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Abnormal endothelial function in female patients with hypothyroidism and borderline thyroid function☆

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Abstract

Background: It has been suggested that hypothyroidism is associated with an increased risk for cardiovascular disease. The aim of this study was to assess non-invasively NO-dependent endothelial function of resistance arteries in subjects with hypothyroidism of varying severity.
Methods: Ninety-six female subjects (aged: 42 ± 13 years) comprised the study population. Subjects were divided into five groups based on TSH levels at presentation: Group 0 (n = 23) with TSH: 0.3 – 2.0 μU/ml, Group 1 (n = 22) with TSH: 2.1 – 4.0 μU/ml (upper normal), Group 2 (n = 18) with TSH: 4.1 – 10 μU/ml (subclinical hypothyroidism), Group 3 (n = 22) with TSH > 10 μU/ml (overt hypothyroidism). One additional group with well-controlled hypothyroidism on L-thyroxine therapy (Group 4, n = 11, TSH: 0.3 – 2.0 μU/ml) was also studied. Endothelial function of resistance arteries was assessed by measuring forearm blood flow response during reactive hyperemia utilizing venous occlusion strain-gauge plethysmography.
Results: Duration of reactive hyperemia was significantly different among groups of subjects with varying hypothyroidism (83.7 ± 58.3 s, 53.2 ± 35.7 s, 52.8 ± 47.5 s, 12.9 ± 13.3 s and 69.5 ± 26.2 s in Groups 0, 1, 2, 3 and 4, respectively, $p < 0.001$, ANOVA). Duration of reactive hyperemia was significantly shorter in subjects with upper normal TSH values (Group 1) compared to controls (53.2 ± 35.7 s vs. 83.7 ± 58.3 s, $p = 0.013$), while it was comparable to that of subjects with subclinical hypothyroidism (Group 2) (52.8 ± 47.5 s). However, duration of reactive hyperemia in Group 1 was significantly longer compared to Group 3 (overt hypothyroidism) (53.2 ± 35.7 s vs. 12.9 ± 13.3 s, $p = 0.002$). Similarly, duration of reactive hyperemia in subjects with subclinical hypothyroidism was significantly longer compared to subjects with overt hypothyroidism (52.8 ± 47.5 s vs. 12.9 ± 13.3 s, $p = 0.003$). Duration of reactive hyperemia in Group 4 (well-controlled hypothyroidism on L-thyroxine therapy) did not differ significantly compared to controls. There was a highly significant linear correlation between duration of reactive hyperemia and TSH ($r = -0.383$, $p < 0.001$).
Conclusion: Endothelial dysfunction was detected in the microvasculature of patients with hypothyroidism. Duration of reactive hyperemia decreased with increasing TSH levels. Since endothelial dysfunction is a factor leading to atherosclerosis, this abnormality may partly explain predisposition of patients with thyroid failure to cardiovascular disease.

Keywords: Subclinical hypothyroidism; Endothelial dysfunction; Cardiovascular disease; Reactive hyperemia

1. Introduction

Hypothyroidism is known to be associated with increased risk for cardiovascular disease. The population risk attributable to hypothyroidism associated with myocardial infarction was found to be within the range of recognized major risk factors for cardiovascular disease [1]. Considering hypothyroidism's incidence in general population, it is of major importance to clarify its relationship with atherosclerosis. Several conditional mechanisms explaining this association have been proposed. Disturbance in atherogenic lipid metabolism [2,3], enhanced low density

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lipoprotein oxidation [4], triglycerides and lipoprotein-α level [5], hyperomocysteinemia [6], immune-complex-mediated vascular damage [7], altered haemostatic profile [8] have been suggested as mechanisms that could link hypothyroidism with cardiovascular disease.

Endothelium has a pivotal role in cardiovascular system's physiology [9]. A healthy endothelium maintains vascular function and integrity through the production of nitric oxide (NO) [10] and other vasodilatory and vasoconstrictory substances [9–11]. Moreover, there is ample evidence that endothelial dysfunction is an early phenomenon in atherogenesis and occurs in humans before anatomic evidence of atherosclerosis [12]. All known risk factors for atherogenesis are strongly associated with endothelial dysfunction [13,14].

Endothelial dysfunction has been reported in conduit arteries of patients with clinical and subclinical hypothyroidism [15]. Thyrotropin (TSH) levels at which thyroid failure initiates, and therefore detrimental effect of hypothyroidism on cardiovascular system begins, has aroused a lot of speculation for many years [16–18]. Accordingly, no data are available on the impact of mild hypothyroidism on endothelial function of small resistance arteries. Microvasculature regulates blood flow response and NO greatly contributes to tissue adaptations of blood flow. Recently a non-invasive method to assess endothelial function of resistance arteries in humans using NO-dependent changes in reactive hyperemia has been proposed [19].

The aim of this study was to assess non-invasively endothelial function of resistance arteries in subjects with hypothyroidism of varying severity by measuring reactive hyperemia forearm blood flow with venous occlusion strain-gauge plethysmography.

2. Materials and methods

Ninety-six female subjects (mean age: 42±13 years) (Table 1) who were referred for evaluation of suspected hypothyroidism comprised the study population. Subjects were divided into five groups based on TSH levels at presentation: Group 0 (n=23) with TSH levels: 0.3–2.0 μU/ml, Group 1 (n=22) with TSH levels: 2.1–4.0 μU/ml (upper normal), Group 2 (n=18) with TSH levels: 4.1–10 μU/ml (subclinical hypothyroidism) and Group 3 (n=22) with TSH levels >10 μU/ml (overt hypothyroidism). One additional group of women with well-controlled previously diagnosed hypothyroidism (TSH levels: 0.3–2.0 μU/ml on L-thyroxine therapy for at least 3 months) was also included in the analysis (Group 4, n=11). In Groups 2 and 3, plethysmography was performed before any therapeutic intervention and increased TSH values were confirmed twice on separate time intervals of 2 or 3 months. Positive titers of thyroid autoantibodies and/or hypoechogenic pattern in thyroid ultrasound ascertained all cases. In Groups 0 and 1, thyroid antibodies titers were negative. TSH values in the lower end of the spectrum (0.3–4.0 μU/ml) were viewed as two separate groups (0.3–2 and 2–4 μU/ml) based on recent reports suggesting readjustment of normal TSH values to lower levels and on our own previously published data suggesting that upper normal TSH range may in fact represent early stages of subclinical hypothyroidism [15,27,30].

Exclusion criteria were: (1) evidence of atherosclerotic disease (based on clinical history, clinical examination and electrocardiogram), (2) diabetes mellitus, (3) renal failure or (4) arterial hypertension. All premenopausal women were at the follicular phase of their menstrual cycle when studied. None of the participants in Groups 0–3 were receiving any medications. There were 10 smokers who were equally distributed in each group of this study. Smoking was prohibited at least three hours before measurements of endothelial function. Each subject gave informed consent before entering the study and the local scientific committee approved the protocol. The study protocol conformed to the ethical guidelines of Declaration of Helsinki (1975).

2.1. Analytical measurements

Serum TSH, T_3, and T_4 levels were measured in all study participants within 1 week of the vascular studies. Serum TSH was assayed by IRMA, Amerlex hs TSH coated Tube

Table 1
Characteristics of the study population according to TSH values

	Controls, TSH <2 μIU/ml	Upper normal, TSH: 2.01–4 μIU/ml	Subclinical hypothyroidism, TSH: 4–10 μIU/ml	Overt hypothyroidism, TSH>10 μIU/ml	Treated hypothyroidism, TSH<2 μIU/ml
n	23	22	18	22	11
Age (years)	41.8±11.3	45.6±11.8	43.1±13.2	51±12.1[a]	31.7±9[a,b]
TSH (μIU/ml)	1.26±0.5	3.01±0.6[a]	6.2±1.8[a,b]	33.8±21[a,b]	1.2±0.5[b]
Cholesterol (mg/dl)	195±32	232±46	206±39	274±53[a,b]	191±44[b]
Triglycerides (mg/dl)	79±20	105±35	71±23	147±89[a]	63±33
HDL-cholesterol (mg/dl)	56±10	59±12	61±7	59±11	52±7
LDL-cholesterol (mg/dl)	123±29	136±45	120±30	192±68[a,b]	141±40
Lp(a) (mg/dl)	2.3±0.7	3.5±0.7	11.8±15.3[a,b]	4.1±1.1	2.5±0.6
Homocysteine (μmol/l)	7.9±1.04	10.5±1.5	10.1±2.4[a]	11.5±2.5[a]	8.1±0.41[b]

[a] Statistically significant difference compared to group with TSH <2 μIU/ml.
[b] Statistically significant difference compared to group with TSH 2.01–4 μIU/ml.