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The Clinical Benefit of Thyroid Hormone Therapy for Subclinical Hypothyroidism

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PERMISSION

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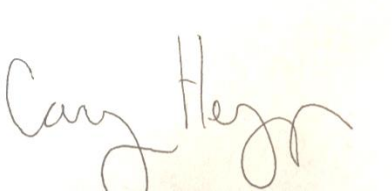
Signature 

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Abstract

Hypothyroidism is a disease that affects about one to two percent of the population in the United States. It is a condition of the thyroid gland that involves inadequate production of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). These changes cause increases in the level of serum thyroid stimulating hormone (TSH). Subclinical hypothyroidism is more prevalent than overt hypothyroidism, involving elevated TSH levels with normal T4 levels. Based on the data from the initial visit, it is unclear if the patient had overt hypothyroidism or subclinical hypothyroidism. Controversy exists in the literature as to whether or not subclinical hypothyroidism in the asymptomatic patient should be treated with synthetic thyroxine replacement. There is also a lack of consensus regarding best practice for initiating treatment. The findings from the literature review support treatment for patients with subclinical hypothyroidism who are aged 65 years or under and have a TSH level that is at or above 7.0 mU/L. There is also evidence to support treatment for patients off all ages with a TSH that is at or above 10 mU/L. In elderly patients taking thyroid replacement therapy, it is important to monitor their TSH levels regularly to avoid overtreatment, as this can lead to adverse effects. When considering treatment for subclinical hypothyroidism it is important to carefully evaluate the patient's health status and current medical conditions.

The Clinical Benefit of Thyroid Hormone Therapy for Subclinical Hypothyroidism

Background

Hypothyroidism is a disease of the thyroid that is common is the United States. Affecting about one to two percent of the US population (Ross, 2017). Thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are produced by the thyroid gland. The release of these thyroid hormones is regulated by thyroid stimulating hormone (TSH), which is produced by the pituitary. Minor changes in serum free thyroxine cause large, reciprocal changes in TSH levels (Ross, 2017). Hypothyroidism occurs when thyroid hormones are low and the TSH is elevated. This is generally determined by drawing a serum TSH and a free T4. The normal values for TSH vary laboratory to laboratory, however the generally accepted normal range of TSH is from 0.45 mU/L to 4.5 mU/L (Rugge, Bougatsos, & Chou, 2015). The normal range for free T4 varies across laboratories also, typical values range from 4.6 to 11.2 mcg/dL (Ross, 2017). The diagnosis of hypothyroidism is based on an elevated level of these lab values. The rationale for providers obtaining a TSH is often based on patient's presenting symptoms, which can be highly variable based on the duration and severity of the deficiency, as well as the age of the patient at onset (Ross, 2017). Some of the common presenting symptoms of hypothyroidism include fatigue, mood changes, constipation, dry skin, intolerance to cold, unexplained weight gain and muscle aches (Feller et al., 2018; Hennessey & Espaillat, 2015). Primary hypothyroidism is diagnosed when the level of thyroid stimulating hormone is elevated and the free thyroxine level is low. TSH levels fluctuate, therefore a serum TSH is drawn initially. If elevated, the TSH is repeated and a free T4 is also drawn to confirm diagnosis of hypothyroidism (Ross, 2017). This is commonly redrawn in four to six weeks after the initial TSH is collected. Treatment for hypothyroidism includes replacement with synthetic thyroxine, which is administered in an oral

pill form called Levothyroxine. The goals of treatment are to return to normal functioning or euthyroid state, which most patients are able to attain with oral levothyroxine. When treated appropriately, the clinical manifestations of the disease are generally reversed (Ross, 2017).

Subclinical hypothyroidism is a form of thyroid dysfunction that is diagnosed when there is an elevated serum TSH, but the free T4 level is normal. Patients with this condition are generally asymptomatic, although some display vague symptoms of hypothyroidism. Patients of advanced age tend to be less symptomatic or their symptoms are sometimes overlooked due to symptoms being associated with the normal aging process (Ross, 2018). TSH levels increase as adults age, therefore subclinical hypothyroidism is more prevalent in the elderly population, accounting for an estimated 15% (Hennessey & Espaillat, 2015). Serum TSH levels can fluctuate and elevated levels can be transient (Hennessey & Espaillat, 2015). When TSH is elevated it is important to draw a repeat TSH, along with a free T4 level to confirm diagnosis of subclinical hypothyroidism (Ross, 2018). The literature is inconsistent in its recommendation regarding the treatment of subclinical hypothyroidism should be treated with thyroid replacement. Specifically, if the TSH is only mildly elevated or if the patient is asymptomatic (Feller et al., 2018). Untreated subclinical hypothyroidism can lead to overt hypothyroidism in some patients and close follow up and monitoring of these patients should be considered (Ross, 2018). Research also suggests untreated subclinical hypothyroidism is associated with an increased risk of cardiovascular disease such as coronary heart disease, atherosclerosis, heart failure, stroke and elevated lipids (Chaker et al., 2015). There is evidence that subclinical hypothyroidism contributes to other medical issues, however the research is conflicting. Reports indicate risk of fractures, fertility problems, nonalcoholic fatty liver disease, and

neuropsychiatric symptoms can be impacted by untreated subclinical hypothyroidism (Chaker et al., 2015; Ross, 2018).

In order to prevent the progression to primary hypothyroidism, most experts agree that if the serum TSH value is at or above 10 mU/L it is appropriate to treat with levothyroxine (Ross, 2018). In patients who have a serum TSH level between 4.5 mU/L and 10 mU/L there is no agreed upon treatment plan (Ross, 2018). Experts argue the clinical benefit of treatment for asymptomatic patients who fall within these ranges may not outweigh the risks. Discrepancy exists among healthcare providers and organizations due to the variation in practice guidelines. Inconclusive data has been extracted from previous systematic reviews exhibiting the clinical benefit of treatment versus no treatment (Feller et al., 2018). Overtreatment can occur with thyroid replacement therapy as TSH levels fluctuate. Overtreatment in subclinical hypothyroidism occurs when initiation of levothyroxine causes an elevation of free T4 causing symptoms of hyperthyroidism including increased risk of fractures or heart arrhythmias. This is especially a concern in the elderly population (Hennessey & Espaillat, 2015). The purpose of this case report is to conduct a literature review to determine if there is clinical benefit of thyroid hormone therapy for subclinical hypothyroidism.

Case Report

The patient was a 38-year-old female who presented to the clinic for evaluation of fatigue and abnormally dry skin. The patient reported that symptoms started about five months prior to the visit. The patient reported brittle nails, dry skin, and increased intolerance to cold. The patient denied starting any new medications recently. Her medications included multivitamins and probiotics. She does not have any known allergies. The patient denied using any new perfumes, detergents or lotions. The patient was 12 months post caesarian section, her third

caesarian section for pregnancy. She denied any personal or family history of thyroid or cardiac disorders. She denied any symptoms of shortness of breath, weakness, or palpitations

The patient was pleasant and cooperative. She was alert and oriented to person, place and time. She did not appear to be in any acute distress. She was well groomed and was a good historian. Vital signs were reviewed and were stable. A physical exam was conducted during the clinic visit and was unremarkable, except for visibly dry skin. The thyroid gland was of normal size and consistency, there were no palpable thyroid nodules or abnormalities. Deep tendon reflexes were intact. Labs were drawn including a complete blood count with differential, a complete metabolic panel, and thyroid stimulating hormone. All labs were unremarkable except the TSH, which was elevated at 6.61 mU/L, with a generally accepted normal range of 0.45 mU/L to 4.5 mU/L. The history and physical exam for this patient were consistent with hypothyroidism; as indicated by the elevated serum TSH level of 6.61 mU/L. There were no previous TSH values available for comparison. The plan included initiating oral thyroid hormone therapy with levothyroxine with a scheduled follow-up appointment in four to six weeks to recheck TSH levels and also draw a free thyroxine (T4) level. At the follow up visit in four to six weeks, the plan will be to evaluate the patient's response to the medication and adjust dosage if needed.

The patient's TSH level is elevated and at this point the subsequent labs have not been completed; the repeat TSH and free T4 level. The results of these labs will determine if the patient has primary hypothyroidism or subclinical hypothyroidism. The following report will evaluate the literature regarding the clinical benefit of thyroid hormone therapy for subclinical hypothyroidism.

Literature Review

A thorough review of the literature was conducted for this case review. Searches consisted of two databases, CINAHL and PubMed. The CINAHL database was searched first using the phrase "subclinical hypothyroidism" in the first box and "treatment" in the second box. Articles were limited to academic journals, geography was set to USA, and the year was limited to 2012 through 2019. This resulted in 56 articles. PubMed was searched next. The first search conducted utilized the terms "subclinical hypothyroidism treatment." This resulted in 2123 articles. To limit the number of results, the search was limited to studies from the past 5 years and only including human studies. This resulted in 438 articles. In reviewing the articles, expert opinion papers and articles from outside the USA were excluded. Articles researching hypothyroidism in pregnancy were also excluded. The results of both databases yielded ten recent articles relevant to this review. The literature reviewed included meta-analyses, systematic reviews, cohort studies and cross-sectional studies.

Untreated subclinical hypothyroidism has been associated as a risk factor for several health conditions including increased weight, increased risk of fractures, increased risk of mortality and cardiac events. Garin, Arnold, Lee, Tracy and Cappola (2014) analyzed weight and body composition in patients ages 65 years and older to determine if subclinical hypothyroidism contributed to weight issues. They concluded that subclinical hypothyroidism was not associated with differences in weight change, lean mass, fat mass, or percent fat when compared to patients with euthyroid. A review by Rugge et al., (2015) also found no evidence to support improved body mass index in patients taking thyroid hormone therapy versus patients who did not receive thyroid hormone treatment. Both studies found no improvement in weight issues with treatment for subclinical hypothyroidism.

Thyroid dysfunction has also been associated with an increased risk of fractures. A systematic review and meta-analysis was conducted by Wirth et al. (2014) to examine the risk of fractures in patients with subclinical thyroid dysfunction. Findings found no statistically significant increased risk for fractures in patients with untreated subclinical hypothyroidism. found no statistically significant increased risk for fractures in patients with untreated subclinical hypothyroidism. It was noted that more research is warranted in this area. Hennessey and Espaillat (2015) report an increased risk of fractures in patients aged 60 and older who are taking levothyroxine and have TSH levels that are greater than 4 mU/L or less than 0.03 mU/L. Indicating the need for close monitoring in elderly patients who are on thyroid hormone therapy.

Untreated subclinical hypothyroidism has also been associated with increased risk of mortality and cardiac events. Hyland et al. (2013) evaluated cardiac risk in elderly patients with untreated subclinical hypothyroidism. They found no association between untreated subclinical hypothyroidism and the incidence of cardiac conditions, specifically: coronary heart disease, heart failure, or cardiovascular death. Hennessey and Espaillat (2015) also reviewed the risk of cardiac events in relation to untreated subclinical hypothyroidism. They concluded that patients with untreated subclinical hypothyroidism, who were ages 65 years and older, were not at an increased risk for cardiac mortality or ischemic heart disease. They did find evidence indicating that patients who were ages 65 or younger with untreated hypothyroidism were at a greater risk for cardiac mortality or ischemic heart disease. This review reports patients with subclinical hypothyroidism aged 70 and younger would benefit from treatment with levothyroxine to improve cardiovascular outcomes, they reported no risk reduction for those patients 70 and older (Hennessey & Espaillat, 2015). Along with younger age, the degree of TSH elevation has shown increased cardiac risk. TSH levels that are 10 mU/L or higher have been associated with

a greater risk of cardiac events and mortality (Hennessey & Espaillat, 2015). Rhee, Curhan, Alexander, Bhan and Brunelli (2013) evaluated over 14,000 people with congestive heart failure and compared outcomes for euthyroid patients to those with hypothyroidism and subclinical hypothyroidism. The results of their study indicate greater risk of death in patients who have congestive heart failure and subclinical hypothyroidism or hypothyroidism that has not been treated. Rugge et al. (2015) performed an evidence review for the U.S. Preventative Services Task Force. The results indicate there is evidence to support treatment of subclinical hypothyroidism to decrease the risk of coronary heart disease. The risk was lower in those treated with thyroid hormone replacement when compared to those whose subclinical hypothyroidism was not treated (Rugge et al., 2015). The evidence supports treatment for subclinical hypothyroidism to prevent cardiac events, especially those aged 65-70 or less and those with TSH levels at or above 10 mU/L.

Rugge et al. (2015) reviewed studies looking at cholesterol levels in patients with subclinical hypothyroidism. They ascertained that there are potentially positive effects on lipid levels with thyroid hormone treatment, however, they concluded that the research available is limited and the results are inconsistent. More research is needed in this area to make an appropriate recommendation.

Subclinical hypothyroidism has also been studied in relation to atrial fibrillation. A study conducted by Baumgartner et al. (2017) reviewed over 30,000 patients to assess the risk of atrial fibrillation and thyroid dysfunction. Their results showed increased risk for atrial fibrillation with elevated free T4 levels. They found that the risk was not increased with elevated TSH levels. In subclinical hypothyroidism, TSH is elevated and free T4 is within normal range. This

study does not correlate untreated subclinical hypothyroidism to the development of atrial fibrillation.

Chaker et al. (2015) conducted a study with over 47,000 participants focusing on subclinical hypothyroidism and the increased risk of stroke. Their data revealed increased risk of fatal stroke in patients with untreated subclinical hypothyroidism that were ages 18 to 49 years of age and in the group aged 50 to 64, but not for those over age 65. They also found that higher concentrations of TSH, those above 7 mU/L, were associated with increased risk of fatal stroke (Chaker et al., 2015). Based on the evidence, they recommend treatment with thyroid hormone replacement in patients who are aged 65 and younger, and also for those with moderately elevated TSH of 7 mU/L or higher This evidence supports previous research that recommends initiating thyroid hormone therapy for patients with subclinical hypothyroidism who are under age 65 and those with moderately elevated TSH levels (Chaker et al., 2015).

Hennessey and Espaillat (2015) found a protective factor of levothyroxine in patients with chronic kidney disease. The report indicates levothyroxine "significantly attenuated the decline in estimated glomerular filtration rates in 113 participants (mean age 63.2) with Stage 2 to 4 chronic kidney disease" (Hennessey and Espaillat, 2015, p. 1671). The use of thyroid hormone treatment may help to slow the progression of chronic kidney disease, identifying a potential benefit for patients with chronic kidney disease and subclinical hypothyroidism to receive treatment with levothyroxine.

A meta-analysis and systematic review conducted by Feller et al. reviewed 21 studies, including over 2,000 patients with elevated TSH levels looking at the benefit of treatment for subclinical hypothyroidism. Authors cited the importance of the study given the "Relatively limited evidence exists from randomized clinical trials (RCTs) to guide therapy for subclinical

hypothyroidism. Systematic reviews have been inconclusive and clinical practice guidelines have varied regarding recommendations for managing subclinical hypothyroidism" (Feller et al., 2018, p. 1350). Results indicated the use of synthetic T4 replacement with levothyroxine was not associated with improvement in overall symptoms. The treatment group and the placebo group exhibited no differences in general quality of life or hypothyroid symptoms (Feller et al., 2018). These findings are consistent with a study conducted by Shah (2017), which found that the use of levothyroxine for treatment of subclinical hypothyroidism did not provide benefit for mood, quality of life, or hypothyroid symptoms. Almost half of the studies participants returned to euthyroid without treatment. Hennessey and Espaillat (2015) looked at cognitive function and mood in elderly adults with subclinical hypothyroidism. They found no significant difference in cognitive function or mood between those treated with levothyroxine and those taking the placebo medication. They also noted that 50% of the patients in the placebo group returned to euthyroid by the end of the 12 months period. These findings are consistent with Rugge et al. (2015) that found no correlation with treatment of subclinical hypothyroid and improvements in quality of life, cognitive function or blood pressure when compared to patients with no treatment.

Treatment guidelines for subclinical hypothyroidism often have variability and depend on a variety of clinical considerations. The recommendations from current clinical guidelines value the current research and support the findings from the research conducted by Feller et al. (2018). Feller et al. (2018) found no statistically significant differences between those treated with thyroid hormone replacement versus those who were not treated in regard to quality of life or signs and symptoms of hypothyroidism. However, there are other risk factors to consider based on the research. Research indicates there is increased risk for cardiac events in patients who are under 65 years of age and those with TSH levels at or above 10 mU/L (Feller et al.,

2018). Recent clinical guidelines report, “observational data show a benefit of T4 treatment in reducing ischemic heart disease events and overall mortality in younger individuals with subclinical hypothyroidism, and we suggest T4 treatment in most patients <65 years of age with a TSH ≥7.0 mU/L” (Ross, 2018, what’s new para 1). Hennessey and Espaillat (2015) recommends consideration for treatment for those patients with TSH level at or above 10 mU/L to decrease the risk of morbidity. These recommendations are appropriate based on the body of research that was reviewed for this case study.

When initiating treatment for subclinical hypothyroidism in the elderly it is recommended to start at lower doses and increase slowly to avoid overtreatment and adverse side effects. In all patients, it is important to evaluate their overall health condition and determine if treatment is indicated. Treatment plans should be tailored to the needs of the individual patient and followed appropriately with consistent follow up and monitoring. Research supports the benefit from thyroid hormone therapy for subclinical hypothyroidism depending on the age of the patient and the concentration of TSH.

Learning Points

- When considering treatment for subclinical hypothyroidism; carefully evaluate the patient’s health status and current medical conditions to determine appropriateness.
- Consider treatment in most patients aged 65 years and younger with a TSH ≥7.0 mU/L.
- Consider treatment for all patients with TSH level at or above 10 mU/L.
- Treatment of elderly patients often requires lower starting doses with closer lab and clinical monitoring to reduce potential adverse effects.

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