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RESEARCH ARTICLE

TSH ACCORDING TO AGE AND SEX, DECREASES THE PRESUMPTIVE DIAGNOSIS OF HYPOTHYROIDISM

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ABSTRACT

Introduction: The reference ranges for classifying a patient as hyperthyroid, normothyroid or hypothyroid vary from one laboratory to another, due to the different techniques used, regional factors, such as race, iodine intake, etc. But there are also other variables, like the age and the sex of the patient that generally are not taken into account, but can play a role in the diagnosis.

Objectives: To apply the formulas from the NHANES III study, to a Madrid (Spanish) population.

Patients and methods: We included 2521 patients: they were requested TSH and thyroid antibodies (antimicrosomial thyroid antibodies and thyroglobulin) by their family physicians. The TSH, T3 and T4 tests were also requested.

Results: Of 181 patients (134 women and 47 men), corresponding to 12% of the total and 63.7 % of patients classified as hypothyroid, which were reclassified as normothyroid. Only 2 patients (100 % men), corresponding to 0.08% of the total and 0.20% of patients initially classified as normothyroid, were reclassified to hyperthyroid.

Discussion: The results of our study show a significant decrease in patients classified initially as hypothyroid and then reclassified as normothyroid depending on their age and sex. All these equations could be programmed into the laboratory´s computer system and would not need further testing.

Conclusions: Classification errors would be reduced in patients with TSH below the 2.5 percentile or above the 97.5 percentile of its reference range of TSH.

INTRODUCTION

Thyroid disorders are an important group of endocrine diseases, and usually the Thyroid-stimulating hormone (also known as thyrotropin, thyrotropic hormone, TSH, or hTSH for human TSH) in serum, is considered to be the most sensitive marker of thyroid dysfunction[1]. Thyroid-stimulating hormone (=TSH) levels may vary depending on pre-analytical factors, like pulsatile secretion, diurnal variation (with a night increase), high levels in the new-borns, lower levels in early pregnancy and variable effects of non-thyroid diseases levels[2-4].

Recent data from the analysis of National Health and Nutrition Examinations Survey III (NHANES III) in the United States suggest that in the absence of thyroid disorders, serum TSH concentrations increase with age[5-8]. The TSH reference limits are controversial (especially upper limits). The usual method used to set these limits, is based on the distribution of non-thyroid disorder subjects. This distribution curve is not

Gaussian, and it is biased at higher concentrations, even after the logarithmic transformation, the levels of the biased area are assumed to reflect mild hypothyroidism. Nonetheless, there is no evidence available that the limits resulting from this curve are applicable to everyone. However, some studies point out that different subpopulations have unique distribution of TSH, and their reference limits are different (with statistical significance) from the limits set by the traditional approach[9-12]. Further evidence show that changes in the population distribution limits and reference TSH can change according to age and ethnicity. The traditional TSH distribution curve is composed from several curves for specific subpopulations. These last data point out that using reference limits specific for age and ethnicity should attenuate the misclassification of subjects with TSH outside the reference range[13]. The establishment of the new reference limits for specific subpopulations, would be a task that should require measurements of TSH to a large number of individuals in each subpopulation that are free from thyroid disorders. According to NACB´s (National Academy of Clinical Biochemistry) guidelines[1], those individuals should be free from any thyroid disorder, should not take thyroid medication or drugs that may interfere thyroid function, and should be free of circulating antithyroid antibodies. Other authors have even point out that subjects with ultrasound abnormalities in the thyroid gland should also be excluded[14].

Boucai *et al*[13] have used the NHANES III database, evaluating quantitatively the contribution of age, ethnicity and gender in the reference limits of TSH, that are classically defined as percentiles 2.5 and 97.5 of the TSH distribution. These analyses led to the development of equations that could predict the percentiles 2.5 and 97.5 for each combination of demographic factors. This could be programmed into the laboratory´s hardware, which will evaluate the formulas provided in this article in our environment and will assess whether there are significant changes in normal range or not.

OBJECTIVES

To apply the formulas from the NHANES III study, which established reference ranges for TSH for the specific subpopulations in the United States (with the finding that age, sex and race were independent factors from the average TSH and reference ranges), to our environment, in a Madrid (Spanish) population.

To ascertain if these formulas to determine new TSH reference ranges, could allow us to avoid checking the result, not needing further testing, as T4, T3 or antithyroid antibodies.

To reduce classification errors in patients with TSH below the 2.5 percentile or above the 97.5 percentile of its reference range of TSH. This should improve the quality of care in individuals evaluated by thyroid disorders.

PATIENTS AND METHODS

We included 2521 patients, who were requested TSH and thyroid antibodies (antimicrosomial thyroid antibodies [anti-TPO] and thyroglobulin) by their family physicians. TSH was determined, and if appropriate, also the hormone thyroxine (T4) and triiodothyronine hormone (T3). The TSH, T3 and T4 tests were performed using chemiluminescent microparticle immunoassay (CMIA) in ARCHITECT i2000 (ABBOTT) and anti-TPO and anti-thyroglobulin by Enzyme-linked immunosorbent assay (ELISA) in InmunoCAP250 (PHADIA).

The reference range used in our laboratory (University Hospital "Ramón y Cajal") for TSH is between 0.35 and 4.94 mUI/mL, so adapting the formulas described in the paper by Boucai[7] *et al*, the following formulas were obtained to study:

TSH (percentile 2,5) = 0,35 + 0,00073*Age – 0,031*Sex

TSH (percentile 97,5) = 4,94 + 0,05*Age – 0,223*Sex

Considering the age in years, and sex should be "0" for men and "1" for women.

The reference ranges for antibodies are listed in Table 1.

Table 1

Antibodies	Negative	Uncertain	Positive
Anti-TPO	< 60 UI/mL	60 – 100 UI/mL	> 100 UI/mL
Antithyroglobuline	< 280 UI/mL	280 – 344 UI/mL	> 344 UI/mL

RESULTS

Our 2521 patients correspond to 456 men (18.1%) and 2065 women (81.9 %) with a mean age of 50.0 ± 19.7 years. The study group was divided in three sections based on the results of antithyroid antibodies (Table 2).

Table 2

		Negative	Uncertain	Positive
Anti-TPO/Antithyroglobuline		Negative/Negative	Uncertain /Negative Negative/ Uncertain	Positive/Positive Positive/ Uncertain Positive/Negative Negative/Positive Uncertain /Positive
Patients		1513 (60,0%)	91 (3,6%)	917 (36,4%)
Sex	Male	340	8	108
	Female	1173	83	809

The design of the formula was developed with patients who had negative antithyroid antibodies. Therefore, our study population should be only those with negative anti-TPO and negative thyroglobulin, i.e. 1513 patients out of 2521 patients included at first.

With our reference range, our classification of the thyroid function is in Table 3.

Table 3

Hyperthyroid patients	Normothyroid patients	Hypothyroid patients
120 (7,9%)	1109 (73,3%)	284 (18,8%)

Applying the formulas to be studied the following results in Table 4.

Table 4

Hyperthyroid patients	Normothyroid patients	Hypothyroid patients
122 (8,1%)	1288 (85,1%)	103 (6,8%)

Of 181 patients (134 women [74 %, mean age 57.4 ± 18.7 years] and 47 men [26 %, mean age 55.9 ± 21.4 years]), corresponding to 12% of the total and 63.7 % of patients classified as hypothyroid, which were reclassified as normothyroid. Only 2 patients (100 % men), corresponding to 0.08% of the total and 0.20% of patients initially classified as normothyroid, would be reclassified to hyperthyroid.

DISCUSSION

The formulas used in this study, were developed from the NHANES III study, which established reference ranges for TSH for the specific subpopulations in the United States. They

found that age, sex and race were independent factors from the average TSH and reference ranges.

As strong points of our study, we must say that those formulas had been adapted to our environment, with a Spanish population. Along with the large sample of patients with joint determinations of TSH, T4, T3, and antithyroid antibodies, the result of this study is a significant decrease in patients classified initially as hypothyroid and then reclassified as normothyroid depending on their age and sex.

Three studies of subjects free of clinical thyroid disease demonstrated that exclusion of people who had antithyroid antibodies and thyroid ultrasound abnormalities did not influence median TSH or TSH reference limits[15-17]. It is well known, that anti-thyroid antibodies and some thyroid ultrasound abnormalities may happen in subjects with thyroid disease and thyroid dysfunction, so these results are not obvious.

These formulas to determine new TSH reference ranges are attractive, because theoretically could allow us to avoid checking the result, not needing to request more tests such as T4, T3 or antithyroid antibodies. These equations can be programmed into the laboratory´s informatics system, and as explaining before, not needing further testing.

Thus the number of patients initially diagnosed with hypothyroidism presenting negative antithyroid antibodies and having a TSH above the normal range, was significantly reduced. According to their age and sex, these patients should fall now in the normal thyroid function range.

The main limitation of our study is the need to validate this model in other centres of the country, and thus extend this analysis to other unstudied subpopulations or the NHANES III.

Increasing evidence points out to the fact that classical methods for determining TSH reference limits may not reflect properly the TSH distribution of groups. This can vary with age, ethnic, or genetic composition[12].

CONCLUSIONS

Whenever possible, it is of capital importance to provide clinicians with population-specific reference limits. Our findings will help clinicians to reduce classification errors in patients with TSH below the 2.5 percentile or above the 97.5 percentile of its reference range of TSH. These results should provide a useful and reliable tool in the laboratory´s computer systems. The laboratory can then provide clinicians with more accurate population-specific TSH reference limits, which should also improve patient care.

Conflict of Interests

The authors declare no conflict of interest.

References

1. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF *et al*. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid.* 2003 Jan;13(1): 3–126.
2. Keffer, JH. Preanalytical considerations in testing thyroid function. Clinical Chemistry. 1996; 42: 125–34.
3. Soldin OP, Chung SH, Colie C. The use of TSH in determining thryroid disease: how does it impact the practice of medicine in pregnancy? *J Thyroid Res*. 2013; 148–57. http://dx.doi.org/10.1155/2013/148157
4. Santos Palacios S, Pascual-Corrales E, Galofre JC. Management of Subclinical hyperthyroidism. *Int J Endocrinol Metab.* 2012; 10 (2): 490–6.
5. Hollowell JG, Staehling NW, Flanders WD. Serum TSH, T, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002; 87: 489–99.
6. Deary M, Buckey T, Soldin OP. TSH – Clinical aspects of its use in determining thyroid disease in the elderly. How does it impact the practice of medicine in aging? *Adv Pharmacoepidemiol Drug Saf*. 2012;1(119): 9369.
7. Atzmon G, Barzilai N, Hollowell JG, Surks MI, Gabriely I. Extreme longevity is associated with increased serum thyrotropin. *J Clin Endocrinol* 2009; 94:1251–4.
8. Fontes R, Coeli CR, Aguiar F, Vaisman M. Reference interval of thyroid stimulating hormone and free thyroxine in a reference population over 60 years old and in very old subjects (over 80 years): comparision to young subjects. *Thyroid Res.* 2013;6:13.
9. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. *J Clin Endocrinol Metab.* 2010;95(2): 496–502.
10. Taylor PN, Razvi S, Pearce SH, Dayan CM. Clinical review: A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab*. 2013 Sep;98(9): 3562–71.
11. Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP. Age-specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. *Clin Endocrinol (Oxf).* 2012 Nov;77(5): 773–9.
12. Surks MI, Hollowell JG. Age-specific distribution of serum tryrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2007; 92: 4575–82.
13. Boucai L, Hollowell JG, Surks MI. An approach for development of age, gender, and ethnicity-specific thyrotropin reference limits. *Thyroid.* 2011;21(1): 5–11.
14. Wartofsky L, Dickey RA. Review The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab*. 2005; 90(9): 5483–8.
15. Kratzsch J, Fiedler GM, Leichtle A, Brügel M, Buchbinder S, Otto L, *et al.* New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. *Clin Chem* 2005;51:1480–6.
16. Eskelinen S, Suominen P, Vahlberg T, Löppönen M, Isoaho R, Kivelä SL, *et al*. The effect of thyroid antibody positivity on reference intervals for thyroid stimulating hormone (TSH) and free thyroxine (FT4) in an aged population. *Clin Chem Lab Med* 2005; 43:1380–5.
17. Hamilton TE, Davis S, Onstad L, Kopecky KJ. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. *J Clin Endocrinol Metab* 2008; 93:1224–30.