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Critical Comments

The subject of the Rhineland Study as described in the article is highly relevant (1).

We have critical comments regarding three points:

- The benchmark for undertreatment was a TSH concentration above 4.27 mU/L.
  - This is not consistent with the recommendations of the German College of General Practitioners and Family Physicians (DEGAM) guideline on this subject (2). The guideline provides that a TSH concentration in 70–80 years old is considered elevated at a level of >5 mU/L and in those older than 80 at a level of >6 mU/L.
  - Up to 10 mU/L, no substitution is recommended and in people older than 75 years, this is not needed in concentrations up to 20 mU/L.

Consequently there will be much less undertreatment.

- A TSH concentration between 0.56 mU/L and 4.27 mU/L is not confirmation of successful substitution. In many patients without a clear indication, the L-thyroxin dose can be tapered out under TSH monitoring.
- According to some statements, not enough TSH monitoring controls are carried out. In 2022, 22.5 million measurements were taken (personal communication from the Zentralinstitut für die kassenärztliche Versorgung [ZI, the central institute for statutory health insurance provision/care provision], dated 22 June 2023).
- Monitoring TSH concentrations is costly, at €3 for the laboratory expenditure. In older persons—except in acute decompensation and/or dose finding periods—much longer monitoring intervals are sufficient (every 5 years) (3).

Tracing overtreatment and undertreatment with thyroid hormone and putting a stop to it requires a high level of commitment. The article raises awareness of the subject, but it underestimates overtreatment and overestimates undertreatment.

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JS and KV are authors of and GE served as an expert reviewer for the DEGAM guideline "Elevated TSH levels in general practice". All three are conducting research into the care for patients with thyroid disease. The research projects are financed with public funds. GE and JS are general practitioners.

In Reply:

Levothyroxine treatment requires careful adjustment; manifest hypothyroidism inevitably requires treatment, whereas latent hypothyroidism requires decisions made on an individual basis. Independent of age, asymptomatic patients (TSH≤ 10 mU/L) should not receive any substitution treatment. Patients older than 75 years should be treated if their TSH level exceeds 10 mU/L. For those older than 75 with latent hypothyroidism (TSH<20 mU/L), substitution is not required (1).

In treated patients, the guideline recommends a THS range of 0.4–4.0 mU/L (laboratory reference ranges vary [inter]nationally) (1).

Levothyroxine dosages should be determined based on age, weight, cardiac status, and severity of hypothyroidism (1). TSH is the primary marker for thyroid function and is considered the most sensitive indicator for thyroid hormone changes . Many epidemiological studies therefore use the TSH level to categorize overtreatment or undertreatment with levothyroxine (2, 3). However, treatment success depends not only on the TSH level but also on the well-being, potential adverse effects, and patients' adherence.

Population-based studies enable insights into the quality of drug treatment in the general population and

can uncover potential problems. The Rhineland Study identified a high prevalence of levothyroxine use (23%), with 18% overtreatment (TSH<0.56 mU/L) and only 4% undertreatment (TSH>4/27 mU/L) (4). The high prevalence of participants with suppressed TSH is particularly concerning, as subclinical hyperthyroidism is associated with negative health outcomes such as atrial fibrillation and osteoporosis (5). The number of overtreated individuals could—as mentioned in our publication—be underestimated, since persons with a TSH level in the lower reference range and low dosages of levothyroxine might remain euthyroid after discontinuation. Furthermore, it is unclear how many participants had manifest hypothyroidism before starting treatment, as many might not have needed levothyroxine substitution.

In individuals aged 70–80 years, TSH levels should not exceed 5.0 mU/L, whereas it should not fall below 6.0 mU/L in those older than 80 (1). In our sample, the number of individuals categorized as undertreated was low (n=27, mean age: 59.5±15.5 years). Only three undertreated participants aged between 70 and 80 years had a TSH level >5/0 mU/L, and only one participant >80 years had a TSH >6/0 mU/L. For this reason, a potential overestimation of undertreated participants appears negligible here.

We investigated the prevalence and determinants of overtreatment and undertreatment with levothyroxine and emphasized in our article that despite numerous TSH controls, treatment often seems inadequate. Although treatment success depends not only on TSH levels but also on factors such as age, sex, and biological variation, the high number of participants with suppressed TSH levels is concerning. We agree that TSH alone is not sufficient to comprehensively assess the quality of levothyroxine substitution. Nonetheless, our study provides insight into the current overall situation and aims to sensitize the medical community to the ongoing challenges of overtreatment or undertreatment.

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The author declares that no conflict of interest exists.