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Original Article

Biochemistry Section

Relationship between Lipoprotein(a) and Thyroid Hormones in Hypothyroid Patients

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ABSTRACT

Background and Objective: Changes in plasma lipid concentrations are well known metabolic consequences of thyroid dysfunction. The alterations are most prominent in hypothyroidism which is typically associated with pronounced hypercholesterolaemia and frequently with moderate hypertriglyceridaemia. In cases of hypothyroidism, how the serum Lp(a) levels are influenced by thyroid hormone remains unknown and contradictory results on the effect of thyroid hormone on serum Lp(a) levels have been reported. There is substantial evidence to suggest that elevated serum Lp(a) levels contribute significantly to the development of CHD. The present study was designed to determine the lipoprotein(a) [Lp(a)], lipid profile and thyroid hormone levels in newly diagnosed hypothyroid patients and to find any correlation that existed between Lp(a) and other parameters.

Materials and Methods: Untreated hypothyroid (n=50) patients were included in the study. We also included 40 normal healthy subjects as controls. Lipid profile, Lp(a) and thyroid profile were estimated by using autoanalyzers.

Results: The results of this study showed that levels of HDL-cholesterol were significantly decreased ($p<0.001$), whereas those of other lipid parameters and Lp(a) levels were found to be significantly increased ($p<0.001$) in hypothyroid patients as compared to those in controls. Correlation study revealed a significant positive correlation between Lp(a) and TSH levels in hypothyroid patients.

Conclusion: Our present findings indicated that hypothyroidism could be strongly associated with lipid abnormalities that enhanced the development of cardiovascular diseases. Also, Lp(a) and non-HDL-C should be estimated with other lipid parameters as a useful index for measuring the cardiac risk in hypothyroid patients. A recommended screening should be advised for any patient with thyroid dysfunction, especially hypothyroidism, to assess lipid abnormalities by using Lp(a) and non- HDL-C and he/she should treated at the earliest.

Keywords: Cardiovascular disease, Non-HDL-C, Hyperlipidaemia

INTRODUCTION

Hypothyroidism is a common metabolic disorder which is existent in the general population. Levels of total and LDL cholesterol tend to increase as the thyroid function declines. Hypothyroidism is associated with an increased prevalence of coronary heart disease (CHD), presumably because of the hyperlipidaemia which is frequently associated with this disease, which is characterized in most cases by hypercholesterolaemia.

Much attention has been paid to the clinical significance of lipoprotein(a) [Lp(a)]. Lp(a) is an LDL-like particle which has been linked to a glycoprotein which has been named as apolipoprotein(a). There is substantial evidence to suggest that elevated serum Lp(a) levels contribute significantly to the development of CHD [1–5].

Nevertheless, the physiological role and metabolism of Lp(a) are not entirely clear. In cases of hypothyroidism, how the serum Lp(a) levels are influenced by thyroid hormone remains unknown and contradictory results on the effect of thyroid hormone replacement on serum Lp(a) levels have been reported [6–13]. Although an altered lipid profile is frequently observed in patients with thyroid dysfunction, published data on the relationship between Lp(a) and thyroid status are controversial [14].

In a number of previous studies, investigators have reported the effect of the thyroid status on the changes in the serum lipoprotein concentrations, whereas reports on serum Lp(a) concentrations are limited and the results are controversial. Recently, non-high-density lipoprotein cholesterol (non-HDL-C), a measure of Total Cholesterol (TC) minus HDL-C, has emerged as a predictor of cardiovascular disease. Elevated levels of low-density lipoprotein cholesterol (LDL-C) have been consistently associated with an increased risk for development of cardiovascular disease. The present study was done to determine the lipoprotein (a), lipid profile and non-HDL-C levels in hypothyroid patients and to find any significant correlation which existed between Lp(a) and non-HDL-C and thyroid hormones.

MATERIALS AND METHODS

Study Design

The correlation analysis study design was performed on hypothyroid and healthy individuals. We recruited 50 newly diagnosed hypothyroid patients who had been referred to a reputed hospital and 40 healthy individuals who served as controls. Blood samples were collected in sterile plain tubes after an overnight fast and they were centrifuged at 3000 rpm for 10 minutes. The fresh serum samples were then analyzed for specific parameters which have been mentioned further.

Methods

The levels of TC, HDL-C, and triglycerides (TG) were measured by enzymatic assays. The non-HDL-C levels were calculated as TC-HDL-C. The LDL-C levels were measured by direct homogenous assay. The serum Lp(a) concentration was measured by using a latex turbidimetry method. All the above parameters were analyzed by using auto analyzer Olympus AU400. Serum concentrations of free T4 (reference range, 0.8 - 1.8 ng/dL), free T3 (2.1-4.2 pg/mL), and TSH (0.5 - 5.0 μIU/mL) were measured by two-site immunoenzymometric assay by using TOSOH AIA 360 system analyzer.

The study protocol was in accordance with the Helsinki Declaration of 1975, that was revised in 2000 and with the institutional ethics committee's guidelines. Informed consents were obtained from all patients and healthy volunteers before they entered the study.

STATISTICAL ANALYSIS

The data were expressed as Mean ± SD for [Table/Fig-1] and as Mean ± SE for [Table/Fig-2]. Statistical analysis was performed by employing t-test. The correlation of parametric values was performed by using Pearson's correlation analysis. p values which were ≤ 0.05 were considered to be statistically significant.

Parameters	Healthy Controls (n = 40)	Hypothyroid Patients (n = 50)	p Value
Age	47±13.5	50.3±8.8	0.24 (NS)
BMI	20.4±2.8	23.2±7.4	0.02*
Male/Female	16/24	14/36	

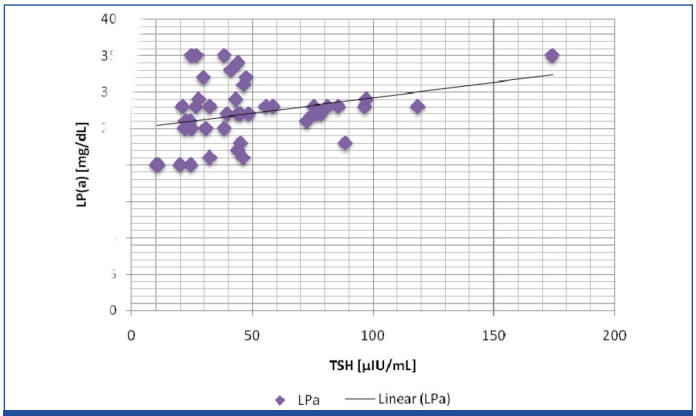
[Table/Fig-1]: General parameters of both patients and controls.
*Correlation is significant at the 0.05 level (2-tailed).
NS: Not significant,**Correlation is significant at the 0.01 level (2-tailed)

Parameters	Controls	Patients	p Value
FT4	1.35±0.05	0.36±0.02	0.0001**
HDL - C	41.1±0.78	30.54±0.88	0.0001**
LDL - C	105.9±2.32	159.10±4.91	0.0001**
LDL/HDL - C	2.62±0.08	5.09±0.23	0.0001**
Lp(a)	18.65±0.72	27.02±0.58	0.0001**
non-HDL	128.55±2.61	201.06±5.15	0.0001**
TOTAL CHOLESTEROL	169.65±2.59	232.12±5.12	0.0001**
TRIGLYCERIDES	112.95±4.49	219.34±9.16	0.0001**
TSH	2.14±0.09	47.82±4.39	0.0001**
VLDL	22.59±0.89	43.86±1.83	0.0001**

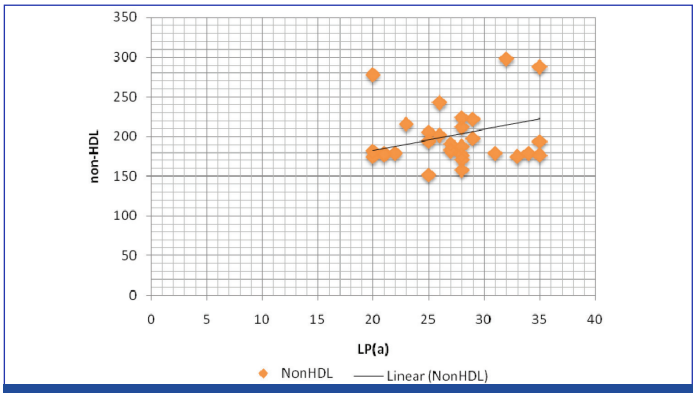
[Table/Fig-2]: Parameters of patients compared with controls
*Correlation is significant at the 0.05 level (2-tailed)
NS: Not significant,**Correlation is significant at the 0.01 level (2-tailed)

Parameters	r-Value	p-Value
FT4 & Lp(a)	-0.303	0.03*
Lp(a) & TSH	0.320	0.02*
Lp(a) & LDL	0.282	0.04*
Lp(a) & non-HDL	0.305	0.03*
LDL & non-HDL	0.880	0.0001**

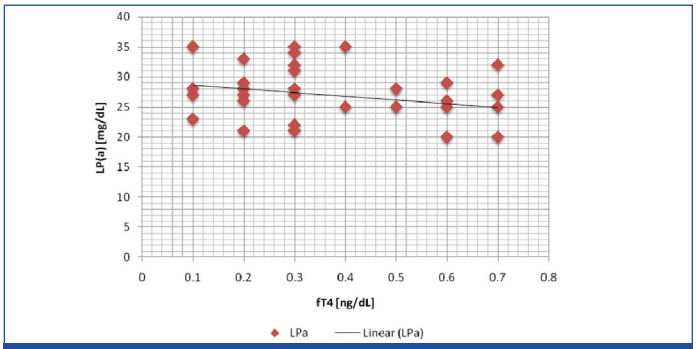
[Table/Fig-3]: Correlation between parameters in hypothyroid patients
* Correlation is significant at the 0.05 level (2-tailed)
NS: Not significant,**Correlation is significant at the 0.01 level (2-tailed)



[Table/Fig-4]: A positive correlation between TSH and Lp(a) in hypothyroid patients Lp(a) - Upto 14 mg/dL; TSH - 0.5 - 5.0 µIU/mL



[Table/Fig-5]: A positive correlation between LP(a) and non-HDL in hypothyroid patients Lp(a) - Upto 14 mg/dL; non- HDL - < 130 mg/dL



[Table/Fig-6]: A negative correlation between fT4 and Lp(a) in hypothyroid patients fT4 - reference range, 0.8 - 1.8 ng/dL; Lp(a) - Upto 14 mg/dL

RESULTS

Though levels of FT4 and HDL - C were lower as compared to those of controls, we found higher levels of LDL - C, LDL/HDL - C, Lp(a), non-HDL, TC, TG, TSH and VLDL in patient group [Table/Fig-2], with a high statistical significance. LP(a) showed a positive correlation with TSH, LDL and non-HDL [Table/Fig-3], as has been depicted through the correlation graphs [Table/Fig-4,5]. Whereas a negative correlation was observed between LP(a) and FT4 levels in hypothyroid patients [Table/Fig-6]. These results thus provided valuable information that LP(a) had a strong relationship with thyroid hormones and alterations in it could reflect the levels of thyroid hormone in thyroid patients.

DISCUSSION

Lipoprotein(a) [Lp(a)] is a cholesterol-enriched lipoprotein particle, which is receiving growing attention as a potential, independent risk factor for cardiovascular diseases [15]. Several studies, including the present one, have indicated an interaction between Lp(a) and LDL levels [16- 24]. Our study showed a significant positive correlation between Lp(a) and LDL in hypothyroid patients, suggesting that various mechanisms such as a direct interaction of apo(a) with other apoB100-containing particles facilitated lipoprotein aggregate formation [25], or the trapping of LDL particles after Lp(a) bound to proteoglycans of the arterial wall by its apoB component, or after uptake of Lp(a) particle by macrophages after contact of these cells with minimally oxidized LDL [26]. These could play a role in contributing to the rise in Lp(a) levels.

There is a preponderant genetic influence that supports the concept of metabolic independence and hypothyroidism could have little effect on Lp(a) levels. However, Lee et al., observed no significant differences in serum Lp(a) levels in different thyroid function groups [27]. Although there are contradictory data on the fluctuations in Lp(a) levels, some authors [18,19] think that they are affected by thyroid function, and several others think that they are unaffected [17, 20, 26]. Our study done on hypothyroid patients showed a negative correlation between fT4 and Lp(a), which was contradictory to the findings of study conducted by Lee et al.

The potential association between Lp(a) and thyroid function status in the general population might be regarded as an important aspect for cardiovascular risk prediction and prevention. We and some other authors have pointed out the correlation between TSH (47.82±4.39) and Lp(a) (27.02±0.58) levels in non-treated hypothyroid subjects, which suggested the influence of thyroid hormones on Lp(a) metabolism. This hypothesis was supported by De Bruin et al., [7], who demonstrated an almost perfect correlation between free thyroxine index and Lp(a).

The correlation analysis in our study also revealed that there was an influence of TSH on Lp(a) levels in hypothyroid patients. Our findings, in combination with previously reported data, therefore, suggest that in severe hypothyroid state, an impairment of the catabolism of the apo B-containing particles, including Lp(a), predominates; and that an elevated secretion of apo B and Lp(a), probably in combination with decreased catabolism, might be postulated. This influence could have been caused by lesser lipolytic activity of lipase enzymes [28].

Studies done on non–HDL-C by Edward J. Shahady showed that it was a more precise therapeutic target than LDL-C [29]. In our study, the positive correlation between LDL and non-HDL-C and with Lp(a) revealed that non - HDL-C could serve as an excellent proxy for assessing the total number of circulating atherogenic particles. Our study may also suggest that non–HDL-C may be superior to LDL-C in predicting cardiovascular disease and that it can be used as the primary lipid target, with patients having characteristic dyslipidaemia that consisted of decreased HDL-C levels, elevated TG levels, and normal to elevated LDL-C levels.

CONCLUSION

Hypothyroidism severely disturbs the lipid homeostasis in liver and adipose tissue, thus contributing to an alteration in circulating lipids, as was expressed in our correlation study. Our present findings indicated that hypothyroidism could be strongly associated with lipid abnormalities that enhanced the development of cardiovascular diseases.

Though our study provided clear insights on lipid parameters and their levels, in future, studies done should be focused on understanding the molecular mechanisms behind the dependence or independence on thyroid receptors for regulation of target genes which are involved in lipid homeostasis, that may entail therapeutic potentials, not only for the prevention and treatment of thyroid disorders, but also for prevalent diseases in the world, such as obesity and cardiovascular disease.

As an outcome of this correlation study, a recommended screening can be advised for any patient with thyroid dysfunction, especially hypothyroidism, to assess lipid abnormalities by using Lp(a) and non- HDL – C, which may prevent them from secondary diseases. Vice versa, in any case of unexplained hyperlipdaemia, thyroid screening can be done to assess the underlying disease.

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