Thyroid ultrasound: beyond the diagnosis of thyroid nodules

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In this issue of the *Archives of Endocrinology and Metabolism*, there are two articles in which thyroid ultrasound was used to clarify some physiopathological aspects of the thyroid, evidencing the notable usefulness of this method beyond its routine use in the diagnosis of nodules and thyroiditis.

The first article, "Should human chorionic gonadotropine treatment increase thyroid volume?", by Ayten Oguz and cols. from the Sutcu Iman University in Kahramanmaras, Turkey, presents a very interesting and pioneering observation showing that the administration of human chorionic (hCG) in the treatment of isolate hypogonadotropic hypogonadism (IHH) in men induced increased thyroid volume (1).

This original observation confirms classical endocrinological evidence on the cross-reactivity between hCG and TSH. Both substances are glycoprotein hormones with structural similarity and whose thyrotrophic activities have been known for a long time (2). TSH and hCG are made up by two subunits (alpha and beta), that are linked to each other, forming active heterodimeric structures; the alpha subunit of both compounds is identical, but the beta subunits also show high structural homology. Similarly, TSH receptors show structural homology with LH/CG receptors, which are bound to protein G (3). Thus, hCG thyrotrophic activity may be explained by either the structural homology between hCG and TSH or between the LH/CG and TSH receptors. Therefore, hCG is able to bind to TSH receptors of thyroid follicular cells and activate intracellular messengers, such as cyclic AMP, and induces growth of follicular cells in culture (3).

In normal pregnancy, when hCG is high, TSH decreases, mirroring the hCG peak (3,4); besides, women with hyperemesis gravidarum show high levels of hCG, which cause transitory thyrotoxicosis (4). Finally, it is know that several pathological conditions, such as hydatidiform moles, choriocarcioma, and other types of cancer that are characterized by high levels of hCG and may induce thyrotoxicosis, which disappears after the tumor is removed (3).

In fact, hCG behaves as a "weak" thyroid stimulator; it is estimated that a 10,000 IU/liter increase in circulating hCG corresponds to a 0.6 pmol/L (0.1 ng/dL) elevation in T4, leading to a TSH decrease of 0.1 mU/L (3). Besides, for clinical hyperthyroidism to ensue, a patient has to show prolonged elevation of hCG levels (4).

Oguz and cols. treated 44 men (18 to 54 years old) carriers of IHH with testosterone (n = 19) or hCG (n = 25) for about 6 months, and compared them with a matched healthy control group, evaluating thyroid function and volume. They did not mention the doses of testosterone or hCG that were employed.

Individuals treated with hCG showed, after 6 months, higher serum levels of testosterone and increased T4 (from 1.16 ± 0.19 ng/dL to 1.34 ± 0.49 ng/dL, p = 0.024) and thyroid volume (from 8.76 ± 1.13 mL to 9.02 ± 0.99 mL, p = 0.001).

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TSH values remained unchanged. Patients treated with testosterone did not show changes in TSH, T4, and thyroid volume.

It is important to emphasize that the study was based on the methodology that is routinely used for thyroid volume calculation, which assumes an ellipsoid shape for each lobe, and the volume is obtained by multiplying the three axes (length, breadth, and thickness) by 0.523 (result of the pi/6 ratio) (5,6).

Therefore, the observation shown in this report, that hCG treatment may induce increased thyroid volume, is original and important for clinical practice. It is a pity that the authors did not mention the hCG dose used.

The other study, "Genetic and environmental influence on thyroid gland volume and thickness of thyroid isthmus: a twin study", from the Semmelweis University in Budapest, Hungary, Tarnoki and cols. analyzed if the most important factor influencing thyroid size was genetics or the environment (7).

This is an ambitious and difficult question, once it has already been demonstrated that several factors, besides genetics, influence thyroid size. Among them, the ingestion of iodine and selenium, TSH concentration, age, sex, body mass index, parity, smoking, and alcohol intake (8).

The study of Tarnoki and cols. has limitations when compared with similar studies in the literature (8-10). They carried out thyroid ultrasound in 114 pairs of Hungarian twins (69 monozygotic, MZ and 45 dizygotic, DZ), and observed, using the twin methodology (11,12), which familial factors were important for thyroid measurements. However, they did not reach a conclusion on the most important factor, if genetics or the environment, in the determination of isthmus thickness and volume of thyroid lobes.

Modelling in twin studies compares phenotypical similarities between MZ and DZ twins, and is based on the principle that MZ twins are genetically identical and, as a consequence, differences between them are related to environmental factors. On the other hand, DZ twins share, in average, about 50% of the genes and, as a consequence, the differences between them are caused by a combination of genetic and environmental factors (11,12).

When I mention the limitations of this study, I consider the methodology and results interpretation. From the methodological viewpoint, the authors employed a methodology for the evaluation of thyroid volume that was different from that used by most of the authors, with the formula length, breadth, and thickness of the lobes multiplied by 0.63. Besides, it seems that the measurement of the isthmus is inadequate for conclusions, as there is a wide anatomical variability in the formation of this segment, which sometimes is filiform, sometimes a little thicker, and the margin of error of measurements may be too large, without even considering the existence of a pyramidal lobe, found in 30-40% of the individuals (5,6). Still, in terms of the methodology based on modelling in twin studies, there was no thyroid function evaluation or data on TSH, free T4 values, and antithyroid antibodies, which weakens the method when it is considered that other studies in the literature employed more factors in the analysis (8-10).

From the standpoint of data interpretation, we considered that the sample is small when compared with Danish data (8). Thus, Hansen and cols. studied 104 MZ and 107 DZ from the same sex and, besides ultrasound measurements, they also included TSH, free T4, anti-TPO and anti-Tg antibodies, BMI, sex, age, familial history of thyroid disease, pregnancy, use of estrogen replacement therapy, and smoking to evaluate modelling in twin studies (11,12), concluding that genetic factors were responsible for 71% of the individual differences in thyroid volume (8).

As a conclusion, I consider that the study of Tarnoki and cols. needed a larger sample, besides information on thyroid function evaluation in order to better define the most important factor influencing thyroid size, if genetics or the environment. This limitation is admitted by the authors in their conclusion and discussion.

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