



# Levothyroxine Treatment of Central Hypothyroidism Has a Beneficial Influence on Cardiovascular Risk Factors

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Klose M, Marina D, Hartoft-Nielsen ML, Klefter O, Gavan V, Hilsted L, Rasmussen AK, Feldt-Rasmussen U. Central hypothyroidism and its replacement have a significant influence on cardiovascular risk factors in adult hypopituitary patients. J Clin Endocrinol Metab. 2013;98:3802-10. Epub June 24, 2013; doi: 10.1210/jc.2013-1610.

**Background** Central hypothyroidism is a relatively rare disorder, occurring mainly in patients with pituitary tumors; it is often a consequence of the treatment of the tumor. The incidence of central hypothyroidism is estimated at 1:20,000 to 1:80,000 in the general population (1). Because of its rarity, the effect of central hypothyroidism on cardiovascular risk factors is difficult to assess. The current paper is a retrospective study of cardiovascular risk factors in growth hormone (GH)–deficient patients who also had central hypothyroidism in a single Danish

SUMMARY • • • • • • • • • • • • • • •

### Methods

hospital over a 20-year period.

The study included 209 patients with baseline thyroid function, uninterrupted GH therapy, and no Cushing's disease. Forty-six patients were TSH-sufficient (euthyroid) and 163 patients were characterized as TSH-deficient because they had an FT<sub>4</sub> <12 pmol/L (0.93 ng/dl). The TSH-deficient patients were divided into tertiles according to their FT<sub>4</sub> levels on levothyroxine therapy: the first tertile had the lowest FT<sub>4</sub> (<13.1 pmol/L), the second tertile an intermediate FT<sub>4</sub> (13.1 to 16.7 pmol/L), and the third tertile the highest FT<sub>4</sub> (>16.8 pmol/L) before commencing GH therapy. The 46 patients who were TSH-sufficient were compared with 54 patients in each tertile with regard to lipid parameters and body composition.

### Results

At baseline,  $FT_4$  was inversely associated was associated with a higher body-mass index (BMI) (r = -0.15; P = 0.03), waist circumference (r = -0.19; = 0.03), hip circumference (r = -0.20; P = 0.05), and directly associated with HDL (r = 0.28; P < 0.001), independent of age, sex, and IGF-I. No significant correlations were observed between  $FT_4$  and other body-composition or lipid markers.

Follow-up data were available for 192 patients at a median follow-up time of 4.1 years (range, 2.5 to 5.8) after initiation of GH therapy. At follow-up, 31 patients (16%) were categorized as TSH-sufficient and 161 (84%) as TSH-deficient. Twelve patients (21%) initially defined as TSH-sufficient were on levothyroxine treatment; 32 (64%) first-tertile, 28 (54%) secondtertile, and 17 (33%) third-tertile patients received an increased levothyroxine dose as compared with baseline, whereas 12 (27%) had a dose reduction and 2 had stopped levothyroxine treatment. An increase in  $FT_4$  was associated with a decrease in BMI (r = -0.16; P = 0.03), lean body mass (r = -0.21; P<0.01), diastolic blood pressure (r = -0.17; P = 0.03), total cholesterol (r = -0.27; P < 0.01), and LDL cholesterol (r = -0.26;P<0.01). These associations remained after adjustment for the change in IGF-I.

### Conclusions

The data indicate the importance of optimal levothyroxine replacement to reduce cardiovascular risk in patients with central hypothyroidism.

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

The rarity of central hypothyroidism makes it difficult to accumulate a significant number of patients to study its cardiovascular risk and nearly impossible to study its effects on cardiovascular events. Because these patients were part of a group also treated with GH and carefully followed with regard to various cardiovascular risk parameters, the data could be analyzed for the effects of levothyroxine therapy on these parameters. Since all of the patients were treated with GH, leading to an optimal level of IGF-I, the effects were considered to be unrelated to the GH therapy. However, the significant effects, mainly associations, were relatively modest. On the other hand, this is a somewhat heterogeneous group of patients. With regard to the lipid parameters, patients on lipid-lowering drugs were excluded from the analysis. Although the patients did not receive a dose of levothyroxine aimed at a specific target FT<sub>4</sub>, a dose that achieves an FT<sub>4</sub> of >13 pmol/L (1.0 ng/dl) is generally considered euthyroid. In our clinic, we aim for the

levothyroxine dose in patients with central hypothyroidism to achieve an  $FT_4$  of >1.2 ng/dl.

A recent paper pointed out that there are patients with subclinical central hypothyroidism who can be diagnosed by echocardiography, even though their  $FT_4$  is in the normal range (2) (reviewed in the June 2012 issue of Clinical Thyroidology). Treatment of these patients with levothyroxine improved the echocardiographic parameters. This finding is consistent with the results showing that the first tertile of patients with hypothyroidism in the current report had less desirable anthropomorphic and lipid measurements and that additional treatment with levothyroxine improved these parameters.

Because of the commercial importance of GH therapy, the beneficial effect of much cheaper therapy with levothyroxine in patients with hypothyroidism is often overlooked. This study shows the significant benefit of this simple therapy, which is widely accepted by these patients in contrast to the daily injection required for treatment with GH.

#### References

- 1. Price A, Weetman AP. Screening for central hypothyroidism is unjustified. BMJ 2001;322:798.
- Doin FC, Rosa-Borges M, Martins MR, Moisés VA, Abucham J. Diagnosis of subclinical central hypothyroidism in patients with hypothalamicpituitary disease by Doppler echocardiography. Eur J Endocrinol 2012;166:631-40. Epub January 20, 2012.