
Lipid profile and Arterial Walls Properties in Hypothyroidism

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Abstract:

Background: The link between lipid profile and ischemic heart disease was known long ago but more recently this link has been extended to include blood clotting factors.

Objective: Because hypothyroidism was considered as an example of atherosclerosis. The aim of this study is to investigate the relation between atherosclerosis in hypothyroidism and lipid profile, factor VII, von Willebrand factor, and finally common carotid artery distensibility.

Methods: Plasma lipid profile including: total cholesterol (TC), triglyceride (TG), high density lipoprotein(HDL), low density lipoprotein (LDL) and oxidized low density lipoprotein (OXLDL), in addition to that factor VII and von Willebrand factor studied biochemically, while common carotid artery distensibility coefficient (CCADC) studied ultrasonographically in group I (euthyroid subjects) and group II (hypothyroid subjects).

Results: The present study showed an increase in all biochemical markers excepted for HDL who has decreased in addition to the decrease in CCADC in group II as compared to group I. Changes in lipid profile was blamed to be the cause behind atherosclerotic changes in hypothyroidism, while increased triglyceride may play a role in the increase in factor VII. The increase in plasma cholesterol, LDL and OXLDL linked with the increase in von Willebrand factor. However, atherosclerotic arterial wall was the possible extra-hepatic source of the above factors in hypothyroidism. The CCADC decreased could be due to increase in LDL or OXLDL.

Conclusion: both factors VII and von Willebrand could play a role in atherosclerotic changes in hypothyroidism which could be evaluated by CCADS.

Key words: Hypothyroidism, Factor VII, Von Willebrand Factor, lipid profile, common carotid artery distensibility coefficient

Introduction:

The relations between triglyceride and myocardial infarction have been investigated by many authors. Most case-control and prospective cohort studies that have examined the relationship of fasting triglyceride on risk of cardiovascular disease have reported strong association^[1]. The oxidized low density lipoprotein (OXLDL) has been blamed to be one of the most important causative factors for the development of atherosclerotic diseases including stable coronary disease^[2] in human. Ehara et al measured the levels of OXLDL in patients with different manifestation of coronary artery disease, they observed that plasma level of OXLDL was significantly elevated in patients with coronary artery disease, compared with control group. In addition, they showed that OXLDL levels correlated with severity of clinical presentation i.e. the patients with acute myocardial infarction had the highest levels, followed by those with unstable angina and then those with stable angina^[3].

Evidence has been mounting that plasma coagulation factor are risk factors for cardiovascular diseases in middle-aged population. The finding that factor VII is an independent risk factor for ischemic heart disease has been supported by others^[4]. To date, virtually all results are consistent with the hypothesis that measuring of coagulation, possibly as estimate of thrombotic potential, are predictors of cardiovascular diseases in middle-aged men and women. VW factor is a marker to many adaptive conditions, including the chronic phase response where the raised

concentration of VW is strongly associated with an increased risk of chronic heart disease^[5].

Atherosclerosis and its risk factors can alter vascular wall properties and thereby distensibility^[6]. Arterial distensibility can be studied non-invasively in vivo and measures of arterial stiffness have been proposed as surrogate markers for atherosclerosis^[7]. It is well established that arterial distensibility decreases with aging^[6]. Furthermore, it has been shown that subjects with advanced coronary artery disease or hypertension have more rigid arteries than healthy controls^[6]. However, there is a lack of data concerning arterial distensibility in the other causes of atherosclerosis as in hypothyroidism.

Hypothyroidism but not hyperthyroidism represents an important risk factor for atherosclerosis and coronary heart disease^[8]. The most compelling data suggesting a greater cardiovascular risk in patients with sub-clinical hypothyroidism come from the Rotterdam Study^[9]. In a cross-sectional analysis of 1149 women, those with sub-clinical hypothyroidism had a higher prevalence of aortic atherosclerosis on chest radiographs and a higher prevalence of myocardial infarction than euthyroid women. Furthermore, the transition of coagulation parameters from a bleeding tendency in severe hypothyroidism to hypercoagulability in moderate hypothyroidism could precipitate acute thrombosis and myocardial infarction^[10].

Because there is a lack of information for role of factor VII and von Willebrand factor in the development of atherosclerotic changes in

hypothyroidism and the evaluation of this change by arterial distensibility, the aim of this study is to fill this gap.

Methods:

Ten patients with hypothyroidism (group II: 5 males and 5 females with mean age 45.5 ± 7.5 years) and 23 euthyroid, control subjects (group I: 13 males and 10 females with mean age 43.3 ± 8.9 years). Subjects in accord with inclusion and exclusion criteria were consecutively selected from the population referred to the AL-Yarmouk teaching hospital, Baghdad, IRAQ. Groups were matched for age and sex. None of the subjects enrolled in this study used any medication known to interfere with lipid metabolism; blood coagulation; and none used a special diet. The patients were studied before treatment with levo-thyroxine sodium. Overt hypothyroidism was defined as an increase plasma thyroid stimulating hormone concentration in combination with a decrease plasma thyroxine concentration; euthyroid state was defined as thyroid stimulating hormone and thyroxine levels being within the indication reference intervals.

Each subject agreed to participate in the study after being informed of its nature and purpose. The protocol of the study was approved by the local ethics committees of the institutions involved.

Plasma thyroid stimulating hormone, thyroxine determined by radioimmunoassay (Immunotech, A Backman Coulter company, Czech Republic), while serum TC, TG, and HDL were determined by totally enzymatic methods (Bio Merieux Company – France). LDL was calculated from Friedewald's Formula^[11]. Determination of OXLDL was done to follow the procedure of Harris et al^[12]. The factor VII test was performed by HEMOLAB co-factor

VII (Biomerieux, France), while VW factor was determined by ELISA using commercial kit supplied by DIAGNOSTICA STAGO. The data for the factors VII and VW were expressed as percentage.

The right common carotid artery distensibility coefficient was measured ultrasonographically (530D model VOLUSON 530D with 7.5 MHz linear array transducer) as described Henry et al^[13]. Distensibility was calculated from diameter, distension and pulse pressure as follows:

$$\text{Distensibility coefficient} = \frac{(2\Delta D.D + \Delta D^2)}{(\Delta P.D^2)} \text{ in } 10^{-3}. \text{KPa}^{-1}$$

Where ΔD is distention, D is diameter and ΔP is pulse pressure.

All analyses were carried out with SPSS (SPSS version 11). Results are expressed as Mean $\pm$ SD (Mean $\pm$ Standard Deviation). Comparisons among groups were conducted by using student t test. For correlation analysis, Person's correlation coefficients were calculated. $P < 0.05$ was considered statistically significant.

Results:

The results of the present study have shown a definite difference in lipid profile between control group (group I) and hypothyroid subjects (group II). Plasma TC, TG, LDL, and OXLDL were significantly higher in group II than group I. However, the reverse to the above observation was for high density lipoprotein which was significantly lower in group II than group I (table 1).

Plasma factor VII and von Willebrand factor was significantly higher in group II than group I by (14% and 21% higher respectively). This was not true for common carotid artery distensibility coefficient (CCADC) where it was significantly lower in group II than group I by 13 % (table 2).

Table 1: Mean $\pm$ SD for lipid profile, where: TC: Total Cholesterol, HDL: High Density Lipoprotein, TG: Triglyceride, LDL: Low Density Lipoprotein, OXLDL: Oxidized Low Density Lipoprotein in group I and II.

	TC (mg/dL)	HDL (mg/dL)	TG (mg/dL)	LDL (mg/dL)	OXLDL (μ mol/L)
Group I	197.4 $\pm$ 16.6	52.0 $\pm$ 12.3	147.3 $\pm$ 16.8	115.8 $\pm$ 24.5	0.21 $\pm$ 0.06
Group II	223.1 $\pm$ 22	42.4 $\pm$ 5.1	199.8 $\pm$ 19.2	140.7 $\pm$ 19.1	0.37 $\pm$ 0.16
P	**	*	**	**	**

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$P < 0.05$, **: $P < 0.01$.

Table 2: Mean $\pm$ SD for factor VII, von Willebrand factor, and distensibility in Group I and II.

	Factor VII %	Von Willebrand factor %	Distensibility coefficient $10^{-3}.KPa^{-1}$
Group I	106.9 $\pm$ 16.9	102.3 $\pm$ 17.1	13.2 $\pm$ 1.9
Group II	124.7 $\pm$ 18.0	129.0 $\pm$ 28.0	11.5 $\pm$ 1.8
P	*	**	*

*: P<0.05, **: P<0.01.

Discussion:

The data of the present study has shown a definite increase in plasma concentration of VW factor and factor VII and decrease in CCADC, where it was not possible to compare those results with others since it was the first time to obtain such results in hypothyroid subjects.

The increased in the level of TC, TG and decreased in the level of HDL in hypothyroidism have been observed by others ^[14]. Furthermore, hypothyroidism associated with a increase in LDL quantitatively^[15] and qualitatively through an increase in OXLDL ^[15], where hypothyroidism was associated with increase susceptibility of LDL to oxidation compared to that in euthyroid state^[16]. Enhanced LDL oxidation may play a role in the cardio-vascular diseases process seen in these patients ^[16].

The abnormal lipid profile observed in this study including high LDL and low HDL have been blamed for the cause of atherosclerosis associated with hypothyroidism. Some studies have shown that hypothyroidism is associated with a lower HDL level. In a report comparing 52 patients with sub-clinical hypothyroidism and 18 with overt hypothyroidism with 46 euthyroid controls matched for age, sex, Althaus et al ^[17] found a significant lower HDL in even the sub-clinically hypothyroid patients. Caron et al ^[18] also reported that the HDL level was significantly decreased among 29 women who had sub-clinical hypothyroidism, compared with 41 women matched for age and metabolic parameters. Furthermore, Caron et al ^[18] observed a significant increased in the HDL level with thyroxin therapy. Elevated levels of TC and LDL are well documented features of overt hypothyroidism ^[19]. One rationale for treating hypothyroidism is to lower levels of LDL cholesterol and thereby decrease atherosclerotic risk ^[20].

Activation of factor VII and the subsequent increase in activated factor VII is partly due to an

elevation of the hemostatic balance by interactions between lipoproteins and coagulation factors. A correlation between factor VII levels and TG as well as TC has been shown in several studies ^[21]. Dietary fat intake increased factor VII in animal ^[22], whereas supplementation of omega-3 fatty acid reduced the degree of postprandial hyperlipidemia (mainly triglyceride) and reduces the activity of factor VII concentration appearing during postprandial hyperlipidemia in human. Higher levels of factor VII in hyperlipidemic patients may be due to enhanced synthesis of factor VII; on the other hand, this may be due to a larger proportion of the activated form of factor VII ^[23]. The correlation between factor VII and lipoproteins may be explained by the binding of factor VII to triglyceride-rich particles ^[24].

A Wilcox et al ^[25] experiments provide evidence that factor VII is synthesized outside of the liver and is found in a variety of cells in atherosclerotic vessels. Their results have shown that normal vessels showed only weak staining for factor VII, possibly associated with some tissue injury during surgical isolation, while in early and advanced atherosclerotic lesions, however, there were extensive deposits of factor VII, mostly found in smooth muscle cells and macrophage-rich regions co-localized with tissue factors. Foam cells and macrophages in the necrotic core adjacent to the cholesterol clefts and foamy macrophages in early intimal thickenings all showed strong cytoplasmic staining with Factor VII antibodies. By that a finger can be pointed out to TG as a hidden cause for the increase in factor VII seen in hypothyroidism.

It was previously shown that during intimal thickening, the immunoreactivity for VW factor increases in the endothelial cells and that VW factor is deposited in quantities in the extra-cellular space of the intimal thickening^[26]. The glycoprotein VW factor is synthesized by only 2 cell types: endothelial cells and megakaryocytes. One can

discriminate the following 3 pools of VW factor in the body: soluble plasma VW factor, basement membrane (extra-cellular matrix) VW factor, and cellular VW factor found in storage granules of endothelial cells and platelets (Weibel-Palade bodies and α -granules)⁽²⁷⁾. The 3 pools contribute to adhesion of platelets and formation of a platelet plug during blood vessel injury.

De Meyer et al⁽²⁸⁾ study showed that rabbits fed a cholesterol-rich diet for 26 weeks induced plaque formation in the aorta. The endothelial cells, showed a dense immunoreactivity for VW factor, a pronounced rough endoplasmic reticulum, and numerous Weibel-Palade bodies. There were sub-endothelial VW factor deposits in the plaques and VW factor mRNA was significantly increased as compared with controls. Similar changes were seen after collar-induced intimal thickening. After cholesterol withdrawal, both VW factor mRNA and the ultra-structural morphology of the endothelial cells normalized, and the VW factor deposits disappeared from the plaque. By that the atherosclerotic arterial wall could be the source of the excess amount of VW factor seen in this study.

Hypercholesterolemia may be a factor that can regulate VW factor gene transcription, as suggested by De Meyer et al⁽²⁸⁾ study. This could be explained by the presence of inflammatory mediators in atherosclerotic plaques⁽²⁹⁾ or by a direct action of cholesterol on VW factor synthesis. It has been shown that activated transcription factor nuclear factor- κ B (NF- κ B) is present in the endothelial cells covering an atherosclerotic lesion⁽³⁰⁾. Activation of NF- κ B by OXLDL may lead to transcription and enhanced synthesis of adhesion molecules⁽³¹⁾ but possibly also of VW factor. In addition, in cultured endothelial cells, LDL enhances the concentration of cell-related VW factor⁽³²⁾. According to the above observation cholesterol, LDL and OXLDL could be blamed singly or collectively as the cause behind the increase in von Willebrand factor seen in hypothyroidism.

Evidence suggests a crucial role of native LDL and OXLDL in the hypercholesterolemia – related endothelial dysfunction and strongly links the decreased nitric oxide production to lipoprotein interaction with the arterial wall and to circulating L-arginine⁽³³⁾. Some studies also suggest an impaired endothelial nitric oxide synthase gene expression or a decreased activity of the normally expressed enzyme. Endothelial cells exposed for prolonged period to native – LDL or OXLDL begin to produce super-oxide⁽³⁴⁾. Vergnani et al⁽³⁵⁾ finding demonstrate that native LDL and OXLDL alter nitric oxide generation even at their physiological concentration.

The loss of nitric oxide due to LDL or OXLDL could be the cause behind the loss of expansion ability of the artery during cardiac cycle and

decrease in distensibility of common carotid artery seen in hypothyroidism.

From above observations we could conclude that factor VII and von Willebrand factor may play a role in the process of atherosclerosis associated with hypothyroidism, which could be extended to affect the arterial tree monitored through the decreased common carotid artery distensibility coefficient.

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