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RESEARCH ARTICLE

Lipoprotein(a) Levels in Thyroid Disorders

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Objective: The aim of this study was to assess the serum levels of Lipoprotein(a) [Lp(a)] in subjects with thyroid disorders, as well as to investigate their relationship with lipid profile and the markers of thyroid function and autoimmunity, admitting that elevated Lp(a) levels and dyslipidemia caused by thyroid disorders synergistically increased the atherogenic process.
Methods: This study enrolled 38 subjects with hypothyroidism, 30 with hyperthyroidism and 55 with euthyroidism. The following parameters were measured: Lp(a), apolipoprotein AI (apo AI), apolipoprotein B (apo B), total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), thyroid stimulating hormone (TSH), free thyroxine (FT4), triiodothyronine (T3), thyroid-peroxidase antibody (TPO-Ab).
Results: Lp(a) was found with increased mean serum levels in hypothyroid subjects (483.28 ± 281.55 mg/L). Hyperthyroid subjects showed normal levels (253.13 ± 94.29 mg/L) of Lp(a), but significantly lower than those with hypothyroidism and slightly increased levels in the euthyroid subjects (305 ± 100.44 mg/L). In hypothyroidism a significant positive correlation between Lp(a) and TSH, apo B, TC, TG, TC/HDL, VLDL levels and a negative correlation with FT4, T3 and apo AI/B ($p < 0.05$) was observed. No correlations were found between serum Lp(a) levels, lipids profile and thyroid function parameters in hyperthyroid subjects, neither with TPO-Ab.
Conclusions: The association of hypothyroidism with increased levels of Lp(a) seems to increase the already high cardiovascular risk in the hypothyroid subjects, while increased levels of Lp(a) represents independently a relevant cardiovascular risk factor.

Keywords: hypothyroidism, hyperthyroidism, Lipoprotein(a)

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Introduction

Lipoprotein(a) [Lp(a)] was found in human plasma by Berg in 1963 as a genetic variant of low-density lipoprotein (LDL) [1], subsequently proving to be a significant independent risk factor for cardiovascular disease (CVD) [2,3,4]. The power of this correlation appears to be similar to that of systolic blood pressure and serum triglycerides (TG), but less significant than LDL, total cholesterol (TC) and apolipoprotein AI (apo AI) [2]. Lp(a) is a particle in which apolipoprotein B-100 (apo B100) is linked by a single interchain disulfide bridge to a unique glycoprotein apoLipoprotein(a) [apo(a)] [3]. Apo(a) is homologous to plasminogen, and its similarity to plasminogen indicates a prothrombogenic role for Lp(a), whereas the similarity of Lp(a) to LDL suggests a proatherogenic role [4,5]. It has been shown that high plasma Lp(a) levels are closely associated with arterial thrombosis, such as myocardial infarction and cerebral infarction [2–8]. Thyroid disorders are associated with lipid alterations, through different mechanisms, in almost all stages of lipid metabolism, mainly concerning TC and LDL and not so often for high-density lipoprotein (HDL), TG, Lp(a), apo A1, and apo B. Qualitative alterations of lipids have been also reported, including atherogenic and oxidized LDL and HDL particles [8]. In thyroid disorders dyslipidemia coexists with various metabolic abnormalities and induces insulin resistance and oxidative stress via a vicious cycle [9]. In association, hemodynamic alterations induced by thyroid hormones might explain the increased risk of coronary artery disease, cerebral ischemia, and angina pectoris in elderly, and possibly ischemic stroke in younger patients with overt or subclinical hyperthyroidism [10]. Even within the normal range of thyroid-stimulating hormone (TSH) values, a linear increase of TC, LDL and TG and a linear decrease in HDL levels has been noticed, all these being correlated with the increasing levels of TSH [11]. There is a general interest whether Lp(a) is under hormonal control. The role of thyroid hormones in the plasma concentration of Lp(a) has not been fully clarified, the results of different studies being contradictory.

The aim of this study was to assess the serum levels of Lp(a) in subjects with thyroid disorders, as well as to investigate their relationship with lipid profile and the markers of thyroid function and autoimmunity, admitting that elevated Lp(a) levels and dyslipidemia caused by thyroid disorders synergistically increased the atherogenic process.

Methods

The investigated parameters were: Lp(a), apo AI, apo B, TC, TG, LDL, HDL, very-low-density lipoprotein (VLDL), TSH, free thyroxine (FT4), triiodothyronine (T3) and thyroid-peroxidase antibody (TPO-Ab) after a written informed consent. Apo AI/B, TC/HDL and LDL/HDL ratios were calculated. We analyzed the correlations between serum levels of Lp(a) and investigated parameters in subjects with hypothyroidism, hyperthyroidism and euthyroidism.

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Table I. Clinical variables and Lp(a) levels of the study groups

Patients	Euthyroid	Hypothyroid	Hyperthyroid
No.	55	38	30
BMI (kg/m^2)	23.82 ± 4.51	24.62 ± 2.42	22.18 ± 3.19
Mean age	38.30 ± 13.52	48.6 ± 13.25	41.53 ± 12.29
Gender	44 F : 11 M	23 F : 15 M	25 F: 5 M
	Lp(a) mg/dL		
Mean±SD	305 ± 100.44	483 ± 281.55	253 ± 94.3
Range	150–830	214–1550	140–530

BMI – body mass index, F – females, M – males

The study groups included 38 subjects with overt hypothyroidism, 30 with hyperthyroidism and 55 with euthyroidism. The study was randomized, descriptive case-control type.

The hypothyroid group included subjects with overt hypothyroidism, where other causes of secondary dyslipidemia were excluded and who have not received hormone replacement therapy within 6 months prior to their inclusion in the study. In the hyperthyroid group we enrolled subjects with different clinical forms of hyperthyroidism who did not follow any specific antithyroid treatment until inclusion in the study. In the control group we included euthyroid patients without any secondary cause of dyslipidemia.

Subjects with severe obesity, diabetes, nephrotic syndrome, renal failure, liver disease, those who were receiving thiazides, chlorthalidone, beta-blockers, anabolic steroids, glucocorticoids, estrogen, progesterone, androgens, oral contraceptives, tamoxifen, raloxifene, retinoids (isotretinoin), cyclosporine, phenobarbital, phenytoin, carbamazepine were not included in the study.

Lp(a) was determined by an immunoturbidimetric method, using a specific antiserum-immunoprecipitation in liquid phase. Quantitative measurements were made using a photometer at a wavelength of 340 nm. Values for individual samples were compared with a calibration curve prepared from a reference serum with a concentration of 950 mg/L. Normal values for Lp(a) were < 300 mg/L.

The statistical analysis included descriptive indicators as: mean and standard deviation, minimum and maximum of investigated lipid parameters. Kruskal-Wallis H test was applied to prove that there are statistical differences between the three groups. Post-hoc Tukey test was applied to specify between which groups there are significant differences. Spearman's correlation coefficient r was calculated. A value of $p<0.05$ was considered statistically significant.

Table II. Post-hoc Tukey test for study groups – multiple comparissons between all pairs of two groups

Variable	(I) group	(J) group	Difference (I-J)	Standard Error	P
Lp(a)	Hypothyroidism	Hyperthyroidism	230.15	43.09	< 0.001
		Euthyroidism	178.28	37.22	< 0.001
	Hyperthyroidism	Hypothyroidism	–230.15	43.09	< 0.001
		Euthyroidism	–51.86	40.04	0.401

Results

The characteristics, clinical variables and mean levels of Lp(a) in the study groups are presented in Table I.

Serum levels of Lp(a) in hypothyroid patients (483.28 ± 281.55 mg/L) were significantly higher than the values of patients from the control group (305 ± 100.44 mg/L), and also higher than the levels found in the hyperthyroid patients (253.13 ± 94.29 mg/L), $p < 0.05$ (Table II).

In patients with hypothyroidism we found a strong significant positive correlation between Lp(a) levels with TSH, Apo B, TC/HDL, TC, TG, VLDL levels, and a significantly mild correlation both with the LDL/HDL ratio and with LDL levels. Lp(a) levels were significantly negatively correlated with Apo AI/B, FT4 and T3 ($p < 0.05$), as presented in Table III.

No correlation was found between TPOAb and Lp(a) levels.

In hyperthyroid female subjects we found a significant positive correlation between Lp(a) and the LDL/HDL ratio ($r = +0.398$, $p = 0.049$). In hyperthyroid male subjects, there was a highly significant negative correlation between Lp(a) and TG ($r = –0.900$, $p = –0.037$), and Lp(a) and VLDL levels ($r = –0.900$, $p = –0.037$). In patients with hyperthyroidism, no correlation was found between Lp(a) levels and the other analyzed parameters.

Table III. Correlations between Lp(a), lipid profile and thyroid function parameters in hypothyroid patients

Patients	Euthyroid	Hypothyroid
TC	+0.574	< 0.001
TG	+0.765	< 0.001
LDL	+0.370	< 0.05
VLDL	+0.768	< 0.001
TC/HDL	+0.542	< 0.001
LDL/HDL	+0.380	< 0.001
Apo B	+0.673	< 0.001
Apo A/B	–0.537	0.001
TSH	+0.542	< 0.001
FT4	–0.587	< 0.001
T3	–0.572	< 0.001

Discussions

The plasma concentration of Lp(a) is genetically determined (depending on the sequences of the apo(a) gene in chromosome 6q26–27) and relatively stable over time, not influenced by age, sex, diet, or most pharmacological interventions that modify other plasma lipids, except for fish oil, nicotinic acid, colestipol, neomycin and atorvasta-

Table IV. Lp(a) levels and cardiovascular risk [13,19]

Lp(a)	Desirable	Borderline risk	High risk	Very high risk
mg/dL	< 14	14–30	31–50	> 50
nmol/L	<35	35–75	75–125	> 125

tin [12–15]. Drugs that inhibit the hepatic production of apo B, intense physical activity and moderate alcohol consumption tend to lower serum Lp(a) levels [13]. The mean plasma concentration of Lp(a) is 30 mg/dL. Average levels Lp(a) and the distribution curve of these levels are very different according to the considered ethnic group. One recent study showed that in different ethic groups, different genetic alterations were associated with increased Lp(a) levels [13,15]. The metabolic determinants of increased serum levels of Lp(a) are unknown. Diabetes and kidney disease are associated with increased levels of Lp(a) [16].

Various authors have admitted that high serum Lp(a) level is a risk factor for coronary heart disease (CHD), cere-brovascular disease (CVD), atherosclerosis, thrombosis, and stroke [4,5,17,18]. Lp(a) levels that increase the cardiovascular risk are presented in Table IV [13,19].

The association of Lp(a) with the incidence of cardiovascular events was studied in patients with familial hypercholesterolemia. In these subjects there was a net increase both in the frequency and the precocity of coronary accidents, Lp(a) levels being found twice as high in individuals who had hypercholesterolemia and associated CHD [2,7].

Data from the literature are contradictory regarding levels of Lp(a) in patients with thyroid dysfunction and on different series results with discrepancies were reported. In thyroid disorders, data obtained by us are partly in agreement with data obtained by De Bruin et al. (1993), who found in a cross-sectional study high levels of Lp(a) in patients with overt hypothyroidism (255 mg/L) and lower levels in hyperthyroid patients (75 mg/L), compared to euthyroid patients (150 mg/L) and a reference population group from a local blood collection center (155 mg/L) [20]. In another study, hyperthyroid patients (with severe thyrotoxicosis, especially with high levels of antithyroid antibodies) had elevated levels of Lp(a) compared to euthyroid subjects. Hypothyroid subjects showed elevated serum levels Lp(a) [22]. Regarding thyroid autoimmunity, it has been reported that euthyroid males and postmenopausal females with evidence of thyroid autoimmunity (increased titers of TPO-Ab and/or thyroglobulin autoantibodies) had increased Lp(a) levels [21,23]. Another study compared the levels of Lp(a) of 22 euthyroid subjects (9 male and 13 postmenopausal female subjects) with thyroid autoimmunity, with those of 64 age- and sex-matched controls without thyroid autoimmunity [24]. There were no significant differences in the values of lipid parameters, including Lp(a), between the two groups, even when apo(a) phenotypes were taken into account [24,25,26]. In subclinical hypothyroidism patients (n = 38) a significant negative correlation was observed between FT3 levels and Lp(a) [26,27].

Lee et al. compared patients covering the whole spectrum of thyroid function and found no differences of Lp(a) levels between groups. No correlation was found between Lp(a) and TSH or FT4 levels [28]. Multiple regression studies showed that 65.5% of the variability in levels of Lp(a) were influenced by the changes in phenotype Lp(a) (60.5%), TSH (3.5%) and age (0.8%). A subgroup analysis of patients with major isoforms of Lp(a) showed that 28% of the variability in concentrations of Lp(a) might be explained by changes in thyroid function (19.1%), age (6.5%) and TG (3.5%). Higher correlations were found with TSH, TC, LDL and apo B levels [11,29–32].

Conclusions

The association of hypothyroidism with increased levels of Lp(a) seems to increase the already high cardiovascular risk in hypothyroid subjects, while increased levels of Lp(a) represents independently a relevant cardiovascular risk factor. This fact can be another argument in favour of the active evaluation of dyslipidemic patients for thyroid dysfunctions, and for unhesitating treatment of hypothyroidism. Thyroid hormones are significant modulators of Lp(a) levels, and there are multiple mechanisms responsible for changing Lp(a) levels.

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