CLINICAL STUDY

Changes in cerebral blood flow velocity in patients with hypothyroidism

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Abstract

Background: At present, hypothyroidism is a well-known risk factor for cardiovascular disorders. The aim of this study was to assess the effects of hypothyroidism on cerebral blood flow velocity with transcranial Doppler (TCD) ultrasonography.

Design and methods: In this study, 30 subjects were enrolled for clinical, subclinical, and healthy control groups. Bilateral middle cerebral artery (MCA) peak-systolic, end-diastolic, and mean blood flow velocities; Gosling's pulsatility index values; and Pourcelot's resistance index values were recorded and compared with each other. TCD was performed in clinical hypothyroid patients after they became euthyroid with thyroid hormone replacement therapy (HRT). The initial and post-HRT results for the clinical hypothyroid group were then compared and evaluated.

Results: There were 30 subjects in each group. Men/women ratio and mean age in clinical hypothyroid, subclinical hypothyroid, and control groups were 3/27, 4/26, and 5/25, and 37.4, 34.4, and 36.7 respectively. Peak-systolic, end-diastolic, and mean blood flow velocities of bilateral MCA were similar in clinical and subclinical hypothyroid groups but significantly higher when compared with the control group. After adequate thyroid HRT in clinical hypothyroid group, the peak-systolic, end-diastolic, and mean blood flow velocities were significantly decreased.

Conclusions: Increased cerebral blood flow velocities were observed in clinical and subclinical patients with hypothyroidism. The normalization of increased blood flow velocity with thyroid HRT suggests a reversible condition.

European Journal of Endocrinology 165 465–468

Introduction

Hypothyroidism modifies the risk factors of atherosclerosis, and indirectly affects atherogenesis and also has direct effects on the vasculature (1). Epidemiological studies have suggested that patients with hypothyroidism have accelerated coronary atherosclerosis. Hypercholesterolemia, hyperhomocysteinemia, increased C-reactive protein, hypertension, and impaired endothelial function in hypothyroid state enhance the atherogenesis (2, 3). The Rotterdam study showed a higher prevalence of myocardial infarction in women with subclinical hypothyroidism compared with euthyroid women (4). Nagasaki *et al.* (5) showed a decrease in carotid intima-media thickness in hypothyroid patients after normalization of thyroid function. There is some suspicion that atherosclerosis due to hypothyroidism may cause a stroke, but this condition is not yet clear (6, 7). Ojamaa *et al.* (8, 9) reported that thyroid hormone induced relaxation of vascular smooth muscle cells have a direct effect and hence increased arterial stiffness is seen in hypothyroidism. To date, there

is no study about cerebral blood velocity change in hypothyroidism. As a consequence, we investigated whether cerebral blood flow velocities changed in hypothyroidism.

Materials and methods

Subjects

The study was conducted in the outpatient clinics of Endocrinology and Neurosonology Laboratory of our hospital. Newly diagnosed 30 patients with clinical hypothyroidism and 30 patients with subclinical hypothyroidism were included. Thirty healthy control subjects were also enrolled in the study. Age and gender of the control group were similar to the other groups. Diagnosis of clinical and subclinical hypothyroidism was made by endocrinology physicians according to physical findings of patients and laboratory levels of their thyroid hormones. Patients who had possible risks for atherosclerosis, such as diabetes, hypertension, and

Table 1 Transcranial Doppler data of clinical hypothyroid group compared with control group.

	Clinical hypothyroid	Control	P
L-peak-systolic BFV	120.0	101.4	0.009
L-end-diastolic BFV	49.3	38.1	<0.001
L-mean BFV	77.3	59.6	<0.001
L-PI	0.9	0.9	0.9
L-RI	0.58	0.59	0.3
R-peak-systolic BFV	120.8	95.8	<0.001
R-end-diastolic BFV	49.7	37.1	<0.001
R-mean BFV	77.1	58.7	<0.001
R-PI	0.9	0.9	0.3
R-RI	0.57	0.58	0.9

L, left; R, right; PI, pulsatility index; RI, resistance index; BFV, blood flow velocity.

coronary artery disease; age > 50 years; hypothyroidism following thyroidectomy; and hypothyroidism in pregnancy or *postpartum* period were excluded. Consent was obtained from the local ethics committee, and all participants had signed informed consent forms.

Transcranial Doppler examination

Transcranial Doppler (TCD) ultrasonography examination was performed with Multi-Dop X DWL, TCD machine after the subjects rested in a supine position for 10 min. The right and the left middle cerebral artery (MCA) were insonated from the temporal windows at 50–65 mm depth with 2 MHz pulsed Doppler probes. Bilateral MCA peak-systolic, end-diastolic, and mean blood flow velocities; pulsatility index values, and resistance index values were recorded and then compared with each group. TCD was performed again when the patients with clinical hypothyroidism became euthyroid between 3 weeks and 3 months due to thyroid hormone replacement therapy (HRT). Before and after thyroid HRT, TCD findings were also compared in the clinical hypothyroid group.

Statistical analysis

The data was analyzed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) 15.0 program. Paired *t*-test, one-way ANOVA, and Bonferroni analysis as *post hoc* test were used at statistical analysis. In all the analysis, *P* value <0.05 was considered significant.

Results

This study comprised 30 clinical hypothyroid patients, 30 subclinical hypothyroid patients, and 30 healthy control subjects. Men/women ratio and mean age in clinical, subclinical hypothyroid, and control groups

were 3/27, 4/26, and 5/25 and 37.4, 34.4, and 36.7 respectively. Diagnosis was made in accordance with physical findings of patients and laboratory levels of their thyroid hormones. Fatigue, hoarseness, constipation, weight gain, hair loss, cold intolerance, and depression were most commonly seen in patients with clinical hypothyroidism in our study. Mean thyroid stimulating hormone (TSH) and free thyroxine (T₄) levels were 19.8 µIU/ml (range 0.4–4.0 µIU/ml) and 0.5 ng/dl (range 0.8–1.9 ng/dl), respectively, in clinical hypothyroid group. They all had autoimmune thyroiditis (also called Hashimoto's disease). Serum anti-thyroglobulin antibody was investigated in 27 of the 30 patients with clinical hypothyroidism and in 20 of the 30 patients with subclinical hypothyroidism. Their antibody results were all positive. Mean TSH and free T₄ levels were 6.3 µ/ml (range 0.4–4.0 µ/ml) and 1.2 ng/dl (range 0.8–1.9 ng/dl), respectively, in subclinical hypothyroid group. This group had abnormal thyroid hormone levels without clinical symptom and sign.

TCD findings of clinical and subclinical hypothyroid groups compared with the control group are summarized in Tables 1 and 2. Peak-systolic, end-diastolic, and mean blood flow velocities were significantly higher in clinical and subclinical hypothyroid groups compared with control group (*P*<0.05). However, peak-systolic, end-diastolic, and mean blood flow velocities were similar in clinical and subclinical hypothyroid groups (*P*>0.05). In addition, the pulsatility index and resistance index values were not significantly different in all groups.

When the patients with clinical hypothyroidism became euthyroid after thyroid HRT, TCD was performed again, and the peak-systolic, end-diastolic, and mean blood flow velocities were significantly decreased after thyroid HRT in clinical hypothyroid group (*P*<0.05; Table 3). However, the pulsatility index and resistance index values were not significantly different.

Table 2 Transcranial Doppler data of subclinical hypothyroid group compared with control group.

	Subclinical hypothyroid	Control	P
L-peak-systolic BFV	121.3	101.4	0.005
L-end-diastolic BFV	49.6	38.1	<0.001
L-mean BFV	78.5	59.6	<0.001
L-PI	0.9	0.9	0.9
L-RI	0.5	0.59	0.9
R-peak-systolic BFV	125.0	95.8	<0.001
R-end-diastolic BFV	51.9	37.1	<0.001
R-mean BFV	80.0	58.7	<0.001
R-PI	0.89	0.9	0.1
R-RI	0.5	0.58	0.8

L, left; R, right; PI, pulsatility index; RI, resistance index; BFV, blood flow velocity.

Table 3 Transcranial Doppler data of clinical hypothyroid group before and after thyroid hormone replacement therapy.

	Clinical hypothyroid group		P
	Before treatment	After treatment	
L-peak-systolic BFV	120.0	89.0	<0.001
L-end-diastolic BFV	49.3	33.8	<0.001
L-mean BFV	77.3	57.1	<0.001
L-PI	0.9	0.9	>0.05
L-RI	0.58	0.60	>0.05
R-peak-systolic BFV	120.8	91.1	<0.001
R-end-diastolic BFV	49.7	33.8	<0.001
R-mean BFV	77.1	58.3	<0.001
R-PI	0.9	0.9	>0.05
R-RI	0.57	0.60	>0.05

L, left; R, right; PI, pulsatility index; RI, resistance index; BFV; blood flow velocity.

Discussion

The relationship with hypothyroidism and atherosclerosis was presented for the first time in an autopsy of myxedematous woman in 1878 (3). In 1967, Vanhaelst *et al.* (10) first made a case-control study and compared 25 autopsies with myxedema and 50 autopsies without myxedema. They found that coronary artery atherosclerosis was more common in the hypothyroid group (10). Following this, some investigators found that atherosclerosis in hypothyroidism was associated with hypercholesterolemia, hyperhomocysteinemia, increased C-reactive protein, hypertension, and impaired endothelial function (2, 3).

Nagasaki *et al.* (5) reported that carotid intima-media thickness was significantly higher in patients with clinical hypothyroidism than in euthyroid control subjects. Carotid intima-media thickness measured by ultrasonography represents early atherosclerotic changes and is generally accepted as a surrogate marker of future cardiovascular events (5, 11). Patients with hypothyroidism have been reported to have greater radial wall thickness and compliance than euthyroid healthy age- and sex-matched controls (12). Changes in the arterial wall, reducing elasticity, and increasing stiffness could induce increased systolic and diastolic blood pressure (3).

Thyroid hormones control blood pressure. In a study, it was found that hypertension increased threefold in patients with clinical hypothyroidism compared with the euthyroid group (13). Increased diastolic blood pressure was reported after thyroidectomy in normotensive persons (14). The potential mechanisms under this condition are increased peripheral vascular resistance and arterial stiffness (9, 15). Arterial stiffness is an important determinant of arteriosclerosis (16). Lekakis *et al.* (17) found that endothelium-associated vasodilatation was impaired in patients with hypothyroidism and they showed that it was improved by adequate thyroid HRT (18).

In this study, we investigated the effects of hypothyroidism on cerebral blood flow parameters. First, peak-systolic, end-diastolic and mean blood flow velocities and pulsatility index and resistance index values were similar in clinical and subclinical hypothyroid groups. However, the systolic, end-diastolic, and mean blood flow velocities were significantly higher in both clinical and subclinical hypothyroid groups than in the control group ($P < 0.05$). When patients with clinical hypothyroidism became euthyroid by thyroid HRT, the peak-systolic, end-diastolic, and mean blood flow velocities were significantly decreased ($P < 0.05$). In our study, TCD measurements were taken on proximal segments of right and left MCA. We did not observe a focal stenotic finding in any patients during TCD examination. The high MCA velocities on both hypothyroid groups may be a result of diffuse vessel abnormalities such as increased arterial stiffness or changes in systemic blood pressure. Vasomotor response to increased systemic blood pressure is an increase in cerebral blood flow velocity. It is reported that increased mild-to-moderate cerebral blood flow velocity is due to diffuse atherosclerosis or vasoconstriction secondary to systemic hypertension (19). In our study, the mechanisms that underlie significantly increased blood flow velocities of both the hypothyroid groups is most likely to be due to mild diffuse subclinical atherosclerosis and/or MCA vasoconstriction secondary systemic hypertension. Actually, we do not know the level of systemic blood pressure in both hypothyroid groups because we did not measure the patients' blood pressure during this study. Unfortunately, this may be a shortcoming of this study.

In our study, normalization of blood flow velocities in patients with clinical hypothyroidism was seen between 3-week and 3-month period with adequate thyroid HRT, suggesting that it is a reversible condition.

The pulsatility index and resistance index values were not significantly different in each group (Tables 1–3; $P > 0.05$). The pulsatility index and resistance index are arithmetic values that depends on vascular parameters. They are calculated as follows: pulsatility index = (peak systolic velocity–end diastolic velocity)/mean blood flow velocity. Resistance index = (peak systolic velocity–end diastolic velocity)/peak systolic velocity. These parameters reflect the flow velocity waveform and indicate the cerebrovascular resistance (20, 21). Pulsatility index and resistance index may change with proximal or distal occlusion, high intracranial pressure, and decreased compliance in older age. Kwate *et al.* (22) pointed a relationship between pulsatility index and resistance index and systemic arterial stiffness in atherosclerotic population. A normal pulsatility index and resistance index value in our study may be explained by mild or early phase of vascular changes due to hypothyroidism. There are also some SPECT studies on hypothyroidism in which demonstrated reversible regional cerebral blood flow changes but

cerebral blood flow does not change with cerebral blood velocity (23).

In conclusion, increased cerebral blood flow velocities were seen in patients with clinical and subclinical hypothyroidism. Normalization of increased blood flow velocities with adequate thyroid HRT can suggest a reversible condition.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 19 March 2011

Revised version received 29 June 2011

Accepted 6 July 2011