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Monotherapy versus Combination Therapy in the Treatment of Hypothyroidism: A Case Report

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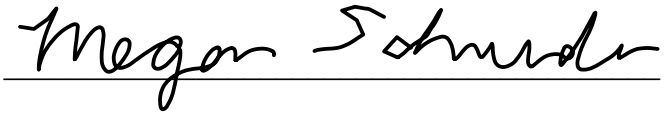
Signature 

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Abstract

Hypothyroidism is a common disorder in the United States which is often caused by disease of the thyroid gland, resulting in inadequate serum thyroxine (T4) and triiodothyronine (T3) levels. With the use of L-thyroxine, most patients will return to an euthyroid state with cessation of hypothyroid symptoms. Some, however, will continue to experience hypothyroid symptoms despite the use of L-thyroxine and normal thyroid hormone levels. The case report presents a 38-year-old, Caucasian, female who was diagnosed with hypothyroidism and prescribed levothyroxine. She was advised to follow-up in four to six weeks following her initial visit to evaluate the effectiveness of the medication. The clinician may encounter a challenging situation if, upon follow-up, the patient presents with continued complaint of hypothyroid symptoms, but normal thyroid hormone levels. Controversy remains on whether to treat those who return with persistent hypothyroid symptoms with combination therapy (L-thyroxine plus liothyronine). The literature review will discuss current recommendations on the use of monotherapy versus combination therapy for hypothyroidism, including the potential risks and benefits of combination therapy and suggestions for future research.

Monotherapy versus Combination Therapy in the Treatment of Hypothyroidism: A Case Report

Background

A 38-year-old, Caucasian, female presented to the clinic with complaint of fatigue and dry skin. Further evaluation of her subjective symptoms revealed she was experiencing irregular menstrual periods, cold intolerance, and having difficulty losing weight. Her physical exam was relatively unremarkable, but blood tests revealed her thyroid stimulating hormone (TSH) was elevated. She was diagnosed with hypothyroidism and prescribed levothyroxine 100mcg by mouth daily. She was advised to follow-up in four to six weeks to recheck her TSH and free T4 levels.

Hypothyroidism is a common disorder that affects 4.6% of the United States population, occurring more often in women (Tariq, Wert, Cheriyath, & Joshi, 2018). Hypothyroidism can be caused by a disruption anywhere in the hypothalamic-pituitary-thyroid pathway but is most often caused by a disease in the thyroid gland resulting in decreased secretions of T4 and T3 (Ross, 2019). This leads to decreased serum levels of T4 and T3 and, due to compensatory mechanisms, increased levels of TSH. The altered hormone levels may cause symptoms involving several organ systems and tissues in the body. Common symptoms of hypothyroidism may include weight gain, fatigue, neurologic dysfunction, constipation, and dry skin (Surks, 2019).

Most people will return to a euthyroid state, with normal thyroid hormone levels and cessation of hypothyroid symptoms, with the sole use of levothyroxine, a synthetic version of T4. However, 5% to 10% of patients will continue to experience hypothyroid symptoms while on L-thyroxine (LT4) monotherapy despite normal TSH and free T4 levels (Tariq et al., 2018). There is evidence in the literature that suggests patients with persistent hypothyroid symptoms should be treated with a combination therapy, consisting of synthetic liothyronine (LT3) in

addition to LT4. Combination therapy for the treatment of hypothyroidism has been an interest for many years, but inconsistent evidence remains as to the benefit of the use of combination therapy (LT4 plus LT3) versus monotherapy (LT4). This case report will review the literature to further determine the risks and benefits of combination therapy versus monotherapy in the treatment of hypothyroidism.

Case Report

A 38-year-old, Caucasian, female with no remarkable medical history presented with complaint of fatigue and abnormally dry skin. She is a reliable historian and provided the information for the encounter. She stated symptoms of excessive fatigue and dry skin started five months prior. She noted she drinks one pot of coffee every day to help give her energy and admitted to inadequate water intake. She denied rashes or pigmentation changes in her skin. In addition to the fatigue and dry skin, she noted she had been having irregular menstrual periods. She stated her periods were becoming more frequent and she experienced heavier flows. She noted her last menstrual period was 22 days prior. She also complained of not being able to lose weight after having her third child, one year ago. Her current medications include a daily multivitamin and probiotic with no known allergies. She admitted to a family history of thyroid dysfunction. She lives at home with her three children and works full-time. She denied use of tobacco products, drugs or alcohol. Her review of systems revealed she experienced cold intolerance. She otherwise denied fever and respiratory, gastrointestinal, genitourinary, and psychological symptoms. Her vital signs on the day of the visit were stable: blood pressure, 130/80, heart rate, 76, temperature, 97.8 ° F, and respirations, 16.

Upon physical exam, she was pleasant, cooperative and in no acute distress. She exhibited normal mood and affect. Her neck was supple with no adenopathy, thyromegaly or

palpable thyroid nodules. Her heart rate and rhythm were regular with no discernable murmurs, rubs or gallops. Lungs were clear to auscultation throughout. Her skin was noted to be dry with no rashes or unusual moles or lesions. No pallor was noted. She exhibited 2+ patellar deep tendon reflexes, bilaterally. A complete blood count (CBC), complete metabolic panel (CMP), TSH level and free T4 level were ordered. The CBC, CMP and free T4 labs were unremarkable while the TSH was elevated at 6.61mIU/L. She was diagnosed with hypothyroidism and prescribed levothyroxine 100mcg by mouth daily. Education about hypothyroidism, including clinical manifestations, was provided. Information about levothyroxine and possible adverse side effects were discussed. She was advised to decrease caffeine intake and to increase water intake and to apply lotion for her dry skin. It was recommended that she follow-up in four to six weeks to check her TSH and free T4 levels and to evaluate symptoms.

Literature Review

The literature is inconsistent with its recommendations for the treatment of hypothyroidism with monotherapy versus combination therapy. A literature search was conducted using the CINAHL and PubMed search engines. Search terms included: "hypothyroidism", "monotherapy", "combination", and " liothyronine". Results were limited to literature published within the last 5 years and in the United States. The literature search resulted in a review of 11 articles that explore the topic of combination therapy versus monotherapy for the treatment of hypothyroidism. The articles included primary and secondary literature, which consist of original studies, review articles, systematic reviews and practice guidelines. The literature review will discuss current recommendations for the treatment of hypothyroidism and will include alternative causes for persistent hypothyroid symptoms, limitations to current studies, and recommendations for future studies.

The clinical practice guidelines supported by the American Association of Clinical Endocrinologists and the American Thyroid Association state those with hypothyroidism should be treated with LT4 monotherapy because current evidence does not support the use of LT4 and LT3 combination therapies (Garber et al., 2012). These recommendations are congruent with the majority of 13 other national practice guidelines published worldwide (Kraut & Farahani, 2015). The European Thyroid Association and the British Thyroid Association are the only organizations who have indicated LT3 may be considered for experimental treatment but include several caveats including the patient must have persistent hypothyroid symptoms, have a normal TSH for over six months, and other autoimmune conditions must be ruled out (Kraut & Farahani, 2015). In a comprehensive review of several national practice guidelines, the use of combination therapy was dismissed with several of the organizations not providing supporting evidence for their recommendations.

The literature included in this review is consistent in its support and recommendation for the use of levothyroxine monotherapy for treating hypothyroidism, with the exception of one retrospective study that supports the use of combination therapy and one study that states combination therapy should not be ruled out as a treatment option (Jonklaas & Burman, 2016; Tariq et al., 2018). The retrospective study included a chart review of 100 patients being treated with combination therapy compared to 2400 patients receiving monotherapy. Data was collected for clinical signs and symptoms which included thyroid hormone levels and responses to a Medical Outcomes Study Short Form-20 questionnaire (Tariq et al., 2018). The authors state symptoms of hypothyroidism improved significantly in the group receiving combination therapy and did not cause hyperthyroidism (Tariq et al., 2018). Based on the collected data, the authors concluded the addition of LT3 is a safe and effective way to improve quality of life in those with

persistent hypothyroid symptoms (Tariq et al., 2018). Jonklaas and Burman (2016) have indicated peaks and troughs of T3 serum levels in their studies when adding LT3 into treatment regimens which do not replicate the natural serum T3 levels produced by the throid. They hypothesize the lack of evidence of improving health outcomes using combination therapy may be caused by the inconsistent T3 levels during therapy (Jonklaas & Burman, 2016). Their findings suggest that combination therapy cannot be ruled out as a beneficial treatment option until there have been studies that administer extended release LT3 or at least three times daily doses (Jonklaas & Burman, 2016).

The literature reviewed was highly consistent with supporting LT4 monotherapy for the treatment for hypothyroidism (Escobar-Morreale, Botella-Carretero, & Morreale de Escobar, 2015; Foeller & Silver, 2015; Hennessey & Espaillat, 2018; Jonklaas, 2016; Kraut & Farahani, 2015; Linder & Clements, 2015). In addition to the lack of consistent evidence supporting combination therapy, several articles cited adverse effects of LT3 and provided alternative causes of persistent hypothyroid symptoms as arguments against the use of combination therapy (Duntas & Wartofsky, 2016; Escobar-Morreale et al., 2015; Foeller & Silver, 2015; Hennessey & Espaillat, 2018; McAninch & Bianco, 2016). It has been shown through earlier clinical trials that LT3 administered at 100 to 175mcg/day can be associated with thyrotoxicosis (McAninch & Bianco, 2016). Though lowered dosages of LT3 resulted in resolution of symptoms, a trial of LT4 80mcg combined with LT3 20mcg resulted in symptoms of hyperthyroidism, including increased palpitations, tremor, perspiration, and anxiety, when compared to high doses of LT4 (McAninch & Bianco, 2016). Combination medications with LT3 dosages as low as 7.5 to 8.5mcg have been associated with the presence of bone-remodeling markers in the urine, indicating even small doses of LT3 may cause adverse effects (Escobar-Morreale et al., 2015).

This is important to consider when educating patients about the use of over-the-counter thyroid supplements. Even though the supplements are under the Food and Drug Administration supervision, they are likely to contain amounts of T4 and T3 that may increase risk of hyperthyroidism (Duntas & Wartofsky, 2016). One 17-year-long observation study found no significant difference in death, cardiovascular disease, arrhythmias, or diabetes in those who received LT3, though there was an increase in the use of antipsychotic drugs (Hennessey & Espaillat, 2018). It is advised not to treat hypothyroidism with combination therapy in pregnant women due to the risks of adverse effects to the fetus. The addition of LT3 causes serum T4 levels to decrease which results in less T4 available for placental transport (Foeller & Silver, 2015). Fetal neurogenesis is dependent on maternal T4 levels, therefore, a reduction in maternal T4 can put the fetus at risk for delayed intellectual development (Foeller & Silver, 2015).

There are potential alternative causes for persistent hypothyroid symptoms that would not indicate the initiation of combination therapy. Some symptoms of hypothyroidism, such as fatigue, cognitive difficulties, and anxiety, can be vague and difficult to measure. Many patients with these vague symptoms may be screened and diagnosed with subclinical hypothyroidism. Subclinical hypothyroidism is defined as having an elevated TSH concentration in the presence of a normal serum T4 concentration (Ross, 2019). Those with subclinical hypothyroidism have a TSH level <10mIU/L and do not have symptoms of hypothyroidism (Ross, 2019). "In many cases, this finding prompts the conclusion that the subclinical hypothyroidism is the case of the nonspecific symptoms, and thyroid hormone therapy is initiated. The patients in whom the cause-effect was incorrect contribute to the increasing number of euthyroid but symptomatic patients" (McAninch & Bianco, 2016, p. 53). Two review articles indicate physical, psychological, social and economic factors that may present with similar symptoms. Examples

include diabetes mellitus, pernicious anemia, vitamin deficiencies, obesity, stressful life events, poor sleep habits, depression and anxiety (Hennessey & Espaillat, 2018; Jonklaas, 2017). Assumption that persistent symptoms are caused by hypothyroidism could lead to a misdiagnosis of a serious condition.

Although most of the sources recommend the use of LT4 monotherapy to treat hypothyroidism, several of the articles listed an alternative cause for persistent hypothyroid symptoms that may indicate the need for the addition of LT3: polymorphisms in the deiodinase type 2 gene (DIO2). Thyroid hormone, T4, is converted to T3 by deiodinases at the cellular level in the periphery (Hennessey & Espaillat, 2018). Two single-nucleotide polymorphisms in the DIO2 have been found which may inhibit the enzyme activity, reducing the ability to convert T4 to T3 (Duntas & Wartofsky, 2016; Hennessey & Espaillat, 2018). Up to 10% to 16% of the population are homozygous for this polymorphism (Jonklaas, 2017). In a large clinical trial, those with a known polymorphism of DIO2 reported increased levels of well-being while on combination therapy (McAninch & Bianco, 2016). Personalized medication, based on genetics, may have a role in the treatment of hypothyroidism.

There are limitations identified throughout past studies comparing monotherapy to combination therapy in hypothyroidism. Several studies have limitations that include employing pre-study LT4 requirements and administering doses of LT3 that were not congruent with the natural ratios produced by the human thyroid (Linder & Clements, 2015). Several studies were limited by their small sample size and restrictive inclusion criteria (Jonklaas, 2017; Linder & Clements, 2015). It is advised for future studies to use standardized outcomes and measures to validate the effects of quality of life between the two study groups (Jonklaas, 2017). Two review articles and one original study suggest trialing extended release LT3 or dosages of three times a

day. Synthetic T3 has a short half-life and once daily, or even twice daily, dosing is not sufficient to maintain steady levels throughout the body (Duntas & Wartofsky, 2016; Jonklaas, 2016; Jonklaas & Bianco, 2014). Maintaining a constant level of T3 in all tissues may increase patient satisfaction and outcomes (Jonklaas, 2016). Though only one article clearly stated a recommendation for the use of combination therapy for hypothyroidism, several of the other articles acknowledge the limitations of past studies and the potential for future studies that may reveal beneficial results for combination therapy.

Learning Points

The following are important learning points that may be concluded from the literature review:

1. Currently, the practice guidelines supported by the American Association of Clinical Endocrinologists and the American Thyroid Association state to use LT4 monotherapy in the treatment of hypothyroidism.
2. It is important to educate patients about the possible adverse effects related to the use of other-the-counter thyroid supplements due to the potential for exceeding average T4 and T3 levels.
3. Though combination therapy is not recommended, it has become more popular in recent years and clinicians may encounter more patients with hypothyroidism on a combination therapy. It is important to discuss the possible risks of combination therapy, especially in those who are pregnant or who are trying to conceive.
4. Combination therapy may be considered for those with polymorphisms of DIO2.
5. Future randomized controlled studies, with the use of extended release LT3 or three times a day dosing, is recommended since past studies tested LT3 dosages that produced lower serum T3 levels then what is naturally produced by the thyroid.

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