

## PRELIMINARY REPORT

# Treating Hypothyroidism Improves Endothelial Function

Georgios I. Papaioannou, Marie Lagasse, Jeffrey F. Mather, and Paul D. Thompson

**Hypothyroidism patients have increased cardiovascular risk, although the mechanism is not defined. Endothelial dysfunction may initiate atherosclerosis, is present in patients with hypothyroidism, and therefore may link hypothyroidism and vascular disease. We are unaware of studies examining the effect of thyroid replacement therapy on endothelial function in hypothyroid patients. The present study examined the effect of treatment of hypothyroidism on brachial artery reactivity. Consequently, we measured endothelium-dependent (EDV) and endothelium-independent (EIV) vasodilation using brachial artery ultrasonography in 8 hypothyroid patients (5 men, mean age  $48.9 \pm 5.5$  years; mean thyrotropin [TSH]  $49.0 \pm 37.0$  mIU/L) before and after thyroxine treatment. Thyroxine treatment reduced average TSH to  $2.9 \pm 0.5$  mIU/L and improved EDV ( $8.0\% \pm 4.4\%$  v  $3.4\% \pm 2.5\%$ ,  $P < .05$ ), whereas EIV was unchanged ( $20.3\% \pm 6.1\%$  v  $19.2\% \pm 9.4\%$ ,  $P =$  not significant [NS]). Thyroxine treatment did not alter serum lipids. Thyroid replacement therapy improves endothelium-dependent vascular reactivity in patients with hypothyroidism irrespective of lipid changes.**

© 2004 Elsevier Inc. All rights reserved.

**D**YSLIPIDEMIA is common in hypothyroidism<sup>1-2</sup> and is generally assumed to be a major factor in accelerating atherosclerosis in these patients. On the other hand, atherosclerotic risk is also increased in borderline hypothyroid women after adjusting for serum lipids, so that other factors may contribute to the increased vascular risk.<sup>3</sup> Endothelial dysfunction occurs early in the atherosclerotic process and may be a key initiating event.<sup>4</sup> Endothelial dysfunction is also present in hypothyroid patients, thereby providing an additional link between hypothyroidism and vascular disease.<sup>5</sup> Although treatment of hypothyroidism improves cardiovascular health,<sup>6</sup> we are unaware of studies examining the effect of such treatment on endothelial function. Thus, the aim of the present study was to determine whether thyroid replacement therapy improves endothelial function in patients with hypothyroidism.

### PATIENTS AND METHODS

Eight patients with newly diagnosed hypothyroidism (thyrotropin [TSH]  $> 4.20$  mIU/L) underwent measurements of endothelium-dependent (EDV) and endothelium-independent (EIV) brachial artery vasodilation, TSH, total thyroxine ( $T_4$ ), triiodothyronine uptake ( $T_3U$ ), serum lipids, homocysteine (HCS), and high-sensitivity C-reactive protein (hs-CRP) before and after  $7.4 \pm 4.0$  (mean  $\pm$  SD) months of  $T_4$  treatment to normalize their TSH. No other changes in the medical regimen were permitted during the study. All participants provided written informed consent.

Serum TSH,  $T_4$ ,  $T_3U$ , HCS, and hs-CRP were assayed by nonisotopic immunoassays. The TSH assay is a high-sensitivity, third generation assay with intra- and interassay coefficients of variation of 3% and 5%, respectively. Brachial artery reactivity measurements were obtained in the morning after an overnight fast with all medications

held the morning of the test. Images were obtained using an Acuson 10.0 MHz linear array transducer and an Aspen cardiac ultrasound system (Acuson, Elmwood Park, NJ) using standard technique. EDV and EIV were calculated as the percent maximal increase in arterial diameter at 1-minute post lower arm occlusion and 3 minutes post nitroglycerine, respectively. Two different interpreters, who were unaware of the treatment status, analyzed all scans independently using CVI Analysis Software (Data Translation Inc, Marlboro, MA). The intra- and interobserver variability in our laboratory is 1.1% and 2.1%, respectively.

Differences between continuous variables before and after treatment were compared with the paired-samples *t* test or the Sign test. Results were considered statistically significant at  $P < .05$ . Analysis was performed with the statistical package SPSS 10.1 (SPSS, Chicago, IL).

### RESULTS AND DISCUSSION

The age of the subjects was  $48.9 \pm 5.5$  years (mean  $\pm$  SD) and included 5 men (62.5%), with TSH  $49.0 \pm 37.0$  mIU/L. Several patients were treated with other cardiovascular medications, but no changes in medications or doses were permitted during the study (Table 1).

$T_4$  treatment (mean dose  $53 \pm 16$   $\mu$ g) reduced average TSH to  $2.9 \pm 0.5$  mIU/L, increased EDV ( $3.4\% \pm 2.5\%$  to  $8.0\% \pm 4.4\%$ ,  $P < .05$ ) (Fig 1), but did not affect brachial artery diameter ( $3.7 \pm 0.4$  v  $3.8 \pm 0.4$  mm,  $P = .47$ ) or the EIV response to nitroglycerin (EIV,  $20.3\% \pm 6.1\%$  v  $19.2\% \pm 9.4\%$ ,  $P = .97$ ). Systolic and diastolic blood pressure,

**Table 1. Baseline Characteristics and Medications of the Subjects**

Characteristics	N = 8 (%)
Age, yr (SD)	$48.9 \pm 5.5$
Gender (males)	5 (62.5)
Hypertension	6/8 (75)
Hyperlipidemia	6/8 (75)
Smoking	1/8 (12.5)
Diabetes	1/8 (12.5)
ACE inhibitors	3/8 (37.5)
Statins	4/8 (50)
Antihyperglycemic agents	1/8 (12.5)

Abbreviation: ACE, angiotensin-converting enzyme.

From the Division of Cardiology, Hartford Hospital, Hartford, CT. Submitted June 25, 2003; accepted October 20, 2003.

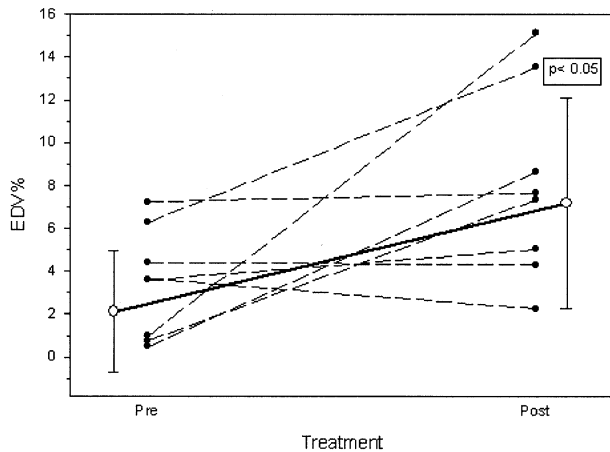
Supported by a grant from Hartford Hospital research administration.

Address reprint requests to Georgios I. Papaioannou, MD, Hartford Hospital, Cardiology Division, 80 Seymour St, PO Box 5037, Hartford, CT 06102-5037.

© 2004 Elsevier Inc. All rights reserved.

0026-0495/04/5303-0003\$30.00/0

doi:10.1016/j.metabol.2003.10.003



**Fig 1. Endothelium-dependent brachial artery vasodilation pre- and post-thyroxine treatment in all 8 hypothyroid subjects (dashed lines denote individual response to treatment and solid lines mean ± SD).**

serum lipids, hs-CRP, and HCS did not change with treatment (Table 2).

The increased cardiovascular risk associated with hypothyroidism has generally been attributed to concomitant increases in serum lipids. However, atherosclerotic risk is also increased 70% to 130% in women with borderline hypothyroidism (TSH > 4 and normal T<sub>4</sub>) and 90% to 210% in those with additional presence of antibodies to thyroid peroxidase, even after adjusting for lipid levels.<sup>3</sup> This raises the possibility that other factors contribute to vascular disease risk in patients with hypothyroidism. Endothelial dysfunction is an early event in atherosclerosis and may actually initiate the atherosclerotic process. Endothelial dysfunction is also present both in hypothyroid and in hyperlipidemic subjects, making it difficult to discern whether hypothyroidism per se or associated lipid abnormalities are responsible for the endothelial dysfunction.

**Table 2. Results of Biochemical Markers and Brachial Artery Reactivity Testing Before and After T<sub>4</sub> Treatment**

	At Enrollment	After Treatment	P Value
TSH (mIU/L)	49.0 ± 37.0	2.9 ± 0.5	—
T <sub>4</sub> (μg/dL)	5.6 ± 1.6	7.0 ± 0.8	.12
T <sub>3</sub> U (U)	0.7 ± 0.9	0.8 ± 0.1	.45
TC (mg/dL)	203 ± 56	211 ± 37	.56
LDL (mg/dL)	114 ± 40	121 ± 31	.61
HDL (mg/dL)	54 ± 16	56 ± 16	.66
TG (mg/dL)	171 ± 133	198 ± 156	.58
HCS (μmol/L)	11.2 ± 2.1	12.1 ± 1.9	.30
hs-CRP (mg/L)	0.8 ± 0.6	0.3 ± 0.1	.90
SBP	121 ± 18	123 ± 20	.63
DBP	69 ± 10	70 ± 7	.99
Baseline diameter (mm)	3.7 ± 0.4	3.8 ± 0.4	.47
EDV (%)	3.4 ± 2.5	8.0 ± 4.4	<.05
EIV (%)	20.3 ± 6.1	19.2 ± 9.4	.97

Abbreviations: TSH, thyrotropin; T<sub>3</sub>U, T<sub>3</sub> uptake; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; HCS, homocysteine; hs-CRP, high-sensitivity C-reactive protein (mean ± SEM); SBP, systolic blood pressure, DBP, diastolic blood pressure; EDV, endothelium-dependent vasodilation; EIV, endothelium-independent vasodilation.

In the present study, endothelial function improved with thyroid replacement therapy. This agrees with animal studies suggesting that thyroid hormone exerts part of its vascular effect through an endothelium-mediated mechanism. Specifically, the vascular contractile response to norepinephrine is reduced in hyperthyroid rats only when the vascular endothelium is intact.<sup>7</sup> Furthermore, the improvement in endothelial function in the present study occurred without change in medications, blood pressure, serum lipids, homocysteine levels, or hs C-reactive protein levels. If confirmed, our results suggest that thyroid replacement therapy may have a direct effect on endothelial function, an effect that may contribute to reduced cardiovascular risk independent of changes in serum lipids.

REFERENCES

1. Klein I, Ojamaa K: Thyroid hormone and the cardiovascular system. *N Engl J Med* 344:501-509, 2001
2. Elder J, McClelland A, O' Reilly DS, et al: The relationship between serum cholesterol and serum thyrotropin, thyroxine and triiodothyronine concentrations in suspected hypothyroidism. *Ann Clin Biochem* 27:110-113, 1990
3. Hak AE, Pols HAP, Visser TJ, et al: Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women. *Ann Intern Med* 132:270-278, 2000
4. Ludmer PL, Selwyn AP, Shook TL, et al: Paradoxical coronary

- vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 315:1046-1051, 1986
5. Lekakis J, Papamichael C, Alevizaki M, et al: Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism and high-normal thyrotropin (TSH) values. *Thyroid* 7:411-414, 1997
6. Cooper DS: Subclinical hypothyroidism. *N Engl J Med* 345:260-265, 2001
7. McAllister RM, Grossenburg VD, Delp MD, et al: Effects of hyperthyroidism on vascular contractile and relaxation response. *Am J Physiol* 274:E946-E953, 1998