Lipoprotein (a), Lipid Profile and Mean Platelet Volume in Hypothyroid Patients in Sana'a, Yemen: A Case-Control Study

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ABSTRACT

Objectives: This study aimed to measure lipoprotein (a) [Lp(a)], lipid profile and mean platelet volume (MPV) in hypothyroid patients compared to healthy controls.

Methods: An unmatched case-control study was conducted involving 100 subjects (50 overt hypothyroidism patients and 50 healthy controls admitted to the University of Science and Technology Hospital, Al-Thawra Hospital and Al-Jomhori Hospital- Sana'a, Yemen during the period from May 2013 to March 2014. Data were collected by in-person interview using a structured questionnaire followed by weight and height measurements. Fresh blood samples were collected and analyzed using electrochemiluminescent, spectrophotometric and immunoturbidimetric methods for estimating Lp(a), lipid profile and MPV parameters.

Results: Hypothyroid patients had a significantly higher concentration of Lp(a) compared to the control. Total cholesterol (TC), triglycerides and low-density lipoprotein-cholesterol (LDL-C) levels were also significantly higher in hypothyroid patients. Serum level of free triiodothyronine (FT3) was negatively correlated with Lp(a), TC and LDL-C ($r=-0.380$, $p=0.007$; $r=-0.354$, $p=0.012$; $r=-0.350$, $p=0.013$, respectively). However, serum thyroid-stimulating hormone was positively correlated with Lp(a), TC and LDL-C ($r=0.344$, $p=0.015$; $r=0.299$, $p=0.035$; $r=0.405$, $p=0.004$, respectively) among hypothyroid patients. MPV levels, on the other hand, showed a strong positive correlation with ($r=0.611$, $p=0.001$).

Conclusions: These findings indicate that overt hypothyroidism patients tend to have increased Lp(a) and atherogenic lipids that may contribute to increasing risk of atherosclerosis. However, hypothyroid patients showed no significant difference compared to the controls regarding the MPV

Keywords: Hypothyroidism, Lipoprotein (a), Lipid profile, Mean platelet volume, Yemen

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1. Introduction

Thyroid disorders influence lipoprotein metabolism (1–3). Changes in plasma cholesterol concentrations are primarily due to changes in the low-density lipoprotein (LDL) fraction. In hyperthyroidism, mRNA for LDL receptors is increased, leading to an increase in the number and activity of these receptors (2, 3), and therefore to a decrease in concentrations of LDL and total cholesterol (TC) (2). However, inversed changes occur during hypothyroidism. The increase in apolipoprotein B (apoB) and LDL concentrations is due to decreased removal rates rather than an increased secretion (3). In addition, conflicting results have been reported with regard to lipoprotein (a) [Lp(a)] changes during thyroid dysfunction (4).

Lp(a) was first identified as an LDL by Berg (5) in 1963, who succeeded in separating it into its lipid and protein components. The molecule consists of a lipid similar to that found in LDL and is the most complex and polymorphic of the lipoprotein particles. It has been later found that apolipoprotein A (apoA) was linked to apoB100 of LDL by disulfide linkages (4). The apoA structural gene is located on chromosome 6 with the gene for plasminogen, indicating that both might have arisen from a common ancestral gene (5, 6).

It is noteworthy that Lp(a) is homologous to plasminogen, a protein causing the lysis of blood clots. Moreover, Lp(a) competes for the binding sites of plasminogen on the endothelium and may induce atherosclerosis by interfering with thrombolysis (7). In contrast to plasminogen, however, apoA cannot be converted to the proteolytic form. Therefore, Lp(a) can be expected to be a potentially thrombogenic and atherogenic agent. Because Lp(a) also shares the apoB antigen with LDL, it may be metabolized through the LDL cholesterol (LDL-C) receptor pathway (8).

The mean platelet volume (MPV) can reflect the platelet activity (9). Increased MPV has been associated with atherosclerotic lesions and cardiovascular diseases (CVD) (10, 11) as well as with diabetes, hypertension, dyslipidemia, smoking and obesity, which are CVD risk factors (12). Platelets play a critical role in thrombus formation and myocardial infarction after the rupture of an arteriosclerotic plaque in a coronary artery (10). Therefore, increased MPV may represent a risk factor for myocardial infarction. However, this is still controversial, where the majority of studies addressing the MPV role compared patients suffering from myocardial infarction with healthy controls (12). The available data regarding the relationship between thyroid function and MPV are conflicting and limited to small-scale case-control studies (18). The increased risk of atherosclerosis and ischemic heart disease associated with hypothyroidism has been partially attributed to dyslipidemia. Information on the effect of thyroid disorders on Lp(a) and MPV is limited and gives no final conclusion. It was reported that hypothyroidism abnormalities do not lead to consistent changes in lipoproteins (15); however, some studies reported that hypothyroidism affects the level of lipoproteins (16, 17).

In the present case-control study, the association of overt hypothyroidism with Lp(a), lipid profile and MPV was examined by determining their serum levels. There is increasing evidence that increasing Lp(a), lipid profile and MPV play a pivotal role in developing coronary artery disease (18). Thyroid dysfunction alters the lipid profile through its effect on lipid metabolism. Investigators have reported the effect of thyroid status on the changes in the serum lipoproteins, whereas reports on Lp(a) are limited, but the results remain controversial. Therefore, the aim of this study was to deter-

mine Lp(a), lipid profile and MPV in patients with overt hypothyroidism compared to healthy controls.

2. Methods

2.1. Study design, subjects and ethical clearance

Fifty subjects with over hypothyroidism and 50 apparently healthy controls were recruited in the present unmatched case-control study. The study was performed in the University of Science and Technology Hospital, Al-Thawra Hospital and Al-Jomhori Hospital- Sana'a, Yemen during the period from May 2013 to March 2014.

Patients aged between 18 and 65 years old with overt hypothyroidism detected on screening who agreed to participate were selected as cases. It was ensured that they had not taken anti-lipidemic drugs or oral contraceptives. In addition, patients with existing cardiovascular or renal diseases, type 2 diabetes mellitus or with a history of alcohol intake were excluded from the study. The control subjects were selected from the hospitals excluding those who are coming from cardiology and diabetology departments to avoid possible confounders. The study protocol was approved by the Ethical Committee for Research on Human Subjects of the Faculty of Medicine and Health Sciences, Sana'a University. The purpose of the study was explained to all participants, and investigations were carried out after their written, informed consent. All subjects were categorized into two groups: Cases of overt hypothyroid subjects with thyroid-stimulating hormone (TSH) ≥5.0 µIU/mL, free triiodothyronine (FT3) <1.45 pg/mL and free thyroxin (FT4) <0.71 pg/dL and controls of healthy subjects with normal TSH, FT3 and FT4.

Anthropometric parameters were evaluated as follows: weight was determined using electronic scales, height was measured with a stadiometer, and body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Approximately 10 mL of venous blood were drawn from patients after 12-hour fasting. Blood samples were then immediately centrifuged at 2700 rpm for 10 minutes at 4°C. Freshly separated serum was used for the determination of TSH, FT3 and FT4, while the remaining aliquots of serum were stored at –70°C until they were analyzed for Lp(a) and lipid profile. Blood samples were also collected into tripotassium EDTA-anticoagulated tubes for the measurement of MPV to avoid platelet swelling.

2.2. Biochemical analyses

Serum TSH, FT3 and FT4 were measured by electrochemiluminescence immunoassay using Elecsys autoanalyzer (Roche Diagnostics, Germany). Serum TC, triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C) and Lp(a) were measured automatically using Cobas C501 analyzer (Roche Diagnostics, Germany). LDL levels were calculated according to the Friedwald formula (20), where LDL (mg/dL) = TC−(HDL+1/5 × TG).

2.3. MPV measurement

The MPV was measured by Sysmex XE-2100 Automated Hematology Analyzer (Sysmex XE-2100, Buckinghamshire, United Kingdom).

2.4. Statistical analysis

The data were analyzed by the Statistical Packages for Social Sciences (SPSS) software version 20.0 (IBM Inc., New York, USA). Continuous data were checked for normality of distribution by the Kolmogorov-Smirnov statistical test and the results were expressed as mean ± Standard de-

viation (SD) or as median ± interquartile range (IQR). Student's independent *t*-test or Mann-Whitney U test, whichever suitable, was used to compare the continuous variables of the two groups. Categorical variables were analyzed with the chi-square or Fisher's exact tests. Correlation was measured using Spearman's rank correlation coefficient (*r*). All *p*-values were two-sided, and a *p*-value <0.05 was considered statistically significant.

3. Results

Table (1) shows the sociodemographic characteristics of cases and controls. There was no significant difference between cases and controls with regard to cigarettes smoking. However, there was a significant difference between patients with overt hypothyroidism and healthy controls regarding age (*p*=0.001) and BMI (*p*=0.002), whereas a borderline significance (*p*=0.045) was found between the two groups regarding the educational level.

Table 1. General characteristics of the study and control groups*

Variable	Hypothyroid group n (%)	Control group n (%)	p-value
Median age (years)	37 (32~43)	30 (24~38)	0.001
Median BMI (kg/m²)	24.8 (23.9~26.6)	22.4 (20.8~25.7)	0.002
Sex			
Male	11 (**22**)	20 (**40**)	0.083
Female	39 (**78**)	30 (**60**)	
Marital status (%)			
Single	10 (**20**)	9 (**18**)	
Married	36 (**72**)	39 (**78**)	0.657
Widow	4 (**8**)	2 (**4**)	
Cigarette smoking			
Never	44 (**88**)	43 (**86**)	
Past	0 (**0**)	1 (**2**)	0.603
Current	6 (**12**)	6 (**12**)	
Educational level			
Illiterate	20 (**40**)	9 (**18**)	
Basic education	12 (**24**)	10 (**20**)	
High school	8 (**16**)	10 (**20**)	0.045
University and above	10 (**20**)	21 (**4**)	

*Number of cases and controls are 50 each; BMI; body mass index; (...~...), interquartile range

Table (2) compares the laboratory findings of thyroid hormones, Lp(a), lipid profile and MPV among hypothyroid patients and healthy controls. Serum TSH was significantly (*p*=0.001) higher in the hypothyroid group by 33.6-fold, while FT3 and FT4 were significantly (*p*<0.001) lower in hypothyroid patients by 67.4 and 65.8%, respectively, as compared to controls. The levels of TC, TG and LDL-C were significantly higher by 1.12-, 1.7- and 1.2-fold, respectively, compared to controls, but there was no significant difference in HDL-C levels between the two groups. Hypothyroid patients also had significantly higher Lp(a) by about two-fold compared to controls, but there was no significant difference in MPV between the two groups.

Table 2. Comparison of thyroid hormones, Lp(a), lipid profile and MPV between hypothyroid patients and controls in Sana'a, Yemen*

Parameter	Hypothyroid group	Control group	p-value
TSH (µIU/mL)	56.1 (23.3~95)	1.67 (1.26~2.62)	0.001
FT3 (pg/mL)	1.05 (1.0~1.31)	3.23 (2.9~3.70)	0.001
FT4 (pg/mL)	0.41 (0.30~0.60)	1.20 (1.31~1.32)	0.001
TC (mg/dL)	217 (201~260)	192.5 (169~220)	0.001
TG (mg/dL)	188 (115~237)	116.5 (103~159)	0.001
HDL-C (mg/dL)	45.1±8.42	43.2±8.56	0.256
LDL-C (mg/dL)	132 (99~163)	109.5 (92~122)	0.004
Lp(a) (mg/dL)	38.3 (26.8~44.3)	17.5 (12~23)	0.001
MPV (fL)	10.7±1.18	10.9±1.15	0.568

*Number of cases and controls are 50 each; TSH, thyroid-stimulating hormone; FT3, Free triiodothyronine; FT4, free thyroxin; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MPV, mean platelet volume; (... ~...), interquartile range

Table (3) shows the correlation of thyroid hormones with Lp(a), lipid profile and MPV in hypothyroid patients. Serum FT3 was negatively correlated with Lp(a), TC and LDL-C ($r=-0.380$, $p=0.007$; $r=-0.354$, $p=0.012$; $r=-0.350$, $p=0.013$, respectively). However, serum TSH was positively correlated with Lp(a), TC and LDL-C ($r=0.344$, $p=0.015$; $r=0.299$, $p=0.035$; $r=0.405$, $p=0.004$, respectively). On the other hand, FT4 was positively correlated with MPV ($r=0.611$, $p=0.001$). Table (4) shows that Lp(a) was positively correlated with TC and LDL-C ($r=0.453$, $p=0.001$; $r=0.430$, $p=0.002$, respectively).

Table 3. Correlation of thyroid hormones with biochemical parameters, MPV and BMI among hypothyroid patients in Sana'a, Yemen

Variable	TSH		FT3		FT4	
	r	p-value	r	p-value	r	p-value
TC	0.299	0.035	–0.354	0.012	–0.125	0.387
TG	0.037	0.796	–0.045	0.757	0.208	0.146
HDL-C	0.114	0.432	0.070	0.629	0.091	0.528
LDL-C	0.405	0.004	–0.350	0.013	–0.051	0.726
Lp(a)	0.344	0.015	–0.380	0.007	–0.231	0.106
MPV	0.015	0.920	0.102	0.480	0.611	0.001
BMI	–0.152	0.292	0.223	0.119	0.269	0.059

r, Spearman's correlation coefficient; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); MPV, mean platelet volume; BMI; body mass index

Table 4. Correlation of lipoprotein (a) with lipid profile among hypothyroid patients in Sana'a, Yemen

	TC		TG		HDL-C		LDL-C	
	r	p-value	r	p-value	r	p-value	r	p-value
Lp(a)	0.453	0.001	–0.006	0.966	0.012	0.932	0.430	0.002

r, Spearman's correlation coefficient; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a)

4. Discussion

The significant increase in Lp(a) levels in hypothyroid patients is in line with previous studies (16, 21). A cross-sectional study conducted in Seoul, Korea by Lee et al. (22) on 33 cases of overt hypothyroidism and 190 cases of subclinical hypothyroidism showed non-significantly different Lp(a) levels among the two groups. The effect of thyroid hormones on Lp(a) is still controversial. These discrepant results may be attributed to genetic polymorphism of apoA (23), study design, collection and storage of samples, statistical analysis, and population differences that reflect the known ethnic variability in the distribution of Lp(a) levels (24). Additionally, the disagreement may also be related to the apoA size heterogeneity that greatly affects the accuracy of Lp(a) antibody-based analytical methods that recognize the variably repeating kringle IV type 2 (24). Moreover, the results of Lp(a) raise doubt about its role as an independent risk factor for CVD, suggesting its synergistic contribution to CVD by enhancing the effect of other lipid risk factors. It is evident that Lp(a) and LDL can act additively in the development of CVD (24). In addition, a high serum Lp(a) level can be a risk factor for coronary heart disease, atherosclerosis and thrombosis (21).

The findings of the present study are in agreement with those obtained by Pop-Radu and Glig (21), who found a significant positive correlation between TSH and Lp(a) in hypothyroid patients in a randomized, descriptive case-control study in Romania. However, the present findings disagree with those reported by Lee et al. (22), who found no correlation between Lp(a) and TSH or FT4 between hypothyroid patients and normal controls. This discrepancy may be due to polymorphisms in the apoA gene, which can cause considerable inter-individual variations in the production of Lp(a), or may be

due to the differences between the study groups. Furthermore, the effect of thyroid hormones on Lp(a) may depend on the degree of thyroid failure (26).

The findings of the present study are consistent with that of Pop-Radu and Glig (21), who reported a significant negative correlation between FT3 and the levels of Lp(a), suggesting the influence of thyroid hormones on Lp(a) metabolism. Because of the sequence homology of apoA with plasminogen, Lp(a) may compete for plasminogen by binding to its receptors, indicating its link to thrombus formation and being an independent, genetically-determined risk factor for arteriosclerosis (23). In contrast to the finding of Pop-Radu and Glig (21), no significant correlation was found between FT4 and Lp(a) in the present study.

In the present study, the MPV showed a non-significant difference between hypothyroid patients and normal controls. This finding is similar to that observed by Torun et al. (27), who found no significant difference in MPV levels between overt hypothyroidism (10.2 fL) and subclinical hypothyroidism (9.4 fL) among non-obese women patients of reproductive age in Sanliurfa, Turkey. On the other hand, some researchers reported elevated MPV levels in hypothyroid patients (18). Large platelets with increased MPV values are active and release more thromboxane A2 than smaller ones, leading to an increased tendency to thrombosis (18). The absence of a significant difference in the MPV levels in the present study could be attributed to the different strategy of case selection. It is noteworthy that there is a limited number of contradictory reports in the literature that deal with this matter. Macey et al. (46) showed that the changes in MPV were greatest between 30 and 60 minutes in blood stored at ambient temperature. However, blood samples were analyzed within 5 minutes in the present study, considerably strengthening the accuracy of the present MPV results.

Elevated MPV levels have been reported in subclinical hypothyroidism as a risk factor for cardiovascular complications. Van Doormaal et al. (14) demonstrated in a study conducted in the Netherlands that hypothyroidism leads to smaller platelets, whereas Ford and Carter (28) reported opposing results. The MPV cut-off value for predicting of future cardiovascular events is not clear (27). Some reports suggest values as high as 10.3 fL while others suggest 9 fL as an MPV cut-off value (29–31).

In the present study, there was a significant positive correlation between FT4 and MPV in hypothyroid patients compared to controls, but no correlations were found with TSH and FT3. This is in agreement with a recent study by Atile et al. (32), who reported the absence of association between MPV levels and TSH and FT3 in hypothyroid patients. Limited and conflicting data on the association between thyroid function and MPV have been reported in small-scale case-control studies (18). However, the potential usefulness of MPV as a prognostic marker for venous thromboembolism and various types of arterial thrombosis was concluded in a population-based metanalysis, making it acceptable as a new risk factor for atherosclerosis (32).

In the present study, the significant increases in TC and LDL-C in hypothyroid patients are in line with those reported by Shashi et al. (16), Kaliaperumal et al. (33) and Regmi et al. (34). This increase may be attributed to the raised serum LDL-C concentration (23), the effect of thyroid hormones on lipoprotein lipase activity that hydrolyzes the TG-rich lipoprotein (35) and the decreased activity of LDL receptors, leading to decreased catabolism of LDL and intermediate-

density lipoprotein (IDL) (36). Furthermore, the promoter of the LDL receptor gene contains the thyroid hormone response element, which allows the FT3 to upregulate the gene expression of LDL receptors (23). These could contribute to atherogenesis. Moreover, thyroid hormones induce the hepatic *de novo* cholesterol synthesis by stimulating the enzyme 3–hydroxy–3–methyl-glutaryl-CoA (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate leading to an increased cholesterol synthesis in hyperthyroidism and a decreased one in hypothyroidism (23). In addition, thyroid hormones control the expression of surface LDL-C receptors, affecting protein synthesis and lipoprotein metabolism (37). Hypothyroidism also increases total fatty acids, apoB–100 content of LDL and LDL oxidation, and the increased cholesterol levels can be considered as a substrate for the oxidative stress, increasing the risk of atherosclerosis (23).

The absence of correlation between TSH level and BMI in the present study is in contrast to that reported by Dipankar et al. (39), who found that TSH correlated positively with BMI in the hypothyroid compared to the lean group, considering BMI as a reliable indicator for the body adiposity assessment. Therefore, decreased thyroid hormones in hypothyroid patients may well explain the significant increase in BMI of these patients compared to controls. However, the effect of TSH on lipids is different in overweight and normal weight populations and between men and women. Serum TSH, sex and BMI have significant effects on serum lipid profile (40). The present study revealed a significant positive correlation between TSH and TC, supporting the data reported by Risal et al. (17). This correlation indicates that lipid abnormalities can result from thyroid dys-

function (26).

Serum HDL-C in the present study was non-significantly lower in hypothyroid patients compared to the controls, which is in agreement with previous studies (38, 39). However, this finding differs from other studies (41, 42), which reported a significant increase in serum HDL-C levels in hypothyroid patients. These conflicting results may be partly because of the reported regulation of cholesteryl ester transfer protein and hepatic lipase activity by thyroid hormone (23).

The observed significant increase in TG in hypothyroid patients in the present study is similar to that reported by Shashi (16), who found significantly increased TG levels in overt and subclinical hypothyroidism patients compared to normal controls in Punjab, India, and this could be explained by a reduced removal rate of TG from plasma and the accumulation of IDL (23). Hypertriglyceridemia is frequently associated with premature coronary artery disease (43, 44), which is defined by the occurrence of a myocardial infarction or the need for a coronary artery procedure (42).

The findings of the present study are limited by the small sample size that might not detect the real diversity of MPV levels between hypothyroid patients and controls and the lack of an accurate measurement method for Lp(a) that could affect the biochemical analysis due to the heterogeneity of apoA. In addition, the measurement of Lp(a) in frozen sera is likely to result in a falsely lower Lp(a) concentrations.

5. Conclusions

Hypothyroid patients in Yemen may be at particular risk of atherosclerosis and CVD. Therefore, screening for Lp(a) levels could be useful in patients with hypothyroidism to reduce the as-

sociated disease. In addition, further studies with larger sample sizes are required to accurately determine the alterations in Lp(a) and MPV levels as well as the actual risk for CVD in hypothyroid patients.

Authors' contributions

SAA designed the study, performed experiments, interpreted data and wrote the initial draft. BAS and EA supervised the work and helped in editing the manuscript. All authors read and approved the final manuscript.

Acknowledgments

Competing interests

The authors declare that they have no competing interests associated with this article.

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