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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.

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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

women with inadequate calcium intake are at risk (Kung and Yeung, 1996).

The second longitudinal study (Jodar et al., 1998) reviewed by Heemstra et al. reported an increased risk for postmenopausal women of "minimal," although statistically significant, reduction in appendicular bone density in one of five areas that were measured. However the authors of the original study, Jodar et al., concluded that error variations of the DXA measurements made it unlikely that these minimal differences were meaningful.

Following the publication of that most recent review article, three more studies have assessed the risk to BMD when HDT was used to suppress the return of DTC. A 2008 study compared 66 patients to 66 healthy controls individually matched to the patients for age, gender, and menopausal status. Each group contained 11 men, 22 premenopausal women and 33 postmenopausal women. The levothyroxine treated group was followed for an average of 15 months, and experienced no decrease in BMD compared to the controls. Notably there was no difference in any of the subgroups, including the postmenopausal women (Eftekhari et al., 2008).

The most recent study, conducted in Japan, enrolled 225 women in a randomized controlled trial that evaluated the effects of postoperative HDT therapy on disease-free survival for papillary thyroid carcinoma, while prospectively evaluating the effects of TSH suppression on BMD (Sugitani and Fujimoto, 2011). The group who received HDT had a mean TSH level of 0.07 ± 0.10 mU/L, while the control group were kept within the normal range, and had a mean TSH of 3.14 ± 1.69 mU/L. After one year of follow up, changes in BMD did not differ significantly between groups for younger women (<50 years old), but significant differences were seen for older women (≥50 years old). However, the authors did not report such results at the 3 and 5 year measurements for women over 50. Overall the study found no significant differences in BMD between the control group and the treatment group at any time period.

Daily calcium intake was not reported in this study, which is problematic because the average intake of calcium per day among women in Japan is significantly less than among women in the United States and Europe. Japanese women average only 607 mg/day, which may confer greater vulnerability to the adverse effects of HDT compared to women who receive at least 1200 mg/day of calcium (Higashiguchi et al., 2009). From a clinical point of view, in which calcium supplementation can be routinely included with HDT, data used to support evidence-based decision making should be limited to samples that have adequate calcium intake.

The remaining study is the most important from the point of view of differentiating hyperthyroidism from HDT treatment. Four groups of postmenopausal women were studied, each with approximately 20 subjects (Belaya et al., 2007). The first group had toxic multinodular goiter, and the second had Graves' disease. The third group received HDT after thyroidectomy due to DTC (mean treatment duration 3 years, range 1.5–6 years), and the fourth consisted of healthy women matched for age and duration of menopause. The mean TSH values for the four groups were 0.198 (toxic multinodular goiter), 0.084 (Graves' disease), 0.060 (TSH suppressive therapy), and 1.862 (healthy controls).

Biochemical markers of bone turnover were significantly higher in all the patient groups compared to the control group, however only the first two groups had significantly lower BMD. There was no difference in BMD between the control group and the patients who were treated with HDT. Although it is a relatively small study, this head-to-head comparison provides important evidence that there are fundamental differences between hyperthyroidism and HDT. It is particularly notable for finding no effect of HDT on BMD even in a sample consisting entirely of postmenopausal women.

Four psychiatry studies have addressed the effects of HDT on BMD. None of the studies showed a clinically significant decline in BMD. One of the four studies contained a subgroup of postmenopausal women who also showed no decline in BMD (Gyulai et al., 1997, 2001; Ricken et al., 2012). In the postmenopausal subgroup of the 1997 Gyulai et al. study, women were treated for an average of 6.8 years with an average T_4 dose of 356 mcg a day, achieving a blood level of 14.3 mcg/l. As a comparison, studies of hyperthyroidism have reported a 12–20% reduction in BMD in hyperthyroid subjects (Lakatos, 2003).

3.2. Review of the cardiovascular and morbidity risks of HDT

Three studies found no increased risk of premature death in patients treated with HDT. A multisite study done in the United States evaluated the effects of thyroidectomy, administration of radioactive iodine, and HDT on the survival of patients with DTC. A total of 2936 patients who suffered from DTC were treated with HDT (Jonklaas et al., 2006). The median duration of follow up was three years, although some patients were followed as long as 14 years. HDT treatment increased survival for patients with stage II, III, and IV DTC. Excluding patients who died from a recurrence of thyroid cancer, the overall mortality rate of the high-dose thyroid group was 1.9%, and the death rate of patients treated only with replacement doses of thyroid was 3%. Among patients with Stage I DTC, there was no survival benefit for either HDT or radioactive iodine. The authors noted that their data suggested that radioactive iodine may have been harmful in that group, but did not see a similar pattern with HDT.

The Sugitani and Fujimoto study discussed above in relation to BMD also evaluated cardiovascular mortality. It followed 225 patients for five years. Roughly half of the patients were treated with HDT to prevent the return of DTC, and a control group of patients with DTC were treated with replacement doses of thyroid hormone. There were no reported deaths from cardiovascular causes, although three patients in the HDT group were dropped from the study because they developed unspecified cardiovascular disease. Excluding patients who died due to the return of thyroid cancer, there was only one death in the HDT group (0.8%), while the control group suffered four deaths (3.8%) (Sugitani and Fujimoto, 2011).

A study done in the Netherlands followed 504 patients in complete remission from DTC who were being treated with HDT therapy. The median follow up period was 9 years, and survival was compared to the baseline mortality rate in the general population (Links et al., 2005). There was no significant difference in the number of cardiovascular related deaths or all causes of death in individuals treated for DTC who did not have a thyroid cancer recurrence. The authors concluded that disease-free patients after thyroid carcinoma have a normal residual life span, and that high dose thyroid and other treatments for DTC do not shorten life expectancy.

Only one prospective study reported increased cardiovascular deaths associated with DTC (Hesselink et al., 2013). The authors stated that their study included a substantial number of patients from the earlier Links study, reported above. With a mean age at baseline of 49 years old, 524 patients were followed for a median of 8.5 years. The authors reported 22 cardiovascular related deaths, representing 4.2% of the study population. Hazard ratios based on death rates in the general population were calculated to be 3.15 for cardiovascular death and 4.40 for all-cause mortality, which included recurrence of thyroid cancer.

The authors acknowledged a number of problems with the data. Most importantly, data sources for the cause of death among the study sample included public health records (Statistics Netherlands), hospital records, outpatient records, autopsy reports, and information from general practitioners. Comparison data for the general public came from a single source: Statistics Netherlands. The authors stated that "the cause of death as reported by Statistics Netherlands or the patient record and general practitioner may not be fully in accordance with each other." This discrepancy makes calculation of hazard ratios problematic, because hazard ratios are generally considered valid only when the data for the treatment group and the control group are similar.

Only a single paper could be found that purported to show increased AF with HDT (Abonowara et al., 2012). No other cardiac arrhythmias were reported in the study. A group of 136 patients, average age 52 at the start of the study, were treated with HDT to prevent the return of DTC, and followed for an average of 11 years. The prevalence of AF in this population then was compared against the prevalence of AF in the age-adjusted general population. The mean TSH level of the study participants was 0.17 mIU/L. Two patients were found to have long-standing AF with 12 patients developing paroxysmal AF. Seven of the 14 patients who developed AF also had concurrent hypertension (50%), while only 31% of the non-AF patients suffered from hypertension. The authors concluded "TSH suppression is associated with a high prevalence of AF ($p < 0.0001$)."

These results must be interpreted with caution because the authors used different definitions of AF in the DTC population than was used for the general population. The general population data was obtained from a 2001 study in which only non-transient atrial fibrillation was counted (Go et al., 2001). In order for the comparison to be valid, Abonowara et al. should have excluded from their calculations the 12 patients with paroxysmal AF. Proper classification leaves only two patients with AF, and indicates that the risk of AF is not increased by HDT. It should be noted that over the mean duration of 11 years (range 1 to 21) no deaths were reported among subjects exposed to HDT. No other papers could be located showing an increase in arrhythmias, AF or otherwise. Arrhythmias other than AF are rare among people living with endogenous hyperthyroidism (Fadel et al., 2000).

3.3. Cardiovascular risks associated with endogenous hyperthyroidism

In contrast to HDT, hyperthyroidism is associated with a plethora of cardiovascular problems that can be lethal. These include myocardial structural changes, arrhythmias, pulmonary hypertension, cardiac valve prolapse, thromboembolic episodes and other cardiomyopathies (Biondi and Kahaly, 2010; Brandt et al., 2011; Klein and Danzi, 2007; Vallabhajosula et al., 2011). The mortality of patients with hyperthyroidism is 20% higher than that of the general population (Fazio et al., 2004).

Graves' disease is an autoimmune disorder, and the most common cause of hyperthyroidism in the setting of sufficient dietary iodine. This disease is triggered by autoimmune antibodies that mimic TSH. TSH receptors are not exclusively found on the thyroid gland. They can be found in other tissues including fat, fibroblasts, bone, brain, kidney, testis, heart and cells of the immune system (Drvota et al., 1995; Gershengorn and Neumann, 2012). The effects of Graves' disease are not limited to the thyroid gland; 90% of patients have one or more other pathologies such as orbitopathy (exophthalmos), dermopathy, Marie's Disease, myxoid degeneration and cardiac valve prolapse (Biondi and Kahaly, 2010). Prospective studies have revealed a high prevalence (40%) of pulmonary arterial hypertension in patients with hyperthyroidism (Biondi and Kahaly, 2010). AF is the most common cardiovascular sequela of hyperthyroidism, developing in 10–28% of patients compared with 0.5–9.0% of the general population (Biondi and Kahaly, 2010).

4. Discussion

Hyperthyroidism carries a multitude of health risks. In contrast, the evidence shows that high circulating levels of thyroid hormone from external sources carry little or no medical risks. When compared to the risks of most of the medications used to treat bipolar disorders HDT appears to be less risky (Kelly, 2014, 2015). The large body of studies evaluating the risks of HDT has found a profound discordance between HDT risks and the risks of hyperthyroidism. Although more work needs to be done, at this time the evidence leads to the conclusion that the major medical sequelae associated with hyperthyroidism are not caused by high circulating levels of thyroid hormone used in the reviewed studies. Since the doses of HDT that were studied caused suppression of TSH, it can also be concluded that low levels of TSH play little or no role in the medical sequelae associated with hyperthyroidism.

4.1. Discussion of osteoporosis risk and HDT

Some studies appear to support the hypothesis that high circulating levels of thyroid hormone cause the medical sequelae associated with hyperthyroidism. The best example of this is the high bone turnover markers found with elevated levels of thyroid hormone; however, high bone turnover markers are not inevitably linked with a decrease in BMD. In the one study that directly compared hyperthyroidism with HDT treatment (Belaya et al., 2007), bone turnover markers were elevated for both, however even in the presence of high bone turnover markers, the HDT group did not have a decrease in BMD.

The possible deleterious effect of thyroid hormone therapy on BMD has been debated for the last three decades (Lakatos, 2003). There is general agreement that treatment with HDT does not represent a risk for decreasing BMD in men or premenopausal women. This is reflected in the American Thyroid Association guidelines for the treatment of DTC. It warns of a risk of osteoporosis from HDT only for postmenopausal women (Cooper et al., 2009), but after a close inspection of the studies purportedly showing decreased BMD in postmenopausal women, the effect of HDT on postmenopausal women should be reconsidered.

A review of the original studies used by Hemmstra et al. to implicate HDT as a risk for ostioperosis data indicates that none of the long term studies showed a decrease in BMD among postmenopausal women (Heemstra et al., 2006). In one of the two studies only women with inadequate calcium intake experienced bone loss. The simple addition of 1000 mg/day of calcium resulted in stable BMD. In the other study "subtle" effects on BMD were found in only one of five areas measured, and the authors of the original paper, Jodar et al., discounted the findings based on the margin of error in the measurements.

While the Sugitani and Fujimoto study reported decreased BMD at the one year time period for women over 50 taking HDT, there was no report of decreased BMD for women over 50 at the 3 and 5 year time period (Sugitani and Fujimoto, 2011).

It has been accepted that HDT does not pose a risk for decreased BMD for men and premenopausal women (Cooper et al., 2009). Based on this and the above considerations, the most reasonable interpretation of the data appears to be that there is an absence of risk of osteoporosis with HDT therapy. Postmenopausal women who have inadequate calcium intake may need supplemental calcium. In contrast, studies of hyperthyroidism have consistently reported a 12–20% reduction in BMD in hyperthyroid subjects (Lakatos, 2003).

4.2. Cardiovascular and mortality risks of HDT

Hyperthyroidism is associated with a number of potentially lethal medical complications (Brandt et al., 2011). The mortality rate among those living with hyperthyroidism is 20% higher than in the general population (Fazio et al., 2004). In contrast to these findings, the three studies that reported mortality data associated with HDT found no indication of increased mortality. One study was a population study, and two studies had control groups of patients with DTC treated only with replacement doses of thyroid. In the studies with control groups, which represent a more valid study design, there is a numeric trend toward fewer deaths among patients taking HDT, when deaths related to cancer recurrence are excluded. Overall, the absence of increased mortality indicates either no or minimal risks from HDT.

4.3. An alternative explanation for the medical sequelae of hyperthyroidism

There is mounting evidence that the sequelae of Graves' disease, including pulmonary arterial hypertension, cardiac valve involvement, and specific cardiomyopathies, are linked to an autoimmune process

(Biondi and Kahaly, 2010). The high circulating levels of thyroid hormone are caused by a TSH receptor autoantibody that mimics TSH. Graves' disease, like most autoimmune diseases, is frequently accompanied by multiple autoimmunities. More and more sequelae of Graves' hyperthyroidism are being linked to an autoimmune process (Biondi, 2012). Exophthalmos (Wall and Lahooti, 2010) and Graves' dermopathy (Topliss and Eastman, 2004) have conclusively been shown to be the result of an autoimmune process. In hyperthyroidism, the risk of autoimmune mediated problems does not end with the suppression or ablation of the thyroid gland. Radioiodine therapy may double TSH receptor antibody levels. At the end of five years 50% of patients treated with radioiodine and 10% of those treated with surgery or by medical suppression of the thyroid gland have persistently elevated TSH antibodies (Laurberg et al., 2008).

An abnormally high plasma level of thyroid hormone is associated with heart arrhythmias and osteoporosis when it occurs in the context of hyperthyroidism, but not with DTC. Determining whether these adverse events will occur with bipolar disorder requires additional research. The majority of the patients in the studies we reviewed did not have bipolar disorder, so a similar safety profile is not guaranteed. Immune dysfunction is found in patients with bipolar disorder (Ortiz-Domínguez et al., 2007) and in this respect it is similar to hyperthyroidism. On the other hand, thyroid hormone is given in pill form with bipolar disorder, which is the same with DTC. Overall, the immune system abnormalities in bipolar disorder are more subdued and have a different profile from those found in patients with hyperthyroidism. Consequently, it is more likely that administration of the hormone in pill form accounts for the differences in safety. This alternative is supported by the three bipolar disorder studies reviewed that did not find increased risk of osteoporosis with high dose thyroid hormone (Gyulai et al., 1997, 2001; Ricken et al., 2012).

Given the large number of studies related to hyperthyroidism and the fact that high circulating levels of exogenous thyroid hormone are often incorrectly referred to as “hyperthyroidism,” searching for relevant studies was complex and some relevant studies may have been missed. This risk is likely minimized by the inclusion of review papers. The conclusions made in this paper are based on the blood levels achieved by usual treatment doses of HDT. In practice this means doses that were limited by thyrotoxic side effects.

5. Conclusion

Exogenous thyroid hormone used in the treatment of illnesses, even when resulting in high circulating levels, does not show a correlation with the sequela of the disease of hyperthyroidism. Historically, when and how high dose exogenous thyroid hormone was conflated with hyperthyroidism is unclear. Failure to adhere to the strict definitions of thyrotoxicity and hyperthyroidism may have played a role in the process. Even today, HDT therapy is routinely referred to as “hyperthyroidism” (Perros et al., 2014). This belief that high circulating hormones are equivalent to hyperthyroidism has continued despite the robust body of evidence reviewed in this paper that contradicts that assumption. There is more than sufficient evidence to conclude that HDT is not a risk factor for decreased BMD among men, premenopausal women, and postmenopausal women with adequate calcium intake. No quality studies have shown that HDT increases mortality or cardiovascular risks. Contrasting the health risks of actual hyperthyroidism with the absence of evidence that HDT causes major health problems, there is sufficient reason to conclude that high circulating levels of thyroid hormones are not the cause of the medical sequelae of hyperthyroidism. The most viable alternative explanation is that the sequelae of hyperthyroidism are related to an autoimmune process. It is essential that careful differentiation between hyperthyroidism and high levels of circulating thyroid hormone be maintained in order to promote clear communication, accurate diagnostic assessment, and optimal treatment planning.

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Conflicts of interests

Tammas Kelly has no conflicts of interest other than a part time contract employer of Lawrence Denmark.

Lawrence Denmark has no conflicts of interest other than a part time contract employee of Tammas Kelly.

Daniel Z. Lieberman has no conflicts of interest.

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