THYROID
Volume 33, Number 8, 2023

DOI: 10.1089/thy.2023.0307

Symptoms in Patients Being Treated for Hypothyroidism: New Data in a Continuing Controversy

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The recognition that myxedema was due to deficiency of a substance or substances made by the thyroid gland, and the successful treatment of this formerly devastating condition using extracts from the thyroid gland in the late 19th century, was revolutionary. The enthusiasm of clinicians is aptly noted in the 1898 edition of the iconic medical textbook written by Sir William Osler, *The Principles and Practice of Medicine*: In referring to the treatment of myxedema he stated ''That we can restore to life the hopeless victims of myxedema is a triumph of experimental medicine. The results, as a rule, are most astounding—unparalleled by anything in the whole range of curative measures.''[1]

With the advent of reliably standardized dosing using synthetic sodium levothyroxine, monotherapy replaced animal thyroid extract as first-line therapy over the course of the 20th century (reviewed in Kahaly and Gottwald-Hostalek[2]). The subsequent availability of sensitive thyrotropin (TSH) assays combined with precise control over the prescribed dose made it theoretically possible to target a narrow range of serum TSH level, with the goal of restoring the patient to a clinical and biochemical euthyroid state. In the United States in 2020, ~100 million prescriptions for levothyroxine were written for ~20 million patients,[3] and in the United Kingdom, in 2019–2020 there were ~33 million prescriptions written for thyroxine (T4) for ~1.4 million patients.[4]

While most patients appear to be doing well with this therapeutic approach, Saravanan et al.[5] found that even among those with normal serum TSH levels, hypothyroid patients responding to a survey were more likely than controls to have a significant symptom burden, based on scores on a validated general health questionnaire and a thyroid symptom-specific questionnaire. Similar concerns about dissatisfaction have been obtained more recently in an online survey sponsored by the American Thyroid Association with >12,000 respondents.[6]

The reasons for this dissatisfaction are not known, but hypotheses include an inability to normalize thyroid function using T4 monotherapy in some patients, an ''autoimmune'' diathesis with chronic inflammation that does not respond to thyroid hormone, increased diagnostic scrutiny in symptomatic persons leading to a higher detection of unrelated subclinical hypothyroidism, and coexisting somatic symptom disorder (SSD).

In this issue of *Thyroid*, there are two articles that explore the possible factors responsible for persistent dissatisfaction with thyroid hormone replacement therapy, and the relationships among serum TSH levels, symptoms, and patient factors including medication adherence. In the article by Perros et al.,[7] volunteers were asked to complete an online tool to assess symptomatology, and in the study by Mehuys et al.,[8] patients were surveyed after an invitation to participate by a pharmacist when they refilled their levothyroxine prescriptions.

In the first study,[7] the authors conducted a multinational online survey of people with hypothyroidism using the Patient Health Questionnaire-15, a self-administered instrument that is a screening tool for somatization disorder. Thirteen of the 15 questions refer to physical symptoms and 2 assess for low-energy and trouble sleeping. Symptoms were scored as 0, 1, or 2 (not bothered at all, bothered a little, bothered a lot), and a score of ≥10 was considered consistent with having probable somatic symptom disorder (pSSD).

Other survey questions included (1) whether the patient attributed the symptoms to hypothyroidism or thyroid medication, (2) whether symptoms were controlled with their thyroid medication, (3) how satisfied they were with their thyroid medication and overall treatment of hypothyroidism, and (4) the impact of hypothyroidism on daily living. The survey was publicized and promoted online for 4 months by Thyroid Federation International, a network of patient groups, and required 30–45 minutes to complete. A total of 3516 valid responses were received, the vast majority of which were from white women over the age of 40 years who were employed, had other comorbidities, and were being treated with levothyroxine.

The prevalence of pSSD was 58.6% compared with an historic rate of 7.2% in the general population. Women had higher scores than men, and higher scores were correlated with being unemployed; having low household income; having one or more comorbidities; and being treated with

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levothyroxine rather than combination T4 + triiodothyronine (T3), T3 alone, or desiccated thyroid. Patients with pSSD were more likely to express dissatisfaction with their care and the treatment of their hypothyroidism, and such patients were also more likely to feel that their hypothyroidism impacted negatively on their daily living.

Based on the very high prevalence of a pattern of symptoms consistent with pSSD in those expressing dissatisfaction with thyroid therapy, the authors concluded that a ''biopsychosocial'' approach to the presence of persistent symptoms could be effective for many of these patients. Interestingly, the authors point out that pSSD typically has its onset by age 30 years, often decades before the diagnosis of hypothyroidism is made, which may explain how this diagnosis could contribute to the lack of symptom resolution with thyroid hormone in patients who appear to be adequately treated with levothyroxine.

Study limitations include the fact that those answering questionnaires were self-selected, as well as the sample size being minuscule compared with the universe of people taking levothyroxine, and a lack of information on thyroid functional status.

The second article[8] used pharmacy dispensing data to target eligible patients across Belgium with at least a 2-year history of taking levothyroxine monotherapy for conditions other than thyroid cancer (43.6% reported specifically having a diagnosis of Hashimoto's thyroiditis). Five adult patients were sequentially recruited at each of 183 pharmacies to take a self-administered questionnaire about their practices taking levothyroxine and their quality of life. Of the 1523 patients screened for participation, 72.9% were eligible and 77% of those agreed to participate for a total of 856 subjects.

The mean age was 61 years and 86% were women. Less than one-third had seen an endocrinologist in the past year. Twenty-five percent had out-of-range serum TSH levels recorded in the medical record within 6 months of the study administration, 28% were nonadherent based on filling <80% of their prescriptions, and 25% self-reported problems with adherence, mostly forgetfulness. However, quality of life was generally rated as being satisfactory. Overall the population did not find thyroid symptoms bothersome and only 4.1% of the population reported a score consistent with poor symptom control.

In this study, there was no correlation among medication adherence, serum TSH, and quality-of-life scores. Despite the apparent lack of an effect on symptoms, this study documents that patients often have suboptimal adherence to their medication regimens. Since there is harm associated with undertreatment of more advanced hypothyroidism even when still subclinical,[9] novel strategies to improve patients' prescription management are sorely needed.

The goal of a physician is to improve health, and help people to feel better. We know from many population-based studies that thyroid hormone dosing is not always well adjusted[10–12] and some patients remain dissatisfied even when their serum TSH levels are on target. In this setting, the results from Mehuys et al.[8] are reassuring that when self-selection is reduced in the sample, most patients have minimal symptoms even when TSH levels are not within the reference range. Nonetheless, important questions remain about how to help those in whom symptoms persist.

One hypothesis relates persistent symptoms to the ability of monotherapy to normalize pituitary TSH secretion without fully normalizing peripheral serum T3 levels. Single nucleotide polymorphism variations in deiodinase-2 and monocarboxylate transporter-10 transporter genes correlated with patient preference for combination therapy in one study.[13] Thus, in a subgroup of patients it may be appropriate to try balanced combination therapy that continues to target a reference range TSH, as recently discussed by the American Thyroid Association.[14] However, it is important to note that even on combination therapy, symptomatic complaints persist in many patients.[7,13]

At the same time, the fact of a response to a biologically active hormone does not prove the presence of a physiological deficit. Stimulating responses to pharmacological doses should not be used to justify excessive treatment in hypothyroid patients. The conversation between physicians and symptomatic biochemically euthyroid patients is, therefore, complex, and requires both detail and compassion to help patients achieve a nuanced understanding of the data surrounding symptoms and thyroid hormone levels. Important findings include the high prevalence of ''hypothyroid'' symptoms among those who are euthyroid, with a low positive predictive value for even four or more such symptoms in the Colorado Thyroid Disease Prevalence Study.[10]

And on the opposite side, randomized controlled trials that manipulate the TSH between the euthyroid and subclinical hypothyroid level have not demonstrated an effect on symptoms,[15,16] even when serum TSH levels ranged between 1.85 and 9.49.[16] In support of alternative approaches for patients with persistent symptoms, a recent randomized trial showed that exercise (60 minutes of aerobic activities [bike and treadmill], 3 times a week, for 16 weeks) had a significant positive impact on symptoms in subclinical hypothyroid patients who were not treated with levothyroxine.[17]

Furthermore, a small randomized controlled trial of women with treated hypothyroidism and poor quality-of-life scores demonstrated significantly improved symptoms in those who received eight sessions of cognitive behavioral therapy.[18] Thus, as a growing literature and the articles reviewed here support, most patients are doing well on monotherapy. For those who are not, which includes some on combination therapy with T3, having an alternative construct for somatic complaints may help doctors and patients reframe residual problems and pursue more effective interventions once appropriate physiological thyroid hormone replacement is achieved.

Authors' Contributions

J.S.M. and D.S.C. shared equally in the conceptualization, writing, and editing of this article.

Author Disclosure Statement

Both authors have no relevant financial disclosures.

Funding Information

No funding was received in support of this study.

References

1. Osler W. The Principles and Practice of Medicine. D. Appleton and Co.: New York, NY, USA; 1898.
2. Kahaly GJ, Gottwald-Hostalek U. Use of levothyroxine in the management of hypothyroidism: A historical perspec-

tive. Front Endocrinol (Lausanne) 2022;13:1054983; doi: 10.3389/fendo.2022.1054983.
3. ClinCalc DrugStats Database. Available from: https://clincalc.com>drugstats [Last accessed: May 1, 2023].
4. Stedman M, Taylor P, Premawardhana L, et al. Liothyronine and levothyroxine prescribing in England: A comprehensive survey and evaluation. Int J Clin Pract 2021; 75(9):e14228; doi: 10.1111/ijcp.14228.
5. Saravanan P, Chau WF, Roberts N, et al. Psychological well-being in patients on ''adequate'' doses of l-thyroxine: Results of a large, controlled community-based questionnaire study. Clin Endocrinol 2002;57(5):577–585.
6. Peterson SJ, Cappola AR, Castro MR, et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. Thyroid 2018;28(6):707–721; doi: 10.1089/thy.2017.0681.
7. Perros P, Nagy EV, Papini E, et al. Hypothyroidism and somatization: Results from E-mode patient self-assessment of thyroid therapy, a cross-sectional, international online patient survey. Thyroid 2023;33(8):927–939; doi: 10.1089/thy.2022.0641.
8. Mehuys E, Lapauw B, T'Sjoen G, et al. Investigating levothyroxine use and its association with thyroid health in patients with hypothyroidism: A community pharmacy study. Thyroid 2023;33(8):918–928; doi: 10.1089/thy.2023.0066.
9. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010;304(12):1365–1374; doi: 10.1001/jama.2010.1361.
10. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160(4):526–534.
11. Parle JV, Franklyn JA, Cross KW, et al. Thyroxine prescription in the community: Serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment. Br J General Pract 1993;43(368):107–109.
12. Aoki Y, Belin RM, Clickner R, et al. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid 2007;17(12):1211–1223; doi: 10.1089/thy.2006.0235.
13. Carle A, Faber J, Steffensen R, et al. Hypothyroid patients encoding combined MCT10 and DIO2 gene polymorphisms may prefer L-T3 + L-T4 combination treatment—Data using a blind, randomized, clinical study. Eur Thyroid J 2017;6(3):143–151; doi: 10.1159/000469709.
14. Jonklaas J, Bianco AC, Cappola AR, et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: A consensus document. Thyroid 2021; 31(2):156–182; doi: 10.1089/thy.2020.0720.
15. Stott DJ, Rodondi N, Kearney PM, et al. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 2017;376(26):2534–2544; doi: 10.1056/NEJMoa1603825.
16. Samuels MH, Kolobova I, Niederhausen M, et al. Effects of altering levothyroxine (L-T4) doses on quality of life, mood, and cognition in L-T4 treated subjects. J Clin Endocrinol Metab 2018;103(5):1997–2008; doi: 10.1210/jc.2017-02668.
17. Werneck FZ, Coelho EF, Almas SP, et al. Exercise training improves quality of life in women with subclinical hypothyroidism: A randomized clinical trial. Arch Endocrinol Metab 2018;62(5):530–536; doi: 10.20945/2359-3997000000073.
18. Rezaei S, Abedi P, Maraghi E, et al. The effectiveness of cognitive-behavioral therapy on quality of life in women with hypothyroidism in the reproductive age: A randomized controlled trial. Thyroid Res 2020;13:6; doi: 10.1186/s13044-020-00080-z.

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