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ORIGINAL PAPER

Coronary flow reserve after L-thyroxine therapy in Hashimoto's thyroiditis patients with subclinical and overt hypothyroidism

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Abstract *Backgound/Aims* Overt and subclinical hypothyroidism are reported to be associated with increased cardiovascular disease risk. We have used coronary flow reserve (CFR) measurement by trans-thoracic Doppler echocardiography (TTDE) to determine coronary microvascular function in Hashimoto's thyroiditis patients with overt and subclinical hypothyroidism and to evaluate effects of L-thyroxine replacement on coronary endothelial function. *Methods* In total, 10 overt hypothyroid patients, 10 subclinical hypothyroid patients, and 10 controls were enrolled. FT4, TSH, anti-thyroid antibodies, lipid profile, insulin, glucose, HOMA-IR, physical parameters, and CFR measured by TTDE were recorded before and after 6 months of L-thyroxine replacement in all groups. *Results* CFR values of all hypothyroid patients at baseline were significantly lower than those in controls. After L-thyroxine, CFR increased significantly in overt and subclinical hypothyroidism with respect to the baseline measurements ($P < 0.05$). When baseline and second measurements were evaluated collectively for patients and controls, CFR was positively correlated with FT4 levels ($r = 0.31$, $P = 0.01$) and negatively correlated with TSH and HOMA-IR ($r = -0.38$, $P = 0.002$ and $r = -0.42$, $P < 0.001$, respectively). *Conclusion* Subclinical as well as overt hypothyroid patients have impaired coronary microvascular function which improved after L-thyroxine therapy. Treatment of Hashimoto's thyroiditis patients with subclinical hypothyroidism should be considered to improve cardiovascular disease risk.

Keywords Cardiovascular disease · Coronary flow reserve · Echocardiography · Hashimoto's thyroiditis · Hypothyroidism · Thyroxine

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Introduction

A number of studies indicated increased cardiovascular morbidity and mortality in patients with overt and subclinical hypothyroidism. Increased cardiovascular disease risk is also reported in euthyroid patients with Hashimoto's thyroiditis (HT) [1–3]. Although data indicating associations between subclinical hypothyroidism and adverse clinical cardiac outcomes are less clear, mechanisms such as abnormal lipid profile, hyperhomocysteinemia, abnormal hemostatic profile, autoimmune reactivity are suggested to be related with increased cardiovascular risk [3–7].

Endothelial dysfunction is an early and reversible key event of cardiovascular disease and has been used to predict future coronary artery disease prior to atherosclerotic changes in arteries [8–11]. Inflammation has a critical role in the pathogenesis of atherosclerosis and endothelial dysfunction [12–14]. The importance of endothelial dysfunction as a precursor of vascular pathology in autoimmune thyroid

disease has been recently recognized [3]. In a recent study, endothelial abnormality was reported to be dependent on the serum levels of anti-peroxidase antibodies as well as abnormalities of thyroid function and lipid profile in HT, however other reports did not support it [3, 15].

Thyroid hormone replacement therapy has been recently demonstrated to improve endothelium-dependent vasodilation in both subclinical and overt hypothyroidism [16, 17]. Therefore it was suggested that cardiovascular morbidity and mortality due to hypothyroidism will be decreased after L-thyroxine (L-T4) therapy.

Coronary flow reserve (CFR) represents the capacity of the coronary circulation to dilate following an increase in myocardial metabolic demands. Although CFR was used to be measured invasively until recently, CFR has been evaluated in echo-lab recently by using Doppler and vasodilator stress such as dipyridamole or adenosine [18–21]. By this method, impairment of CFR can be assessed before development of angiographically detectable stenosis in epicardial coronary arteries and we are able to investigate early coronary microvasculature pathology [22]. Measurement of CFR has predictive power for future cardiovascular events and therefore could be used as a surrogate marker for early atherosclerotic changes of coronary arteries [23, 24].

The aim of our study was to evaluate coronary microvascular circulation and endothelial function of epicardial coronary arteries before and after thyroid hormone replacement therapy by the measurement of CFR via a noninvasive technique, trans-thoracic Doppler echocardiography (TTDE), in patients with subclinical and overt hypothyroidism due to HT and compare them with controls.

Materials and methods

Subjects

Ten patients with overt hypothyroidism due to HT (1 male/9 female and mean age 46.3 ± 3.9 years), 10 adults with subclinical hypothyroidism due to HT (1 male/9 female and mean age 44.3 ± 12.6 years), and 10 healthy controls (1 male/9 female, and mean age 42.4 ± 6.6 years) were enrolled in in this prospective follow-up study. Overt hypothyroidism was defined as free thyroxine (FT4) < 12.0 pmol/L, serum TSH > 4.2 mIU/L, subclinical hypothyroidism was defined as TSH > 4.2 mIU/L while FT4 concentration is normal limits (12.0–22.0 pmol/L), and the healthy control group was chosen among individuals with normal FT4 and TSH (0.27–4.20 mIU/L) levels. TSH and FT4 levels of all subjects were consistent with their diagnoses. Hypothyroid patients were given L-T4 replacement therapy, at a dose of 25 μg/day per oral in the morning, 30 min before breakfast. Dosage was adjusted every 2 weeks in follow-up period until the target dosage was achieved. For hypothyroid patients, the recommended replacement doses (1.6 μg/kg/day) were reached. For subclinical hypothyroid patients, half of the recommended replacement doses were reached. After that, target dose was defined as the dose which was lowered serum TSH level < 4.2 mIU/L after at least 4 weeks of treatment. FT4 and TSH levels were measured every 4 weeks. At the end of 6 months, euthyroidism (i.e., TSH concentration < 4.2 mIU/L) was established in all hypothyroid patients. All measurements were taken two times in all groups; (i) basal measurements before starting therapy, (ii) measurements after 6 months L-T4 therapy. Subclinical and overt hypothyroid groups were selected from baseline groups (subclinical hypothyroid group n:16, overt hypothyroid group n:18) reported in *Int. J. Cardiol.* among the patients accepted to participate in a longer follow-up study [25]. The diagnosis of HT was established on the basis of elevation in serum thyroid peroxidase antibody (TPO-Ab) with or without thyroglobulin antibody (Tg-Ab), associated with the presence of goitre. Dimensions of thyroid glands of control subjects were in normal limits and TPO-Ab and Tg-Ab were not detected in serum tests. The control subjects were age and sex matched and all the study subjects (both patients and controls) were nonsmokers. Subjects in hypothyroid group or in control group with established cardiovascular disease, with overt clinical evidence of atherosclerotic cardiovascular disease, other chronic disease that could accelerate atherosclerosis such as diabetes mellitus, chronic renal failure and hypertension or severe disorders such as cancer were excluded from the study. None of the subjects permitted to drink caffeine-rich beverages at least 12 h before the procedure. None of the women in the patient and control groups was postmenopausal.

Biochemistry

Each subject was studied following a 12-h overnight fast with measurement of lipid profile, free T4, TSH, insulin, glucose without taking the usual morning replacement therapy.

All biochemical analyses including glucose, total cholesterol, LDL, HDL, plasma triglyceride (TG) concentrations were performed by an oxidase-based technique at Roche/Hitachi Modular System (Tokyo, Japan) in the Central Biochemistry Laboratory.

TPO-Ab and Tg-Ab were measured by chemiluminescent microparticle immunoassay using ARCHITECT® *i* System.

Basal insulin, free T4, TSH concentrations were analyzed by using electro-chemiluminescence at Roche/Hitachi Modular Analytics System (Tokyo, Japan).

Insulin resistance (IR) was calculated by a computer-derived Formula [26]: HOMA (homeostasis model assessment) IR = fasting insulin (mcU/ml) × fasting glucose (mmol/l)/22.5

Anthropometric and physical parameters

Body mass index (BMI) was calculated as the ratio of weight (kg) divided by height (cm) squared.

Systolic and diastolic blood pressures were measured on the right arm of subjects in an upright sitting position after at least 5 min of rest using a sphygmomanometer with appropriate cuff size. Two readings were recorded for each individual. The average of two readings was defined as the subject's blood pressure (BP).

Coronary flow measurement

A single, experienced investigator (H.O.), performed coronary flow velocity recordings during this data acquisition. The principal investigator (H.O.) was not aware of the groups of subjects and is experienced in coronary flow measurements and evaluation of CFR in different clinical situation. Recently, the same Cardiology team has published the results of two other studies [27, 28].

Coronary flow reserve recordings were performed with the Vivid 7 echocardiography device (General Electrics, Wisconsin, USA) using a middle-range frequency (3–8 MHz) broadband transducer. CFR recordings were performed in the left-anterior descending (LAD) coronary artery by TTDE, as previously described [29]. The acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left-lateral decubitus position. The LV was imaged in the long-axis cross section and the ultrasound beam was inclined laterally. The coronary blood in the mid-to-distal LAD was searched by color Doppler flow mapping guidance with the optimal velocity range (+12 to + 15 cm/sec). Then, the sample volume (1.5 or 2.0 mm wide) was positioned on the color signal in the LAD artery. We measured variables of LAD artery velocity using fast Fourier transformation analysis. After baseline recordings of flows, dipyridamole (0.56 mg/kg, Persantin, Boehringer Ingelheim, Barcelona, Spain) was infused over a 4-min period. An additional infusion of dipyridamole (0.28 mg/kg over a 2-min period) was used if the heart rate did not exceed a %10 increase from the baseline. Two minutes after the end of the infusion, hyperemic spectral profiles in the LAD artery were recorded. All images were recorded for playback analysis and were later measured off-line. Average diastolic peak velocity (ADPV) and average mean diastolic velocity (AMDV) were measured at baseline and under hyperemic conditions. CFR was defined as the ratio of ADPV at hyperemia: ADPV at baseline. The intra-observer variability of CFR measurement was % 3.6 in the current study.

All of the measurements were performed between 08:00 h and 09:00 h, and all of the subjects abstained from caffeine-containing drinks for at least 12 h before testing. The typical symptoms during dipyridamole infusion such as severe headache, nausea, vomiting, gastrointestinal irritation, dizziness, flushing, syncope, hypotension occurred in none of our study subjects (both patients and controls). Only transient mild headache was reported in two patients and three controls. ECG monitoring was routinely performed for all subjects during the procedure. No significant tachycardia or ST/T changes were observed. In our echocardiography laboratory, aminophylline was kept at hand for intolerable side effects. But none of our subjects necessitated aminophylline infusion.

The study was approved by the local institutional ethics committee and all participants gave informed consent.

Statistical analysis

Data are expressed as mean ± SE, with significance level $P < 0.05$. The Kruskal–Wallis with post-hoc test and one-way analysis of variance with Scheffe post-hoc test evaluated unrelated observations between groups, whereas repeated measures analysis of variance with Scheffe post-hoc analysis determined group differences between repeatedly measured variables. Relationships were determined with Pearson's correlation coefficient.

Results

Comparison of baseline values between overt hypothyroid, subclinical hypothyroid, and control groups

Age, gender, and baseline BMI values of three groups were similar. The biochemical, physical, and echocardiographical characteristics of study population are demonstrated in Table 1. Hemodynamic parameters, lipid profiles, blood glucose levels were normal and similar among three groups. Insulin and HOMA-IR values were significantly higher in patients with overt hypothyroidism than those in controls, but were similar in patients with subclinical hypothyroidism to those in controls ($P < 0.05$). Serum FT4 levels of subclinical hypothyroid and control groups were in normal limits and similar; whereas serum FT4 levels were significantly lower in overt hypothyroid group than those in other two groups ($P < 0.05$). TSH levels were significantly higher in both overt and subclinical groups

Table 1 Characteristics of overt hypothyroid patients, subclinical hypothyroid patients, and control subjects before and after L-thyroxine therapy

Parameters	Control group ($n = 10$)		Overt hypothyroidism group ($n = 10$)		Subclinical hypothyroidism group ($n = 10$)	
Treatment	Baseline	At sixth month	Baseline	At sixth month	Baseline	At sixth month
Total cholesterol (mg/dl)	170 ± 10	167 ± 9	206 ± 10	208 ± 9	190 ± 10	185 ± 9
Triglyceride (mg/dl)	117 ± 19	114 ± 21	130 ± 19	166 ± 21	132 ± 19	96 ± 21
LDL (mg/dl)	98 ± 9	97 ± 6	131 ± 9	122 ± 6	111 ± 9	97 ± 6
HDL (mg/dl)	48 ± 4	47 ± 3	48 ± 4	47 ± 3	42 ± 4	45 ± 3
Glucose (mg/dl)	81 ± 2	82 ± 1	85 ± 2	84 ± 1	85 ± 2	83 ± 1
Insulin (μIU/ml)[a,e]	4 ± 1.42	3.74 ± 0.71	9.89 ± 1.41	6.32 ± 0.71	7.81 ± 1.43	5 ± 0.71
HOMA-IR[a,d,e]	0.72 ± 0.28	0.74 ± 0.15	2.12 ± 0.28	1.34 ± 0.15	1.65 ± 0.28	1.04 ± 0.15
F-T_4 (pmol/L)[a,c,d]	14.42 ± 0.35	14.57 ± 0.77	9.78 ± 0.35	16.57 ± 0.77	14.2 ± 0.35	15.41 ± 0.77
TSH (mIU/L)[a,b,c,d,e]	1.75 ± 3.67	1.83 ± 0.27	24.31 ± 3.67	2.56 ± 0.27	7.64 ± 3.67	2.36 ± 0.27
TPO-Ab (IU/ml)[a,b]	5.7 ± 17.4	5.3 ± 26.1	245 ± 17.4	222.7 ± 26.1	189.5 ± 17.4	197.9 ± 26.1
Tg-Ab (IU/ml)[a,b]	16.9 ± 27.7	17 ± 35.7	355.5 ± 27.7	337 ± 35.7	319.5 ± 27.7	300.1 ± 35.7
BMI (kg/m^2)	24.2 ± 2.4	24.4 ± 3.1	25.2 ± 2.2	24.6 ± 2.2	24.5 ± 2.2	24.4 ± 2.3
Systolic BP (mmHg)	116 ± 3	116 ± 6	114 ± 3	116 ± 6	113 ± 3	102 ± 7
Diastolic BP(mmHg)	74 ± 2	74 ± 2	71 ± 2	79 ± 2	73 ± 2	73 ± 2
ADPV-basal (cm/sn)	35.1 ± 3.1	35.5 ± 3.5	32.2 ± 3.1	32.1 ± 3.5	36.3 ± 3.1	35.9 ± 3.5
ADPV-hyperemia (cm/sn)[a,d,e]	91 ± 7.3	91.2 ± 9.2	91 ± 7.3	72.6 ± 9.2	91 ± 7.3	92.9 ± 9.2
AMDV-basal (cm/sn)	27.3 ± 2.4	28.9 ± 2.7	25.6 ± 2.4	24.2 ± 2.7	29 ± 2.4	29.1 ± 2.7
AMDV-hyperemia (cm/sn)[a,d,e]	67.1 ± 4.9	68.3 ± 5.8	42.3 ± 4.9	52 ± 5.8	50.6 ± 4.9	70 ± 5.8
CFR[a,b,d,e]	2.64 ± 0.13	2.63 ± 0.18	1.59 ± 0.13	2.36 ± 0.18	2.03 ± 0.13	2.54 ± 0.18

Data are mean ± SE. HOMA-IR: fasting insulin (mcU/ml) x fasting glucose (mmol/l)/22.5, BMI: body-mass index, BP: blood pressure, ADPV: average diastolic peak velocity, AMDV: average mean diastolic velocity, CFR: coronary flow reserve

Symbols were presented significant difference ($P < 0.05$)

[a] Between overt hypothyroidism and control groups at before treatment

[b] Between subclinical hypothyroidism and control groups at before treatment

[c] Between subclinical and overt hypothyroidism groups at before treatment

[d] Between before and after treatment in overt hypothyroidism group

[e] Between before and after treatment in subclinical hypothyroidism group

than those in controls ($P < 0.05$), but as expected, were much more higher in overt hypothyroidism than those in subclinical hypothyroidism ($P < 0.05$). TPO-Ab and Tg-Ab were not significantly different between the two hypothyroid groups, but were significantly higher in hypothyroid groups than those in controls ($P < 0.05$). CFR values were lower in overt and subclinical hypothyroid groups than those in control group ($P < 0.05$), whereas significantly much more lower in overt hypothyroid group than those in subclinical group ($P < 0.05$).

Study parameters after L-T4 therapy

In group with overt hypothyroidism; hemodynamic parameters, lipid profiles, and serum glucose levels were not changed significantly. HOMA-IR values improved significantly ($P < 0.05$) after L-T4 therapy, whereas serum insulin levels decreased, but the decrement did not reach statistical significance. FT4 ve TSH improved significantly and reached normal levels after therapy ($P = 0.05$). TPO-Ab and Tg-Ab levels unchanged and remained high. CFR values increased significantly after L-T4 replacement ($P < 0.05$).

In group with subclinical hypothyroidism; no significant difference between the baseline and after L-T4 treatment in hemodynamic parameters, glucose and lipid profile except TG was detected. TG levels decreased significantly after L-T4 therapy ($P < 0.05$). Serum insulin levels and HOMA-IR values decreased significantly ($P < 0.05$). FT4 levels were not changed, whereas TSH levels decreased significantly and reached normal limits ($P = 0.05$). TPO-Ab and Tg-Ab unchanged and had remained high. CFR values increased significantly after L-T4 replacement ($P < 0.05$).

In control group; all measurements, repeated during 6 months follow-up period, were not changed according to baseline measurements.

When baseline and after 6 months measurements were considered in a whole group (both patients and controls),

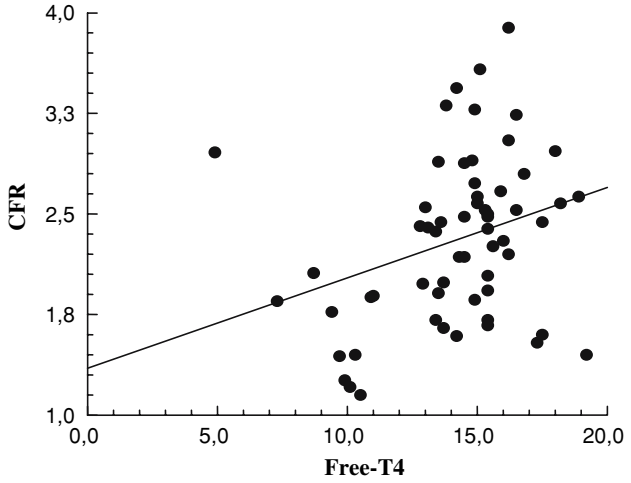

Fig. 1 Relationship between coronary flow reserve (CFR) values and free-T4 concentrations (pmol/L) of all subjects in study group, measured both before and after L-thyroxine (L-T4) therapy ($r = 0.31$, $P = 0.01$)

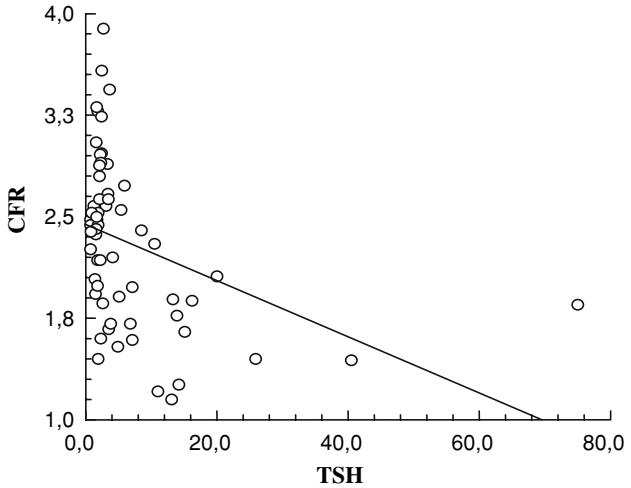

Fig. 2 Relationship between coronary flow reserve (CFR) values and TSH concentrations (mIU/L) of all subjects in study group, measured both before and after L-thyroxine (L-T4) therapy ($r = -0.38$, $P = 0.002$)

CFR was positively correlated with FT4 levels ($r = 0.31$, $P = 0.01$) and was negatively correlated with TSH and HOMA-IR values ($r = -0.38$, $P = 0.002$ and $r = -0.42$, $P < 0.001$, respectively) (Figs. 1–3). Changes in CFR at the end of treatment were compared with changes in other study parameters at the end of follow-up. Changes in CFR (Δ change) were significantly and negatively correlated with Δ TSH ($r = 0.509$; $P < 0.05$) (Fig. 4).

Discussion

To the best of our knowledge, this is the first time that a study, using a non-invasive method, shows the improvement

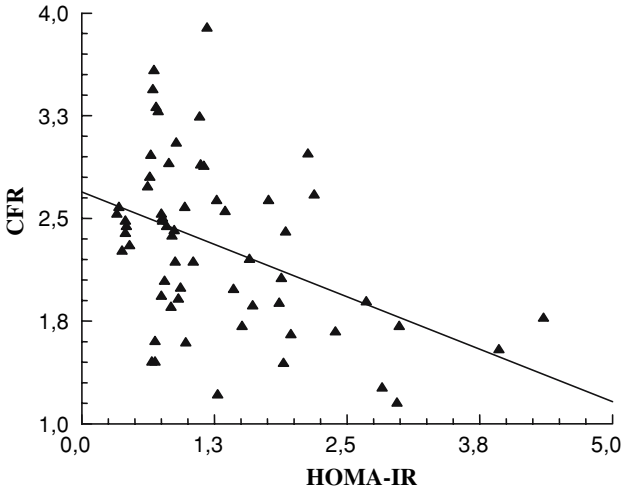

Fig. 3 Relationship between coronary flow reserve (CFR) values and homeostasis model assessment—insulin resistance (HOMA-IR) values of all subjects in study group, measured both before and after L-thyroxine (L-T4) therapy ($r = -0.42$, $P < 0.001$)

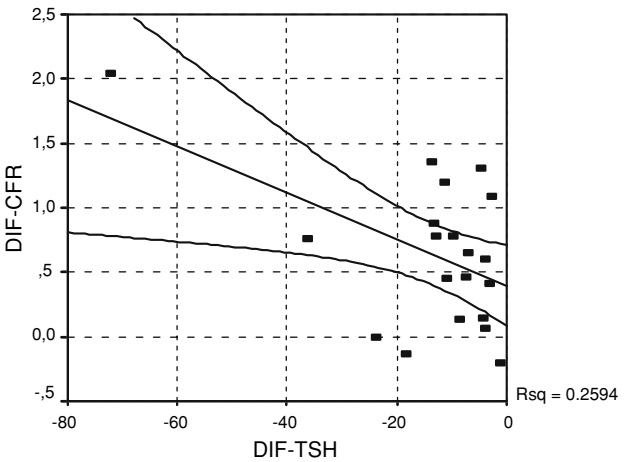

Fig. 4 Comparison of changes in CFR (DIF-CFR = Δ change of CFR) with changes TSH (DIF-TSH = Δ change of TSH) ($r = 0.509$; $P < 0.05$)

of impaired CFR in HT patients with subclinical hypothyroidism and overt hypothyroidism after L-T4 therapy and supports the previous studies which pointed out the significance of L-T4 replacement on cardiovascular function in patients with subclinical hypothyroidism [16, 30].

Overt hypothyroidism usually leads to cardiovascular abnormalities. The subclinical hypothyroidism is a condition characterized by normal serum concentrations of FT4 and slightly elevated serum concentrations of TSH [31]. Hak et al. [1] reported that subclinical hypothyroidism is a strong indicator of atherosclerotic cardiovascular disease. In that large population study, about 10% of the elderly women have been reported to develop subclinical hypothyroidism and to have thyroid autoimmunity. A more

recent evaluation by Surks et al. [7] underlined the paucity of data about the long-term adverse effects of untreated subclinical hypothyroidism on important cardiovascular outcomes. Subclinical hypothyroidism could have potentially important healthcare implications, although beneficial cardiovascular effects of treatment of subclinical disease are not yet confirmed by randomized clinical trials.

The CFR measurement that reflects coronary microvascular function and endothelial function of epicardial coronary arteries by TTDE, as a cheaper and easy screening test, may be used as a detection method in the assessment of major epicardial coronary arteries [19–22]. A CFR of <2 may be evidence of severe coronary artery disease. In a recent report, Rigo [18] suggested that the use of CFR measurement as a sole diganostic criterion has structural limitations because of sampling only LAD. In addition, discrimination between microvascular and macrovascular disease could not be made by CFR measurement alone. However, CFR can identify mild to moderate stenosis (reduced flow reserve to subischemic levels) and coronary microvascular dysfunction (reduced flow reserve with angiographically normal coronary arteries). Microvascular dysfunction could lead to myocardial ischemia and cardiovascular disease [18]. Therefore measurement of CFR has value to predict future coronary events [23].

In our study, CFR measurements of HT patients with overt and subclinical hypothyroidism were found to be lower than those of control subjects ($P < 0.05$) like the results of baseline measurements reported in *Int. J. Cardiol.* [25].

The exact mechanism by which hypothyroidism affects endothelial function is not clear. But well-kown atherosclerotic risk factors such as hemostatic alterations, hypercholesterolemia, and hyperhomocysteinemia have been shown to contribute endothelial dysfunction in hypothyroidism [4–6]. Despite lipid profiles and hemodynamic parameters in subclinical hypothyroidism and overt hypothyroidism were similar to each other before and after L-T4 treatment in our study, impairment of CFR was significantly higher in overt hypothyroid and subclinical hypothyroid patients than those in controls, and was significantly higher in overt hypothyroid patients than those in subclinical ones ($P < 0.05$). In our study the negative association between changes in TSH and CFR is worth-mension. The role of TSH on endothelial function is subject to debate. A previous study clearly demonstrated that recombinant human thyrotropin administration impaired endothelium-dependent dilation acutely [32]. Therefore decrement in TSH may be responsible for the improvement in endothelium-dependent dilation of coronary arteries and may further support the treatment of even subclinical hypothyroidism [32]. Factors other than dyslipidemia and hypertension not measured in our study should be taken into consideration to explain the more severely impaired coronary flow measurement in overt hypothyroid patients such as hemostatic and/or inflammatory alterations [33, 34].

Association between subclinical-overt hypothyroidism and IR gave conflicting results in previous studies. In a recent study by Owecki et al. [35], there was no correlation between hypothyroidism due to total thyroidectomy and insulin sensitivity. But, Dessein et al. [36] reported that subclinical hypothyroid patients with rheumatoid arthritis (RA) had increased IR and suggested that thyroid function test should be used while assesing cardiovascular risk in RA. In our study, insulin and HOMA-IR values were significantly higher in overt hypothyroid group than those in controls, however there was no statistically significant difference in insulin and HOMA-IR values between overt and subclinical hypothyroidism and between subclinical hypothyroidism and control group. We found that in overt hypothyroid group, HOMA-IR values decreased significantly ($P < 0.05$) after L-T4 therapy. In subclinical hypothyroid group, serum insulin levels and HOMA-IR values decreased significantly ($P < 0.05$). We could not find any correlation between TSH and HOMA-IR levels, but CFR showed significant negative correlation with HOMA-IR in the whole group. Improvement in HOMA-IR in HT patients with subclinical and overt hypothyroidism after L-T4 replacement has not been reported previously [16, 17]. But Roos et al. [37] reported that HOMA-IR is increased in euthyroid subjects in the lowest tertial of FT4. In Roos et al.'s study, FT4 and TSH were significantly associated with HOMA-IR (beta $= -0.133$; $P < 0.001$ and beta $= 0.055$; $P = 0.024$, respectively). Therefore reduction of fasting insulin and HOMA-IR after LT4 replacement support findings reported by Roos et al. in euthyroid patients [37].

Wells and Hueston [15] demonstrated that TPO-Ab does not correlate with cardiovascular disease risk in patients with subclinical hypothyroidism. In the present study, we found that TPO-Ab and Tg-Ab were significantly higher in hypothyroid groups than those in controls ($P < 0.001$). However we also could not demonstrate any correlation between TPO-Ab and Tg-Ab, and CFR levels, measured both at the baseline and after L-T4 therapy. This study like the one by Wells and Hueston [15] does not support the measurement of TPO-Ab antibodies in subclinical hypothyroidism as a strategy for guiding treatment or assessment of cardiovascular disease risk.

Inflammation is well known to participate in atherogenesis in many diseases which have increased cardiovascular mortality and morbidity [38]. It is recently postulated that endothelial dysfunction in HT with euthyroid status could occur as a result of inflammation [3]. Recently Taddei et al. [39] reported that in subclinical hypothyroid patients with autoimmune thyroiditis, low-grade chronic inflammation

causes endothelial dysfunction and impaired nitric oxide availability by a COX-2-dependent pathway leading to increased production of oxidative stress.

It is concluded that subclinical as well as overt hypothyroid patients with HT had impaired coronary microvascular function evaluated noninvasively by CFR measurement, compared with controls. L-T4 therapy both in overt and subclinical hypothyroid patients led to improvement in coronary microvascular dysfunction. In addition, HOMA-IR values decreased significantly in both subclinical and overt hypothyroid group after L-T4 replacement therapy. Large, population-based studies with clinical cardiac end points and longer duration of follow up after L-T4 replacement therapy are required—in particular—in subclinical hypothyroid groups, to reveal the beneficial cardiac effects of L-T4 treatment.

References

1. A.E. Hak, H.A. Pols, T.J. Visser, H.A. Drexhage, A. Hofman, J.C. Witteman, Ann. Intern. Med. **132**, 270–278 (2000)
2. G.J. Kahaly, Thyroid **10**, 665–679 (2000)
3. G.D. Xiang, Y.S. He, L.S. Zhao, J. Hou, L. Yue, H.J. Xiang, Clin. Endocrinol. **64**, 698–702 (2006)
4. A.W. Kung, R.W. Pang, E.D. Janus, Clin. Endocrinol. **43**, 445–449 (1995)
5. W.I. Hussein, R. Green, D.W. Jacobsen, C. Faiman, Ann. Intern. Med. **131**, 348–351 (1999)
6. B. Muller, D.A. Tsakiris, C.B. Roth, M. Guglielmetti, J.J. Staub, G.A. Marbet, Eur. J. Clin. Invest. **31**, 131–137 (2001)
7. M.I. Surks, E. Ortiz, G.H. Daniels, C.T. Sawin, N.F. Col, R.H. Cobin, J.A. Franklyn, J.M. Hershman, K.D. Burman, M.A. Denke, C. Gorman, R.S. Cooper, N.J. Weissman, JAMA **291**, 228–238 (2004)
8. R.F. Furchgott, J.V. Zawadzki, Nature **288**, 373–376 (1980)
9. R. Ross, N. Engl. J. Med. **314**, 488–500 (1986)
10. A.H. Henderson, Br. Heart. J. **65**, 116–125 (1991)
11. P.O. Bonetti, L.O. Lerman, A. Lerman, Arterioscler. Thromb. Vasc. Biol. **23**, 168–175 (2003)
12. M.J. Jarvisalo, M. Juonala, O.T. Raitakari, Curr. Opin. Clin. Nutr. Metab. Care **9**, 547–552 (2006)
13. B. Erzen, M. Sabovic, M. Sebestjen, I. Keber, P. Poredos, Cardiology **107**, 111–116 (2006)
14. A.T. With Noto, E. Bogeberg Mathiesen, J. Amiral, A.M. Vissac, J.B. Hansen, Thromb. Haemost. **96**, 53–59 (2006)
15. B.J. Wells, W.J. Hueston, Clin. Endocrinol. **62**, 580–584 (2005)
16. S. Taddei, N. Caraccio, A. Virdis, A. Dardano, D. Versari, L. Ghiadoni, A. Salvetti, E. Ferrannini, F. Monzani, J. Clin. Endocrinol. Metab. **88**, 3731–3737 (2003)
17. G.I. Papaioannou, M. Lagasse, J.F. Mather, P.D. Thompson, Metabolism **53**, 278–279 (2004)
18. F. Rigo, Cardiovasc. Ultrasound **3**, 8 (2005)
19. M. Galderisi, B. Capaldo, M. Sidiropulos, A. D'Errico, L. Ferrara, A. Turco, P. Guarini, G. Riccardi, O. de Divitiis, Am. J. Hypertens. **20**, 1283–1290 (2007)
20. Y. Kataoka, S. Nakatani, N. Tanaka, H. Kanzaki, S. Yasuda, I. Morii, A. Kawamura, S. Miyazaki, M. Kitakaze, Circ. J. **71**, 891–896 (2007)
21. S. Shimada, K. Harada, M. Toyono, M. Tamura, G. Takada, Circ. J. **71**, 1912–1917 (2007)
22. K.L. Gould, K. Lipscomb, Am. J. Cardiol. **34**, 48–55 (1974)
23. M.B. Britten, A.M. Zeiher, V. Schachinger, Coron. Artery Dis. **1585**, 259–264 (2004)
24. A.C. Rodrigues, C.C. Frimm, F. Bacal, V. Andreolli, J.M. Tsutsui, E.A. Bocchi, W. Mathias Jr., S.G. Lage, Int. J. Cardiol. **103**, 201–206 (2005)
25. H. Oflaz, R. Kurt, A. Cimen, A. Elitok, I. Onur, E. Golcuk, M. Demirturk, S. Batmaz, E. Kasikcioglu, Int. J. Cardiol. **120**, 414–416 (2006)
26. D.R. Matthews, J.P. Hosker, A.S. Rudenski, B.A. Naylor, D.F. Treacher, R.C. Turner, Diabetologia **28**, 412–419 (1985)
27. E. Kasikcioglu, A. Elitok, I. Onur, A. Cimen, A. Ucar, H. Oflaz, Int. J. Cardiol. Aug 24; [Epub ahead of print] (2007)
28. H. Oflaz, F. Sen, A. Elitok, A.O. Cimen, I. Onur, E. Kasikcioglu, S. Korkmaz, M. Demirturk, F. Kutluturk, B. Pamukcu, N. Ozbey, Clin. Endocrinol. **66**, 524–529 (2007)
29. T. Hozumi, K. Yoshida, Y. Ogata, T. Akasaka, Y. Asami, T. Takagi, S. Morioka, Circulation **97**, 1557–1562 (1998)
30. M. Yazici, S. Gorgulu, Y. Sertbas, E. Erbilen, S. Albayrak, O. Yildiz, C. Uyan, Int. J. Cardiol. **95**, 135–143 (2004)
31. M.I. Surks, E. Ocampo, Am. J. Med. **100**, 217–223 (1996)
32. A. Dardano, L. Ghiadoni, Y. Plantinga, N. Caraccio, A. Bemi, E. Duranti, S. Taddei, E. Ferrannini, A. Salvetti, F. Monzani, J. Clin. Endocrinol. Metab. **91**, 4175–4178 (2006)
33. H. Masaki, M. Nishikawa, M. Urakami, M. Yoshimura, N. Toyoda, Y. Mori, N. Yoshikawa, M. Inada, J. Clin. Endocrinol. Metab. **75**, 721–725 (1992)
34. R. Chadarevian, E. Bruckert, A. Ankri, I. Beucler, P. Giral, G. Turpin, Thromb. Haemost. **79**, 99–103 (1998)
35. M. Owecki, E. Nikisch, J. Sowinski, Acta. Clin. Belg. **61**, 69–73 (2006)
36. P.H. Dessein, B.I. Joffe, A.E. Stanwix, Thyroid **14**, 443–446 (2004)
37. A. Roos, S.J. Bakker, T.P. Links, R.O. Gans, B.H. Wolffenbuttel, J. Clin. Endocrinol. Metab. **92**, 491–496 (2007)
38. O. Serri, P. St-Jacques, M. Sartippour, G. Renier, J. Clin. Endocrinol. Metab. **84**, 58–63 (1999)
39. S. Taddei, N. Caraccio, A. Virdis, A. Dardano, D. Versari, L. Ghiadoni, E. Ferrannini, A. Savletti, F. Monzani, J. Clin. Endocrinol. Metab. **91**, 5076–5082 (2006)