Section: Biochemistry

Original Research Article

SERUM NON HDL A BIOMARKER FOR EVALUATION OF CARDIOVASCULAR RISK IN HYPOTHYROID PATIENTS

P. Sunithapriya[1], C.Anbumani[2], D. Alamelumangai[3], N. Santhi[4]

[1]*Associate Professor, Department of Biochemistry, Thanjavur medical College, Thanjavur, India.*
[2]*Assistant Professor, Department of Biochemistry, Thanjavur medical College, Thanjavur, India.*
[3]*Assistant Professor, Department of Biochemistry, Thanjavur Medical college, Thanjavur, India.*
[4]*Associate Professor, Department of Biochemistry, Government Medical College, Pudukkottai, India.*

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Corresponding Author:
Dr. N. Santhi,
Associate Professor, Department of Biochemistry, Government Medical College, Pudukkottai, India.
Email: shara.29m@gmail

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ABSTRACT

Background: Thyroid disorders are the most common endocrinopathies seen in the world. It is estimated that nearly 42 million people in India suffer from thyroid related disorders. Hypothyroidism is prevalent to the extent of 9.45-11.73% among Indian population as reported in a recent survey. Hypothyroidism is a condition where the thyroid gland doesn't produce enough thyroid hormones resulting in weight gain, cold intolerance, tiredness and other metabolic disturbances. Dyslipidemia is commonly encountered in hypothyroidism with high serum Total Cholesterol (TC) levels, elevated Low Density Lipoprotein-Cholesterol (LDL-C) levels and increased triglyceride levels. Non HDL-C includes all the cholesterol in lipoprotein particles that is considered to be atherogenic. Untreated hypothyroidism impairs quality of life and also a potential risk for cardiometabolic complications. Hence early screening and management of hypothyroidism is essential to reduce the cardiometabolic risk. **Aims and Objectives:** To estimate the levels of Non-HDL-C in hypothyroid patients as compared to normal subjects and to assess its reliability as a simple cost effective biomarker to predict the future cardiovascular risk in hypothyroid patients.

Materials And Methods: The present study is Observational- Case control study. This study is conducted in the Department of Biochemistry, Thanjavur medical college, Thanjavur. 70 known hypothyroid patients attending General medicine OPD, TMCH are selected as cases and the corresponding age and gender matched 70 healthy individuals are selected as controls. Total sample size selected for each group is 70. Thyroid profile – TSH, T3, T4 estimation is done by ELISA method. Lipid profile is estimated in ERBA XL640 Fully automated analyzer by enzymatic method. Non- HDL-C (mg/dl) = Total Cholesterol – HDL cholesterol.

Statistical Analysis: The data were entered in MS office excel sheet and analyzed using SPSS version 21. Continuous data with normal distribution was expressed as mean with standard deviation. Unpaired 't' test was used to compare the means between the controls and cases. Pearson's correlation was used to determine the direction and degree of association of N-HDLC with TSH. P <0.05 was considered statistically significant.

Results: In the present study it was noted that Non-HDL-C was significantly high in hypothyroid patients (137.57± 40.26) when compared to healthy controls (107.05± 26.38) and the p value is statistically significant.

Conclusion: Non-HDL-C significantly predicts cardiometabolic risk factors in patients with hypothyroidism and could be used as a feasible biomarker to assess atherogenic risk in patients with hypothyroidism.

Keyword: Hypothyroidism, Dyslipidemia, Non HDL

INTRODUCTION

Hypothyroidism, also called underactive thyroid, is the condition where thyroid gland does not make enough thyroid hormones to meet the body's demand. The classic symptoms of hypothyroidism include fatigue, lethargy, weight gain and cold intolerance. However, these symptoms are non-specific and the diagnosis is typically made on biochemical grounds through serum thyroid function tests.[1] If an underactive thyroid is not treated, it can lead to complications like heart disease, goiter and myxoedema coma, a life-threatening condition.

Prevalence of hypothyroidism in India is around 10.95% as compared with 4.6% in USA and 2% in UK. Higher prevalence and different characteristics of thyroid dysfunction in Indians are likely indicative of underlying different biological factors along with rapid changes in dietary habits, decreased physical activity and sedentary lifestyle.[2,3] Iodine deficiency remains a common cause of hypothyroidism worldwide. In areas of iodine sufficiency, autoimmune disease and iatrogenic causes are foremost aetiologies causing hypothyroidism.[4]

Hypothyroidism is a common cause of secondary dyslipidemia which is characterized by an imbalance of different circulating lipids, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). This pathological condition is a major risk factor for atherosclerosis and cardiovascular diseases.[5]

The composition and the transport of lipoproteins are seriously altered in thyroid diseases. Overt hypothyroidism is characterized by hypercholesterolaemia and a marked increase in low-density lipoproteins (LDL) because of a decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver. Moreover, a decrease in LPL activity is found in overt hypothyroidism, decreasing the clearance of TG-rich lipoproteins. Therefore hypothyroid patients also present with elevated TG levels associated with increased levels of VLDL and occasionally fasting chylomicronemia. Alterations in lipoprotein fractions have also been reported in patients of Sub Clinical Hypothyroidism.[6] Most of the lipid abnormalities, the potential risk factors for cardio vascular diseases will resolve with thyroid hormone replacement therapy. Hence there is always a need felt to have a simple, reliable and cost effective marker to assess the cardiometabolic risk in hypothyroid patients.[7]

Modern laboratory diagnosis of lipid disorders and cardiovascular risk should be based on the use of indicators which present full impact of all plasma lipid components involved in atherogenesis. Non HDL-C includes all cholesterol present in lipoprotein particles considered to be atherogenic, including LDL, lipoprotein (a), IDL and VLDL remnants and it is calculated using a simple equation:

Non-HDL-C (mg/dL) = TC – HDL-C

Actually, little attention is being paid to the use of non-HDL-C but the latest Guidelines for both European and American Cardiological Societies emphasize the importance of this parameter for assessing the risk of atherosclerosis and coronary heart disease.

In view of the above facts, the present study is done to estimate the levels of Non-HDL-C in hypothyroid patients as compared to normal subjects and to assess its reliability as a simple cost effective biomarker to predict the future cardiovascular risk in hypothyroid patients.

MATERIALS AND METHODS

The present study is Observational- Case control study. This study is conducted in the Department of Biochemistry, Thanjavur medical college, Thanjavur.

The Institutional Ethics Committee approval was obtained prior to commencement of the study (Ethical Clearance Certificate no.1111/2023). An informed consent was taken from all the subjects recruited into the study. 70 known hypothyroid patients attending General medicine OPD, TMCH are selected as cases and the corresponding age and gender matched 70 healthy individuals are selected as controls.

Inclusion Criteria

Patients with hypothyroidism with age > 18 years irrespective of sex are included in the study

Exclusion Criteria

The subjects were excluded if they have, Diabetes mellitus, Chronic kidney disease, Nephrotic syndrome, Cushing's syndrome, Cholestatic liver disease, Familial hypercholesterolemia, Malignancy and Pregnancy

Sample size

According to N. Chandrika *et al.* study, considering the mean ($\mu 1$ = 133.13) and standard deviation ($\sigma 1$=42.57) for the cases and the the mean ($\mu 2$= 114.7) and standard deviation ($\sigma 2$= 34.7) for the controls

Power = 80%

Absolute Precision = 5%

Confidence interval = 95%

n = 140

Total sample size selected for each group is 70

After approval of ethical committee, the blood samples are collected from hypothyroid patients and the controls are attending General Medicine OPD, Thanjavur Medical College Hospital, Thanjavur.

Parameters analyzed

2 mL of fasting venous blood is taken from antecubital vein, thyroid parameters and lipid profile are estimated in serum. Thyroid profile namely, TSH, T3, T4 estimation is done by ELISA method.

Lipid profile is estimated in ERBA XL640 Fully automated analyzer by enzymatic method.

Blood lipid profile includes the following parameters.

Total Cholesterol(TC), HDL-C, NON HDL, LDL-C, Triglycerides.

Total cholesterol (mg/dl) is estimated by cholesterol oxidase-peroxidase method (CHOD-POD).

HDL-C (mg/dl) is estimated by modified polyvinyl sulfonic acid (PVS) and polyethylene- glycol methyl ether (PEGME) coupled classic precipitation method.

Triglycerides (mg/dl) is also estimated enzymaticaly by GPO method. VLDL (mg/dl) is calculated by the formula TGL/5.

Non- HDL-C (mg/dl) = Total Cholesterol – HDL cholesterol.

LDL –C is estimated by calculation (Friedwald` s formula)

LDL-C (mg/dl) = TC-(HDL +TGL/5)

Statistical Analysis

The data were entered in MS office excel sheet and analyzed using SPSS version 21.

Continuous data with normal distribution was expressed as mean with standard deviation. Unpaired 't' test was used to compare the means between the controls and cases. Pearson's correlation was used to determine the direction and degree of association of N-HDLC with TSH. P <0.05 was considered statistically significant

RESULTS

The Mean±SD of biochemical parameters studied were compiled and compared between controls and cases as shown in Table :1

Table 1: Descriptive Data of Cases and Controls

S.No	Parameters	Controls (n=70) mean±SD	Cases(n=70) mean±SD	p value
1.	TOTAL T3 (ng/mL)	1.05 ± 0.42	0.88 ± 0.49	0.028 (<0.05)
2.	TOTAL T4 (µg/dL)	8.55 ± 2.81	3.55± 1.21	0.001 (<0.05)
3.	TSH (mIU/L)	2.51 ± 2.87	22.73 ± 13.69	0.00 (<0.05)
4.	TOTAL CHOLESTEROL (mg/dl)	139.35 ± 26.40	171.91 ± 39.90	0.00 (<0.05)
5.	HDL-C (mg/dl)	32.30 ± 9.60	34.45 ± 9.60	0.18
6.	NON HDL- C (mg/dl)	107.05± 26.38	137.57± 40.26	0.00 (<0.05)
7.	LDL-C(mg/dl)	67.27±30.72	107.62±43.03	0.00 (<0.05)
8.	TGL(mg/dl)	128.13 ± 59.44	155.16 ± 93.68	0.04 (<0.05)
9.	VLDL-C (mg/dl)	39.42±30.84	31.61 ± 18.57	0.07

Table 2: Pearsons Correlation Between TSH and Non HDL Cholesterol in Both Cases and Controls

COMPARING VARIABLES	PEARSON'S CORRELATION COEFFICIENT	p- VALUE
Serum TSH & Non HDL cholesterol in controls	0.132	0.277
Serum TSH &Non HDL cholesterol in cases	0.157	0.194

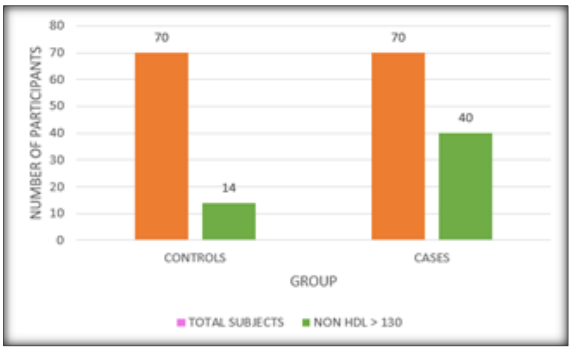

Figure 1: Number of Sublets with non HDL Cholesterol>130 Mg/Dl

DISCUSSION

Thyroid hormones significantly affect lipoprotein metabolism and other cardiovascular risk factors. Normally thyroid hormones induce the HMG-CoA reductase, upregulates LDL receptors by controlling the LDL receptor gene activation and also protects LDL from oxidation. Thyroid hormones can influence HDL metabolism by increasing cholesteryl ester transfer protein (CETP) activity and stimulates lipoprotein lipase (LPL), which catabolizes the TG-rich lipoproteins like VLDL and chylomicron.

The most common abnormalities of lipoprotein metabolism associated with hypothyroidism are elevated levels of TC and LDL-C. This is due to the decreased LDL receptors, resulting in decreased catabolism of LDL and IDL resulting in hypercholesterolemia.[8,9,10]

In our present study, the thyroid profile test between the two groups were stratified and it shows a significant differences in T4 and TSH levels. When mean and SD values of Total Cholesterol and Non-HDLC was compared between case and control group, it was observed that both the serum TC and Non-HDLC, the parameter of interest, were found to be significantly increased in hypothyroid patients than in healthy controls and the p value is statistically significant. We also observed high levels of TG in our study which may be due to the

decreased activity of lipoprotein lipase (LPL), which results in decreased clearance of TG rich lipoprotein.[11,12,13] The profound effect of thyroid status on lipid metabolism can be illustrated by several cross-sectional studies showing that as TSH increases even within the reference range, serum TC, LDL-C, Non HDL –C and TG all increase, and HDL-C decreases.[14] Regarding guidelines for management in dyslipidemia, National Cholesterol Education Program (NCEP) has recommended a target for LDL-C to be <100 mg/dl followed by a target of non-HDL cholesterol <130 mg/dl as a secondary target if triglyceride level remains elevated (>200 mg/dl). Furthermore, LDL-C alone is not sufficient to estimate atherogenic risk in patients with elevated triglycerides as it could be misleading if triglycerides > 400mg/dl. One cohort research trial had demonstrated that non-HDL cholesterol was a better predictor of CVD than LDL cholesterol. Non HDL cholesterol can provide a single index of all apolipoprotein-B containing lipoproteins and can provide overall cardiovascular risk index. If non-HDL-C is higher, especially in the presence of hypothyroidism, treatment to lower lipids should be considered to prevent cardiovascular disease and nephropathy progression. Estimation of Non HDL is usually ignored in general busy clinical practice and should be considered among hypothyroid patients.[15,16.] Our study provided clear insight on lipid parameters and their levels and correlates with the study conducted by Gonzalez *et al.* which reported that 96.1% of hypothyroid patients have dyslipidemia and mostly have low HDL-C and high TG. It was further suggested that hypothyroidism with obesity is a significant risk factor for the development of dyslipidemia.[17] These observations from the present study clearly states that non-HDL-C significantly predicts cardiometabolic risk in patients with hypothyroidism. This assault can be prevented with a timely detection of dyslipidemia by a simple cost effective Non HDL-C test which represents the atherogenic lipids.

Limitations of The Study

The limitations of the study include its relatively small sample size, which may restrict the generalizability of the findings to a broader population. Further studies are required to confirm our findings and strengthen the hypothesis that hypothyroidism is strongly associated with cardiometabolic risk factors.

CONCLUSION

The present study results highlights the importance of Non-HDL-C in replacing the traditional lipid profile assays for assessment of dyslipidemia in hypothyroid patients. It is superior to LDL-C in predicting the major adverse cardiovascular events.

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