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Elevated levels of circulating thyroid hormone do not cause the medical sequelae of hyperthyroidism

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ABSTRACT

Background: Clinicians have been reluctant to use high dose thyroid (HDT) to treat affective disorders because high circulating levels of thyroid hormone have traditionally been equated with hyperthyroidism, and understood as the cause of the medical sequelae of hyperthyroidism, such as osteoporosis and cardiac abnormalities. This conclusion is not supported by (HDT) research.
Methods: A literature review of research related to the morbidity and mortality of HDT treatment was performed.
Results: There exists a large body of research involving the use of HDT treatment to prevent the recurrence of differentiated thyroid cancer and to treat affective disorders. A review of this literature finds a lack of support for HDT as a cause of osteoporosis, nor is there support for an increase in morbidity or mortality associated with HDT. This finding contrasts with the well-established morbidity and mortality associated with Graves' disease, thyroiditis, and other endogenous forms of hyperthyroidism.
Discussion: The lack of evidence that exogenous HDT causes osteoporosis, cardiac abnormalities or increases mortality compared with the significant morbidity and mortality of hyperthyroidism requires an alternative cause for the medical sequelae of hyperthyroidism. One possibility is an autoimmune mechanism.
Conclusion: High circulating levels of thyroid hormone is not the cause of the sequela of hyperthyroidism. The reluctance to using high dose thyroid is unwarranted.

Contents

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1. Introduction

The assumption that high dose thyroid (HDT) causes iatrogenic hyperthyroidism affects the adoption of T3 or T4 to treat affective disorders. Although high levels of circulating thyroid hormone have been accepted as the cause of most medical sequelae associated with hyperthyroidism, recent review papers have not supported this assumption, suggesting that high dose thyroid (HDT) treatment is unlikely to lead to the same sequelae as hyperthyroidism. This calls into question the belief that the morbidity and mortality of hyperthyroidism are caused directly by high circulating levels of thyroid hormone, and raises the possibility that HDT treatment is substantially safer than conventionally believed (Kelly, 2014, 2015).

HDT is routinely used to prevent the recurrence of thyroid cancer (Cooper et al., 2009; Perros et al., 2014) and to treat affective disorders (Bauer et al., 1998, 2003, 2005; Bauer and Whybrow, 1990, 2001). A randomized double blind placebo controlled study showing the efficacy of HDT was recently published (Bauer et al., 2015). HDT is specifically recommended in multiple treatment guidelines for bipolar disorders (Crismon et al., 2007; Hirschfeld, 2010; Sachs et al., 2000; Yatham et al., 2013).

It is critically important to distinguish hyperthyroidism from high circulating levels of thyroid hormone caused by thyroid medication. Although the two are often confused, the latter does not meet the formal definition of hyperthyroidism discussed below. Surprisingly, some examples of this confusion are found in authoritative endocrine guidelines. In the *British Thyroid Association Guidelines for the Management of Thyroid Cancer* (Perros et al., 2014), the guidelines cite three studies as evidence of the cardiovascular risks of HDT, however all three studies evaluated patients with subclinical hyperthyroidism.

Similarly, the *Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer* (Cooper et al., 2009), states that "Adverse effects of TSH suppression may include the known consequences of subclinical thyrotoxicosis, including exacerbation of angina in patients with ischemic heart disease, increased risk for atrial fibrillation in older patients." A single study is cited to support this conclusion. Like some other studies discussed in this article, this study made the crucial error of conflating the disease of hyperthyroidism with high dose thyroid treatment. The authors studied a mixed group of patients with hyperthyroidism and those receiving thyroid hormone therapy (Sawin et al., 1994). Consequently, no conclusions can be drawn regarding the risk of clinical administration of thyroid hormone, separate from the disease of hyperthyroidism. This guideline also asserts a risk of osteoporosis (among postmenopausal women only) with HDT. However, the cited study concludes that subclinical hyperthyroidism is a risk factor but the evidence for external thyroid "is inconclusive" (Toft, 2001). Once again, the authors failed to distinguish high dose thyroid treatment from the disease of hyperthyroidism, invalidating their conclusion that the former causes osteoporosis.

2. Methods

Google Scholar (which includes PubMed) was used to search for all relevant articles pertaining to the use of HDT to treat differentiated thyroid cancer (DTC) or bipolar disorders. The following keywords were searched both individually and in combination: risks of, etiology of, cause of, HDT, supraphysiologic, liothyronine (T3), levothyroxine (T4), thyroid stimulating hormone (TSH), TSH suppression, TSH receptors, cardiovascular, cardiac, pulmonary hypertension, atrial fibrillation (AF), stroke, osteoporosis, osteopenia, morbidity, mortality, bipolar, affective disorders, major depression, augmentation, thyroid cancer, autoimmune, and hyperthyroidism. Once key articles were identified, the citations of those papers were examined for relevancy using the PubMed "Related Citations" feature to identify other relevant articles. Only statistically significant findings in the various studies were reported unless otherwise noted. Approval for the study was obtained from the institutional review board of the Poudre Valley Health Hospital.

2.1. Definition of terms

The joint task force of the American Thyroid Association and the American Association of Clinical Endocrinologists' management guidelines on hyperthyroidism treatment provides the following definitions: Hyperthyroidism is defined as the overproduction of endogenous thyroid hormone with accompanying signs and symptoms of thyrotoxicosis. Thyrotoxicosis is the presence of signs and symptoms of high circulating levels of thyroid hormone. Both must be confirmed by laboratory studies. Hyperthyroidism is a subtype of thyrotoxicosis, while subclinical hyperthyroidism is a mild form of hyperthyroidism (Bahn et al., 2011). When high doses of thyroid are used to treat specific illnesses, the terminology used in the literature varies. This paper will use the term "high dose thyroid" (HDT) to describe treatment with high doses of exogenous thyroid.

3. Results

A significant amount of experience with HDT has been accumulated because it is routinely used to suppress the recurrence of DTC (Cooper et al., 2009; Heemstra et al., 2006; Quan et al., 2002), and for the treatment of affective disorders. The use of HDT to successfully treat bipolar disorders and, to a lesser extent, refractory major depression has a long history in psychiatry, and is recommended in multiple treatment guidelines (Crismon et al., 2007; Hirschfeld, 2010; Sachs et al., 2000; Yatham et al., 2013). For example, the "Texas Algorithms Procedural Manual for the Treatment of Bipolar Disorders" recommends doses of T3 up to 160 mcg and T4 doses up to 500 mcg (Crismon et al., 2007).

3.1. The effects of HDT on bone mineral density

There is a large body of literature on HDT used to suppress the return of DTC that includes data on changes in bone mineral density (BMD). The most recent review was done in 2006 by Heemstra et al. The authors evaluated 21 studies of HDT used to prevent the recurrence of DTC. The authors concluded, "…our data suggest that postmenopausal women with subclinical hyperthyroidism (sic) are most at risk, whereas no increased risk was observed in men and premenopausal women." (Heemstra et al., 2006).

Increased risk in postmenopausal women is widely accepted, however the data supporting this conclusion is questionable. Heemstra et al. reviewed 16 studies that included postmenopausal women (Heemstra et al., 2006). Twelve were cross sectional, two used a more rigorous longitudinal design, and two studies included elements of both. Among the cross sectional designs only four found a decrease in BMD, whereas ten did not. Among the longitudinal studies two found a decrease in BMD, and two found no change.

One of the two longitudinal studies that reported decreased BMD among postmenopausal women included 46 participants who were followed for two years. Calcium intake among these women was low, averaging 507 mg/day, less than half of the recommended amount of 1200 mg/day. All received HDT for the treatment of thyroid cancer. The participants were randomized into three groups: one group received 200 mcg of intranasal calcitonin plus 1000 mg of calcium daily, another received calcium alone, and the third received placebo. Only the women in the placebo group showed significant bone loss at the end of the study. The other two groups had stable BMD and there was no additional benefit from calcitonin compared to calcium alone. Therefore, only women with inadequate calcium intake, a known risk factor for osteoporosis, showed decreased BMD. Women with adequate calcium intake did not experience decreased BMD. The conclusion that HDT caused the decrease in BMD is not supported. This indicates that only