

## SCIENTIFIC LETTER

Reference values for serum thyroglobulin in healthy individuals<sup>☆</sup>

## Valores de referencia para tiroglobulina sérica en individuos sanos

Dear Editor,

I have read the article "Definition of the reference ranges for free T4, TSH and thyroglobulin among healthy subjects of the Health District of Jaén" submitted by Olmedo-Carrillo et al.<sup>1</sup> with interest, and would like to make a number of comments on the study.

One of the main objectives of the study was to determine the reference values (RV) for serum thyroglobulin (Tg-S) in the general population. In 2013, the National Academy of Clinical Biochemistry published the laboratory guidelines for the diagnosis and monitoring of thyroid gland diseases, establishing the criteria for selecting the adequate reference population for determining the RVs referring to TSH, antithyroid antibodies and Tg-S. In relation to the latter parameter, the recommended selection criteria were to establish RVs from healthy, non-smoking euthyroid (TSH 0.5–2.0 mIU/l) individuals under 40 years of age, with no personal or family history of thyroid disease, and no evidence of antithyroglobulin antibodies (TgAb) or thyroid peroxidase antibodies.<sup>2</sup> Although these criteria for selecting the reference population may be questionable from several points of view, it is clear that when determining the Tg-S values it is necessary to specify the presence of TgAb, due to their known interference with the Tg-S measurements. With regard to the system used in this study (immunometric assay), one of its main disadvantages is a propensity toward interference—even with low TgAb concentrations—and the fact that interference is characterized by undetectable or falsely reduced Tg-S values.<sup>2</sup> The presence of TgAb in the general population is variable and ranges between 5% and 15%. These figures can moreover increase in populations transiting from dietetic

iodine deficiency to sufficiency, as in the population of this study. The increase in thyroid autoimmunity following an increase in iodine intake in previously iodine-deficient areas has been described in different populations.<sup>3</sup> Experimental studies indicate that iodine induces the production of TgAb by incrementing thyroglobulin immunogenicity and promoting lymphocyte proliferation.<sup>3</sup> As a result, the measurement of TgAb in iodine-deficient populations can also be regarded as an intermediate biochemical indicator in monitoring the impact of iodoprophylaxis programs upon thyroid function.

Although some authors conducting epidemiological studies to evaluate the usefulness of Tg-S in assessing iodine nutritional status have considered that the determination of TgAb may be obviated, these studies referred to children, in whom the prevalence of TgAb is very low.<sup>4</sup> In the case of adults the situation depends on the type of test used and on the nature of the interference.<sup>5</sup> Serum thyroglobulin is recommended as a sensitive biomarker of iodine nutritional status, because it reflects the improvement in thyroid function weeks or months after iodine repletion. Few studies have been made to establish RVs for Tg-S, though these values have been previously defined for children<sup>4</sup> and pregnant women,<sup>6</sup> with similar intervals: a median of <13 µg/l or <3% of the population with thyroglobulin >40 µg/l, and a median of <10 µg/l or <3% of the population with >44 µg/l, are indicative of sufficiency in these populations, respectively. In other iodine-sufficient adult, non-pregnant populations, the same median thyroglobulin concentration of <10 µg/l has been established, together with an upper limit of <40 µg/l, as indicative of nutritional iodine sufficiency.<sup>7</sup> These same criteria had already been used by the World Health Organization. On considering these values and applying them to the results of this study, the population would appear to be iodine-deficient, since the median thyroglobulin concentration is >10 µg/l, and >3% of the values are >40 µg/l. However, these results may have been influenced by thyroid gland volume, which is strongly correlated to Tg-S levels<sup>8</sup>—a circumstance not controlled for in this study, and which is evident in women >65 years of age, possibly in relation to an increased frequency of multinodular goiter. Nevertheless, women of fertile age (15–40 years) show iodine deficiency according to Tg-S, which is a cause for concern. This observation was already analyzed by the authors.<sup>9</sup> The complementary information added by Tg-S to ioduria in population-based studies of iodine nutritional status has recently been examined by several authors,<sup>4,6–8</sup>

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and although ioduria is a good population indicator of iodine nutritional status, it should always be taken into account that it largely reflects iodine intake during a short period of time before sampling—hence its important day-to-day intra-individual variation. This situation worsens with the use of urine iodine concentration (UIC) in casual urine samples, since individual iodine intake cannot be determined by measuring ioduria in a point urine sample. Therefore, a relationship between ioduria and the thyroid parameters should not be expected, especially when ioduria is expressed as UIC and the dilution of the sample has not been corrected,<sup>10</sup> and particularly when investigating adults. For this reason, different authors have advocated the estimation of 24-hour urine excretion based on formulas, with urine creatinine in casual samples or in 24-hour urine collections ( $\mu\text{g/d}$ ).<sup>8,10,11</sup> Accordingly, 24-hour urine iodine excretion is a better predictor of the thyroid parameters, including Tg-S,<sup>8,10</sup> in contrast to UIC (which was used in this study), for which no correlation is observed between ioduria and Tg-S.

The study data are of great value and interest, and the efforts of the authors are laudable; however, the RVs for Tg-S must be viewed with caution.

## References

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