Letters to the Editor regarding the article

Over- and Undertreatment With Levothyroxine

Findings of the Population-Based Rhineland Study

by Nersi Alaeddin, Dr. Rutchanna M.S. Jongejan, and Prof. Dr. med. Julia C. Stingl, et al. in issue 42/2023

Contrary to the Guideline

Postulating over- or undertreatment independently of age and merely because a TSH concentration falls below or exceeds a TSH reference range (1) is in contradiction of the guideline "Raised TSH concentrations in general practice [Erhöhter TSH-Wert in der Hausarztpraxis]" compiled by the Association of the Scientific Medical Societies in Germany (AWMF) (2) and, also, to best practice in the treatment. Individual TSH concentrations need to be assessed in consideration of a patient's life age, fT4 measurement, clinical symptoms, body mass index (BMI), medication, impairment to health related quality of life, and general health (acute illnesses/disorders, comorbidities). Disease mongering on the basis of a deviation from the reference range for TSH concentrations is unjustifiable. For low TSH concentrations this is equally true: the reference range is not the criterion for treatment, but clinical symptoms, etiology, comorbidities, and—where applicable—additional medication and laboratory variables have to be considered. When interpreting TSH measurements, dietary/nutritional, environmental, geographical, genetic as well as endogenous and exogenous factors have to be considered, including iodine intake, age, sex, biological variations, pregnancy, ethnic background, and testing method used. In older persons the upper threshold of the TSH reference range increases (3). According to (1), independently of age, asymptomatic elevated TSH≤ 10 mU/L should not be substituted and hormone substitution can be omitted in patients >75 years who have latent hypothyroidism up to <20 mU/L. The levothyroxine dose has to be guided in the individual case by thyroid readings determined in laboratory tests as well as subjective wellbeing or symptoms. It was shown that in patients ≥85 years, latent hypothyroidism is not associated with higher mortality and confers no survival advantage compared with TSH concentrations <4 mU/L.

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Conflict of interest statement
The author declares that no conflict of interest exists.

TSH Concentration by Itself Does not Reflect Successful Treatment

We read the results of the Population-Based Rhineland Study (1) of thyroxine (T4) treatment with great interest. The authors reported on almost 3000 participants, of whom 23% received T4 treatment. Comparison with the resultant TSH concentrations showed a high proportion of improper treatment, with 18% categorized as overtreated. We agree with the authors that this result is striking and unsatisfactory. The same applies, however, for the selected criterion for classifying treatment success, since the TSH concentration does not necessarily reflect successful treatment.

A substantial proportion—5–10% of patients having substitution treatment—complain of a sustained low quality of life on monotherapy with T4, in spite of reaching TSH reference values (2). Genetic variability in the genes for thyroid hormone transporters, receptors, and selenium dependent deiodinases, which control the metabolism of T4 and T3, are considered as potential causes (3). Negative feedback regulation of TSH, for example, is dominated primarily by the beta-isoform of the thyroid hormone receptor, whereas many peripheral organs depend on the alpha-isoform. Further to genetic variability, thyroid hormone resistance has been described in patients with chronic fatigues syndrome, which can be explained by autoimmunity against the selenium transporter and impairs the deiodination of T4 in the target organs (4).

In this setting too, the deficiency was not reflected in the TSH concentrations, which underlines that, in order to assess the success of any substitution, additional variables need to be measured, such as quality of life and alternative biomarkers for the effect of thyroid hormone. We therefore agree with the authors that overtreatment should be avoided, but TSH as the only parameter is not sufficient to classify the success of T4 substitution. This is a relevant limitation of the study, which should be mentioned and borne in mind.

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