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Elevated TSH and Obesity: Cause or Consequence?

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Abstract

Obesity rates are becoming a worldwide epidemic. Elevated body mass index is largely associated with increased risk for diseases and laboratory abnormalities, including elevations in thyroid stimulating hormone (TSH). In many obese patients, the elevation in TSH exists with normal peripheral thyroid hormones, such as free T4. The case presented in this paper involves a 38-year-old morbidly obese female who presents to the clinic with fatigue. Laboratory results reveal an increased TSH level and normal free T4 level. Does this constitute a diagnosis of subclinical hypothyroidism, and should this patient receive thyroid supplementation as treatment? This paper explores and analyzes research conducted on subclinical hypothyroidism as it relates to obesity, identifies potential causes of elevated TSH in the setting of obesity, and discusses implications of treating elevated TSH in obese patients.

Elevated TSH and Obesity: Cause or Consequence?

Background

Obesity, as defined by a body mass index (BMI) greater than 30, is estimated to affect almost 40% of U.S. adults as of 2016 (Centers for Disease Control, 2019). Elevated BMI can have negative impacts on hormone levels and metabolism (Rotondi, Magri, & Chiovato, 2011). Hypothyroidism, a disease commonly associated with obesity, is estimated to affect over 20 million Americans (American Thyroid Association, 2019). Both of these rates of prevalence are on the rise. In patients with both diagnoses, obesity is oftentimes believed to be caused by hypothyroidism. New research suggests increased levels of thyroid stimulating hormone (TSH) could be a consequence of obesity, especially in those patients with subclinical hypothyroidism.

The purpose of this paper is to explore the controversial link between hypothyroidism and obesity to determine whether obesity is the cause or consequence of elevated TSH levels. It will compare and contrast evidence of cause and consequences with a brief literature review. This paper will also explore the differences in overt hypothyroidism and subclinical hypothyroidism in the obese patient. Implications for treatment of subclinical hypothyroidism will also be discussed.

Case Report

The research questions and foundation for this paper are centered around LT, a 38-year-old female who presents with chief complaints of fatigue and dry skin. LT endorses that over the last few months she has become increasingly more fatigued. She is getting about seven hours of sleep per night and takes naps with her children during the day. LT is 12 months post-partum and has just stopped breastfeeding. She complains of intermittent constipation. The patient describes hair loss consistent with her post-partum status. She has never been diagnosed with depression

but wonders if perhaps that could be causing her fatigue. LT endorses no purposeful exercise and states, “I have been somewhat overweight my entire life.” She describes a diet high in simple carbohydrates and sugar. She wonders if her diet could be contributing to her symptoms. LT has a past medical history positive for two normal spontaneous vaginal deliveries. Her current medications include a multivitamin and probiotic daily. She has no known allergies.

Upon examination, the patient’s vital signs are within normal limits. She is 62 inches tall and weighs 120 kg, making her BMI 48.3. Her physical examination is greatly benign with the exception of dry cracked skin on her hands, elbows, knees and lower legs. Her nails are short and have a peeled appearance. On auscultation, her bowel tones are normal. Her deep tendon reflexes are 2+ and brisk. The NP questions hypothyroidism but cannot rule out anemia or depression in her differential. She orders a CBC, CMP, TSH and free T4. The CBC and CMP are unremarkable. However, TSH is 6.6 and free T4 is 1.27. Given these lab values, the NP diagnoses LT with subclinical hypothyroidism and levothyroxine therapy is initiated. With a normal free T4, LT is started at 25 mcg of levothyroxine daily. She will return to the clinic in 6-8 weeks for a repeat TSH and free T4 for potential dose adjustment.

The NP also spends time discussing LT’s BMI and recommends she start 30 minutes of physical activity three times per week and gradually increase to a goal of 30-45 minutes of activity at least five times per week. She also refers her to a registered dietician to address her diet. A goal of 5-10% reduction in body weight by her follow up appointment is set.

Literature Review

The relationship between obesity and thyroid hormones is a contentious issue for patients and providers alike. In the case study presented above, the patient's elevated TSH, or hyperthyrotropinemia, was a differential diagnosis for the chief complaint of fatigue. However, morbid obesity complicates her case which poses an important question; does her hyperthyrotropinemia contribute to her obesity or did her increased body mass cause her elevated TSH? Furthermore, is mildly elevated TSH in obesity worrisome, and should it be treated?

Thyroid hormones have a well-known relation to body mass, temperature regulation, and metabolism. Basal metabolic rate is regulated by the thyroid, which plays an important role in promoting thermogenesis (Sanyal & Raychaudhuri, 2016). Thyroid hormones also influence several other metabolic pathways including hunger, lipid and glucose breakdown, and energy expenditure from fat stores (Sanyal & Raychaudhuri, 2016). The thyroid gland produces thyroxine, or free T4, which has a direct effect on cell metabolism influencing the rate of ATP production in the mitochondria, having an effect on the "conversion of caloric energy to heat" (Martin & Blair, 2015). Both overt hypothyroidism (elevated TSH and decreased free T4) and subclinical hypothyroidism (slightly increased TSH and normal free T4) are associated with cellular changes that can affect metabolism (Biondi, 2010). While the thyroid gland does not directly affect weight control feedback mechanisms in the body, thyroid dysfunction has been associated with obesity or weight loss resistance (Martin & Blair, 2015).

Much of the research from the last 15 years on obesity and thyroid hormones has been focused on whether increased body mass trends are related to thyroid dysfunction or disturbance (Michalaki et al., 2006; Rotondi et al., 2009; Marzullo et al., 2010). In these studies, elevations in TSH were seen frequently in obese patients, so a positive correlation between elevated BMI and

elevated TSH was shown. Research argues that even marginally elevated TSH levels, suggestive of mild thyroid failure, are associated with increased body mass and increased obesity rates (Knudsen et al., 2005).

Several hypotheses to explain the cause of increased TSH levels in obesity exist. These include subclinical hypothyroidism (e.g. caused by iodine deficiency or autoimmune thyroiditis), imbalance in the hypothalamic-pituitary axis, thyroid hormone resistance, or an adaptation process to increase energy expenditure (Reinehr, 2010). In two large cohort studies, research examined morbidly obese patients (BMI >40) who had elevated TSH. The data presented found no correlation to positive thyroid antibodies or iodine deficiency and obesity, suggesting subclinical hypothyroidism may not be the cause of elevated TSH in obese patients (Rotondi et al., 2010; Reinehr et al., 2007).

Leptin is a hormone produced by fat cells that helps regulate appetite and energy expenditure (Biondi, 2010). It is also "an important neuroendocrine regulator of the hypothalamic-pituitary-thyroid axis, by regulation of TRH gene expression in the paraventricular nucleus. In turn, TSH will stimulate leptin secretion by human adipose tissue" (Biondi, 2010). This causes constant high levels of circulating leptin, which may lead to leptin resistance (Biondi, 2010). Leptin also affects the conversion of T4 to T3 (Biondi, 2010). Both of these factors support the idea that leptin and thyroid hormones are related, and increased levels of thyroid hormones could cause decreased leptin action (or vice versa), leading to increased appetite, and therefore increased body mass. There has not been any experimental research done on this topic, however, so this idea is very hypothetical.

Thyroid hormone resistance is another explanation for elevated TSH in obesity. Although plasma TSH levels are elevated, TSH receptors are less expressed on the fat cells of obese

patients in comparison to those with a normal BMI (Biondi, 2010). Reduced receptor expression could cause a down-regulation of hormone receptors and their action (Biondi, 2010). Furthermore, this would "increase plasma TSH and free T3 concentrations and constitute a condition of peripheral thyroid hormone resistance" (Biondi, 2010). Interestingly, weight loss would restore fat cells to their normal size and this process could be reversed.

In addition, there is the possibility of the body increasing TSH levels to increase resting energy expenditure (Reinehr, 2010). This theory is substantiated by the research that shows TSH levels normalize after significant weight loss (Reinehr, 2010; Reinehr et al., 2008; Janssen et al., 2015). In a well-designed study by Janssen et al. (2015), researchers analyzed TSH and free T4 levels from obese patients undergoing Roux-en-Y gastric bypass (RYGB). In their study, elevated TSH and normal free T4 levels were present in 71 out of 503 patients (Janssen et al., 2015). They did not include patients already on thyroxine therapy. These levels were drawn prior to surgery and then 12 months post-RYGB. The patients' mean BMI prior to surgery was 47 and 12 months post-operatively it was, on average, 34. In approximately 90% of the patients included in the study, TSH levels normalized after the 12-month post-operative period (Janssen et al., 2015). This data strongly suggests these patients did not need thyroxine supplementation as significant weight loss normalized their TSH levels. This study recommends those patients who were on thyroxine therapy for subclinical hypothyroidism pre-operation should wean off thyroxine after significant weight loss and recheck TSH levels, which they postulate, would be normal (Janssen et al., 2015). In those patients whose TSH did not normalize with weight loss, researchers tested thyroid antibodies to further rule out autoimmune causes of subclinical hypothyroidism (Janssen et al., 2015). This study had eight patients whose TSH did not normalize and went on to have anti-TPO and anti-Tg levels drawn. Of the eight tested, only one

patient was diagnosed with Hashimoto's Thyroiditis and was started on thyroxine therapy. No reliable experimental data has been published on non-surgical weight loss and the effect on thyroid levels.

Untreated overt hypothyroidism can have serious cardiac implications, however, there is much debate over the effects of subclinical hypothyroidism on cardiac diseases. Hypothyroidism causes relaxation of vascular smooth muscle which decreases cardiac output (Udovic, Pena, Patham, Tabatabai, & Kansara, 2017). Over time, this leads to a myriad of other cardiac issues including increased systemic vascular resistance, arterial stiffness, and hypertension (Udovic, Pena, Patham, Tabatabai, & Kansara, 2017). Bradycardia is often seen in hypothyroidism due to the effects thyroid hormones have on pace-maker cells (Udovic, Pena, Patham, Tabatabai, & Kansara, 2017). Elevated total cholesterol and low-density lipoprotein levels are often seen in hypothyroid states (Udovic, Pena, Patham, Tabatabai, & Kansara, 2017). This is due to the "decreased expression of hepatic LDL receptors and reduced activity of cholesterol-α-monooxygenase, which breaks down cholesterol, resulting in decreased LDL clearance" (Udovic, Pena, Patham, Tabatabai, & Kansara, 2017). Overt hypothyroidism leads to this "deranged lipid profile" and research has focused on whether subclinical hypothyroidism can cause these changes in lipid levels as well.

Over time, observational studies have aimed to answer this question. In the early 2000s, research focused on drawing connections between subclinical hypothyroidism and hyperlipidemia. However, a recent randomized controlled trial in Iran demonstrates no differences in lipid profiles exist in subclinical hypothyroid patients when compared to euthyroid patients (Alamdari et al., 2016). Similar data was published by Pirich, Mullner, & Sinzinger (2000). The National Health and Nutrition Examination Survey III gathered demographic and

health information from about 40,000 Americans during the years 1988 through 1994 (Hueston & Pearson, 2004). From this study, researchers were able to examine any association between hyperlipidemia and subclinical hypothyroidism. Data from adults aged 40 or older, who did not have diagnosed thyroid dysfunction were included. Lipid panels from patients who had subclinical hypothyroid and euthyroid states were analyzed and compared (Hueston & Pearson, 2004). In this population-based study, there did not appear to be a correlation between subclinical hypothyroidism and elevations in total cholesterol or low-density lipoproteins when compared to the euthyroid cohort (Alamdari et al., 2016; Hueston & Pearson, 2004). While it does not appear subclinical hypothyroidism in itself can cause an elevated lipid profile, no experimental research has been conducted to include obesity as a factor.

Perhaps the most recent and relative data on the treatment of subclinical hypothyroidism comes from a systematic review and meta-analysis conducted by the Journal of the American Medical Association. Authors of this analysis aimed at proving or disproving the association of thyroid supplementation on quality of life and other thyroid-related symptoms in subclinical hypothyroid adults (Feller et al., 2017). They included 21 of 3,088 randomized controlled trials that compared placebo with thyroid supplementation in non-pregnant subclinical hypothyroid adults. They explored thyroid-related factors such as outcomes on body mass index, systolic blood pressure, cognitive function, and quality of life and mood-related outcomes (Feller et al., 2017). It was concluded that thyroid supplementation in subclinical hypothyroidism, for non-pregnant adults, does not improve thyroid-related outcomes and/or general quality of life (Feller et al., 2017). The authors summarize the outcomes of this analysis with the following recommendation for practice: “these findings do not support the routine use of thyroid hormone therapy in adults with subclinical hypothyroidism” (Feller et al., 2017).

With increasing obesity rates worldwide, clinicians must be privy to the idea that a patient's body mass index can affect their TSH levels. This author believes subclinical hypothyroidism is a consequence, rather than a cause of obesity. More experimental research is needed to create a new reference range for TSH levels in people with an elevated BMI. Supplementing thyroid hormones in subclinical hypothyroidism is not beneficial for weight loss or other thyroid-related problems. Subclinical hypothyroidism in obesity is better treated with significant weight loss, which warrants referrals from primary care to specialists such as registered dieticians, lifestyle medicine practitioners, mental health practitioners, and in some cases bariatric surgeons.

As for LT, presented in the case study, the NP chose to supplement her elevated TSH with levothyroxine. Perhaps a better course of action would have been to rule out potential causes of subclinical hypothyroidism, such as thyroid autoimmunity or iodine deficiency. If these studies were negative, educating LT and exploring ways to better support weight loss efforts would have been more beneficial for lasting outcomes.

Learning Points

- Obesity is associated with elevations in TSH levels; more research is needed to develop a new reference range for TSH in obese non-pregnant adults
- The increase in TSH levels in obese patients could be attributed to leptin, peripheral hormone resistance, or adaptation to increase energy expenditure; more research is needed to identify the exact cause
- Specific causes of subclinical hypothyroidism, such as autoimmunity or iodine deficiency should be ruled out
- Non-specific subclinical hypothyroidism in nonpregnant adults should not be treated with thyroid supplementation; treatment does not affect thyroid-related diseases or quality of life
- Treatment of elevated TSH in obese adults should be focused on lifestyle modifications to decrease BMI; more research is needed to determine a specific percentage of weight loss to see normalization in TSH

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