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Why Do Patients with Subclinical Hypothyroidism Get Overtreated?

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SUMMARY

Background

There is growing concern about patients with subclinical hypothyroidism receiving too much L-T_4, a problem found both in specialty and in primary care settings. Too much circulating thyroid hormone can increase the risk of atrial fibrillation and bone fragility, especially in the elderly. For patients who have a normal free T_4 level and whose TSH is above the upper limit of normal yet below 10 mU/L, the American Thyroid Association recommends considering treatment if the patient has symptoms suggestive of hypothyroidism, a positive anti-TPO titer, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases (1). British guidelines indicate that if screening thyroid-function tests have been performed for nonspecific symptoms in a normal healthy adult and the TSH is between 4 and 10 mU/L but the FT_4 is normal, L-T_4 is not recommended as routine therapy. However, repeat thyroid-function testing should be done in 3 to 6 months, after excluding nonthyroidal illness and drug interference (2). If the second test results are similar to the first, and if the anti-TPO titer is normal, a repeat measurement of TSH every 3 years is all that is required (2). In the United Kingdom, primary care physicians take care of most patients receiving L-T_4 for hypothyroidism. A computerized thyroid disease register assists physicians in keeping track of all the patients with hypothyroidism receiving L-T_4 and to ensure that physicians obtain thyroid-function tests on these patients every 12 months. The current study assessed how instituting these practice targets influenced L-T_4 prescribing behavior and whether this policy may have had unintended consequences.

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Methods

About 52,000 patients given an initial L-T_4 prescription within 90 days of a TSH determination were identified in the General Practice Research Database between 2001 and 2009, after excluding patients known to be taking thyroid-altering medications, those receiving L-T_4 for pregnancy, and those with a known history of hyperthyroidism, pituitary disease or thyroid surgery. Pretreatment TSH levels, L-T_4 prescriptions, and subsequent TSH levels were analyzed every 6 months for up to 5 years (if more than one determination had been obtained within a 6-month period, the most recent value was used). An "interpretable" free T_4 determination was available in about 35,000 cases at the time of the initial prescription of L-T_4, while in 21,000 cases a free T_4 level was available at the end of a patient's study. Unfortunately, no "interpretable" anti-TPO data were available. Other symptoms, clinical findings, diagnoses, clinic appointments, tests, and procedures were reviewed for the 3 months prior to initiating treatment with L-T_4, and, along with age and sex, were factored into the analyses. No information concerning mortality was provided. Logistic-regression analysis was used to assess the odds of a patient being given an L-T_4 prescription for a TSH of 10 mU/L or less. The odds of suppressed TSH developing at 5 years were also assessed by univariable logistic regression.

Results

The median TSH for which a new patient received L-T_4 fell steadily over the study period, from 8.7 mU/L in 2001 to 7.9 mU/L in 2009. After adjusting for multiple variables, the odds ratio for as of a patient receiving L-T_4 for a TSH of 10 mU/L or less was 1.30 (95% CI, 1.19 to 1.42; P<0.001) in 2009 as compared with 2001. In 2001, 42% of patients had a TSH above 10 mU/L, whereas in 2009, only 36% had a TSH above 10 mU/L (P<0.001). Of the patients whose initial TSH was between 4 and 10 mU/L, about 20,000 had an interpretable free T_4 before L-T_4 treatment was started. Strikingly, 83% of them had a normal free T_4. True, those who were given L-T_4 despite a normal free T_4 were more likely to be older and to have had pretreatment cardiovascular risk factors, but the majority (11,000) did not have a history of hypertension, diabetes, or elevated lipids and had no symptoms consistent with hypothyroidism. After 6 to 12 months of treatment, 2.7% of patients had a suppressed TSH (<0.1 mU/L), whereas after 54 to 60 months of treatment, the fraction with a frankly suppressed TSH had more than doubled (5.8%). Furthermore, the fraction of patients with a TSH between 0.1 mU/L and 0.5 mU/L rose from 6.3% after 6 to 12 months to 10.2% after 54 to 60 months of treatment. Patients who noted fatigue or depression before the initial prescription of L-T_4 were significantly more likely to have a suppressed TSH at 5 years, as were women whose initial TSH was either under 4 mU/L or over 10 mU/L. Although those with cardiac risk factors were less likely to have a suppressed TSH level, more than 10% of those with cardiac risk factors did have a low TSH level. The risk of being given a new prescription for a TSH between 4 and 10 mU/L was greatest in those 80 to 100 years old.

Conclusions

In the United Kingdom, the fraction of patients with marginal degrees of hypothyroidism treated with L-T_4 increased progressively between 2001 and 2009, apparently associated with the institution of new targets for general practitioners. The risk for a patient with a suppressed TSH or a TSH below the lower limit of normal was substantially greater after 5 years' treatment than after only 6 to 12 month's treatment.

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ANALYSIS AND COMMENTARY

The risks associated with having an elevated T_4/free T_4 appear to exceed the risks of having a TSH between 4 and 10 mU/L. Older patients are at particular risk for overtreatment, since their upper limit of normal for the level of TSH is slightly higher than that in younger patients (3). A review of records on 3900 community-dwelling apparently euthyroid Caucasian Australian men over 70 years of age found that those whose free T_4 was normal but in the highest quartile were 20% more likely to have died (odds ratio, 1.19; 95% CI,1.02 to 1.39) over 6 years of follow-up (4). In contrast, there was no altered risk of mortality associated with any quartile of TSH within the normal range (4).

What leads to overtreatment of patients with hypothyroidism? Patients who reported tiredness and depression at the initiation of treatment in this study were significantly more likely to have a suppressed TSH at the end of the study, perhaps because they requested extra L-T_4 to make them feel less lethargic or less depressed. (This may reflect U.K. guidelines on the use of thyroid-function tests, which states "The primary target of thyroxine replacement is to make the patient feel well and to achieve a serum TSH that is in the reference range. … The corresponding free T_4 will be within or slightly above its reference range" (2). In other cases, a fall in a patient's TSH level, a patient's failure to get a scheduled repeat TSH test, or some change in the patient's medications, co-morbid conditions, or diet that have reduced a patient's L-T_4 requirement may have escaped the physician's notice. Rarely, a patient with hypothyroidism can turn to hyperthyroidism because of a change in the activity of thyroid-stimulating antibodies versus the activity of thyroid-blocking antibodies (5). Similarly, a new hot nodule can turn hypothyroidism to hyperthyroidism. There is also evidence that the amount of L-T_4 a patient requires correlates with lean body mass, which tends to decrease with age.

Interestingly, almost 10% of the patients were no longer taking L-T_4 at the end of the study period. In one third of the patients with a TSH between 4 and 10 mU/L, only that single determination had been obtained before L-T_4 was given. Thus some of the patients may actually have had thyroid-function abnormalities, reflecting nonthyroidal illness. Furthermore, it is not unusual for a slightly elevated TSH level in an elderly patient to spontaneously normalize (6). On the other hand, some patients may have stopped taking L-T_4 and begun taking another form of thyroid hormone obtained online, such as a desiccated thyroid preparation.

Patients who may have had a TSH between 4 and 10 mU/L, but who did not receive a prescription for L-T_4 were not included in this study. The absence of anti-TPO data also weakens the interpretation of the data. Furthermore, several different TSH assays were being used during the study, and simply combining the results is not ideal, since some third-generation TSH assays can have a steeper TSH dose–response slope than others (3). More problematic, different free T_4 assays were being used: the consistency and reliability of different T_4 analog methods can be quite uneven, and results may not correlate well those obtained by dialysis (7). Nonetheless, until a large well-controlled, prospective, randomized trial of L-T_4 treatment of patients with subclinical hypothyroidism that includes a wide range of ages and TSH levels is performed, the practitioner needs to be wary of overtreatment with L-T_4.

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