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LETTER TO THE EDITOR

Limitations of current thyroid function tests

Limitaciones de las pruebas actuales de la función tiroidea

Dear Editor,

Current thyroid function tests may have limitations since they only measure the total or free T4 and/or T3 and TSH serum concentrations in peripheral blood and not the effect of T4 or T3 serum on different specific target tissues. Nonetheless, TSH concentration is a good functional marker of the effect of thyroid hormones in the pituitary tissue. We know that tissues take up iodothyronines by surface transporters and deiodinate T4 into the active form T3. The availability of T3 at the tissue level is regulated by three deiodinase isoforms (D1, D2, D3), but due to tissue heterogeneity, pituitary secreted TSH may not reflect what happens in other tissues. Therefore, TSH serum is not an appropriate indicator of peripheral tissue euthyroidism.[1,2] It is also known that pituitary TSH secretion is mainly regulated by the local T4 to T3 conversion through deiodinase 2, which is consistent with the dominant role of T4 rather than T3 in regulating TSH secretion.

From a clinical practice point of view, about 15% of patients treated with levothyroxine monotherapy do not reach clinical euthyroidism and continue to have complaints of psychological impairment, depression, and persistence of symptoms of thyroid hormone deficiency despite biochemical euthyroidism demonstrated by normal TSH concentrations.[3,4]

In a study by Peterson et al.,[5] it was found that individuals in a large population taking levothyroxine while having TSH values within the reference limits, compared to euthyroid individuals, exhibited relatively lower free and total T3 serum level, relatively higher free and total T4 serum level, and consequently lower T3/T4 ratios. This finding is in agreement with previous studies of athyreotic patients treated with levothyroxine monotherapy[6,7]; these patients, despite having TSH concentrations within the reference value, may have inadequate peripheral deiodination to compensate for the absent T3 secretion. Long-term effects of chronic tissue exposure to abnormal T3/T4 ratio are currently unknown. In line with this, a recent report by Ito et al. concluded that in total thyroidectomised patients treated with levothyroxine, those with mildly suppressed serum TSH values were close to euthyroidism, while those with normal or strongly suppressed TSH were mildly hypothyroid.[8]

Another topic of debate in this field is the reference values of TSH, with the suggestion that the upper reference limit should be reduced to 2.5 mIU/L or 3.0 mU/L. The current TSH reference range is too high as it includes patients with thyroid antibodies that are destined for future hypothyroidism. However, not all population studies that exclude risk factors for thyroid diseases report a significant change in the TSH reference range.[9] A recent investigation by Inoue et al. found an increased risk of all-cause mortality, cardiovascular-related mortality, and cancer-related mortality among those with TSH serum concentrations both in the high-normal and low-normal reference ranges, compared to those with mid-normal serum TSH concentrations.[10] This phenomenon raises the question of whether the serum TSH reference range should be re-examined.

The results of the aforementioned studies confirm the limitations of the current thyroid function tests that may influence our clinical practice. To address these limitations, the following recommendations should be noted: 1) total thyroidectomy should be performed only when the risk to benefit ratio is well balanced in order to avoid the risk of harming the patients; 2) in order to achieve euthyroidism in hypothyroid patients, we should pay attention not only to the results of thyroid function tests but also to the symptoms; 3) serum TSH values for athyreotic patients may be at the lower limit of the current normal range.

Disclosure statement

The author has nothing to disclose.

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