DOES EXTREME OBESITY AFFECT THYROID HORMONE METABOLISM?

Michalaki MA, Gkotsina MI, Mamali I, Markantes GK, Faltaka A, Kalfarentzos F, Vagenakis AG, Markou KB. **Impaired pharmacokinetics of levothyroxine in severely obese volunteers.** Thyroid. March 21, 2011 [E-pub ahead of print]. doi: 10.1089/thy.2010.0149.

SUMMARY

BACKGROUND

These authors previously reported that euthyroid but severely obese subjects have higher levels of triiodothyronine (T_3), thyroxine (T_4) and thyrotropin (TSH) than normal controls, and suggested that the morbidly obese have reset their "central thyrostat" (1).

METHODS

The authors assessed the kinetics of serum T_3 and T_4 after giving 600 µg of levothyroxine (L-T_4) as an oral solution to 16 men and 22 women who were apparently euthyroid but severely obese (mean [±SD] body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] 48.6±8.3) and to 24 age-matched controls (mean BMI, 23.3±1.7). None of the study participants was taking any medication, had positive anti-thyroid peroxidase antibodies or any thyroid disease, or had other co-morbidities. There was no mention of smoking status. The mean basal serum TSH was 2.3±1.0 µIU/ml and the mean total T_4 was 8.7±1.3 µg/dl in the obese subjects, as compared with 1.3±0.9 and 7.5±1.3 in the controls (both P<0.001). After a 12-hour fast, the subjects were given 600 of µg L-T_4 in the morning, and blood was sampled for the next 4 hours.

RESULTS

Administering L-T_4 caused the mean serum T_3 to fall 7% in the morbidly obese subjects (from 137±16 to128±14) at 2 hours, whereas it rose 17% (from 133±19 to 155±21) in the controls (P<0.001). The serum T_4 level rose in both groups, but it peaked later in the obese group (2.5±0.9 vs. 1.9±0.1 hr, P<0.01). Based on estimated plasma volume and the assumption that giving exogenous L-T_4 did not suppress the release of endogenous T_4 and TSH and that the endogenous production of T_4 remained constant during the study period, the calculated area under the curve was lower for obese subjects (13.5±7.4 vs. 19.1±5.4 P< 0.01), as was the maximum concentration of T_4 (5.1±2.3 vs. 6.4±1.8, P<0.05) as compared with controls.

CONCLUSIONS

The authors concluded that severely obese individuals may require higher doses of L-T_4 than normal and that impaired L-T_4 pharmacokinetics such as delayed gastrointestinal absorption might be involved. The reason for the small decrease in serum T_3 was not clear.

COMMENTARY

In view of reports of accelerated gastric emptying in morbidly obese patients, it would have been helpful if there was some other evidence of jejunoileal malabsorption to support the authors' suggestion that delayed L-T_4 absorption was involved. Knowing the smoking history of the subjects would have been helpful, in view of the strong correlation between current smoking, BMI, and TSH levels in Norwegian men and women (2). That study also found a strong correlation between BMI and "subclinical hypothyroidism" in current smokers, as well as in never-smokers (2).

Many studies have found a direct correlation between BMI and TSH levels in apparently healthy individuals whose thyroid hormone and TSH levels are in the normal range. There is controversy concerning whether some of these individuals have "subclinical hypothyroidism," however. It has been suggested that elevated antithyroid antibodies need to be present before entertaining the diagnosis in such cases (3).

The L-T_4 dose required to maintain euthyroidism in thyroidectomized subjects has been reported to be directly related to circulating interleukin (IL)-6 levels (4), and cells in adipose tissue from obese subjects

continued on next page

are known to release more IL-6. A recent study on a variety of human cells reported that IL-6 blocks their conversion of T_4 to T_3 while increasing their inactivation of both T_3 and T_4, apparently by depletion of an intracellular thiol co-factor (5). Could the higher levels of IL-6 in severely obese individuals affect the way such individuals metabolize L-T_4?

— Stephen W. Spaulding, MD

References

1. Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, Psyrogiannis Ai, Kalfarentzos FE,. Kyriazopoulou VE. Thyroid function in humans with morbid obesity. Thyroid 2006:16:73-8.
2. Åsvold BO, Bjøro T, Vatten LJ. Association of serum TSH with high body mass differs between smokers and never-smokers. J Clin Endocrinol Metab 2011;94:5023-7. Epub October 21, 2009; doi:10.1210/jc.2009-1180.
3. Rotondi M, Magri F, Chiovato L. Thyroid and obesity: not a one-way interaction. J Clin Endocrinol Metab 2011;96:344-6.
4. Papanas N, Papatheodorou K, Papazoglou D, Gioka T, Antonoglou C, Kotsiou S, Maltezos E. Post-thyroidectomy thyroxine replacement dose in patients with or without compensated heart failure: the role of cytokines. Cytokine 2008;41:121-6. Epub December 31, 2007.
5. Wajner SM, Goemann IM, Bueno AL, Larsen PR, Maia AL. IL-6 promotes nonthyroidal illness syndrome by blocking thyroxine activation while promoting thyroid hormone inactivation in human cells. J Clin Invest 2011;121:1834-45. E-pub April 11, 2011; doi:10.1172/JCI44678.