Clinical THYR<u>OIDOLOGY</u>



# L-T<sub>4</sub> Treatment of Patients With Subclinical Hypothyroidism Can Partially Restore Cardiac Flow Reserve

Traub-Weidinger T, Graf S, Beheshti M, Ofluoglu S, Zettinig G, Khorsand A, Nekolla SG, Kletter K, Dudczak R, Pirich C. Coronary vasoreactivity in subjects with thyroid autoimmunity and subclinical hypothyroidism before and after supplementation with thyroxine. Thyroid. January 10, 2011 [Epub ahead print]. doi:10.1089/thy.2011-0183.

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#### Background

"Subclinical hypothyroidism" is not a disease but a combination of laboratory-test results that may be found in up to 10% of the population, and that has many possible causes. It is characterized by an elevated serum TSH level in the face of  $T_4$  and  $T_3$ levels in the normal range. Test-retest reliability for TSH is +/-40% (1), and it is not uncommon for the TSH in patients with subclinical hypothyroidism to return to normal, although this can take 3 or more years to occur (2). On the other hand, overt hypothyroidism can develop in "euthyroid" patients with an elevated TSH: the risk ranges from 1.2% to 18% per year, depending largely on how high the TSH is (1). Patients with overt hypothyroidism are at increased risk for cardiovascular disease, but whether patients with subclinical hypothyroidism are at increased risk remains controversial, despite literally thousands of papers on the subject. A variety of physiological and biochemical tests have been used to study function and metabolism in the heart and various vessels in such patients, but the findings often have been discordant. The current paper addressed the microvascular function of the heart, using dynamic positron-emission tomography (PET) with <sup>13</sup>N-labeled ammonia, before and after infusing adenosine intravenously for 2 minutes, and then estimating myocardial vascular resistance (MVR), myocardial blood flow (MBF), and coronary flow reserve (CFR).

#### Methods

The 10 patients (28 to 58 years of age) initially recruited for the study had TSH levels ranging from 5 to 34  $\mu$ U/ml (mean, ~17), and their TSH had been elevated for 2 to 9 months. Their mean levels of free

 $T_4$  and free  $T_3$  were within the normal range, although they were significantly lower than the mean levels in 8 controls (38 to 60 years of age). The patients apparently had no major comorbidities, and were deemed to have Hashimoto's thyroiditis because they had positive anti-TPO antibodies (titers and duration of positivity not indicated). Initial baseline and adenosine-stimulated dynamic PET data were obtained in 9 patients, but only 8 received L-T<sub>4</sub> for 6 months. The dose was increased in 25-µg increments until the TSH level was between 1 and 2  $\mu$ U/ ml, which required doses of 150 to 500  $\mu$ g/day. The 8 patients then underwent a second PET study. The peripheral infusion of adenosine does produce vasodilation of the coronary microvascular bed, but it can also transiently lower the systemic blood pressure and change the heart rate. MBF estimated from the dynamic PET images was combined with the heart rate and blood pressure 2 minutes after starting the adenosine infusion and used to correct the calculation of CFR and MVR.

#### Results

The mean myocardial parameters were provided for 8 controls and for 9 patients before L-T<sub>4</sub> treatment, but for only 8 patients after treatment. The mean adenosine stress MBF and corrected CFR values obtained before L-T<sub>4</sub> treatment were significantly lower in the 9 patients than in the 8 controls. Following 6 months of treatment with L-T<sub>4</sub>, the mean CFR increased ~50% and the mean corrected CFR increased 24% (P = 0.043) in the 8 patients, but these mean values remained lower than the mean CFR of the 8 controls. No significant differences in regional CFR or stress MBF were found, indicating that no hemodynamically relevant stenosis was present.

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#### Conclusions

In 9 patients with slightly to substantially elevated TSH values, analysis of 13N-ammonia uptake indicated that several parameters of coronary micro-

vascular function were significantly below control levels. In the 8 patents given 6 months of treatment with L-T<sub>4</sub>, the mean corrected coronary blood flow improved but was not normalized.

#### ANALYSIS AND COMMENTARY • • • • • •

It is somewhat surprising that there was no analysis of pretreatment and posttreatment data for individual patients, since they would have served as their own controls. Nonetheless, the findings seem consistent with recent echocardiographic studies on myocardial microvascular function, and they raise the possibility that myocardial, smooth muscle, endothelial, neural, or stromal changes, rather than major vessel dysfunction, may be present in some patients. Hashimoto's thyroiditis is the commonest cause of subclinical hypothyroidism, but other possible causes include advanced age, obesity, polymorphisms in genes such as phosphodiesterase-8, and TSH-receptor blocking antibodies. An increased TSH level also can occur—usually transiently—after taking certain foods or drugs, or during recovery from subacute, painless or postpartum thyroiditis, or from nonspecific illness. Some of these diagnoses are difficult to confirm, but a positive TPOAb titer does not prove that Hashimoto's thyroiditis caused a patient's subclinical hypothyroidism: for example, in the patient who required 500  $\mu$ g of L-T<sub>4</sub> for 6 months to normalize the TSH, a more obscure diagnosis (or noncompliance) might be possible. Furthermore, the wide range of TSH levels and the small number of subjects makes it difficult to know what to do with these results.

However, over the past 10 years or so, an upper limit of 10 µU/ml TSH for "watchful waiting" in subclinical hypothyroidism has become widely accepted. Patients whose TSH is consistently above 10  $\mu$ U/ml are known to be much more likely to advance to overt hypothyroidism, and a recent analysis of 11 prospective studies indicates that such patients are at increased risk of coronary heart disease and death (3). In a patient who has symptoms consistent with hypothyroidism, which cannot be otherwise unexplained, and whose TSH is slightly above normal but below 10, it seems reasonable to try a "therapeutic trial" of L-T<sub>4</sub>, recognizing that a favorable response does not prove that hypothyroidism was the cause. However, there are two clinical situations that require the physician's special attention when considering treatment of mild subclinical hypothyroidism. 1) In the pregnant patient, there is a clear consensus for giving L-T<sub>4</sub>. 2) In contrast, L-T<sub>4</sub> treatment of elderly patients with mild subclinical hypothyroidism must be closely monitored. TSH levels increase with age regardless of anti-TPO positivity, and some studies have found that slightly elevated TSH levels are associated with increased survival to great age. The dose of L-T<sub>4</sub> given to elderly patients is of special concern, since a recent study found that over 40% of patients aged 65 were receiving overreplacement, and this group is especially at risk for cardiovascular and skeletal side effects (4).

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#### References

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- Karmisholt J, Andersen S, Laurberg P. Variation in thyroid function in subclinical hypothyroidism: importance of clinical follow-up and therapy. Eur J Endocrinol 2011;164:317-323. Epub January 5, 2011.
- Rosário PW, Bessa B, Valadão MM, Purisch S. Natural history of mild subclinical hypothyroidism: prognostic value of ultrasound. Thyroid 2009;19:9-12.

DEDICATED TO SCIENTIFIC INQUIRY, CLINICAL EXCELLENCE, PUBLIC SERVICE, EDUCATION, AND COLLABORATION.

- Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304:1365-74.
- 4. Somwaru LL, Arnold AM, Joshi N et al. High frequency of and factors associated with thyroid hormone over-replacement and underreplacement in men and women aged 65 and over. J Clin Endocrinol Metab 2009;94:1342-5. Epub January 6, 2009.

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