 DOI: 10.18231/2394-6377.2017.0098

Castelli risk indices as useful indicators of atherogenic risk in subclinical hypothyroidism

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Abstract

Introduction: Thyroid hormones play an important role in regulating lipid metabolism. Subclinical Hypothyroidism (SCH) is increased thyrotropin-stimulating hormone (TSH) with normal T3, T4 levels. SCH is associated with derangements in Lipid metabolism, indicated by elevated cholesterol, HDL cholesterol, LDL cholesterol, increased incidence of atherosclerosis, leading to Atherogenic risk in SCH. Significance of dyslipidemia in SCH remains controversial.

Objectives: To quantitatively detect levels of total-cholesterol, HDL-Cholesterol, & LDL-Cholesterol and to assess lipid atherogenic risk based on Castelli risk indexes (CRI) in Subclinical Hypothyroidism**.**

Materials and Method: 30 SCH cases compared with 30 euthyroid controls. Serum T3, T4, TSH estimated by ELISA method, Serum Total-Cholesterol, HDL-Cholesterol by enzymatic CHOD-PAP method, LDL-Cholesterol using Friedewald formula. Systolic and diastolic blood pressure was measured in all cases.

Results: Serum levels of TSH (P<0.001), Total cholesterol (p<0.001), LDL Cholesterol (P<0.001), CRI-I (TC/HDL) (p<0.001) and CRI-II (LDL/HDL) (p<0.001) Systolic & diastolic blood pressure (P<0.001) showed significant increase. No significant change in levels of serum T3, T4, HDL-Cholesterol. Individual analysis revealed that the percentage change was higher for TSH and CRI.

Conclusion: Results contribute to high atherogenic risk as indicated by CRI. So CRI can be used as better indicator of dyslipidemia as compared to isolated lipid profile parameters and highlights cardiovascular risk in SCH.

Keywords: Castelli risk index – I, Castelli risk index – II, Subclinical Hypothyroidism, Atherosclerosis

Received: 3rd August, 2017 **Accepted:** 7th September, 2017

Introduction

Subclinical hypothyroidism is defined as a serum TSH concentration above the upper limit of the reference range when serum T3 and T4 concentrations are within reference ranges.(1) Subclinical hypothyroidism or mild thyroid failure is a common problem, with a prevalence of 3% to 8% in the population without known thyroid disease.(2) Even slight decrease in the levels of T4 within the normal range will lead to increase in serum TSH above the normal range. So, measurement of serum TSH is the important test for diagnosis of subclinical Hypothyroidism when the peripheral thyroid hormone levels are within normal laboratory range.(2) Subclinical thyroid disease is a laboratory diagnosis. Patients with subclinical disease have few or no clinical signs or symptoms of thyroid dysfunction.(1) Subclinical hypothyroidism has been associated with increased risk for atherosclerosis. The data in subjects with subclinical hypothyroidism with atherosclerosis and coronary heart disease (CHD) are conflicting.(3) Although established risk factors explain most cardiac risks, significant attention has been focused on alternative biochemical markers to assist in identifying those at risk of atherogenesis leading to clinical cardiac event.(4) This study underlines the importance of Castelli risk indexes as indicators of atherogenesis in SCH.

Materials and Method

The study was carried out in the Dept. of Biochemistry, BLDEU'S Shri. B. M. Patil Medical College Hospital and Research Centre, Bijapur (Karnataka) India. 30 subclinical hypothy roid cases aged above 35 years and 30 euthyroid controls from the general population were included in the study according to the inclusion and exclusion criteria mentioned below. This study was approved by the Institutional Ethics Committee. All the subjects gave an informed consent before undergoing further investigations. The study was carried out from November 2011 to May 2013.

Inclusion criteria: Subclinical hypothyroidism cases having TSH in the range of 4.50 to 14.99 mlU/L, T3 and T4 within normal limits. The euthyroid controls having normal TSH [0.3-4.5 mlU/L.] were included in the study.

Exclusion criteria: cases with known hypothyroidism, thyroidectomy cases, patient with radiotherapy, previous radioactive iodine therapy, consumption of drugs known to cause SCH, primary or secondary dyslipidemia, patients with diabetes mellitus, patients with other systemic illness, renal and hepatic failure cases, patients on statins were excluded from the study.

Collection of blood samples: Venous blood samples were drawn at 8 a.m. following a 12 hours of fasting, in a plain bulb from the subjects, with all the aseptic precautions. Blood samples were centrifuged within 30

minutes at 3000 rpm for 5 min. and serum was separated. Serum samples were stored at -20°C until assayed. Serum T3, T4, TSH were estimated by ELISA method.[5-7] Serum total cholesterol estimation and HDL-C was done by enzymatic COD-PAP method.[8] LDL-C was calculated by using Friedewald formula.[9]

Table 1: Comparison of Parameters between Subclinical Hypothyroid Cases and Euthyroid Controls

Parameter	Controls	SCH Patients
N	30	30
TSH (µIU/dl)	7.68 ± 2.46	2.64 ± 1.09**
T3 (nmol/dl)	1.36 ± 0.41	1.83 ± 0.97
T4 (nmol/dl)	85.12 ± 16.72	89.27 ± 22.78
TC (mg/dL)	245.72 ± 38.36	183.66 ± 39.13 **
TG (mg/dL)	165.25 ± 18.74	104.37 ± 31.58 *
LDL-C (mg/dL)	185.63 ± 37.94	126.24 ± 36.39 **
HDL-C (mg/dL)	27.03 ± 4.07	36.23 ± 6.63
CRI-I	66.3± 2.02	50.6 ± 1.87 **
CRI-II	45.8 ± 1.22	38.2 ± 1.08 **
SBP (mm Hg)	127.36 ± 5.65	122.73 ± 4.35 **
DBP (mm Hg)	91.43 ± 3.08	80.86 ± 4.16 **

** Indicates p<0.001- Highly Significant, * p<0.01- Significant. T3=Tri-iodothyronine, T4=Tetra iodo-thyronine, TSH=Thyroid stimulating hormone, TC=Total cholesterol, LDL=Low density lipoproteins, HDL=High density lipoproteins, CRI-I = Castelli risk indexe-I, CRI-II=Castelli risk indexeII, SBP= Systolic Blood Pressure, DBP= Diastolic Blood Pressure.

Results

Table 1 shows that serum mean levels of TSH, TC, LDL-C, CRI-I, CRI-II, SBP, DBP were highly signifi cant in SCH patients as compared to controls where as T3 , T4, HDL-C did not show statistically significant difference as compared to controls.

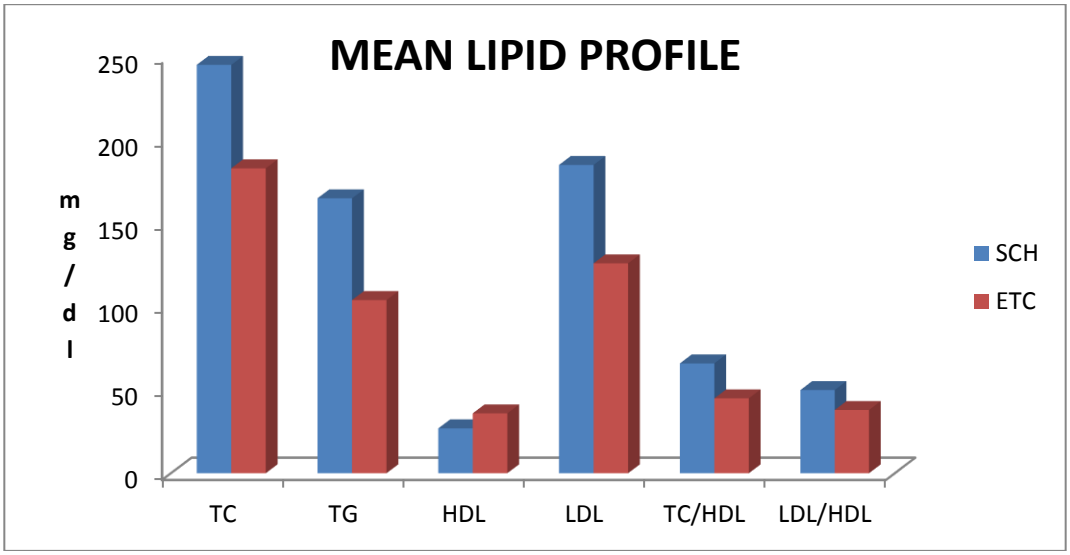

Fig. 1: Comparison of Parameters between Subclinical Hypothyroid Cases and Euthyroid Controls

Discussion

Subclinical hypothyroidism is more common than overt hypothyroidism and is being diagnosed more frequently in the recent times.[4] Despite this, the clinical significance of this disorder is still debatable. Overt hypothyroidism causes secondary hyperlipidemia and atherosclerosis is generally accepted,[11] but studies showing same correlation with SCH less convincing results. Data on coronary heart disease (CHD) in subjects with subclinical hypothyroidism are conflicting.[3]

Mechanisms underlying the development of hypercholesterolemia in hypothyroidism include decreased fractional clearance of LDL-C by a reduced number of LDL-C receptors in the liver in addition to de- creased receptor activity. The catabolism of cholesterol into bile is mediated by the enzyme cholesterol 7 –hydroxylase. This liver specific enzyme is negatively regulated by T3 and may contribute to the decreased catabolism and increased levels of serum cholesterol associated with hypothyroidism. The increased serum lipid levels in subclinical hypothyroidism as well as in overt disease are potentially associated with increased cardiovascular risk. The thyroid hormone replacement therapy is found to restore euthyroidism and reverses the risk ratio.[10] In hypothyroidism, endothelial dysfunction and impaired vascular smooth muscle relaxation lead to increased superior venacaval resistance. These effects lead to diastolic hypertension in nearly 30% of patients, and thyroid hormone replacement therapy restores endothelial-derived vasorelaxation and blood pressure to normal in most.[10] Our study revealed that CRI-I and CRI-II are significantly increased in SCH as compared

to the individual lipid profile parameters. Velkoska Nakova[12] studied Dyslipidaemia and hypertension in patients with subclinical hypothyroidism and concluded that CRI–I and CRI-II were significantly increased in SCH as compared to controls. Paula Herer[13] studied cardiovascular risk in middle aged woman with SCH and found that CRI were not significant in the study group. CRI-I greater than 5.0 contributes to 25% of the cardiovascular events.[14-15] Results of our study are comparable with Rafael Luboshitzky et al[16] who demonstrated that the percentage of subjects with increased CRI-I AND CRI-II were more in study group (Risk Factors for Cardiovascular Disease in Women with Subclinical Hypothyroidism). Our study is similar to the study done by B. U. Althaus, J.-J. Staub et al[17] which showed the significant LDL/HDL ratio but their study showed significant value for HDL and LDL but our study showed significance for only LDL- C as independent parameter. Bindels et al.[14] estimated that an increase of 1 mIU/L in serum TSH was associated with a rise in serum cholesterol of 0.09 mmol/L (3.5 mg/dl) in women and 0.16 mmol/L (6.2 mg/dl) in men. Fernandez M, Webb D[15] have shown that the ratio between these particles predicts cardiovascular disease (CVD) risk better than isolated lipoprotein subfractions. Our study is also similar to the study done by Mala Mahto et al which shows similar results. This highlights the importance of measurement of all the lipid fractions individually and calculating the ratio of the artherogenic and artheroprotective fractions. This would reflect the actual balance between the two fractions and help in better prediction of a cardiovascular risk.

Conclusion

Present study reveals that significantly higher levels of serum TSH, Total Cholesterol, Triglycerides, LDL-C, Castelli risk indices, systolic blood pressure and diastolic blood pressure and lower levels of HDL-C are seen in subclinical hypothyroidism as compared to euthyroid controls. Castelli risk indices are better indicators of atherogenic risk in subclinical hypothyroid cases.

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