Patients with subclinical thyrotoxicosis experience significant improvements in mood and motor learning but have minor declines in self-perceived general and physical health status

Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, mood, and cognition in experimentally induced subclinical thyrotoxicosis. J Clin Endocrinol Metab 2008;93:1730-6.

SUMMARY

BACKGROUND The authors suggest that subclinical thyrotoxicosis, defined as an abnormally suppressed serum thyrotropin (TSH) level with normal serum free T_4 (FT_4) and free T_3 (FT_3) levels may adversely affect mood and cognition. They recently reported that subclinical hypothyroidism leads to decrements in health status, mood, and working memory. The aim of this double-blind, randomized, crossover study was to establish whether subclinical thyrotoxicosis also alters health status, mood, and cognitive function.

METHODS The study subjects were 33 volunteers with adult-onset hypothyroidism, which in 2 cases was caused by radioiodine therapy for Graves' disease and in 31 others by autoimmune hypothyroidism. Subjects were randomly assigned to receive either their usual doses of levothyroxine ($L\text{-}T_4$) (euthyroid arm) or higher doses of $L\text{-}T_4$ aimed at achieving a serum TSH level of 0.01 to 0.4 mU/L (subclinical thyrotoxicosis arm). Six weeks later, $L\text{-}T_4$ compliance was assessed and dose adjustments were made as needed. Twelve weeks after the baseline visit, subjects returned for an extended visit, at which they underwent evaluations of health status, mood, and cognition with Short Form 36 (SF-36) and Profile of Mood States (POMS) and evaluations for thyrotoxicosis symptoms using the Hyperthyroid Symptom Scale. The subjects then crossed over to the second arm of the study, and their new doses of $L\text{-}T_4$ were dispensed. At the end of the study, subjects were asked to identify the high-dose study arm and which arm they preferred.

The SF-36 is a multipurpose health survey with 36 questions that yield an 8-scale profile of functional health and well-being scores as well as a psychometrically based health utility index. Higher scores on SF-36 reflect better health status and well-being. The POMS is a measure of six dimensions of affect or mood, including tension–anxiety, depression–dejection, anger–hostility, vigor–activity, fatigue–inertia, and confusion–bewilderment. Respondents rate 65 adjectives on a 5-point intensity scale, in terms of how they have been feeling in the past week (0 = not at all and 4 = extremely). Except for vigor–activity, the higher the score, the greater the mood disturbance or the more distress. Also a battery of cognitive tests for different forms of memory was administered to assess different cognition areas of the brain.

RESULTS The mean (±SEM) baseline, euthyroid arm, and thyrotoxic arm serum TSH levels were 2.58±0.27, 2.15±0.31, and 0.17±0.06 mIU/L, respectively; the serum FT_4 levels were 1.33±0.04, 1.40±0.04, and 1.70±0.06 ng/dl; and the FT_3 levels were 262.7±6.3, 259.3±6.2, 320.2±11.4 pg/dl ($P<0.001$ for all thyroid tests). Study subjects were unable to reliably predict which arm was the subclinical thyrotoxicosis arm. Fifteen of 33(45.5%) guessed correctly, 10 (30%) guessed incorrectly, and 8 (24%) had no opinion. Sixteen (48.5%) preferred the $L\text{-}T_4$ dose that they perceived was the higher dose, 5 (15%) preferred the dose they perceived was the euthyroid dose, and 12 (36%) had no preference (P not significant)

At the end of the subclinical thyrotoxicosis arm the SF-36 physical health status was slightly worse ($P = 0.01$), the mental component summary scale was slightly but not significantly better ($P = 0.15$) and the mental health subscale was significantly improved ($P = 0.01$, Figure 1). The POMS confusion, depression, and tension subscales were significantly improved during the subclinical thyrotoxicosis arm ($P = 0.04$ to 0.06, Figure 2). There were no other significant effects on the SF-36 or POMS subscales. Changes in the mental component summary and the general health subscale scores of SF-36 were directly related to changes in the serum FT_3 levels between the two study arms; changes in the mental component summary were also related to serum FT_4. The other significant finding was that changes in motor learning, a basal ganglia, and cerebellar function, were observed (Figure 3).

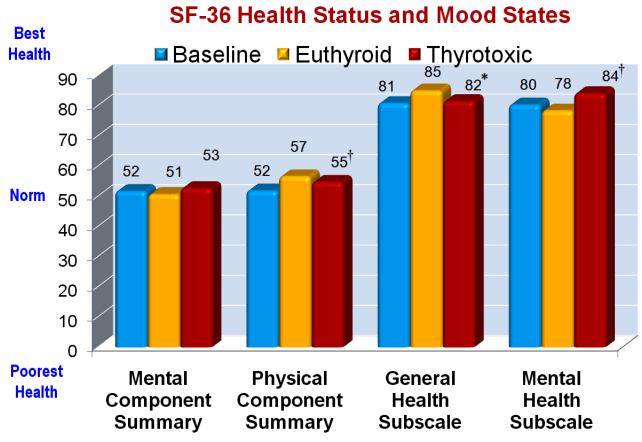

Figure 1. The bars show scores in the SF-36 health status and mood states. †P = 0.01. *P = 0.06 as compared with baseline and the euthyroid arm. Here and elsewhere figures are rounded to the nearest integer. (This figure is drawn from data in Table 2 of Samuels et al.)

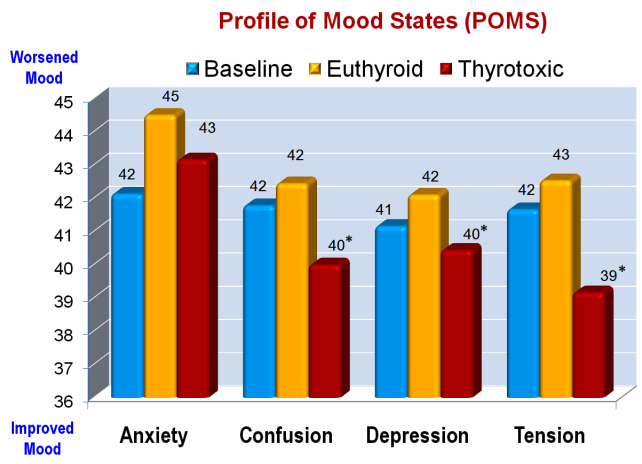

Figure 2. There is a significant improvement in the POMS scores during the subclinical thyrotoxicosis arm. They were significantly improved for confusion, depression, and tension subscales. *P = 0.04 to 0.06, as compared with euthyroid arm (This figure is drawn from data in Table 2 of Samuels et al.)

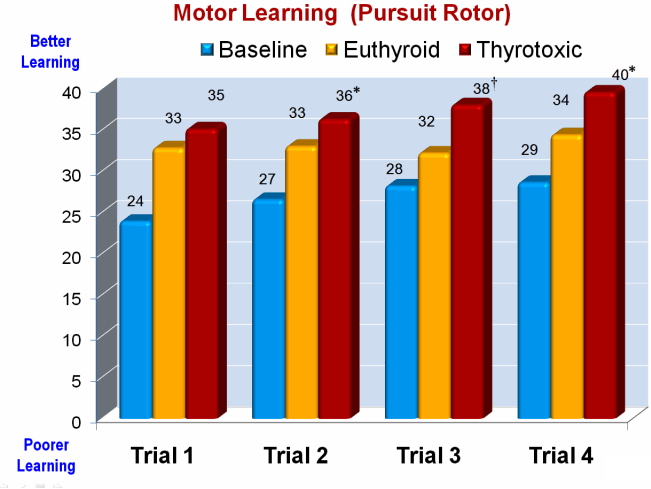

Figure 3. The results of motor learning (pursuit rotor) . In this test, subjects held a photosensitive wand to maintain contact with a 2-cm light disk rotating on a variable-speed turntable. The outcome measured was the mean total time the stylus remained on target during each of four trials *P<0.05 as compared with the euthyroid arm. (This figure is drawn from data in Table 3 of Samuels et al.)

CONCLUSION Patients with subclinical thyrotoxicosis experience improvements in mood and motor learning but have small declines in self-evaluated general and physical health status, suggesting that patients with hypothyroidism should not be treated with suppressive doses of L-T_4.

COMMENTARY

In a similarly designed study with the same outcome measures, Samuels et al. (1) found that subclinical hypothyroidism was associated with decrements in working memory but not in motor learning, as compared with improved motor learning without changes in working memory in the subclinical thyrotoxicosis study. This suggests that different parts of the brain were affected. The authors opine that taken together these studies suggest that there is a "window" of thyroid function of overall health, as defined by the SF-36 physical-component summary and the general health subscale, but that mental health and mood may improve, as defined by the SF-36 mental-component summary and POMS.

One of the interesting findings of the Samuels study is that more than half the subjects were unable to accurately identify when they were in the thyrotoxic arm of the study. This is similar to findings by Walsh et al. (2), who performed a double-blinded, randomized clinical trial of 56 subjects with hypothyroidism who were taking 100 μg or more of L-T_4 daily that was altered by 25-μg increments to stratify patients into low, middle, and high L-T_4 treatment groups. There were no significant treatment effects identified by any of the instruments, such as SF-36, the Thyroid Symptom Questionnaire, and tests assessing well-being, and in quality of life or cognitive function, and there was no significant treatment preference. Small changes in L-T_4 dosage did not produce measurable changes in symptoms of hypothyroidism, well-being or quality of life, despite the changes in serum TSH and other markers of thyroid hormone action.

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References

1. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, mood, and cognition in experimentally induced subclinical hypothyroidism. J Clin Endocrinol Metab 2007;92:2545-51.

2. Walsh JP, Ward LC, Burke V, et al. Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double blind, randomized clinical trial. J Clin Endocrinol Metab 2006;91:2624-30.