

ORIGINAL ARTICLE

Biochemical Changes in Mild Hypothyroidism and its Affiliation with Dyslipidemia in PakistanAYESHA ZUBAIR¹, SABAHA FATIMA², SALEHA AKRAM NIZAMI³, ANAS KHALIL⁴, RABIA SATTAR⁵, BASHIR AHMED SHAHEEN⁶¹Senior Demonstrator, Department of Biochemistry, Islam Medical & Dental College Sialkot²Assistant Professor, Department of Biochemistry, Gujranwala Medical College, Gujranwala³Senior Demonstrator, Department of Biochemistry, Al Aleem Medical College Ferozpur Road, Lahore⁴Assistant Professor, Department of Biochemistry, Wah Medical College, Wah Cantt⁵Associate Professor, Department of Physiology, Sharif Medical & Dental College, Lahore⁶Assistant Professor, Institute of Biochemistry, Gulab Devi Educational Complex, LahoreCorrespondence to Dr. Ayesha Zubair, Email: drayeshazubair@gmail.com Cell: 03361040227**ABSTRACT**

Background: Primary hypothyroidism is associated with the synthesis, metabolism and lipid abnormalities of thyroid hormones. Individuals with hypothyroidism have been shown to have high low density cholesterol and low high density cholesterol. In individuals with normal thyroid the association is usually observed between total cholesterol and thyroid stimulating hormone. Due to lipid abnormalities one group of experts is of the opinion that individuals with TSH ≤ 10 mIU/L having features of hypothyroidism should be started with thyroxine medication. Whereas, the other group does not support this idea making the topic controversial. In Pakistan the association between thyroid function and lipid abnormalities have so far not been studied which leaves a room for research at this topic.

Aim: To explore the association between mild hypothyroidism and lipid abnormalities in Pakistani population.

Methodology: This cross sectional study is carried out at Alfalah Welfare Medical Society, Lahore as part of their medical checkup, all the subjects gave written informed consent. The study was done from January 2021 to July 2021.

Results: Thyroid function test of 2312 (85.4%) of the subjects was found to be normal. Subjects with mild hypothyroidism among Group-I were 324 (11.9%) whereas mild hypothyroidism in group-II were 36(1.3%). Triglyceride (3.99 ± 0.80 compared to 3.79 ± 0.70 mmol/L, $p < 0.0001$), low density lipoprotein (2.59 ± 0.60 compared to 2.29 ± 0.39 mmol/L, $p < 0.0001$) and high density lipoprotein was (1.10 ± 0.14 compared to 1.14 ± 0.15 mmol/L).

Conclusion: In patients with mild hypothyroidism due to deranged lipid profile atherogenesis was observed. In continuation to it low high density lipoproteins were also observed in children and a raised triglyceride and low density lipoprotein in the adult population. On the other hand, in patients with mild hypothyroidism having low TSH levels no such abnormalities were observed.

Keywords: Dyslipidemia, Subclinical Hypothyroidism, Thyroid

INTRODUCTION

The role of thyroid hormone in the synthesis, metabolism and lipid abnormalities is documented with primary hypothyroidism. Studies done previously has shown significant increase in total cholesterol and low density lipoprotein cholesterol in people with reported hypothyroidism. In those individuals with euthyroid there is an association of total cholesterol with thyroid stimulating hormone. A group of experts is of the opinion that individuals with TSH ≤ 10 mIU/L with clinical features of hypothyroidism should be started with thyroxine medication, the reason is due to lipid abnormalities. However, another group of experts do not support this idea and categorize it a controversial subject. In Pakistan thyroid function and lipid abnormalities have not been documented, even though this population is predisposed to atherogenic lipid profile. This study was undertaken focusing different age groups to ascertain abnormalities in lipid profile in subclinical mild hypothyroidism at different level of thyroid stimulating hormone.

MATERIAL AND METHODS

This cross sectional study is carried out at Alfalah Welfare Medical Society, Lahore as part of their medical checkup, all

the subjects gave written informed consent. The study was done from January 2021 to July 2021. As a part of general health evaluation system this study is a sub component of this health system. Total subjects engaged in the study were 3230, written informed consent was signed by all the participates. Those participants with previous history of diabetes, hypertension, hepatic, renal or thyroid disease were excluded from the study. Remaining participants 2150 were included in the study which were further divided into two major groups based on the age of the individual. Group I included participants below 18 years of age and group II included participants above 18 years of age. Sample of blood was taken for analysis of T3, T4, TSH, lipid profile and antithyroid peroxidase antibodies (TPO). These major groups were further subdivided into subgroups.

Subgroup-I Control group with normal thyroid function test.

Subgroup-II Normal T4 level, TSH ≤ 10.0 mIU/L.

Subgroup-III Normal T4 level, TSH ≤ 10 mIU/L.

Lipid profile was done on the same blood sample and reference values according to the manufacturer were considered normal, the kit used for analysis was Hitachi 902 fully automated biochemistry analyzer; Roche, Mannheim, Germany.

Dyslipidemia was considered with the following reference values

Group-I TC N5.18 mmol/L, TG N1.70 mmol/L, HDL b1.04 mmol/L, or LDLN3.37 mmol/L

Group-II TCN6.21 mmol/L, serum TGN1.70 mmol/L, HDL b1.04 mmol/L in males and b1.3 mmol/L in females, or LDLN4.14 mmol/L

Group-III (2.5–5.8 pmol/L), (11.5– 23 pmol/L), and (0.5–5.2 mIU/L) for RIA and (2.8–7.1 pmol/L), (12.0– 22.0 pmol/L), (0.27–4.20 mIU/L)

The normal range of Anti-TPO is g 0.0–34.0 IU/L, anything above N34.0 IU/L is considered positive

Statistical analysis: By using EPI2003 statistical analysis was done. Mean ±SD was used, % or number were also used till specification. All parametric data were analyzed by student's t-test. Kruskal-Wallis test was applied if Bartlett's chi-square test for equality of population variances was b0.05, for non-parametric data analysis chi-square test was used. To assess the correlation between thyroid function test and lipid profile Pearson's correlation was calculated. P-value of b0.05 was considered statistically significant.

RESULTS

Table-I shows the biochemical and hormonal statistics of 3230 participants of the study. Males are 1550 (47.98%) and females were 1680 (52.01%) belonging to different age group.

Table-1: Biochemical and Hormonal statistics of participants.

	Participants (≤18 years)	Participants (>18 years)	p-value
Total participants	1850 (57.27%)	1380(42.72%)	
Average age	16.6±1.9	43.1±17.0	<0.00001
Gender (M:F)	52:48	35:65	<0.00001
S/cholesterol	3.69±0.50	3.98±0.79	<0.00001
S/triglyceride	1.29±0.34	1.70±0.55	<0.00001
HDL	1.15±0.10	1.12±0.17	<0.00001
LDL	2.22±0.31	2.44±0.62	<0.00001
T3	4.71±0.79	4.70±0.87	0.01
T4	15.89±2.19	14.39±1.98	<0.00001
TSH	3.29±3.09	3.37±3.19	0.74
Mild hypothyroidism-I	279(8.4%)	370(18.3%)	
Mild hypothyroidism-II	34(1.1%)	39(1.8%)	

Thyroid function test of 2312 (85.4%) of the subjects was found to be normal. Subjects with mild hypothyroidism among Group-I were 324 (11.9%) whereas mild hypothyroidism in group-II were 36(1.3%). With advancing age there was an increase in the tendency of triglyceride and low density lipoproteins.

Mild hypothyroidism –I when compared with euthyroid in all groups of the study does not showed any gross lipid abnormalities. When these finding were compared with triglycerides, low density lipoprotein and high density lipoprotein gross changes were observed. Significant increase in triglyceride and low density lipoprotein was observed and high density lipoprotein was low in participants of mild Hypothyroidism-I in comparison with the control group. Triglyceride (3.99±0.80 compared to 3.79±0.70 mmol/L, p<0.0001), low density lipoprotein (2.59±0.60 compared to 2.29±0.39mmol/L, p<0.0001) and high density lipoprotein was (1.10±0.14 compared to 1.14±0.15 mmol/L). After weighted gender adjustment, all such differences were static. Individual evaluation

categorizing for BMI showed that lipid profile was also static in subjects with normal BMI.

Table-II reveals that lipid profile effect by mild hypothyroidism-II among different ages. Gross low high density lipoprotein levels were observed in individuals with mild hypothyroidism-II which was the only abnormality in lipid profile when compared among individuals of mild hypothyroidism-I control group.

Table 2: Lipid level in different age group

	Normal TFT	Mild hypothyroidism -I	Mild hypothyroidism-II
Adolescent group	N=3016 (90.5%)	N=280 (8.4%)	N=35 (1.1%)
s/cholesterol	3.68±0.47	3.67±0.46	4.07±0.73
p-value		0.91	0.23, 0.22
s/triglyceride	1.13±0.36	1.26±0.26	1.39±0.34
p-value		0.15	0.22,0.03
HDL	1.14±0.12	1.13±0.10	1.07±0.11
p-value		0.55	0.001,0.001
LDL	2.23±0.32	2.21±0.30	2.44±0.56
p-value		0.16	0.076,0.035
Adult group	N=1607 (79.9%)	N=368 (18.3%)	N=37 (1.8%)
s/cholesterol	4.06±0.84	4.12±1.0	4.33±0.80
p-value		0.258	0.031,0.009
s/triglyceride	1.53±0.51	1.52±0.57	1.40±0.38
p-value		0.29	0.33,0.083
HDL	1.12±0.17	1.14±0.21	1.10±0.14
p-value		0.24	0.33,0.082
LDL	2.44±0.60	2.47±0.63	2.80±0.57
p-value		0.84	0.0001,0.0001

Among adult group a rise level of triglyceride and low density lipoprotein was seen in mild hypothyroidism-II and a decrease in high density lipoprotein was also seen which had no significant value in comparison with individuals of control group of mild hypothyroidism-I.

Data reveals that serum TSH is correlated with serum cholesterol positively (r=0.036, p=0.006) and low density lipoprotein (r=0.029, p=0.017). It was also observed that a negative correlation exists between T3, T4 and serum cholesterol (r=0.069, p<0.0001 and r= - 0.076, p=0.0001).

No correlation was observed between high density lipoprotein and T3 (r= - 0.020, p=0.143) and T4 (r=0.01, p=0.140). No close correlation was observed between thyroid status and triglyceride.

DISCUSSION

In the present study it is observed that as the age increases the prevalence of mild hypothyroidism also increases, in a longitudinal study conducted by Soliman AT, Al Yafei F, Al-Naimi L, Almarri N, Sabt A, Yassin M, et al. on thyroid function in patients with thalassemia major in 2013 and in another study conducted in 2020 by Yamamura H, Kokumai T, Furuya A, Suzuki S, Tanahashi Y, Azuma H aslo confirms our finding^{1,2}. The morbidity and mortality in patients with hypothyroidism is significantly increased with comorbidities as cardiovascular disease which is one of the major factors increasing the number of morbidities, when associated with increased triglyceride and low density lipoprotein levels adds to the morbidity, a study conducted in 2017 by Canbolat IP, Belen E, Bayyigit A, Helvacı A, Kilickesmez K highlights the fluctuation of blood pressure and its effects on the body, in another study conducted in 2020 by Inoue K, Ritz B, Brent

GA, Ebrahimi R, Rhee CM, Leung AM shows the effect of subclinical hypothyroidism and its association with cardiovascular diseases, in a meta-analysis of prospective cohort studies by Moon S, Kim MJ, Yu JM, Yoo HJ, Park YJ in 2018 also highlights the risk of cardiovascular diseases in its association with subclinical hypothyroidism, all these finding confirm the finding in our study³⁻⁵.

Result of different studies have unrevealed the fact that the association between mild hypothyroidism, cardiovascular disease and lipid profile is not strong, this is supported by the study conducted in 2017 by Delitala AP, Fanciulli G, Maioli M, Delitala G and another study conducted by Khan R, Sikanderkhel S, Gui J, Adeniyi A-R, O'Dell K, Erickson M, et al in 2020 which highlights the cardiovascular disease and its association with hypothyroidism^{6,7}. The treatment of patients with thyroxine having mild hypothyroidism does not show any beneficial effects on lipid profile, however, treatment of patients with TSH having lipid profile derangements is recommended and fruitful, a study conducted in 2020 by Yao Z, Zhao M, Gong Y, Chen W, Wang Q, Fu Y, et al. which shows the relation of microbes in GIT and L-thyroxine through changed thyroxine metabolism in mild hypothyroidism subjects, and another study conducted by Hoermann R, Midgley JE, Larisch R, Dietrich JW in 2017 supports the finding of our study^{8,9}.

In children high density lipoprotein showed some significant difference in comparison with the rest of the lipids in the lipid profile, a study conducted in 2020 about condition of the Cholesterol when it get transferred to HDL and Other Parameters in subjects before thyroidectomy due to thyroid cancer Related to Lipoprotein Metabolism by Sigal GA, Tavoni TM, Silva BM, Khalil-Filho R, Brandão LG, Baracat EC, et al supports the finding of our study¹⁰. Such differences were not observed in adults where no gross abnormalities in lipid profile was observed with the control group, in a cohort study conducted in Tehran in 2019 by Ahi S, Amouzegar A, Gharibzadeh S, Delshad H, Tohidi M, Azizi F is similar to our study¹¹. In middle aged and old persons with mild hypothyroidism no strong association was observed in individuals having cardiovascular risks in comparison with individuals having normal thyroid profile, in a study conducted in 2018 by Kim JS, Zhang Y, Chang Y, Ryu S, Guallar E, Shin Y-C, et al shows mild hypothyroidism and its incident depression in age group catering young and middle-age individuals, which is close to our study¹².

In our study a whereas a negative association was observed with HDL. A negative association exists between serum cholesterol, LDL, T3 & T4 among different age groups, gender and wide range of thyroid functions, in a study conducted in 2018 by Jin HY about the preponderance of mild hypothyroidism in overweight children or adolescents and its correlation between thyroid hormone and the portion of metabolic syndrome which supports the finding of our study¹³. This thing has been highlighted in individuals having mild hypothyroidism and also in subjects having normal thyroid a study conducted by Toda A, Hara S, Tsuji H, Arase Y in 2020 shows subclinical hypothyroidism is associated with albuminuria in Japanese nondiabetic subjects and in another study conducted in 2020 by Kara O about the influence of subclinical

hypothyroidism on metabolic parameters in obese children and adolescents which favors our study^{14,15}.

Gross lipid profile changes and metabolism have been observed in autoimmune diseases affecting different systems, a study conducted in 2017 on rheumatoid arthritis and its effect of metabolism by Erum U, Ahsan T, Khowaja D supports the present study¹⁶. In subjects with normal thyroid an elevated serum triglyceride and low density lipoprotein profile was observed with positive anti TPO antibody as compared with negative anti-TPO antibodies.

CONCLUSION

In patients with mild hypothyroidism due to deranged lipid profile atherogenesis was observed. In continuation to it low high density lipoproteins were also observed in children and a raised triglyceride and low density lipoprotein in the adult population. On the other hand, in patients with mild hypothyroidism having low TSH levels no such abnormalities were observed.

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