygmomanometer in sitting position (measured 2 times after a 5-min rest between each measurement).[22]

Laboratory Investigations

The blood was collected from the median cubital vein 10 - 12 hours after the last meal (fasting blood) for the estimation of serum FT4, TSH and lipid profile. The blood samples then centrifuged to separate the serum and divided into 2 parts for thyroid function and lipid profile.

For thyroid function, first part of the serum was analyzed by Advia Centaur CP Imunoassay analyzer. The second part of the serum was analyzed on chemistry analyzer; Dimensions Rx Max by using the Siemens kit for TC, LDL-C, TG and HDL-C.

Statistical analysis

Data were analyzed with Statistical Package for Social Science (SPSS Inc, Chicago, Illinois, USA) software version 18. The means and standard deviations were used to describe continuous data. For categorical data, frequencies and percentages were estimated. Categorical variables were compared with each other using the chi-square test. Pearson correlation test was used to find relationship between TSH and lipid level. Correlation was expressed as Pearson correlation coefficient (r). P value <0.05 was considered as significant.

RESULTS

Baseline characteristics

Among study subjects, 156 subjects were SCH cases, whereas 152 subjects were euthyroid control group. Age, gender, BMI were not different between them (Table I). The mean (±SD) TSH was 7.77±1.61 and 3.03 ± 0.98(μIU/ml) in SCH case and euthyroid control group respectively; [p<0.001] and the mean FT4 (ng/dl) among subclinical hypothyroid patients was 1.04 ±0.16 (±SD) and in euthyroid controls was 1.18 ± 0.18(±SD); [p <0.001] (Table II).

Table I Baseline anthropometric characteristics of case (SCH patients) and controls

Variables		Case(n=156)	Control(n=152)	p value
Age (years)	[Mean ± SD]	40.42 ±6.76	40.27 ±5.65	0.830
Sex[N (%)]	Male	35 (11.4)	47 (15.3)	0.092
	Female	121 (39.3)	105 (34.1)	
Height (meter)	[Mean ± SD]	1.57 ±8.39	1.58 ±8.21	0.394
Weight (kg)	[Mean ± SD]	57.23 ±7.50	57.63 ±6.84	0.630
BMI(kg/m^2)	[Mean ± SD]	22.95 ±1.45	22.90 ±1.39	0.772

SCH: subclinical hypothyroidism; BMI: body mass index. ANOVA & Chi-square analysis was done

Table II Baseline clinical and bio-chemical parameters of case and controls

Variables		Case(n=156)	Control(n=152)	p value
Dyslipidemia	Yes [N (%)]	149 (48.4)	85 (27.6)	<0.001
	No [N (%)]	7 (2.3)	67 (21.8)	
SBP (mm Hg)	[Mean ± SD]	117.95 ±10.33	119.67 ±11.22	0.162
DBP (mm Hg)	[Mean ± SD]	77.59 ±6.65	77.33 ±7.88	0.754
TSH (ìIU/ml)	[Mean ± SD]	7.77 ±1.61	3.03 ±0.98	<0.001
FT_4 (ng/dl)	[Mean ± SD]	1.04 ±0.16	1.18 ±0.18	<0.001

SCH: subclinical hypothyroidism; SBP: systolic blood pressure; DBP: diastolic blood pressure; TSH: thyroid stimulating hormone; FT_4: free thyroxin; Chi square & ANOVA analyses were done

Pattern of lipid profile

Serum TC, LDL-C and TG were higher [Case vs. Control: 184.37±44.72 vs. 162.64±44.16; 117.39±60.64 vs. 99.93±29.57; 183.82±54.46 vs. 168.04±61.14 (Mean ±SD) respectively] and HDL-C was statistically lower [Case vs. Control:37.32 ±7.81 vs. 42.74±8.94 (Mean±SD)] among SCH patients in comparison to euthyroid control group; [p<0.05] (Table III). The presence of dyslipidemia had significant association with SCH group (Table IV).

Table III Comparison of lipid profile between case and control group

Lipid profile (mg/dL)	Case [Mean ± SD]	Control [Mean ± SD]	p value
Total Cholesterol	184.37 ± 44.72	162.64 ± 44.16	<0.001
LDL Cholesterol	117.39 ± 60.64	99.93 ± 29.57	0.002
HDL Cholesterol	37.32 ± 7.81	42.74 ± 8.94	<0.001
Triglyceride	183.82 ± 54.46	168.04 ± 61.14	0.017

SCH: subclinical hypothyroidism; LDL: low density lipoprotein; HDL: high density lipoprotein. ANOVA analysis was done

Table IV Distribution of different categories of dyslipidemia between case and control group

Different categories of dyslipidemia		Case (n=156)		Control (n=152)		p value
		N	%	N	%	
High Cholesterol	Yes	58	18.8	29	9.4	<0.001
	No	98	31.8	123	39.9	
High LDL Cholesterol	Yes	49	15.9	22	7.1	<0.001
	No	107	34.7	130	42.2	
Low HDL Cholesterol	Yes	129	41.9	72	23.4	<0.001
	No	27	8.8	80	26.0	
High Triglyceride	Yes	125	40.6	72	23.4	<0.001
	No	31	10.1	80	26.0	

SCH: subclinical hypothyroidism; LDL: low density lipoprotein; HDL: high density lipoprotein; Chi-square analysis was done; p value <0.05 is significant.

Correlation between TSH and lipid profile

Pearson's correlation coefficient for the relationships between serum TSH and lipid parameters are shown in Figures 1-4. It showed that TSH levels were positively correlated with TC, LDL-C, TG [r = 0.242, P<0.001; r = 0.218, P<0.001; r = 0.150, P=0.008 respectively] and negatively correlated with HDL-C (r = - 0.349, P=<0.001) in SCH patients.

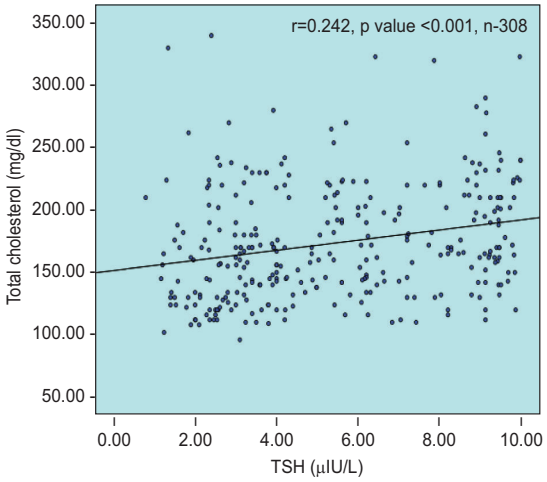

Figure 1 Correlation between total cholesterol and TSH

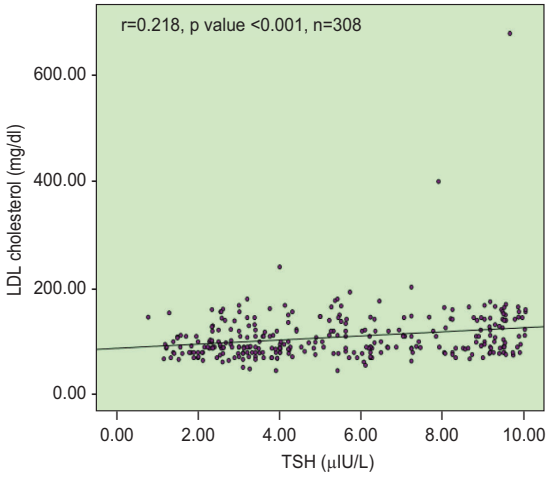

Figure 2 Correlation between LDL cholesterol and TSH

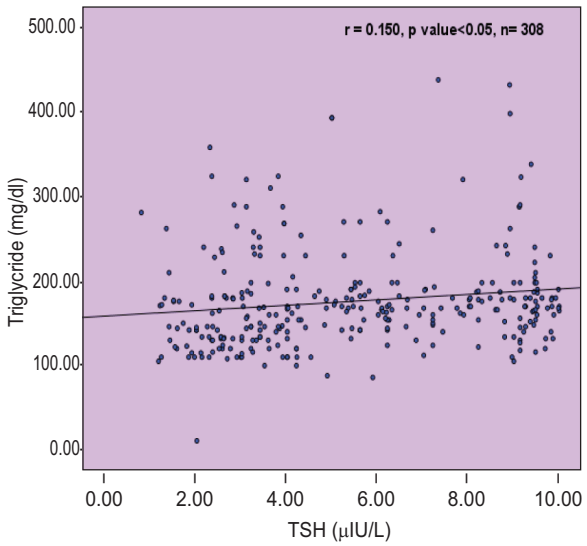

Figure 3 Correlation between triglyceride and TSH

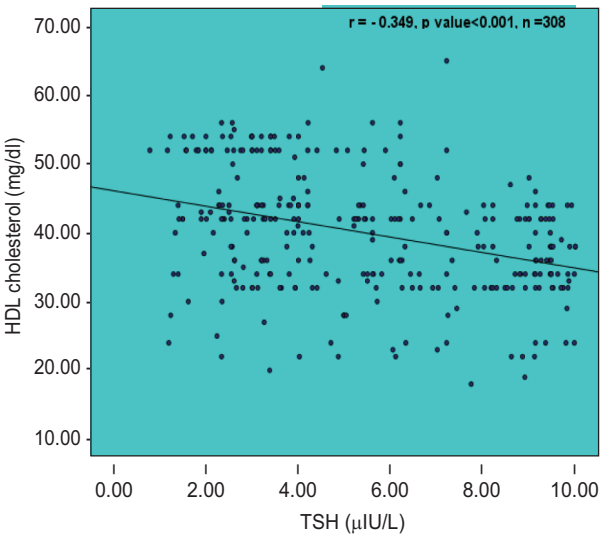

Figure 4 Correlation between HDL cholesterol and TSH

DISCUSSION

It is well known that overt hypothyroidism is linked with increased plasma cholesterol, LDL cholesterol and triglyceride levels.[23] But the linkage between SCH and dyslipidemia is still debatable. Though few large cross sectional studies reported that there were no significant differences among total cholesterol or LDL cholesterol between subjects with SCH and healthy adults but some other studies reported elevation of total cholesterol and LDL cholesterol among SCH compared to healthy subjects.[24] Additionally there is promising evidence that treatment with thyroxin lowers serum lipid in SCH that is why it is pivotal to treat cases of SCH with dyslipidemia.[13]

The lipid profile of 156 subclinical hypothyroid subjects were compared and evaluated with 152 euthyroid subjects in this study. It showed lipid abnormalities were more prevalent in subclinical hypothyroid subjects in comparison to euthyroid group [p <0.001]. Significant association of higher serum levels of TC, LDL-C, TGs and lower levels of HDL-C were observed in subclinical hypothyroid subjects as compared to the euthyroid subjects [p<0.001].

Thyroid hormone has multiple effects on the regulation of lipid synthesis, absorption, and metabolism. Although it is found that 1 to 11% of all patients with dyslipidemia have SCH [25], but the outcoms of SCH on serum lipid values are still not obvious. There are some studies those demonstrated that total cholesterol and LDL-C levels are raised in patients with SCH but also suggest that HDL-C and lipoprotein levels are not altered in subclinical hypothyroid patients.[25]

In this respect, our study subjects with SCH had significantly higher levels of TC, LDL-C, TGs and lower levels of HDL when compared with healthy euthyroid individuals [p <0.001]. Another study [26] also observed that significant high mean serum total cholesterol (TC), triglycerides (TG) and very low-density cholesterol (VLDL-C) in patients with SCH as compared to controls (P<0.05). Similarly Asranna et al [27] found significantly higher mean total cholesterol and LDL-C levels in SCH as compared to controls. Even so they also observed that there was no significant difference in the mean HDL-C, VLDL-C, and TG between SCH and controls.

Though there are many studies which did not find a positive correlation between SCH and dyslipidemia.[28, 29] But our study showed a significant association between TSH and dyslipidemia, as dyslipidemia was much more prevalent in patients with SCH in comparison to control group and this was in accordance with results of many other studies, which also find the same .[30, 31] In our study TC, LDL-C and TGs were positively correlated with TSH level but HDL-C was negatively correlated with TSH level [p <0.001].

Limitation

The cross-sectional nature of the study was conducted in a single center area with a smaller number of

participants. Larger studies are required to clarify the significance of development of dyslipidemias in subclinical hypothyroid subjects before the development of overt hypothyroidism.

Conclusion

The study exhibited significantly higher levels of cholesterol, triglycerides and low density lipoprotein levels and lower level of high density lipoprotein were associated with subclinical hypothyroidism as compared to euthyroid individuals. Majority of the SCH subjects had dyslipidemia and TSH levels showed statistically significant correlation with total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol. So, subclinical hypothyroidism should be a matter for further exploration because dyslipidemia is associated with this thyroid disorder.

Authors' contribution: NA designed the study, drafted manuscript. Both NA and TA revised the manuscript and approved for submission.

Conflicts of interest: Nothing to declare.

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