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Implications for Cardiovascular Diseases by Gender Differences in Lipoprotein and Thyroid Hormone Metabolism

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Abstract

Hypothyroid adults have a high risk of atherosclerosis secondary to increased levels of various cholesterol fractions, particularly, low density lipoproteins cholesterol. The present study was planned to estimate lipoprotein and thyroid hormones and compare the gender-based differences in these parameters. The study was conducted in 100 healthy volunteers in the age group 18-25 years (50 males and 50 females). Lipid profile (Total cholesterol, LDL-C, HDL-C, VLD-C and Triglycerides) and thyroid function tests, Apolipoproteins (Apo) A -1 and B were estimated in these subjects. Total cholesterol, T.G, HDL-C, LDL-C and VLDL-C levels were higher in healthy adult females in comparison with healthy adult males but the difference was not statistically significant ($p > 0.05$). Levels of Apo A-1, Apo-B and atherogenic index (A.I.) were higher in young healthy males as compared to females in our study. Apo-B values were significantly higher in males in comparison to females (p values were significantly higher in male controls as compared to their female counterparts (p levels were also higher in healthy males in comparison to females, but the difference was not statistically significant ($p > 0.05$)). In contrast, TSH levels were higher in female controls ($p > 0.05$). Finding of gender-differences in their metabolism indicate that pattern of cardiovascular and atherogenesis is different in both sexes and there is possible difference and in utero programming of atherosclerosis in both the sexes.

Introduction

Alteration in lipid profile is a well-known phenomenon in thyroid dysfunction. Mild thyroid failure has been extensively evaluated as a cardiovascular risk factor.¹ Hypothyroid adults have a high risk of atherosclerosis secondary to increased levels of various cholesterol fractions, particularly, low density lipoproteins cholesterol (LDL-C).² Coronary heart disease (CHD) risk associated with subclinical hypothyroidism might be mediated by a hypercoagulable state; modulation of lipoprotein(a) [Lp(a)] metabolism; increased C-reactive

protein (CRP) values etc.³ It has been shown that LDL receptor (LDL-R) is regulated at the messenger RNA (m-RNA) level by thyroid hormones.⁴ The promoter of LDL-R contains a thyroid hormone response element (TRE), and T₃ modulates gene expression of LDL-R. changes in plasma levels of high density lipoprotein cholesterol (HDL-C) are due to remodeling of HDL-C particles by hepatic lipase (HL) and cholesterol ester transfer protein (CETP). Both HL and CETP are induced by thyroid hormones and are responsible for remodeling of HDL-C. Activity of both enzymes decreases in hypothyroidism and increase in hyperthyroidism.⁵ Hence the present study was planned to estimate lipoprotein and thyroid hormones and compare the gender-based differences in these parameters.

Material and Methods

The study was conducted in 100 healthy volunteers in the age group 18-25 years (50 males and 50 females). Only those healthy volunteers were included in the study who were not having any history of alcoholism, smoking, hypertension, thyroid disorders, obesity, diabetes and renal diseases.

Sample Collection

Five ml of venous blood was collected aseptically from antecubital vein after a 12 hour overnight fast. Serum was separated by centrifugation (2000 rpm for 15 minutes) and samples were analyzed on the same day. The sera of the healthy volunteers were estimated for the lipid profile (Total cholesterol, LDL-C, HDL-C, VLD-C and Triglycerides) and thyroid function tests. Apolipoproteins (Apo) A -1 and B were also estimated. Routine examinations; blood sugar, blood urea, serum creatinine were carried out.

Method of Assay

TT₃ and TT₄ were estimated by radioimmuno assay and TSH_{10,11} by immuno radiometric assay. Apo A-_{112,13} and B were analyzed using immuno-turbimetric immunoassay kits (Randox - make) in random access autoanalyzer (Konelab 30i). Serum cholesterol¹⁴, triglyceride¹⁵ and HDL-C¹⁶ had been estimated enzymatically. Concentration of VLDL-c and LDL-c were calculated using Friedwald's

formula.17 Statistical Analysis Data thus obtained was expressed in mean + SD values and students t- test was applied . Also regression analysis was carried out.

Results

The mean total cholesterol was 201.01+ 0.09 mg/dl; mean HDL-C was 42.29 + 9.45 mg/dl, mean LDL-C was 133.04 + 39.34 mg/dl; mean VLDL-C was 24.87 + 13.92 mg/dl, mean triglyceride was 120.5 + 67.38 mg/dl. The mean Apo A-1 and Apo-B were 103.02 + 22.16 mg/dl and 78.53 +21.99 mg/dl respectively. Atherogenic index was 0.79 +0.23.The mean TT3 value was 128.27+27.37 ng/dl, mean TT4 values in adult sera were 7.49 + 1.42 µg/dl and mean TSH values were 2.71 + 1.65 µIU/ml. Total cholesterol, T.G, HDL-C, LDL-C and VLDL-C levels were higher in healthy adult females in comparison with healthy adult males but the difference was not statistically significant ($p>0.05$). Apo A-1, Apo-B levels and A.I were higher in healthy adult males in comparison to females ($p>0.05$; $p3$ and TT4 and lower levels of TSH were observed in male controls as compared to female controls. TT3 values were significantly higher in male controls as compared to their female counterparts ($p4$ levels were also higher in healthy males in comparison to females, but the difference was not statistically significant ($p>0.05$). In contrast, TSH levels were higher in female controls ($p>0.05$, Table2). Significant positive correlation was observed between ApoA-1 and HDL-C ($r=0.49$, $p4(r= -0.100$, $p>0.05$); TT4 and A.I ($r= 0.060$), $p>0.05$).

Discussion

LDL-C is the major cholesterol in adults.18 It has been established that despite of the reduced activity of HMG-CoA reductase, there is increase in serum TC, mainly due to raised level of LDL-C which is due to decreased regulation of LDL-R mediated catabolism of LDL. Hypothyroidism has been reported to accompany a lowered fractional clearance of both exogenously and endogenously labeled TG from circulation suggesting impaired TG clearance. Hypertriglyceridemia associated with increased levels of VLDL-C can be explained by decreased activity of hepatic triglyceride lipase and lipoprotein lipase (LPL) resulting in decreased clearance of TG-rich lipoproteins. Elevated HDL-C levels can be explained by decreased activity of CETP resulting in reduced transfer of cholesterol esters from HDL to liver.4 McConathy etal19 have reported high TG level in

males and low TC and free cholesterol levels in males than those in females. Jugner etal20 reported that lipoprotein profile in males was more atherogenic than in females, particularly TG and Apo-B were higher in males than in females whereas HDL-C and Apo A-1 were lower. Also, LDL-C/ Apo-B ratio was significantly lower in males as compared to females.In the present study,TC,HDL-C,LDL-C,VLDL-C and TG were higher in young healthy females as compared to healthy males, though the difference was not statistically significant. Increased Apo-B and elevated Apo-B to Apo A-1 ratio are considered to be important predictors of atherogenesis. Elevation in LDL-C and Apo-B levels in young adults have recently been linked with cardiovascular disease in later life. Apo A-1 and Apo-B have been reported to follow the same trends as HDL-C and LDL-C respectively.21 Levels of Apo A-1,Apo-B and atherogenic index(A.I.) were higher in young healthy males as compared to females in our study. Apo-B values were significantly higher in males in comparison to females($p22$ have reported implications for cardiovascular disease by gender differences in lipoprotein metabolism. The transport of fat in the blood stream is approximately twice as fast in women as in men. Disease states such as obesity and diabetes are associated with greater lipoprotein abnormalities in women as compared with men. A great increment on cardiovascular risk in women is linked to these abnormalities. Knopp etal reported a greater change in triglyceride , Apo A-1, HDL-C levels and a lesser change in LDL –C in women than men with high carbohydrate or high fat feeding and concluded that dietary fat restriction has less beneficial effect on lipoproteins in women than in men.22 Simple negative correlations have been reported between free T4 levels (FT4)and TC ($r = - .45$), LDL-C ($r = - 0.46$), Apo – B ($r = - 0.31$) or HDL – C ($r = - 0.55$) values by Rieu etal23 and they reported that among these lipid parameters, only HDL-C levels ($r = - 0.31$, $p4$ is a strong predictor(p In the present study, TT3 ,TT4 levels were higher in adult males as compared to females($p0.05$ respectively).TSH levels were lower in adult males as compared to their female counterparts, but the difference was not statistically significant.Negative correlation was observed between TC and TT4 and TT4 and A.I. in adults($r=-0.10$, $p>0.05$; $r=-0.06$, $p>0.05$ respectively). The cardiovascular system is a specific target of thyroid hormone, and when thyroid hormone secretion is chronically altered, this is accompanied by profound changes in cardiovascular hemodynamic. Impaired endothelial dysfunction is associated with hypothyroidism, even if it is in subclinical stage. Finding of gender-differences in their metabolism

indicate that pattern of cardiovascular and atherogenesis is different in both sexes and there is possible difference and in utero programming of atherosclerosis in both the sexes.

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