Original Article

DOI: 10.7860/JCDR/2014/10363.4905

Biochemistry Section

Inherent Suppression of Thyroid Stimulating Hormone in Newly Diagnosed Dyslipidemic Patients – Indication for Use of Thyromimetics?

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ABSTRACT

Background: Dyslipidemia triggers a sequel of metabolic derangements such as insulin resistance, hyperglycemia and oxidative stress via vicious cycle. Dyslipidemia is characterised by elevation of plasma cholesterol, triglycerides (TGs), or both, or a low level of high-density lipoprotein (HDL) which in turn can progress to atherosclerosis a forerunner for ischemic heart disease (IHD). Dyslipidemia is seen even in subclinical hypothyroid patients.

Objectives: The aim of the study was to look for thyroid & glycemic abnormalities in dyslipidemic patients and compare it with euthyroid, normolipidemic group.

Materials and Methods: Thirty primarily dyslipidemic patients and 30 euthyroid normolipidemic subjects aged 25-55 years were tested for fasting plasma glucose (FPG), fructosamine, lipid profile, thyroid hormones - T3, T4 and thyroid stimulating hormone (TSH). The values were compared with those of age matched euthyroid normolipidemic control group.

Results: The dyslipidemic pool showed small but significant decrease in the TSH levels with comparable T3, T4 levels as compared to euthyroid group. The group also had significantly higher FPG, total cholesterol (TC), triglycerides (TG), low density lipoprotein (LDL) levels and lower high density lipoprotein (HDL) levels as compared to the euthyroid normolipidemic group. The plasma fructosamine levels were similar in both the groups. The observed results reflected a picture of subclinical hyperthyroidism in dyslipidemic patients.

Conclusion: The observations of the present study preclude a need to assess the thyroid status in patients of primary dyslipidemia as both conditions per se have an increased risk of cardio vascular diseases. A subclinical hyperthyroid state may essentially be helpful in maintaining the lipid metabolism. The prevailing mild hyperthyroid status also makes it important to reconsider the accuracy of long term glycemic indicators like fructosamine and possibly glycated haemoglobin in these patients. Upon establishment of their efficacy and safety, thyromimetics may have a role in the treatment of dyslipidemia.

Keywords: Dyslipidemia, Fructosamine, Lipid profile, Subclinical hyperthyroidism

INTRODUCTION

Dyslipidemia is characterised by elevation of plasma cholesterol, triglycerides (TGs), or both, or a low level of high-density lipoprotein (HDL) which in turn can progress to atherosclerosis a forerunner for ischemic heart disease (IHD) [1,2]. According to a report published by Indian Council of Medical Research, dyslipidemia affects 37.5% adults who are aged between 15-64 years [3]. Dyslipidemia is a frequent comorbidity in diabetes, hypertention, thyroid disorders, CHD, cerebrovascular disease and peripheral artery disease. Dyspilidemia of hypothyroid origin and its reversion on treatment is an entity very well studied. In our previous study we have found dyslipidemia even in subclinical hypothyroid patients [4]. T3 and T4 hormones have influence on synthesis, mobilization and degradation of lipids. Cholesterol synthesis is stimulated by inducing hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A reductase that catalyzes the conversion of HMG-CoA to mevalonate, the first step in the biosynthesis of cholesterol which is also a regulatory step. Thyroid hormones stimulate lipoprotein lipase enzyme, which catabolises the triglycerides into VLDL and chylomicrons to fatty acids and glycerol [5]. Considering the role of thyroid hormones in lipid metabolism, thyromimetics have been tried to treat dyslipidemia [6]. Data from animal studies suggested that thyromimetics can be used in the treatment of obesity, hepatic steatosis, and atherosclerosis. Reports from earlier studies showed that a low dosage of desiccated thyroid lead to marked reduction in plasma cholesterol after 20–30 weeks of treatment. But administration to patients at high doses resulted in tachycardia, angina pectoris, diarrhoea, weight loss, and insomnia with brief overt hyperthyroidism [7]. Despite indications for the use of thyromimetics in dyslipidemia, whether the dyslipidemic patients have associated thyroid dysfunction basically is not well reported. Abnormal carbohydrate metabolism is also frequently associated with dyslipidemia [7] and thyroid hormones have a hyperglycemic action. To understand the mutual dependence of the thyroid hormones, lipids and glucose status, the present study was aimed at investigating whether freshly diagnosed dyslipidemic patient's manifest thyroid and glycemic dysfunction and is the use of thyromimetics justified in them?

MATERIALS AND METHODS

The study consisted of two groups of 30 subjects each aged 25-55 years: Group I: freshly diagnosed dyslipidemic patients before initiation of therapy, Group II: euthyroid normolipidemic controls. Dyslipidemic patients on treatment, patients with known history of diabetes mellitus, hypertension, cerebrovascular disease (CVD) and hypothyroid patients were excluded from the study. Subjects with euthyroid status and normolipidemia served as controls. The study protocol was approved by the Institutional Ethics Committee, Kasturba Medical College, Mangalore, India and informed consent was obtained from selected patients as well as normal subjects.

After an overnight fast of 10 hours, 5ml venous blood was collected in a sterile vacutainer from antecubital vein from each patient and the following parameters were estimated. Fasting plasma glucose was estimated by GOD-POD method (Aspen diagnostics) [8], Fructosamine by NBT reduction method [9], Total cholesterol

Groups	Age	Sex (Male: Female)
Control group (30)	39.00 ± 9.95	15:15
Dyslipidemic group (30)	45.27 ± 7.25	20:10

[Table/Fig-1]: Narrates sex wise distribution of normal patient profile as well as dyslipidemic patients with their mean age

Parameters	Control group (30)	Dyslipidemic group (30)
T3 (ng/dl)	120.94 ± 22.51	131.44 ± 21.33
T4 (µg/dl)	7.82 ± 2.18	8.29 ± 1.98
TSH (µIU/ml)	2.82 ± 1.32	2.04 ± 1.46*

[Table/Fig-2]: Shows the T3, T4 and TSH levels in control group as well as dyslipidemic group
Results were expressed as Mean±SD, * Compared to control
Number in parentheses indicate the number of subjects
p< 0.05 was considered significant

Parameters	Control group (30)	Dyslipidemic group (30)
FPG (mg/dl)	82.79 ± 9.99	92.30 ± 9.71*
Fructosamine (µmol/L)	264.62 ± 20.87	264.93 ± 19.44
TC (mg/dl)	186.93 ± 26.80	269.37 ± 29.12*
TG (mg/dl)	120.69 ± 22.60	205.23 ± 95.83*
HDL (mg/dl)	46.03 ± 5.75	37.93 ± 7.80*
LDL (mg/dl)	94.41 ± 7.82	188.57 ± 41.02*
VLDL(mg/dl)	25.50 ± 6.04	42.43 ± 21.97*
TC/HDL ratio	4.07 ± 0.43	7.48 ± 2.10*
LDL/HDL ratio	2.08 ± 0.32	5.26 ± 1.92*

[Table/Fig-3]: Shows the glycaemic and lipid fractions in control group as well as dyslipidemic group
Results were expressed as Mean±SD, * Compared to control.
Number in parentheses indicate the number of subjects.
p< 0.05 was considered significant

by CHOD-PAP method (Agappe diagnostics) [10], Triglycerides by GPO-PAP method (Agappe diagnostics) [11], HDL cholesterol by CHOD-POD method (Medsource Ozone kit) [10] and LDL cholesterol was calculated by Friedewald's formula [12]. Barring fructosamine, all parameters were estimated using semi-automated analyser – Erba Chem Pro-5. Serum total T3, T4 and TSH were estimated by Chemiluminescence Immunoassay (CLIA) by using 'Roche diagnostics' kits on the Cobas e411 autoanalyser.

STATISTICAL ANALYSIS

The data obtained was expressed as mean ± standard deviation (SD). The results were analysed by using students' independent t-test to compare the two groups using SPSS version 17.0. p<0.05 was considered to be significant.

RESULTS

Sex wise distribution as well as the mean age is depicted in [Table/Fig-1]. The mean age of dyslipidemic patients and control group was found to be 45.25 ± 7.25 years and 39.00 ± 9.95 years respectively. More of males were there in dyslipidemic group (20:10) as compared to control group (15:15).

The thyroid status of the study groups is shown in [Table/Fig-2]. Compared to controls, the dyslipidemic group showed slight higher but statistically insignificant T3 (131.44 ± 21.33 ng/dl) and T4 (8.29 ± 1.98 µg/dl) levels with a small but significant (p < 0.05) decrease in TSH levels.

Glycemic and lipid profiles of the 2 groups are compared in [Table/Fig-3]. Fructosamine levels between the control (264.62 ± 20.87 µmol/L) and dyslipidemic groups (264.93 ± 19.44 µmol/L) were found to be similar. The dyslipidemic pool showed significantly higher fasting plasma glucose, TC, TG, LDL, VLDL, TC/HDL ratio and LDL/HDL ratio and lower HDL (p < 0.05) compared to control group.

DISCUSSION

The hypothesis postulated for assessing thyroid and glycemic profiles in the dyslipidemic patients was; if altered lipids are common in hypothyroid cases, is there a degree of hypo functioning of the thyroid in the dyslipidemic cases? Belying our hypothesis, the dyslipidemic pool showed a slight increase in the free T3 (131.44 ± 21.33 ng/dl) and T4 (8.29 ± 1.98 µg/dl) levels with a significant decrease in TSH levels (2.04 ± 1.46 µ IU/ml) as compared to the controls. However both the sets of values were within the reference range [13,14]. It is well-known that hyperthyroidism is associated with decreased levels of TC, LDL cholesterol and possibly HDL cholesterol. Although, the laboratory values do not fit even in the subclinical hyperthyroid picture [15], in the absence of clinical manifestations, the mild suppression of TSH seen in the dyslipidemic individuals seems like the body's adaptive response to control dyslipidemia.

Although wrought with several unpleasant side effects, statin is the conventional therapy for dyslipidemia. In the search for additional treatment strategies, thyromimetics, selective for the liver or the thyroid hormone receptor isoform β1 (TRβ1) constituted a novel approach to treat dyslipidemia and its clinical sequelae. TRβ1 selective thyromimetics such as Eprotirome and Sobetirome are hepato-selective and might help in the management of hepatic cholesterol metabolism thus correcting dyslipidemia without hyperthyroidism and adverse cardiac consequences [6]. The clinical trials however are yet to be ascertained for the safety and efficacy. Meanwhile, it appears that innately, the body also senses the need to increase the thyroid hormone levels in an attempt to control the abnormal levels of lipids. If selective thyromimetics can be developed without the adverse effects of the excessive thyroid hormones, it may be beneficial to the patients. The proposed mechanisms for their hypolipedimic effect include up-regulation of LDL receptor, inhibition of hepatic transcription factor sterol regulatory binding protein-1 (SREBP1) and promotion of reverse cholesterol transport (Rev-CT). They may also reduce dietary sterols absorption from the intestine and can even stimulate cholesterol 7α-hydroxylase (CYP7A1) a rate-limiting enzyme for bile acid synthesis along with induction of hepatic ABCG5 and ABCG8 ultimately results in biliary cholesterol secretion[6]. Moreover, they are synergistic when combined with 3-hydroxy-3- methyl glutaryl CoA reductase inhibitors. Promising molecules such as MB07811, MB07344, CGS 23425 showed favourable results in preclinical studies and need to be clinically explored [7].

Dyslipidemia triggers a sequel of metabolic derangements such as, insulin resistance, hyperglycemia and oxidative stress via vicious cycle [16,17]. In the present study compared to euthyroid normolipidemic group, patients with dyslipidemia showed a significant elevation in plasma glucose, total cholesterol, triglyceride and LDL levels with an accompanied decrease in HDL cholesterol levels which is in agreement with Cartoni et al., studies [18]. The glycemic adversity found in the newly diagnosed cases (FPG = 92.30 ± 9.71 mg/dl) is well documented. Hyperglycemia is often associated with dyslipidemia. The fructosamine levels (264.62 ± 20.87 µmol/L) and (264.93 ± 19.44 µmol/L) among the controls and the dyslipidemic groups respectively were comparable despite significantly raised plasma glucose levels. As has been previously described [4], fructosamine is a function of both the glycemic status

and turnover rate of proteins over 2-3 wk [19]. The inability of the fructosamine levels to proportionately reflect the hyperglycemic status in the dyslipidemic group also is in support of our finding of a mild hyperthyroid state which could have induced alterations of amino acid metabolism and increased protein turn over in the dyslipidemic patients. Data from animal studies also suggested the presence of low serum fructosamine levels independent of blood glucose concentration [20]. Thus slight excess production of T3 and T4 appears to be an adaptive counter mechanism to control the lipid levels and in turn affects fructosamine levels also, thereby inadvertently reducing the adverse effects of the advanced glycated end products.

The results of the study are limited by the small sample size and the cross sectional design and the same need to be ascertained with an appropriate study protocol. The role of thyroid hormones on lipid and glucose metabolism, the adverse effects of raised lipids on blood glucose levels and their combined effect on glycated proteins demands further elaboration.

CONCLUSION

The observations of the present study preclude a need to assess the thyroid status in patients of primary dyslipidemia as both conditions per se have an increased risk of cardio vascular diseases. A subclinical hyperthyroid state may essentially be helpful in maintaining the lipid metabolism. Upon establishment of their efficacy and safety, thyromimetics may have a role in the treatment of dyslipidemia. The prevailing mild hyperthyroid status also makes it important to reconsider the accuracy of long term glycemic indicators like fructosamine and possibly glycated haemoglobin in these patients.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jun 23, 2014**
Date of Peer Review: **Jul 17, 2014**
Date of Acceptance: **Aug 01, 2014**
Date of Publishing: **Sep 20, 2014**