AUTOIMMUNE THYROID DISEASE IN EUTHYROID SUBJECTS

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Nadie es bueno, quien no quiere ser mejor.
Juan-Manuel Anaya

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CONTENT

1. ABSTRACT

1.1. OBJECTIVE

To determine the prevalence of thyroid autoantibodies and the associated factors in euthyroid subjects.

1.2. METHODS

In this study, 300 euthyroid subjects chosen by stratified sampling from an inception cohort of 1335 individuals were included. None of the subjects was under treatment. Thyroid function was evaluated by measuring serum levels of TSH (0.3-4.5 µIU / ml) and FT4 (5.2-12.7µg / dl). In addition, anti-peroxidase (TPOAbs), anti-thyroglobulin (TgAbs), and anti-TSH receptor (TrAbs) autoantibodies were evaluated together with other 23 autoantibodies and vitamin D levels. The analysis included sociodemographic, clinical, and environmental characteristics. Data were analyzed by chi-square ($\chi 2$), Kruskal-Wallis, Mann-Whitney and logistical regression tests.

1.3. RESULTS

Thyroid autoimmunity was observed in 15.3% of the subjects (TPOAbs in 11.3% and TgAbs in 2%). In six individuals, both autoantibodies were positive. TrAbs were not detected in any individual. Familial thyroid disease (P = 0.021, β = 3.4 CI: 1.2 – 9.5), low libido (P = 0.013, β = 3.8 CI: 1.3 – 10.6), the presence of other ADs (P = 0.014, β = 10.8 CI: 1.6 – 72.9) were associated with thyroid autoantibodies. In addition, VitD insufficiency (P= 0.03), never smoke (P = 0.010, β = 6.9 CI: 1.6 – 30.4), drinking more than 4 cups of coffee (P = 0.036, β = 3.8 CI: 1.1 – 13.1), and higher number of years exposed to wood smoke (P = 0.04), were associated with thyroid autoantibodies. Similar the last analysis, the presence of TPOAbs was associated with familial thyroid disease (P = 0.003, β = 4.9 CI: 1.7 - 14.0), never smoke (P = 0.002, β = 5.7 CI: 1.4 - 21.0), drinking > 4 cups of coffee (P = 0.047, β = 3.6 CI: 1.1 - 13.1), low libido (P = 0.001, β = 5.7 CI: 2.0 - 16.3). In addition, the presence of SS-A / Ro52 (P = 0.009, β = 36.7 CI: 2.5 - 549.9), and Ku (P = 0.046, β = 10.2 CI: 1.1 - 100.7), also was related to these autoantibodies. Regarding TgAbs, the presence of African ancestry (P = 0.01, β = 10.5 CI: 1.7 – 63.2), SS-A / Ro52 (P = 0.03, β = 15.8 CI: 1.2 – 198.6), and CENP-B (P = 0.02, β = 31.2 CI: 1.8 – 565.9) was associated with TgAbs.

1.4. CONCLUSIONS

Subclinical thyroid autoimmunity is not rare. Environmental, genetic, and immunological factors as well as ancestry are associated risk factors. These results will facilitate the implementation of screening strategies in order to provide timely diagnosis and treatment.

1.5. KEY WORDS

Euthyroidism, anti-peroxidase autoantibodies, anti-thyroglobulin autoantibodies, autoimmune thyroid disease.

2. PROBLEM STATEMENT

2.1. PROBLEM FORMULATION

Hypothyroidism, is an endocrine disease characterized by the presence of elevated levels of serum Thyroid-Stimulating Hormone (TSH) with low levels of free thyroxine (FT4). This disorder is described in up to 10% of population and its etiology has mainly an autoimmune origin, being the Hashimoto Thyroiditis (HT) the most important cause (1). One of the main problems lies in the absence of symptoms, therefore a large number of individuals suffer from the disease without knowing it. This high prevalence of undiagnosed hypothyroidism leads to a high rate of associated comorbidities, including cardiovascular disease, hypercholesterolemia, atrial fibrillation and depression (2–4).

Regarding hyperthyroidism, this disorder is the opposite of hypothyroidism. In this case the levels of TSH secreted by adenohypophysis are suppressed, due to the high secretion of T4 by the thyroid gland (5). Its prevalence varies between 0.8% in Europe (6), to 1.3% in the United states (7). As well as hypothyroidism, in hyperthyroidism, the most relevant cause is autoimmune, being Graves' disease (GD), the most important disease (5). Unlike to hypothyroidism, the prevalence of asymptomatic patients is low, therefore in the presence of the disease, the symptoms are very clear. In this case the thyroid hormone excess produces in patients a wide variety of symptoms as fatigue, sweating, tremor, anxiety, disturbed sleep, palpitations, weight loss, and heat intolerance (5).

Epidemiological data, evidences, on one hand, that the prevalence of autoimmune thyroid disease (AITD) is around 5% (8), and on the other hand, that the prevalence of thyroid autoantibodies in healthy subjects, may be even higher (9). This data is relevant, because the presence of thyroid autoantibodies could be a predictive tool of thyroid failure in subjects genetically predisposed. In view of the high prevalence of AITD, many studies have sought to determine the prevalence of thyroid autoimmunity previous overt thyroid disease, documenting the presence of thyroid autoantibodies in healthy subjects (7,10–15). On this wise, the reports ranged from the NHANES III study with a prevalence of 11.3% and 10.4% for TPOAbs and TgAbs, respectively, to a prevalence of 13.1% in Danish population. This is important considering the importance of the thyroid autoantibodies as predictors of AITD. In these sense, several studies have shown its predictive role (16,17).

2.2. JUSTIFICATION

The presence of associated factors with hypo- or hyperthyroidism have allowed to establish strategies that favor its early detection, however, the strategies that allow to determine risk factors associated with the presence of thyroid autoantibodies is still unclear. This is why becomes important the identification and knowledge of AITD, due to its high prevalence in areas with iodine sufficiency, its relationship with various comorbidities as was previously shown and its association with other autoimmune diseases (ADs), (2–4,18–21). In addition to the above, and in view of the high occurrence of undiagnosed thyroid disease, it is necessary to consider the presence of autoantibodies as a cost-effective mechanism for predicting and monitoring AITD in patients with risk factors. This is corroborated by different studies that have shown that the presence of thyroid autoantibodies implies the presence of future thyroid disease. This is the case of the Whickham study, which reported, in patients with TPOAbs and normal TSH, a risk of developing AITD of 2.1 per year (16). In addition to this study, *Li et al.* in a 5-year follow-up, found an accumulated incidence of TPOAbs of 2.8 (17).

In order to determine the possible factors necessary for the appearance of thyroid autoantibodies, it is essential to understand that AITD is a multifactorial disease, which requires a genetic substrate, that together with environmental factors, culminates in an alteration of immunological tolerance and finally in the production of autoantibodies. On this wise, it is necessary to identify the risk population. In first place, it is important to evidence that older people (especially in HT) and women have a greater risk to develop thyroid autoantibodies. This is supported by several studies that have shown ratios female: men between 2:1 to 3:1 (7,11), associated to an increase in thyroid autoantibodies also with age (22).

Other important factor is the genetic condition; such influence could be evaluated observing the family history of AITD or other AD, considering that ADs share genetic factors (23). In these sense, subjects with family history of AITD, or other ADs, screened for thyroid autoantibodies, still with normal TSH might be useful for early detection of AITD. Regarding environmental factors, some of them have been widely described in AITD, such as, iodine, infections, vitamin D (vitD) deficiency, stress, drugs, or tobacco (24). This allows inferring that, evaluating a susceptible population exposed in determined environment, benefits from a serological screening that allows to predict the appearance of AITD. Therefore, it is necessary to know the clinical importance of thyroid function tests, and to consider TSH and

autoautoantibody screening in those groups at risk. In addition, it is necessary to study those patients in whom the presence of AITD is documented, aiming to detect early the presence of other ADs, to initiate an opportune diagnosis and treatment.

2.3. RESEARCH QUESTION

What is the prevalence of thyroid autoantibodies (TPOAbs, TgAbs and TrAbs) and its associated factors in a group of Colombian euthyroid subjects?

2.4. PICO STRATEGY

Population	Subjects without clinical or biochemical hypothyroidism or hyperthyroidism
Intervention	Diagnosis: 1. Previous signature of the consent, healthy individuals were invited to participate in the study by taking a blood sample. 2. Autoantibodies (TPOAbs, TgAbs, and TrAbs) were measured in serum from all target population
Compare	-
Outcome	Prevalence of thyroid autoantibodies (TPOAbs, TgAbs, and TrAbs) and associated factors in a group of euthyroid subjects

3. THEORETICAL FRAMEWORK

3.1. HISTORICAL BACKGROUND AND ANATOMY OF THE THYROID GLAND

Thyroid comes from thyreòs in Greek which means “shield”; also the German name “Schilddrüse” means “shield gland” (25), In the work titled “De Voce”, by Galen, the thyroid gland was described for the first time, as a secreting gland adjacent to thyroid cartilage, although before, Eustachius named it as laryngeal gland (26). Latter, Thomas Whorton named the gland as “thyroid” due to its closeness to the thyroid cartilage (25).

The thyroid, is an endocrine gland medially located between the larynx and the trachea, and between carotid sheath and the sternocleidomastoid muscles laterally. Its weigh is around 15 to 25 g and its dimensions are between 6 to 7 cm long and 3 to 4 cm wide. The gland consists of two lobes connected by an isthmus, which is located between the I and II ring of the trachea (27).

Due to physiological role, the gland is highly vascularized, therefore four arteries irrigates it. Between these vessels there are anastomoses on the surface of the gland, allowing to penetrate the tissue and forming a network of fenestrated capillaries that surrounds each follicle. When veins arise, form a plexus of three groups of veins: inferior, middle, and superior veins (27).

In relation to lymphatic drainage, this is in charge of lymphatic capillaries that communicate with larger lymphatic vessels, which are found in the interlobular connective tissue. These lymphatic vessels drain mainly in a higher group of nodes located above the thyroid isthmus. Other nodes associated with thyroid lymphatic drainage include, pretracheal nodes, located below the isthmus and, other group located along the carotid sheath, and the recurrent laryngeal nerve (27).

In the innervation of the thyroid gland, parasympathetic and sympathetic fibers are related to the follicular cells and around the blood vessels. In fact, some neuropeptides, such as neuropeptide Y, substance P, or vasoactive intestinal peptide, are produced in the nerve fibers distributed throughout the thyroid, regulating follicular cell functions (27).

3.2. SYNTHESIS AND CONTROL OF SECRETION OF THYROID HORMONES

A series of processes enzymatically mediated in the thyrocyte have been described in order to synthesize thyroid hormones. This synthesis begins with the catchment of iodine to the thyroid throughout of sodium-iodide symporter located in the basolateral membrane. Within the thyroid, the iodine passes immediately to follicular lumen thanks to the action of the pendrin transporter. In the lumen, iodine is oxidized by the thyroperoxidase enzyme, and thanks to this process it can bind to tyrosyl residues of thyroglobulin, forming monoiodotyrosine (MIT) or diiodotyrosine (DIT). The binding (also mediated by the thyroperoxidase enzyme) between two DIT or one MIT and one DIT will give rise to T4 and triiodothyronine (T3), respectively. After the formation of thyroid hormones, thyroglobulin enters the thyroid cytosol where T4 and T3 are released (thanks to lysosomal enzymes) to be subsequently secreted into the bloodstream (28).

3.3. THYROID AUTOANTIBODIES

The presence of thyroid autoantibodies evidences an immunological process against the gland. In the case of TPOAbs and TgAbs, these are characteristic of HT, and are associated with lymphocytic infiltration and destruction of the thyroid gland, leading to hypothyroidism (29). In GD, by contrast, the direct stimulation of the TSH receptor by TSH receptor stimulating autoantibodies (TrAbs), is the main cause of the overstimulation of the gland, and hyperthyroidism (30).

3.4. THYROID PEROXIDASE AUTOANTIBODIES

As was explained before, the presence of thyroperoxidase enzyme is crucial for the thyroid hormone synthesis, however is one of the main targets of the immune system when the immunological tolerance against the thyroid is altered. In euthyroid subjects the presence of these autoantibodies is around 12–26% and its levels could be correlated with the degree of lymphocytic infiltration (31). In fact the titers of TPOAbs have been correlated with TSH levels, which could trigger an imminent thyroid failure (31). In overt thyroid disease, these autoantibodies are present in almost all patients with HT, being a hallmark, while in GD may be present in up to 75% (32).

3.5. THYROGLOBULIN AUTOANTIBODIES

Like thyroperoxidase enzyme, the presence of thyroglobulin is critical for the synthesis of thyroid hormones, without it, the formation of the precursors of the T4 and T3 (DIT and MIT), would not be possible. It has been described that thyroglobulin is extremely immunoreactive, mainly due to its extensive glycosylation (33). These autoantibodies are mainly associated with cytotoxicity against thyrocytes, generating destruction and fibrosis of the thyroid tissue (34). Regarding euthyroid subjects, TgAbs, are present in up to 20%, whereas in HT and GD may be present in >90 and up to 70%, respectively (35,36).

3.6. THYROID-STIMULATING HORMONE RECEPTOR AUTOANTIBODIES

Unlike other thyroid autoantibodies, TrAbs are associated with a different immunological response. The presence of these is related to the overproduction or suppression of thyroid hormones through the TSH receptor (35,37).

3.7. AUTOIMMUNE THYROID DISEASE

The appearance of AITD is the combination of genetic and environmental factors, that interact throughout the life and conclude with de breakdown of the immunological tolerance against the thyroid gland (38,39). The spectrum of AITD include the presence of HT to GD (38), two disorders characterized by an immune response that culminates in the production of autoantibodies, intended to cause cytotoxicity and tissue destruction, typical of HT, or overstimulation or blockade of the TSH receptor, common in GD (39).

In relation to genetic susceptibility associated to develop of AITD, the risk of developing it of up to 30% has been observed in siblings of affected patients, with a risk of developing 50% thyroid autoantibodies (40). On the other hand, monozygotic twins show a concordance of 0.3 to 0.7, while for dizygotic twins it is 0.00 to 0.2 (41,42).

Genes associated with AITD susceptibility have been grouped into genes belonging to the thyroid gland and immunoregulatory genes. Thyroid genes such as the TSH receptor genes, are strongly associated with susceptibility to GD while thyroglobulin genes with both, HT and GD (43–45). Regarding immunoregulatory genes, the most important are, PTPN22, HLA class II, and CTLA4. These genes play an important

role in the immunological synapse, during the antigenic presentation between antigen-presenting cells as B-cells or dendritic cells (DCs), and T-cell (46–48). Although these polymorphisms have been related to generate susceptibility to AITD, they are not exclusive to it, since they have been described in other ADs, conferring also a high risk (46–48). In GD, for example, it has been described that a change of an arginine at position 74 of the β-chain, in the cleft of antigen binding of HLA-DR, is associated with this disease (49). To be considered a polygenic disease, there is a wide variety of other immunoregulatory genes associated with AITD, such as HLA class I, HLA-B, and HLA-C genes that provide a different degree of susceptibility and protection according to the population studied (50).

Added to these genetic factors, it has been described the presence of external agents, that could, generate a protective mechanism and prevent the onset of the disease, as is the case of tobacco in HT. On the other hand, it has been described other environmental agents that generate cellular injury and the activation of an irreversible autoimmune response that culminates with the onset of the disease, as the iodine consumption, some infections, or radiation. Far from being explained by a merely genetic component, AITD is considered a complex disease due to the environmental influence as a trigger of the disease. So important is the environmental component in the AITD that it contributes in its occurrence up to 50% (41). Among the most important environmental factors, are iodine, smoking, and vitD, other factors studied are radiation, infection, drugs and stress (39). It seems that in AITD the environmental components have the ability to generate a tissue damage, triggering an immune response initially, from the innate system and later from the adaptive one, initiating a vicious circle and the prolongation of the immune response against the thyroid (50).

Starting with iodine, this component has become relevant given its association with the presence of goiter in areas where iodine lacked. It was for this reason that, as a public health policy, it was decided to supplement the salt with iodine, reducing the goiter rates in the population. However, simultaneously with the decrease in the incidence of goiter in the population, an increase in the incidence of AITD was detected, mainly due to TH. These data have been corroborated by different studies that have demonstrated the different prevalence of AITD before and after supplementing salt with iodine. In fact, one of the studies described the prevalence of thyroid autoantibodies, showing a prevalence before and after the iodization of salt of 13.7 and 19.9% for TgAbs and 14.3 and 23.8% for TPOAbs, respectively (51).

Continuing with tobacco, it is known that the compounds contained in a cigarette have been associated with a large number of diseases, including cancer and some ADs. However, the role of tobacco on AITD is different, due to, its effect on HT but not in GD, have shown an apparently protective effect, decreasing the risk of developing the disease while maintaining an active habit of smoking. Different studies have shown the disparity of the tobacco effect on GD and HT. On the one hand, studies report OR: 3.3 (95% CI, 2.09–5.22) for GD and OR: 4.4 (95% CI, 2.88–6.73) for Graves' ophthalmopathy in current smokers (52,53), nevertheless strikingly, in HT, tobacco seems to have a protective role in current smokers with a OR: 0.54 (95% CI, 0.45–0.66) (54).

Finally, the influence of vitD on AITD is determined by the immunomodulatory effect of this vitamin on immune system. Several immune cells express the vitD-activating enzyme CYP27B1 and the vitD receptor, thus having these cells an immunoregulatory effect (55).

3.8. AUTOIMMUNE THYROID DISEASE PATHOGENESIS

As in many ADs, the synergistic effect between the cellular and humoral immune response is crucial for the appearance of AITD without omitting the necessary participation of the innate immune response as a first step for the development of an aberrant immune response.

Starting with the innate immune response, several results have demonstrated its important role on the pathogenesis of AITD (56). In this sense, it has been observed how the expression of danger-associated molecular patterns (DAMPs) generated by cellular damage in the thyroid tissue, product of external injury, have the ability to stimulate the innate immune system. This mechanism consists in the release of genomic DNA by dying thyrocytes. This DNA are captured by adjacent thyrocytes, generating the production of IFN and pro-inflammatory cytokines, followed by MHC expression and lymphocytic infiltration.(56). Among the most important DAMPS associated with the activation of the innate immune system are, genomic DNA and some thermal shock proteins (56).

In relation to the role of the DCs and AITD, its role was already mentioned along with the innate immune response. Added to the above, it has been observed that these cells are part of the great cellular infiltrate characteristic of AITD, guaranteeing a constant presentation of antigens to the T cells (57,58). Furthermore, several analysis about the phenotypic of this cells in AITD show a lower number of

plasmacytoid DCs associated to a defective expression in its immunoregulatory molecules (59,60).

Turning to the cellular immune response, it has been considered that the Th1 immune response is the hallmark of HT, given the high rate of CD8+ T-cells mediated cytotoxicity and the strong CD4+ T-cells mediated lymphocytic infiltrate characteristic of this disease (61). However, this immune response is not exclusive of HT, in GD, Th1 response plays a very important role. In fact, the expression of mRNA expression of INF-γ, a characteristic interleukin of the TH1 response, has been described in patients with GD (62).

In relation to the Th2 response, this is common, but not exclusive of GD, considering that the constant production of autoantibodies against the TSH receptor is the central axis of the pathophysiology of the GD (63). However, it is important to clarify that HT is not unrelated to the production of autoantibodies, which demonstrates the important role of this response on HT. In fact, it has been shown that the production of thyroid autoantibodies as TPOAbs and TgAbs contributes indirectly to the constant presence of a CD8+ T-cells, activating complement through IgG1 (63).

Apart from the typical group of immune associated to the pathogenesis of AITD, it exists other group of cells strongly associated with the pathogenesis of AITD. This group of cells include, the follicular T cells, which are a subset of T helper cells, and regulatory T cells, which show an alteration in their immunoregulatory function in AITD. Regarding follicular T cells, these cells play an important role in the activation of mature B cells, through the production of IL-21. Given its close relationship with the Th2 immune response, a correlation has been demonstrated between the levels of these cells in peripheral blood with thyroid autoantibody levels (64). On the other hand, the role of Treg-cells in the control of the immune response is known. In AITD, some experiments have shown the poor control that these cells exert over others. In fact, in one experiment it could be evidenced that in AITD, the Treg-cells were unable to inhibit the proliferation of effector T cells evidencing an altered immunoregulatory response (65).

All these mechanisms show a complex immunological response associated with the appearance of AITD, that thanks to damage caused by external agents in a genetically susceptible individual, disturb the delicate balance that keeps the immune system inactive against one's own.

4. HYPOTHESIS

Ho: There are no associated factors with the presence of thyroid autoantibodies
Hi: There are associated factors with the presence of thyroid autoantibodies

5. OBJECTIVES

5.1. GENERAL OBJECTIVE

To determine the prevalence of thyroid autoantibodies and the associated factors in euthyroid individuals

5.2. SPECIFIC OBJECTIVES

To characterize the study population
To describe the associated factors with the presence of thyroid autoantibodies
To analyze the associated factors in light of the prevalence

6. METHODOLOGY

6.1. METHODOLOGICAL APPROACH

This research is based on a quantitative approach since data collection was based on measurement. Additionally, the data analysis was carried out in order to answer a research question. In this way, the previous established hypothesis was tested, relying on numerical measurement, counting, and on the use of statistics to try to establish accurately the patterns of the study population.

6.2. DESIGN

Since this study seeks to describe the characteristics and frequency of an event in health, depending on the characteristics of the subjects and their environment, it is considered an analytical cross-sectional study.

6.3. STUDY PARTICIPANTS

Two hundred Colombian patients from different regions, belonging to different socioeconomic strata, as well as level of education and occupation participated in this study. This group of patients is part of the control group used in the study of ADs of the Center for Autoimmune Diseases Research (CREA).

6.4. SAMPLE DESIGN

The sample size was obtained by randomized stratified sampling paired by age and gender of a population of 1335 individuals using the Epidat ® program, version 4.1, with a confidence level of 95%, with a power of 80% and an estimated prevalence of autoantibodies in euthyroid patients of 1402, obtaining a minimum sample size of 300 subjects (figure 1).

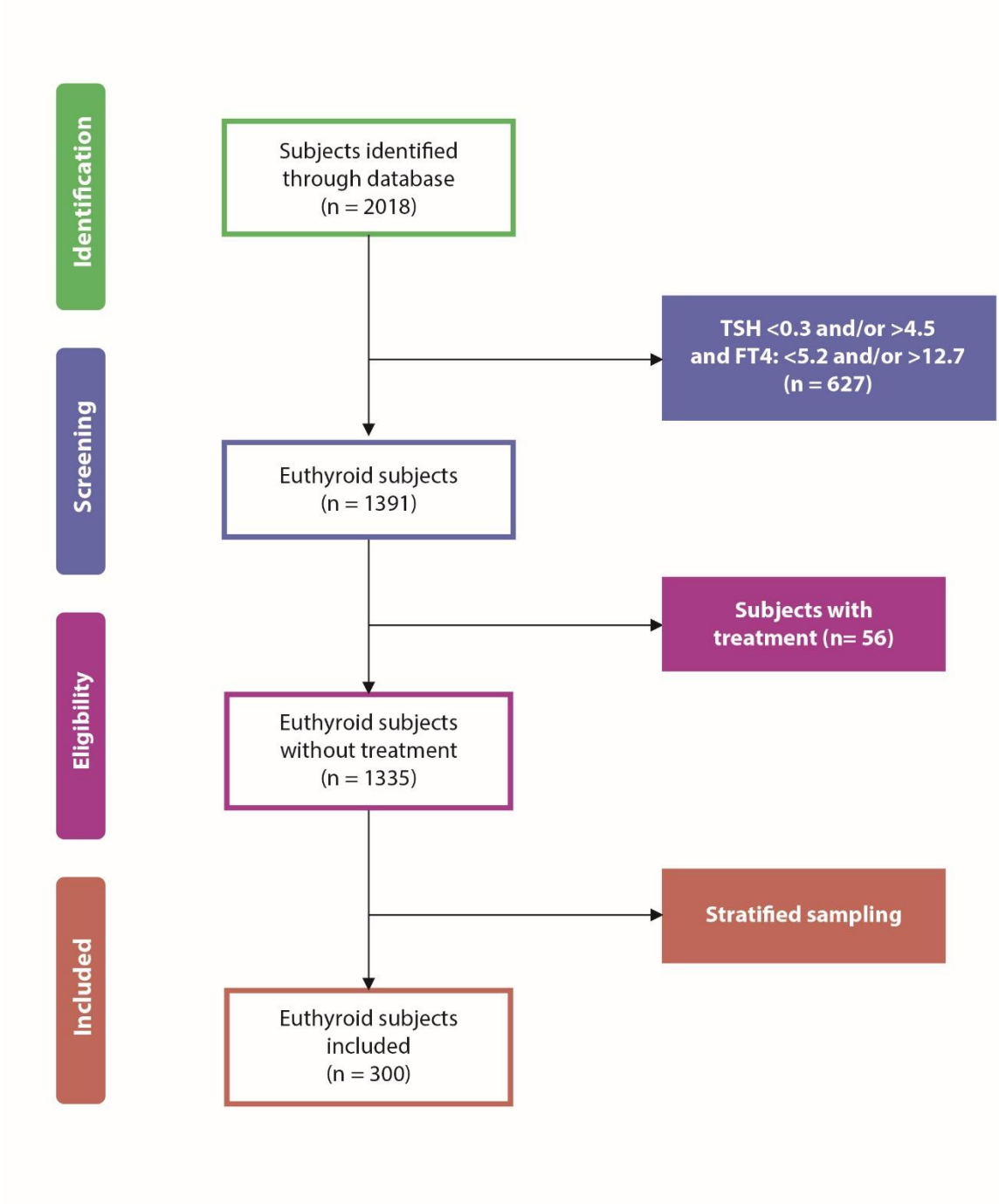

Figure 1. Flow diagram of patient recruitment

6.5. INCLUSION CRITERIA

Euthyroid patients (TSH: 0.3 - 4.5 mIU/ml and FT4: 5.2 - 12.7 IU/dl), without levothyroxine treatment were selected for the study.

6.6. EXCLUSION CRITERIA

Those patients under 18 years, or with undefined thyroid disease, history of hypothyroidism or hyperthyroidism, thyroid disease during pregnancy, previous or current treatment with levothyroxine, thyroid surgery, or history of thyroid cancer were excluded from the study.

6.7. VARIABLE DESCRIPTION

6.7.1. DIAGRAM OF VARIABLES

This variable diagram (figure 2) includes all immunological, biological, environmental, sociodemographic and ethnic factors that can influence the appearance of thyroid autoantibodies

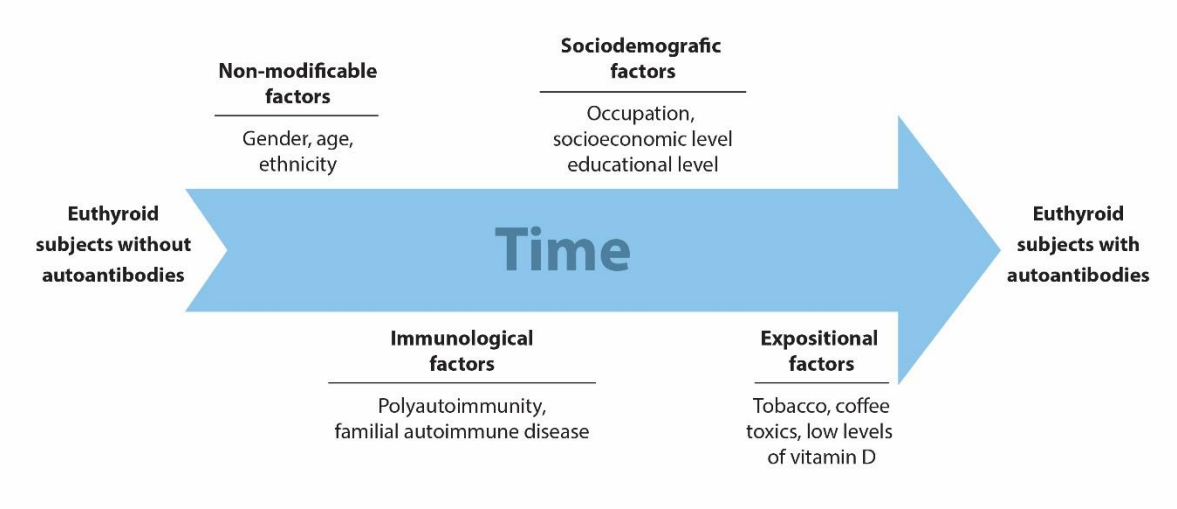

Figure 2. Diagram of variables associated with the appearance of thyroid antibodies

6.7.2. TABLE OF VARIABLES

See appendix 1

6.8. INFORMATION GATHERING TECHNIQUE

6.8.1. SOURCE OF INFORMATION

In this study, all information was obtained from primary sources of information.

6.8.2. INFORMATION COLLECTION INSTRUMENT

Using two medical forms, sociodemographic information as age, gender, ethnicity, socio-economic stratum, and place of origin was obtained (Appendix 2) as previously described (20,66). Additionally, in the same medical form, subjects were inquired about clinical antecedents, such as contraceptive methods, comorbidities, obstetric, surgical and pharmacological antecedents. On the other hand, habits such as consumption of coffee and tobacco, and occupational and home exposures to toxic agents were asked as previously reported (20,66). Finally, the second questionnaire was apply to determine the presence of symptoms related to thyroid dysfunction as well as the presence of hypo or hyperthyroidism (Appendix 3) (1,5).

6.8.3. OBTAINING INFORMATION PROCESS

The clinical evaluation and the data collection was carried out by health personnel (doctors, research assistants) belonging to the CREA between July and November of 2017. The clinical evaluation included the assessment of weight, height, abdominal perimeter, blood pressure and reflex assessment. Additionally, data collection was carried out by applying two medical forms in a self-administered manner, directed by an expert doctor.

The thyroid function was evaluated by measurement of serum TSH and FT4 levels. Additionally, vitD levels, TPOAbs, TgAbs and TrAbs were detected as markers for thyroid autoimmunity and 23 additional autoantibodies were evaluated. TSH, FT4 and vitD levels were measured by electroquimioluminiscence. TPOAbs, TgAbs, rheumatoid factor (RF) IgM, anti-citrullinated protein antibodies (ACPA) IgG, anti-

cardiolipin antibodies (ACA) IgM and IgG, anti-β2glycoprotein-1 (β2GP1) antibodies IgM and IgG were measured using indirect ELISA; while TrAbs with competitive ELISA. The remaining 17 autoantibodies were evaluated by immunoblot assay (double-stranded DNA [dsDNA], nucleosomes, histones, SmD1, proliferating cell nuclear antigen [PCNA], P0, SS-A/Ro60, SS-A/Ro52, SS-B/La, centromere autoantigen B [CENP-B], Scl70, U1-snRNP, AMA M2, Jo-1, PM-Scl, Mi-2, Ku) using IMTEC ANA-LIA Maxx from Human diagnostics.

Blood samples were collected using a tube with EDTA and after 30 min of clot formation was centrifuged at 3500 rpm for 10 minutes. After the sample was kept frozen at -80℃ for further analysis. The following serum measurements were performed: TSH (0.3-4.5 µIU/mL), FT4 (5.2-12.7 UI/dL), antiTPO (positive > 100 IU/mL), and anti-TG (positive > 0.6 IU/mL), RF IgM (positive >6 IU/mL), ACPA IgG (positive >60 IU/mL), ACA IgM and IgG (positive >20 GPL), β2GP1 IgM and IgG (positive >20 GPL). Regarding ANA-LIA, these results were considered positive when the assay results were above a threshold value. Regarding levels of vitD, sufficiency above 30 ng/mL, insufficiency below 30 ng/mL, and deficiency, levels below 20 ng/mL were considered (67).

6.9. ERROR AND BIAS CONTROL

6.9.1. ERROR CONTROL

Sampling error:

- Measurement of autoantibodies to all included patients, independent of previous results.

Measurement errors:

- Measurement by trained personnel.
- Standardized technique (ELISA).
- Quality control by the manufacturer (INOVA Diagnostics).

6.9.2. BIAS CONTROL

- Memory biases: Questioning of the patients was guided.
- Confusion biases: Confusion by age (AITD is more frequent at older age in the general population), gender (AITD is more frequent in women). However, a multivariate analysis model adjusted for gender

and duration of the disease (including age of onset and age at the time of inclusion in the study) was performed.

6.10. INFORMATION PROCESSING AND ANALYSIS TECHNIQUE

As it was described in detail previously (68),"In the univariate analysis, categorical variables will be analyzed by frequencies, and quantitative continuous variables will be expressed as mean and standard deviation (SD) and as median and interquartile range (IQR). To assess associations between outcomes of interest and other variables, the $\chi 2$, and Mann–Whitney U test were used. Logistic and lineal regression were done to aim predict the relationship between the presence of autoantibodies and the risk factors evaluated. The significance level of the study will be set to 0.05 and statistical analyses will be done using SPSS statistics version 2.4".

7. ETHICAL CONSIDERATIONS

7.1. POPULATION

Patients will be contacted by the CREA staff of the Universidad del Rosario. The process was according to the 1581 statutory law of 2012 and the script to contact the patients is shown below: (This writing is in Spanish, having the language of the population)

Buenos días señor / señora (**nombrar el paciente),** un gusto saludarlo/a

Me llamo ***(su nombre)*** soy médico/enfermera del ***Centro De Estudio De Enfermedades Autoinmunes*** (CREA), de la Universidad del Rosario.

En años anteriores usted quedó incluido con nosotros, dentro del grupo de pacientes con lupus eritematoso sistémico. Hoy queremos saludarlo/a y saber cómo ha estado estos últimos meses.

Antes que nada, para nosotros es un placer saber de usted nuevamente. Cuénteme cómo se encuentra……Gracias señor / señora (**nombrar el paciente).** Actualmente estamos llevando jornadas de seguimiento más personalizadas de nuestros pacientes con el fin de actualizar las historias clínicas, reunirnos y conocer otros pacientes que tienen la misma enfermedad y además aprender sobre qué es el Síndrome de Sjögren. ¿Le gustaría venir el día__ a las ___ a esta jornada?

Si responde SI, dar todas las indicaciones. Si responde NO, decir muchas gracias señor / señora (**nombrar el paciente**). Hasta una próxima oportunidad.

7.2. PATIENT VULNERABILITY

Patients in this study are at risk of subordination since all of them have been followed by in the CREA and most of the time they have been contacted by doctors. However, in this time, patients will be contacted by CREA staff, which does not possess medical degree to avoid influencing their decision to attend. Further, if patient rejects the invitation, no retaliation was done, since they followed in the cohort in spite of their decision.

7.3. INFORMED CONSENT

Prior written consent it was asked to take the sample and begin the survey. The informed consent format is shown in the Appendix 4.

7.4. DATA

All collected data was saved in a secure electronic database and all information obtained will be managed according to the 1581 statutory law of 2012. The identity of the patients will not be disclosed. The use and storage of information will be handled according to the resolution 839 of 2017, which states the management of clinical history in Colombia.

7.5. RISK

This study was carried out in compliance with the Act 008430/1993 of the Ministry of Health of the Republic of Colombia, which classifies it as minimal-risk research. The institutional review board of the Universidad del Rosario was asked to approve the study design.

8. RESULTS

8.1. SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The sociodemographic, clinical and laboratory variables are shown in Table 1 and 2. The group of subjects consists mainly of women and young people. Thyroid autoimmunity was observed in 15.3% of the cases; TPOAbs in 11.3% and TgAbs in 2%. Only in 6 individuals, both autoantibodies were described. TrAbs were not detected in any individual. This population is mainly represented by individuals of Amerindian ancestry, although other population groups are described. There is not a large proportion of comorbidities in this population, due to age. In relation to gynecological clinical history, a significant percentage of women with abortions history, menstrual irregularity and infertility is described.

Table 1. Sociodemographic and clinical characteristics

Characteristics	n=300 (%)
Gender	
Women	287 (95.7)
Age	
Median (IQR)	34 (27-40)
Race	
Amerindian ancestry	275/292 (94.2)
African ancestry	13/292 (4.5)
Native	4/292 (1.4)
SES	
1,2,3	294/298 (98.7)
4,5,6	4/298 (1.3)
Comorbidities	
Arterial hypertension	6 (2)
Diabetes mellitus 2	4 (1.3)
Dyslipidemia	6 (2.0)
Cancer	3/299 (1)
Abortion	61/285 (21.4)
Polycystic ovary syndrome	10/282 (3.5)
Biological data	
VitD level (IQR)	15.9 (11.0-23.6)
VitD sufficiency	25/238 (10.5)
VitD insufficiency	70/238 (29.4)
VitD deficiency	143/238 (60.1)

Table 2. Thyroid data	
Characteristics	**n=300 (%)**
Thyroid autoimmunity	
TPOAbs	34 (11.3)
TgAbs	6 (2)
TgAbs and TPOAbs	6 (2)
Biological data	
TSH (IQR)	2.3 (1.7-3.3)
T4 (IQR)	8.4 (7.6-9.1)
Clinical data	
Familial thyroid disease	38 (12.7)
Fatigue	98/297 (33.0)
Anxiety	80/297 (26.9)
Weight gain	75/295 (25.4)
Weight loss	31/298 (10.4)
Cold intolerance	30/299 (10)
Heat intolerance	24/299 (8.0)
Menstrual disorders	105/278 (37.8)
Dry Skin	79/298 (26.5)
Diaphoresis	34 (11.3)
Alopecia	81 (27)
Constipation	83 (27.7)
Voice Alteration	14 (4.7)
Fullness of throat	37 (12.3)
Bradilalia, Bradipsiquia	34 (11.3)
Hyporeflexia	13/297 (4.4)
Tremor	30 (10.0)
Palpitations	50 (10.7)
Diplopia	18 (6.0)
Infertility	9 (3.0)
Low libido	37 (12.3)

8.2. ENVIROMENTAL CHARACTERISTICS

Regarding habits and environmental factors, these are described in Table 2. Unlike tobacco consumption, which is mainly characterized by never smoker, coffee consumption is very important in this population, reaching almost 90%. In contrast, it was found that exposition to organic solvents was the main toxic they have been exposed to throughout life, followed by the use of hair dyes, and exposure to wood smoke. In relation to exposure at work or home, it was found that the main work or housing space to which these individuals were exposed was farms followed by airports and laundries.

Table 2. Environmental characteristics

Characteristics	n=300 (%)
Habits	
Never smoke	232 (77.3)
Former smoker	44 (14.7)
Active smoker	24 (8)
1 – 5 pack-year	20 (6.7)
6 – 15 pack-year	2 (0.7)
More than 15 pack-year	2 (0.7)
Never coffee	22 (7.3)
Former coffee drinker	9 (3.0)
Coffee drinker	266/297 (89.6)
Lees a cup/day	85/299 (28.4)
One cup/day	53/298 (17.8)
2 – 4 cups/day	110/298 (36.9)
More than 4 cups/day	19/298 (6.4)
Environmental exposures	
Organic solvents	255 (85.0)
Hair dyes	184/299 (61.3)
Wood smoke	94 (31.3)
Psychoactive substances	7 (2.3)
Pesticides	8 (2.7)
Asbestos	18 (6.0)
Ever live / work	
Farms	41 (13.7)
Airports	32 (10.7)
Laundry	27 (9)
Factories	13 (4.3)
Garbage deposits	10 (3.3)

8.3. INMUNOLOGICAL CHARACTERISTICS

Immunological data are described in Table 3. The evaluation of these autoantibodies allow to infer that the FR, ACA IgM, and B2GP1 IgM, are the most prevalent autoantibodies in this population. The remaining 6 autoantibodies were not observed in these subjects (Data not shown). Additionally, it was found an interesting percentage of familial autoimmunity and the presence of other ADs.

Table 3. Immunological data

Characteristics	n=300 (%)
Familial autoimmunity	21 (7.0)
Other autoimmune diseases	9 (3.0)
Autoantibodies	
RF	116 (38.7)
ACA IgM	15 (5.0)
B2GP1 IgM	13 (4.3)
SS-B/La	12 (4.0)
SmD1	9 (3.0)
SS-A/Ro60	7 (2.3)
PM-Scl	7 (2.3)
PCNA	7 (2.3)
B2GP1 IgG	5 (1.7)
ACPA	3 (1.0)
Ku	4 (1.3)
SS-A/Ro52	3 (1.0)
CENP-B	3 (1.0)
U1-snRNP	2 (0.7)
Mi-2	2 (0.7)
dsDNA	1 (0.3)
Nucleosome	1 (0.3)

8.4. BIVARIATE AND MULTIVARIATE ANALYSIS

An initial analysis between individuals with thyroid autoimmunity and those without it was carried out. In relation to clinical history and symptoms, the bivariate analysis showed an association between familial thyroid disease *P* = 0.04 (OR: 2.2 95% CI: 1.1-5.0) and low libido *P* = 0.04 (OR: 2.3 95% CI: 1.1- 5.2) with thyroid autoantibodies. On the other hand, regarding to environmental and biological factors, an association between the presence of thyroid autoimmunity, never smoke *P* = 0.04 (OR: 2.7 95% CI: 1.1- 7.1), vitD insufficiency (*P*= 0.03), and higher number of years exposed to wood smoke (*P* = 0.04) was found.

The multivariate analysis included a logistic regression, with the presence of thyroid autoantibodies as the dependent variable. Values of *P* ≤ 0.25 from bivariate analysis were considered within the regression model. The results of the multivariate model analysis under the "forward Wald" option are shown in appendix 5, supplementary table 6. From this analysis, the history of familial thyroid disease, the presence of other ADs, never smoke, drinking more than 4 cups of coffee, and low libido, were the variables significantly associated with the presence of thyroid autoimmunity (Table 4).

Table 4. Associated factors with thyroid autoantibodies

Characteristic	β	95% CI		*P*
Familial thyroid disease	3.384	1.200	9.542	0.021
Other autoimmune diseases	10,811	1,603	72.901	0.014
Never smoke	6.942	1.586	30.378	0.010
Drinking more than 4 cups of coffee	3.776	1.090	13.075	0.036
Low libido	3.753	1.324	10.633	0.013

Considering these findings, the resulting model equation is as follows: $1/1 + e^{3.820 - 1.322 \text{ (low libido)} - 1.329 \text{ (> 4 cups of coffee)} - 1.938 \text{ (never smoke)} - 2.381 \text{ (other ADs)} - 1.219 \text{ (familial thyroid disease)}}$.

This model had a good calibration given by a *P* = 0.61 for the Hosmer and Lemeshow test, with a coefficient of determination R2 of Nagellkerke that indicates that the proposed model explains 18.3% of the variance of the dependent variable (Appendix

5). Additionally, in this model, 83.6% of the predicted cases are accurate, added to a good discriminative capacity given by an area under the curve of 0.70 (Appendix 5, supplementary figure 1). The assumptions of collinearity and monotony of the variables were fulfilled in this model.

The second analysis only included the associated factors with TPOAbs and TgAbs separately. Regarding TPOAbs, the results showed an association between this autoantibody with familial thyroid disease *P* = 0.01 (OR: 2.8 95% CI: 1.2 - 6.2), never smoke *P* = 0.04 (OR: 2.9 95% CI: 1.1 - 8.6), and low libido *P* = 0.009 (OR: 2.9 95% CI: 1.3 - 6.5). Moreover, an association between TSH levels and TPOAbs was described (Figure 3). In relation to TgAbs, the bivariate analysis showed an association between TgAbs with the presence of menstrual irregularity *P* = 0.022 (OR: 0.3 95% CI: 0.08 - 0.9), and SS-A / Ro52 *P* = 0.009 (OR: 13 95% CI: 1.1-154). No association between TSH levels and TgAbs was observed, however there is a trend (Figure 4).

Multivariate analysis, using TPOAbs as the dependent variable are shown in appendix 6, supplementary table 6. The presence of familial thyroid disease, never smoke, drinking > 4 cups of coffee, and low libido, was found. In addition, the presence of SS-A / Ro52, and Ku, was related to the presence of TPOAbs (Table 5).

Table 5. Associated factors with TPOAbs

Characteristic	β	95% CI		*P*
Familial thyroid disease	4.894	1.705	14.049	0.003
Never smoke	5.428	1.397	21.090	0.015
Drinking more than 4 cups of coffee	3.641	1.015	13.055	0.047
Low libido	5.680	2.013	16.028	0.001
SS-A/Ro52	36.729	2.453	549.874	0.009
Ku	10.235	1.040	100.734	0.046

The resulting model equation is as follows: $1/1 + e^{3.820 - 2.326\,(Ku) - 3.604\,(SS\text{-}A/Ro52) - 1.737\,(low\ libido) - 1.292\,(>4\ cups\ of\ coffee) - 1.691\,(never\ smoke) - 1.588\,(familial\ thyroid\ disease)}$. This model had a good calibration given by a *P* = 0.59 for the Hosmer and Lemeshow test, with a coefficient of determination R2 of Nagellkerke that indicates that the proposed model

explains 23.4% of the variance of the dependent variable (Appendix 6). Additionally, in this model, 87.2% of the predicted cases are accurate, added to a good discriminative capacity given by an area under the curve of 0.72 (Appendix 6, supplementary figure 1). The assumptions of collinearity and monotony of the variables were fulfilled in this model.

Multivariate analysis, using the variable TgAbs as a dependent variable are shown in appendix 6, supplementary table 14. The presence of African ancestry, SS-A / Ro52, and CENP-B was associated with TgAbs (Table 6).

Table 5. Associated factors with TgAbs

Characteristic	β	95% CI		*P*
African ancestry	10.500	1.745	63.196	0.010
B2GP1 IgG	7.875	0.761	81.522	0.084
SS-A/Ro52	15.750	1.249	198.573	0.033
CENP-B	31.500	1.753	565.945	0.019

The resulting model equation is as follows: $1/1 + e^{3.820 – 3.450\ (\text{CENP-B}) – 2.757\ (\text{SS-A/Ro52}) – 2.351\ \text{African ancestry})}$. This model had a coefficient of determination R2 of Nagellkerke that indicates that the proposed model explains 17.0% of the variance of the dependent variable (Appendix 6). Additionally, in this model, 94.8% of the predicted cases are accurate, added to an acceptable discriminative capacity given by an area under the curve of 0.67 (Appendix 6, supplementary figure 2). The assumptions of collinearity and monotony of the variables were fulfilled in this model.

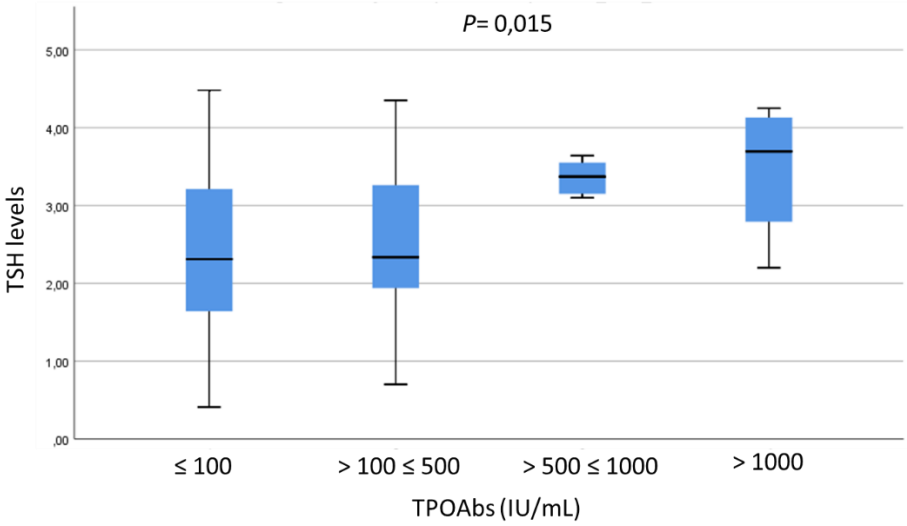

Figure 3. There is a significant association between TSH levels and TPOAbs levels. An increase in TSH levels in same proportion to TPOAbs levels is observed.

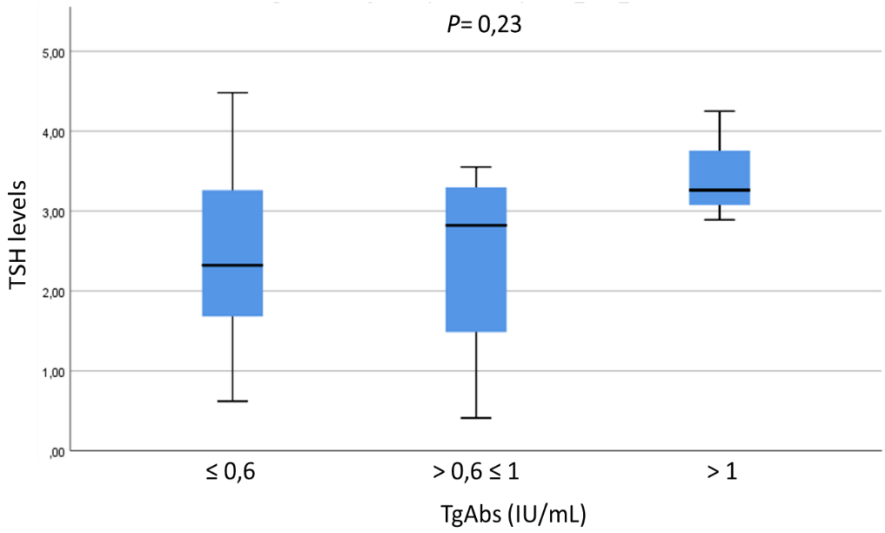

Figure 4. Although there is no statistically significant association between the TSH levels and levels of TgAbs, a trend between the influences of these autoantibodies on TSH levels is described.

9. DISCUSSION

AITD requires a genetic substrate as risk factor for its development. However, this substrate is not enough, it is necessary the existence of external factors that imbalances the immune response, which gives rise to the recognition of self-thyroid antigens. This originates an autoimmune response, which eventually culminates on the overt disease. All these steps are immersed in the natural history of the disease, through a series of states, from the pre-pathogenic phase, which is asymptomatic, to the pathogenic period, characterized by the presence of symptoms (69). In light of the evidence, this study sought to confirm the role of some factors, previously studied in relation to the presence of thyroid autoantibodies, as well as to find new factors that might contribute to the understanding of the risk factors associated to the presence of these autoantibodies during the pre-pathogenic phase of AITD.

The evaluation of these autoantibodies is relevant, considering that in different studies the presence of thyroid autoantibodies in euthyroid subjects implies a higher risk of developing AITD independent of TSH levels, as it was documented by the Whickham survey [OR: 8 (95 % CI 8-19)] and the NHANES III survey [(OR 40; 95% 12-136)] (7,16). In addition, the former study reported an annual risk of developing hypothyroidism of 2.1% per year in the presence of thyroid autoantibodies (7). Although our study does not consist of a cohort, it evidenced a prevalence of autoantibodies comparable with other studies (15).

A relevant finding, was the relationship between autoantibodies and ethnicity, showing that, African ancestry could behave as risk factor to develop thyroid autoantibodies, particularly, TgAbs. These results are controversial, since in other studies the prevalence of TPOAbs in African ancestry population was lower in comparison with other populations and moreover, it has not been associated as risk factor (7,70). In fact, a study done with military personnel in the United States, where the prevalence of AITD by ethnicity was assessed, showed that the incidence of HT was highest in whites, compared with blacks, unlike the GD where the incidence was highest in blacks compared with whites (71). On this wise, given by the link between thyroglobulin locus reported in some studies (72,73), it is possible that the association found in our black population may be caused by this susceptibility genes and the probable thyroid autoantibodies development (74). However, the results that report this association come from non-black population, thus, further studies are needed to analyze the influence of this locus in black population. On the other hand, goes far beyond the ancestry, the environmental factors to which this population are

exposed, could be crucial for the development of these autoantibodies (24). The above supports the importance of identifying patterns of incidence and prevalence, along with relevant environmental factors that may influence the disease's epidemiology in different populations.

Smoking has a significant effect on thyroid function, therefore it has been subject of many investigations (75), and some studies have associated the presence of thyroid autoantibodies with the cessation of smoking (76), which means, that in current-smokers, tobacco could be protective for AITD (77). The first epidemiological descriptions on the effect of tobacco and the presence of thyroid autoantibodies and hypothyroidism are addressed in the NHANES III survey, which showed that active smokers have lower TSH levels compared to non-smokers (77). In addition, other studies have provided new evidence on the role of tobacco on AITD, showing that ex-smokers had higher rates of hypothyroidism attributable to cessation of smoking in up to 85% (76). This information opens the debate on an apparent effect of tobacco on the immunological activity associated with the presence of AITD.

Considering that epidemiological evidence suggests this apparently protective effect of tobacco on the risk of AITD, several experimental studies have been able to show that some components of tobacco have an immunomodulatory effect, such as the alkaloids nicotine and anatabine. Nicotine is widely known for its anti-inflammatory effects (78). This mechanism is mediated by the link between nicotine and its receptor, which is not only expressed centrally and peripherally in pre-ganglionic fibers and neuromuscular synapses, but in immune cells, such as macrophages, DCs and the CD4+ T-cells. In fact, the expression of the nicotinic receptor in these immune cells has been studied as a therapeutic target, enhancing its anti-inflammatory effect on these cells (79).

Another component of tobacco which has been object of recent studies, is anatabine. This alkaloid, like nicotine, has anti-inflammatory properties that could influence the control of an immune response against the thyroid. In addition, unlike nicotine, it is not associated with the toxicity and addiction rates shown with nicotine. Also, it has a longer plasma half-life (80,81). The first studies carried out around anatabine were made in murine models, showing that the mice exposed to this alkaloid had lower incidence and severity of thyroiditis (RR 0.59, P = 0.0174) (82). This study showed a reduction in the immune response mediated by thyroid autoantibodies (TgAbs), and a control of the macrophage production of inducible nitric oxide synthase and cyclooxygenase 2 (82).

Considering the results, a clinical trial was done in order to determine the effect of anatabine in humans. The results obtained from the clinical trial performed in

patients with HT, showed, as in the experimental studies, the effect of anatabine on the production of thyroid autoantibodies, evidencing a significant reduction of TgAbs compared with the placebo group (P = 0.027). This decrease also showed that in the group managed with anatabine, there was a greater number of patients in whom the reduction of thyroid autoantibodies was greater than 20% (P = 0.023), corroborating the effect of anatabine on the Th2 immune response (83).

In relation to this topic, epidemiological data supported by *in vivo* models findings reinforce the hypothesis of an immunomodulatory effect of the tobacco on the thyroid gland, especially on the Th2 response and on the production of autoantibodies (84). In addition, the presence of cyanide contained in cigarette smoke and metabolized to thiocyanate, could be associated with a mild immunomodulatory response given the interference of thiocyanate in the transport and uptake of iodine (77,85). In this sense, it is necessary the elaboration of screening strategies in this population in order to evaluate the presence of thyroid autoantibodies in patients at risk of developing AITD and who moreover, have recently abandoned tobacco.

The relationship between vitD levels and autoimmunity is widely known, since the low levels of this vitamin is associated with the risk of developing ADs, and once the AD is overt, the low levels of vitD has been associated with disease activity (86). However, the prevalence of individuals with vitD insufficiency should be considered a public health problem and not an exclusive matter of ADs (87).

The results exposed in this study confirm the association between low levels of VitD and thyroid autoimmunity. In this sense, it is clear the immunological effect of vitD and its influence on AITD. The role of vitD on the immune response has been widely studied given the direct effect of this vitamin on different immune cells via its receptor in these cells (88). The immunological effects of vitD include stimulation of antimicrobial proteins production, chemotaxis and phagocytosis by macrophages (89,90). Moreover, vitD interferes on the antigenic presentation, since inhibits the expression of co-stimulatory molecules, as well as the expression of MHC-II, and the production of IL-12 and IL-23, especially in DCs (91).

In relation to the different polymorphisms associated with the metabolism of vitD, relevant changes mainly at the level of its receptor, binding protein, CYP27B1 (1-alpha-hydroxylase) and CYP2R1 (VitD 25-hydroxylase) have been described (92,93). On the other hand, in experimental models, it was observed that mice treated with vitD reduced the presence of thyroiditis (94). In addition, in other murine models (BALB/c) deficient for vitD after being immunized againts the TSH receptor they developed hyperthyroidism (95). However, in other ADs it seems that the effect

of vitamin D is not determinant. In one study, vitD levels and the risk of systemic lupus erythematosus and rheumatoid arthritis were evaluated using Mendelian randomization. In this study three independent single-nucleotide polymorphisms on the levels of vitD were studied, nevertheless, causality between the levels of vitD and lupus erythematosus and rheumatoid arthritis was not found (96). In this sense, further functional genetic studies related to variants in the metabolism of vitD will be warranted.

Despite the extensive study of environmental factors associated with AITD, the effect of coffee has been poorly studied. The results of this study reported an association between the presences of thyroid autoimmunity with coffee consumption, especially in those with a consumption greater than 4 cups per day. In relation to these results, it could be presumed that the consumption of coffee in this amount could promote the release of thyroglobulin as previously described (97), triggering an autoimmune response against this antigen.

This study documented a strong association between the presence of familial autoimmune disease, polyautoimmunity and the presence of thyroid autoantibodies. These are validated by different studies that have reported a heritability up to 73% for the presence of thyroid autoantibodies (98). On the other hand, it is clear that this study validates the theory of autoimmune tautology which establishes that all ADs share common mechanisms, which, under the influence of certain genetic, epigenetic and environmental factors, cause a specific AD (21). Based on the foregoing, this study supports this theory by evidencing, an association between thyroid autoantibodies and the association with other ADs and other autoantibodies. Therefore, it is necessary to emphasize the importance of AITD within the framework of autoimmune tautology as a highly relevant disease as possible prediction of other ADs (99).

10. CONCLUSIONS

Subclinical thyroid autoimmunity could be common in Colombian population. There are genetic, environmental, ethnic and immunological factors that seem to influence its development and therefore, in the future appearance of hypothyroidism. The results from the present study will facilitate the implementation of screening strategies in order to provide timely diagnosis and treatment.

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12. APPENDIX

12.1. APPENDIX 1

VARIABLE	NAME	DEFINITION	TYPE	SCALE OF MEASUR EMENT
ID	Identification	ID number	Numerical	-
SEX	Gender	1= Women; 0= Men	Categorical	Nominal
ETHN	Ethnic group	1=half Blood, 2=Afro-Descendant 3=Native NA=Not available	Categorical	Nominal
AGE	Age	(Years) NA= Not available	Numerical	Ratio
EDUCA-LEV	Highest degree of education an individual has completed	1= Primary school 2= Secondary school 3=Technical level 4=Professional 5=Postgraduate degree	Categorical	Nominal
SES	Socioeconomic status	1=1 y 2 2=2 3= 4,5 y 6	Categorical	Nominal
MARIT-STA	Marital status	1= Single 2= Married 3=Widowed 4=Divorced 5= Cohabitation 6= Child, NA= Not available	Categorical	Nominal

OCUP	Occupation	1= Manual exclusive 2=Intellectual Exclusive 3= Mixed	Categorical	Nominal
DM2	Diabetes Mellitus 2	1= Yes 0= No NA= Not available	Categorical	Nominal
DYS	Dyslipidemia	1= Yes 0= No NA= Not available	Categorical	Nominal
AHT	Arterial hypertension	1= Yes 0= No NA= Not available	Categorical	Nominal
CVD	cardiovascular disease	1= Yes 0= No NA= Not available	Categorical	Nominal
TRHOM	Thrombosis	1= Yes 0= No NA= Not available	Categorical	Nominal
DEPRES	Depression	1= Yes 0= No NA= Not available	Categorical	Nominal
ACID-DIS	Peptic acid disease	1= Yes 0= No NA= Not available	Categorical	Nominal
REN-DIS	Renal disease	1= Yes 0= No NA= Not available	Categorical	Nominal
SKIN-DIS	skin disease	1= Yes 0= No NA= Not available	Categorical	Nominal
ANEM	Anemia	1= Yes 0= No NA= Not available	Categorical	Nominal
TBC	Tuberculosis	1= Yes 0= No NA= Not available	Categorical	Nominal
HEP-A	Hepatitis A	1= Yes 0= No NA= Not available	Categorical	Nominal

HEP-B	Hepatitis B	1= Yes 0= No NA= Not available	Categorical	Nominal
POS	Polycystic ovary syndrome	1= Yes 0= No NA= Not available	Categorical	Nominal
CANC	Cancer	1= Yes 0= No NA= Not available	Categorical	Nominal
FAM-CVD	Familial cardiovascular disease	1= Yes 0= No NA= Not available	Categorical	Nominal
FAM-EAI	Familial autoimmune disease	1= Yes 0= No NA= Not available	Categorical	Nominal
EXER	Exercise	1= Yes 0= No NA= Not available	Categorical	Nominal
AGE-MENAR	Age of menarche	Age (years) NA= Not available	Numerical	Ratio
NUM-PREG	Number of pregnancies	Number NA= Not available	Numerical	Ratio
CURR-PREG	Current pregnancy	1= Yes 0= No NA= Not available	Categorical	Nominal
ESP-ABOR	Spontaneous abortion	1= Yes 0= No NA= Not available	Categorical	Nominal
ABOR-<10 W	Abortion before 10 weeks	1= Yes 0= No NA= Not available	Categorical	Nominal
ABOR->10 W	Abortion after 10 weeks	1= Yes 0= No NA= Not available	Categorical	Nominal
CONTRACEP	Current contraception	1= Yes 0= No	Categorical	Nominal

		NA= Not available		
MENS-IRREG	Menstrual irregularity	1= Yes 0= No NA= Not available	Categorical	Nominal
CONTR-HORM	Use of hormonal methods in any time	1= Yes 0=No NA= Not available	Categorical	Nominal
AGE-MENO	Age of menopause	Age (years) NA= Not available	Numerical	Ratio
ALT-MED	Alternative medicine	1= Yes 0= No NA= Not available	Categorical	Nominal
TOBAC	Tobacco	0= Never ; 1= 1-5p/year 2=6-15p/year 3=>15p/year 4= Quit smoking NA= Not available	Categorical	Nominal
TABAC-YEAR	Tobacco years	Years NA= Not available	Numerical	Ratio
CURR-SMOK	Current smoke	1= Yes 0= No NA= Not available	Categorical	Nominal
COFF	Coffee	0= Never ; 1= 1cup/day 2= 2-4cup/day 3= >4cup/day 4= <1cup/day 5= Quit coffee intake NA= Not available	Categorical	Nominal
COFF-YEAR	Coffee years	Years NA= Not available	Numerical	Ratio
CURR-COFF	Current coffee	1= Yes 0= No NA= Not available	Categorical	Nominal

PSICOAC	Use of recreational drugs	1= Yes 0= No NA= Not available	Categorical	Nominal
SOL-ORG	Use of organic solvent	1= Yes 0= No NA= Not available	Categorical	Nominal
HAI-DYE	Use of Hair dye	1= Yes 0= No NA= Not available	Categorical	Nominal
PESTIC	Exposure of Pesticides	1= Yes 0= No NA= Not available	Categorical	Nominal
ASBEST	Exposure of asbestos	1= Yes 0= No NA= Not available	Categorical	Nominal
METAL	Exposure of asbestos metals	1= Yes 0= No NA= Not available	Categorical	Nominal
LIV-FAB	Living close to factories	1= Yes 0= No NA= Not available	Categorical	Nominal
L-FAB-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
LIV-CROP	Living close to crops	1= Yes 0= No NA= Not available	Categorical	Nominal
L-CROP-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
L-ORG	Living close to organic deposits	1= Yes 0= No NA= Not available	Categorical	Nominal
L-ORG-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
LIV-AIR	Living close to airports	1= Yes 0= No NA= Not available	Categorical	Nominal
L-AIR-YEAR	Number of years	Years NA= Not available	Numerical	Ratio

W-CROP	Working in crops	1= Yes 0= No NA= Not available	Categorical	Nominal
W-CROP-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-WOOD	Working in firewood	1= Yes 0= No NA= Not available	Categorical	Nominal
W-WOOD-YEAR	Number of years	Years NA= Not available	Numerical	Ratio l
W-MINE	Working in mines	1= Yes 0= No NA= Not available	Categorical	Nominal
W-MINE-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-AIR	Working in airports	1= Yes 0= No NA= Not available	Categorical	Nominal
W-AIR-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-PLAST	Working with plastics	1= Yes 0= No NA= Not available	Categorical	Nominal
W-PLAST-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-HAI	Working in hairdressing	1= Yes 0= No NA= Not available	Categorical	Nominal
W-HAI-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-GLAS	Working in stained glass	1= Yes 0= No NA= Not available	Categorical	Nominal
W-GLAS-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-LAUN	Working in laundry	1= Yes 0= No NA= Not available	Categorical	Nominal
W-LAUN-YEAR	Number of years	Years NA= Not available	Numerical	Ratio

W-CRAF	Working in crafts	1= Yes 0= No NA= Not available	Categorical	Nominal
W-CRAF-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-PHARM	Working in pharmacies	1= Yes 0= No NA= Not available	Categorical	Nominal
W-PHARM-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-TRANS	Working in transport	1= Yes 0= No NA= Not available	Categorical	Nominal
W-TRANS-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
W-FOOT	Working in footwear factory	1= Yes 0= No NA= Not available	Categorical	Nominal
W-FOOT-YEAR	Number of years	Years NA= Not available	Numerical	Ratio
ABDO-OBE	Abdominal obesity	1= Yes 0= No NA= Not available	Categorical	Nominal
FATI	fatigue	1= Yes 0= No NA= Not available	Categorical	Nominal
ANXIE	anxiety	1= Yes 0= No NA= Not available	Categorical	Nominal
W-GAIN	Weight gain	1= Yes 0= No NA= Not available	Categorical	Nominal
W-LOSS	Weight loss	1= Yes 0= No NA= Not available	Categorical	Nominal
COLD	cold intolerance	1= Yes 0= No NA= Not available	Categorical	Nominal
HEAT	heat intolerance	1= Yes 0= No	Categorical	Nominal

		NA= Not available		
MENST-DIS	Menstrual disorders	1= Yes 0= No NA= Not available	Categorical	Nominal
SKIN	Dry Skin	1= Yes 0= No NA= Not available	Categorical	Nominal
DIAPH	Diaphoresis	1= Yes 0= No NA= Not available	Categorical	Nominal
ALOPE	Alopecia	1= Yes 0= No NA= Not available	Categorical	Nominal
CONSTIP	Constipation	1= Yes 0= No NA= Not available	Categorical	Nominal
ALT-VOIC	Alteration of the voice	1= Yes 0= No NA= Not available	Categorical	Nominal
FULL-THRO	Fullness of throat	1= Yes 0= No NA= Not available	Categorical	Nominal
THY-GROW	Thyroid growth	1= Yes 0= No NA= Not available	Categorical	Nominal
THY-PAIN	Thyroid pain	1= Yes 0= No NA= Not available	Categorical	Nominal
BRADI	Bradilalia, Bradipsiquia	1= Yes 0= No NA= Not available	Categorical	Nominal
PERI-EDE	Periorbital edema	1= Yes 0= No NA= Not available	Categorical	Nominal
REFLEX	Hyporeflexia	1= Yes 0= No NA= Not available	Categorical	Nominal
TREM	Tremor	1= Yes 0= No NA= Not available	Categorical	Nominal

PALPIT	Palpitations	1= Yes 0= No NA= Not available	Categorical	Nominal
HYPERR	Hyperreflexia	1= Yes 0= No NA= Not available	Categorical	Nominal
DIPLO	Diplopia	1= Yes 0= No NA= Not available	Categorical	Nominal
PROP	Proptosis	1= Yes 0= No NA= Not available	Categorical	Nominal
INFERTI	Infertility	1= Yes 0= No NA= Not available	Categorical	Nominal
LIBID	Decreased libido	1= Yes 0= No NA= Not available	Categorical	Nominal
HYPERAC	Hyperactivity	1= Yes 0= No NA= Not available	Categorical	Nominal
TSH	TSH	value	Numerical	Ratio
T4	T4	value	Numerical	Ratio
Vitamin D	Vitamin D	value	Numerical	Ratio
Vitamin D-Suf	Vitamin D-Suf	1= Yes 0= No NA= Not available	Categorical	Nominal
Vitamin D-Insu	Vitamin D-Insu	1= Yes 0= No NA= Not available	Categorical	Nominal
Vitamin D-Defi	Vitamin D-Defi	1= Yes 0= No NA= Not available	Categorical	Nominal
anti-TrAbs	anti-TrAbs	value	Numerical	Ratio
anti-TgAbs	anti-TgAbs	1: Positive 0: Negative	Categorical	Nominal
anti-TgAbs-Num	anti-TgAbs-Num	value	Numerical	Ratio
anti-TPOAbs	anti-TPOAbs	1: Positive 0: Negative	Categorical	Nominal

anti-TPOAbs-Num	anti-TPOAbs-Num	value	Numerical	Ratio
anti-CCP3	anti-CCP3	1: Positive 0: Negative	Categorical	Nominal
anti-CCP3-Num	anti-CCP3	value	Numerical	Ratio
FR	FR	1: Positive 0: Negative	Categorical	Nominal
FR-Num	FR-Num	value	Numerical	Ratio
B2GP1 IgM	B2GP1 IgM	1: Positive 0: Negative	Categorical	Nominal
B2GP1 IgM-Num	B2GP1 IgM-Num	value	Numerical	Ratio
B2GP1 IgG	B2GP1 IgG	1: Positive 0: Negative	Categorical	Nominal
B2GP1 IgG-Num	B2GP1 IgG-Num	value	Numerical	Ratio
ACA III IgM	ACA III IgM	1: Positive 0: Negative	Categorical	Nominal
ACA III IgM-Num	ACA III IgM-Num	value	Numerical	Ratio
ACA III IgG	ACA III IgG	1: Positive 0: Negative	Categorical	Nominal
ACA III IgG-Num	ACA III IgG-Num	value	Numerical	Ratio
dsDNA	dsDNA	1: Positive 0: Negative	Categorical	Nominal
dsDNA-Num	dsDNA-Num	value	Numerical	Ratio
Nucleosomes	Nucleosomes	1: Positive 0: Negative	Categorical	Nominal
Nucleosomes-Num	Nucleosomes-Num	value	Numerical	Ratio
Histones	Histones	1: Positive 0: Negative	Categorical	Nominal
Histones-Num	Histones-Num	value	Numerical	Ratio
SmD1	SmD1	1: Positive 0: Negative	Categorical	Nominal

SmD1-Num	SmD1-Num	value	Numerical	Ratio
PCNA	PCNA	1: Positive 0: Negative	Categorical	Nominal
PCNA-Num	PCNA-Num	value	Numerical	Ratio
P0	P0	1: Positive 0: Negative	Categorical	Nominal
P0-Num	P0-Num	value	Numerical	Ratio
SS-A/Ro60	SS-A/Ro60	1: Positive 0: Negative	Categorical	Nominal
SS-A/Ro60-Num	SS-A/Ro60-Num	value	Numerical	Ratio
SS-A/Ro52	SS-A/Ro52	1: Positive 0: Negative	Categorical	Nominal
SS-A/Ro52-Num	SS-A/Ro52-Num	value	Numerical	Ratio
SS-B/La	SS-B/La	1: Positive 0: Negative	Categorical	Nominal
SS-B/La-Num	SS-B/La-Num	value	Numerical	Ratio
CENP-B	CENP-B	1: Positive 0: Negative	Categorical	Nominal
CENP-B-Num	CENP-B-Num	value	Numerical	Ratio
Scl70	Scl70	1: Positive 0: Negative	Categorical	Nominal
Scl70-Num	Scl70-Num	value	Numerical	Ratio
U1-snRNP	U1-snRNP	1: Positive 0: Negative	Categorical	Nominal
U1-snRNP-Num	U1-snRNP-Num	value	Numerical	Ratio
AMA M2	AMA M2	1: Positive 0: Negative	Categorical	Nominal
AMA M2-Num	AMA M2-Num	value	Numerical	Ratio
Jo-1	Jo-1	1: Positive 0: Negative	Categorical	Nominal
Jo-1-Num	Jo-1-Num	value	Numerical	Ratio
PM-Scl	PM-Scl	1: Positive 0: Negative	Categorical	Nominal
PM-Scl-Num	PM-Scl-Num	value	Numerical	Ratio

Mi-2	Mi-2	1: Positive 0: Negative	Categorical	Nominal
Mi-2-Num	Mi-2-Num	value	Numerical	Ratio
Ku	Ku	1: Positive 0: Negative	Categorical	Nominal
Ku-Num	Ku-Num	value	Numerical	Ratio

12.2. APPENDIX 2

REGISTRO DE CONTROLES SANOS Y FAMILIARES
Centro de Estudio de Enfermedades Autoinmunes (CREA)

Apellidos y nombres:		Fecha de registro:
Documento de identidad:		Sexo[1,7]: F:__ M:__
Edad Actual[1]:	Fecha de Nacimiento:	Cargo en la empresa[1]:
Lugar de Nacimiento: Departamento:	Ciudad Residencia:	Estrato socioeconómico (servicio público)[1,2]:
Escolaridad en años:	EPS:	Prepagada:
Teléfonos:	Dirección:	
Email:	Ayuno: SI:___ NO:___	Muestra: SI:___ NO:___

1.Estado civil
- ☐ Soltero
- ☐ Casado
- ☐ Viudo
- ☐ Divorciado
- ☐ Pareja Estable

2. Tabaco[1,3,4,5]
- ☐ Nunca
- ☐ Exfumador
- ☐ 1-5 paq/año
- ☐ 6-15 paq/año
- ☐ + de15 paq/año
- ☐ Año comienzo
- ☐ Año finalización

3. Café[5,7]
- ☐ Nunca
- ☐ < 1 taza/día
- ☐ 1 taza/día
- ☐ 2-4 tazas/día
- ☐ + de 4 tazas/día
- ☐ Año comienzo
- ☐ Año finalización

4. Ha sido diagnósticado con:

	Año de inicio
Diabetes	
Dislipidemia	
Hipertensión arterial	
Enfermedad arterial oclusiva	
Accidentes cerebrovasculares	
Trombosis	
Depresión	
Epilepsia	
Enfermedad de la arteria carotída	
Enfermedad coronaria	
Enfermedad ácido péptica	
Enfermedad renal	
Ulceras cutáneas	
Anemia	
Tuberculosis[1,9]	
Hepatitis A[1,9]	
Otras hepatitis(B o C)[1,9]	
Malaria[1,9]	
Cáncer (Tipo)	
Otras enfermedades o infecciones	

5. Obstétricos
Menarquia (edad de la primera menstruación):_____Gestaciones:_____
Pérdidas:_____ Espontaneo: SI___ NO___
Pérdidas menos de 10Sem: _____
Pérdidas más de 10 Sem:_____
Partos vaginales:_____Cesáreas:_____ Nacidos vivos:_____
Método de planificación[7]:_____Edad menopausia:_____

	SI	NO
6. ¿Hace ejercicio regularmente al menos 30 minutos 3 veces por semana?[1]	☐	☐
7. ¿En su familia hay alguien con enfermedad cardiovascular diagnósticada antes de los 45 años?[10]	☐	☐

8. Cerca de su residencia actual o previa se encuentran:	**No. Años Exposición**	**Fecha (aaaa-aaaa)**	
Fábricas (Especificar tipo)[1,4]			
Cultivos (Especificar tipo)[1,4]			
Depósitos de elementos orgánicos[1,4]			
Minas[1,4]			
Aeropuertos[1,4]			

9. Agentes tóxicos y drogas	**Año**	**Frecuencia**		**Año**	**Frecuencia**
Sustancias psicoactivas (cocaína, marihuana)			Fenitoína[1]		
Implantes de silicona[1,4,3]			Carbamazepina[1]		
Disolventes orgánicos[1,4,3,8] (Silicona,cetona,arsénico,cloro, otros)			Ácido valproico[1]		
Tintes de cabello (veces/año)[1,4]			Anticoagulantes orales[1]		
Asbestos (Especificar tipo)[1,4]			Hidralazina[1]		
Pesticidas (Especificar tipo)[1,4]			Procainamida[1,4]		
Metales (Mercurio,Oro,Plata)[1,4]			Isoniazida[1]		

Fecha última actualización:17-Jul-17

UNIVERSIDAD CES
Un Compromiso con la Excelencia
Resolución del Ministerio de Educación Nacional No. 1371 del 22 de marzo de 2007

Universidad del Rosario

REGISTRO DE CONTROLES SANOS Y FAMILIARES
Centro de Estudio de Enfermedades Autoinmunes (CREA)

10. Alguna vez ha trabajado en:	**No. Años**	**Fecha de trabajo (aaaa-aaaa)**		**Días a la semana**	**Horas/día**
Cultivo de flores /Pesticidas (Especificar tipo)[4,8]					
Cocina de leña o carbón (Especificar tipo)[4]					
Minería[4]					
Construcción /Aeropuerto (Especificar tipo)[4]					
Plásticos/Caucho (Especificar tipo)[1,3,4]					
Cosmética /Peluquería (Especificar tipo)[1,3,4]					
Pinturas/Vitrales (Especificar tipo)[1,3,4]					
Limpieza/Lavandería (Especificar tipo)[1,3,4]					
Artes gráficas /Artesanías (Especificar tipo)[1,3,4]					
Farmacéutica (Especificar tipo)[1,3,4]					
Odontología[1,3,4]					
Medios de transporte (Especificar tipo)[1,3,4]					
Calzado (Especificar tipo)[1,3,4]					

11. Enfermedades Autoinmunes en la familia[1,8]		
Enfermedades	**Usted**	**Familiar** (Especificar familiar)
Lupus Eritematosos Sistémico		
Artritis Reumatoide		
Síndrome de Sjögren		
Problemas de tiroides: Hipotiroidismo-Hipertiroidismo (Especificar tipo)		
Diabetes Tipo 1 (juvenil)		
Esclerosis Múltiple		
Esclerosis Sistémica (escleroderma)		
Vitíligo		
Psoriasis		
Síndrome Antifosfolípidico		
Hepatitis autoinmune		
Cirrosis biliar primaria		
Espondilitis Anquilosante		
Otras enfermedades autoinmunes		

12. Examen Físico:	
Tensión Arterial	
Talla	
Peso	
IMC	
Perímetro abdominal	

Fecha última actualización:17-Jul-17

12.3. APPENDIX 3

Cumple criterios	Si No	Cuantos		Fecha:

FORMULARIO PARA PACIENTES CON ENFERMEDAD TIROIDEA AUTOINMUNE
CENTRO DE ESTUDIO DE ENFERMEDADES AUTOINMUNES (CREA)

Nombres:	Apellidos:
Documento de identidad:	Edad inicio de síntomas
Forma de inicio:	Edad de diagnóstico:
Tiroiditis de Hashimoto: Si___ No___	Enfermedad de Graves: Si___ No___

CRITERIOS DIAGNÓSTICOS

CRITERIO	POSITIVO	NEGATIVO
TSH alterada		
Suplencia tiroidea		
Anticuerpos anti tiroideos tiroperoxidasa		
Anticuerpos anti tiroideos tiroglobulina		
Anticuerpos anti tiroideos receptor TSH		

MANIFESTACIONES CLINICAS

	Fatiga, letargo		Plenitud en la garganta (sensación de cuerpo extraño en la garganta)
	Ansiedad		Crecimiento tiroideo (coto)
	Ganancia de peso		Dolor tiroideo
	Pérdida de peso		Bradilalia, bradipsiquia (Lento de pensamiento, lento para hablar)
	Intolerancia al frio		Edema periorbitario
	Intolerancia al calor		Hiperactividad
	Alteraciones menstruales		Temblor
	Piel seca		
	Diaforesis (Sudoración excesiva)		Palpitaciones
	Alopecia (perdida de pelo abundante)		Diplopía (Visión doble)
			Mixedema
	Estreñimiento		***Proptosis***
	Alteración de la voz		***Hiporreflexia***

Antecedentes Específicos	SI	NO	Año	Observación
Cirugía de cabeza y cuello				
Exposición a radiación				
Déficit de yodo				
Exposición a medicamentos				

Observaciones:

12.4. APPENDIX 4

CONSENTIMIENTO INFORMADO PARA LA TOMA DE MUESTRAS BIOLÓGICAS Y LA PARTICIPACIÓN EN UN TRABAJO DE INVESTIGACIÓN EN ENFERMEDADES AUTOINMUNES
Centro de Estudio de Enfermedades Autoinmunes CREA - Universidad del Rosario

Es muy importante que usted lea y entienda los siguientes puntos sobre la realización de este estudio:

1. La participación en este estudio es totalmente voluntaria.
2. La naturaleza de esta investigación, sus propósito, sus limitaciones, sus riesgos, sus inconvenientes, incomodidades y cualquier información pertinente al resultado de este, le serán explicados por el grupo de atención clínica.
3. Si tiene algún interrogante sobre el estudio por favor no dude en manifestarlo a alguno de los investigadores, que con mucho gusto, le contestará sus preguntas.
4. **CONFIDENCIALIDAD**: Los registros médicos de cada individuo permanecerán archivados en el **Centro de Estudio de Enfermedades Autoinmunes (CREA)**, perteneciente a la Escuela de Medicina y Ciencias de la Salud de la **Universidad del Rosario**. Las historias médicas, los resultados de exámenes y la información que usted nos ha dado, son de carácter absolutamente confidencial, de manera que, solamente usted y el grupo de atención clínica tendrá acceso a estos datos. Por ningún motivo se divulgará esta información sin su consentimiento. La finalidad y uso de los datos personales por usted suministrados, serán para fines científico de investigación y de contacto con el paciente.
5. En aplicación del artículo 15 de la constitución política de la ley 1581 de 2012, la Universidad del Rosario informa a todos los participantes en este estudio, que sus datos personales se tratarán en concordancia con la política interna de protección de datos personales, puesta a su disposición a través del siguiente link http://repository.urosario.edu.co/bitstream/handle/10336/4503/PoliticaTratamientoProteccionDatosPersonales.pdf. Igualmente se dispuso del siguiente correo para la recepción de solicitudes habeas.data@urosario.edu.co.

EXPLICACIÓN DEL ESTUDIO

OBJETIVO:
El objetivo de este trabajo es identificar qué genes (códigos o huellas dactilares de las células) y cuales mecanismos se presentan más frecuentemente en pacientes con enfermedades autoinmunes, sus familiares sanos o que padezcan también, de alguna enfermedad autoinmune. Estos genes (ADN y ARN) están presentes en todas las células de su organismo, incluidas las de la sangre y la saliva. De estos tipos de muestra, extraeremos los genes, las células y otras sustancias circulantes (moléculas que viajan por la sangre o que están en la saliva) con el fin de analizarlas en un laboratorio respaldado por el CREA perteneciente a la Universidad del Rosario.

PROCEDIMIENTO:
Si Usted decide tomar parte de este estudio, llenaremos un registro con sus datos y la información relevante de su condición de salud. Adicionalmente, le tomaremos una muestra de 20 mililitros de sangre que es necesaria para analizar en el laboratorio y será obtenida de la vena de su brazo. Esta es la manera usual como se obtiene sangre para el análisis. Es posible que sienta un poco de dolor cuando la aguja entre en su brazo. En una de cada 10 personas queda una pequeña cantidad de sangre debajo de la piel, lo cual causará un moretón.

12.5. APPENDIX 5

Supplementary table 1.

Pruebas ómnibus de coeficientes de modelo

		Chi-cuadrado	gl	Sig.
Paso 1	Paso	5,219	1	,022
	Bloque	5,219	1	,022
	Modelo	5,219	1	,022
Paso 2	Paso	5,588	1	,018
	Bloque	10,807	2	,005
	Modelo	10,807	2	,005
Paso 3	Paso	5,254	1	,022
	Bloque	16,061	3	,001
	Modelo	16,061	3	,001
Paso 4	Paso	4,908	1	,027
	Bloque	20,969	4	,000
	Modelo	20,969	4	,000
Paso 5	Paso	3,979	1	,046
	Bloque	24,948	5	,000
	Modelo	24,948	5	,000

Supplementary table 2.

Resumen del modelo

Paso	Logaritmo de la verosimilitud -2	R cuadrado de Cox y Snell	R cuadrado de Nagelkerke
1	191,854[a]	,024	,040
2	186,266[b]	,049	,082
3	181,012[c]	,072	,120
4	176,104[c]	,093	,155
5	172,125[c]	,110	,183

a. La estimación ha terminado en el número de iteración 4 porque las estimaciones de parámetro han cambiado en menos de ,001.
b. La estimación ha terminado en el número de iteración 5 porque las estimaciones de parámetro han cambiado en menos de ,001.
c. La estimación ha terminado en el número de iteración 6 porque las estimaciones de parámetro han cambiado en menos de ,001.

Supplementary table 3.

Prueba de Hosmer y Lemeshow

Paso	Chi-cuadrado	gl	Sig.
1	,000	0	.
2	,001	2	,999
3	,819	2	,664
4	1,065	3	,786
5	1,796	3	,616

Supplementary table 4.

Tabla de contingencia para la prueba de Hosmer y Lemeshow

		COD = 0		COD = 1		
		Observado	Esperado	Observado	Esperado	Total
Paso 1	1	163	163,000	29	29,000	192
	2	14	14,000	8	8,000	22
Paso 2	1	35	35,026	2	1,974	37
	2	5	4,974	1	1,026	6
	3	128	127,974	27	27,026	155
	4	9	9,026	7	6,974	16
Paso 3	1	34	33,702	1	1,298	35
	2	5	4,374	0	,626	5
	3	126	126,736	26	25,264	152
	4	12	12,189	10	9,811	22
Paso 4	1	28	27,283	0	,717	28
	2	10	10,096	1	,904	11
	3	116	117,646	22	20,354	138
	4	12	11,254	5	5,746	17
	5	11	10,721	9	9,279	20
Paso 5	1	26	25,442	0	,558	26
	2	12	11,128	0	,872	12
	3	110	111,958	19	17,042	129
	4	12	11,760	5	5,240	17
	5	17	16,711	13	13,289	30

Supplementary table 5.

Tabla de clasificación[a]

			Pronosticado		
			COD		Porcentaje
	Observado		0	1	correcto
Paso 1	COD	0	177	0	100,0
		1	37	0	,0
	Porcentaje global				82,7
Paso 2	COD	0	177	0	100,0
		1	37	0	,0
	Porcentaje global				82,7
Paso 3	COD	0	175	2	98,9
		1	35	2	5,4
	Porcentaje global				82,7
Paso 4	COD	0	175	2	98,9
		1	33	4	10,8
	Porcentaje global				83,6
Paso 5	COD	0	174	3	98,3
		1	32	5	13,5
	Porcentaje global				83,6

a. El valor de corte es ,500

Supplementary table 6.

Variables en la ecuación

		B	Error estándar	Wald	gl	Sig.	Exp(B)	95% C.I. para EXP(B) Inferior	Superior
Paso 1[a]	LIBID_REG	1,167	,487	5,744	1	,017	3,212	1,237	8,340
	Constante	-1,726	,202	73,383	1	,000	,178		
Paso 2[b]	TABAC/NUN(1)	1,321	,642	4,229	1	,040	3,747	1,064	13,195
	LIBID_REG	1,297	,504	6,611	1	,010	3,659	1,361	9,835
	Constante	-2,876	,627	21,065	1	,000	,056		
Paso 3[c]	PAI_REG(1)	2,194	,938	5,467	1	,019	8,972	1,426	56,442
	TABAC/NUN(1)	1,644	,713	5,323	1	,021	5,177	1,281	20,923
	LIBID_REG	1,313	,510	6,634	1	,010	3,719	1,369	10,102
	Constante	-3,257	,708	21,144	1	,000	,039		
Paso 4[d]	ETI_FAM_REG(1)	1,201	,522	5,287	1	,021	3,325	1,194	9,257
	PAI_REG(1)	2,242	,965	5,395	1	,020	9,409	1,419	62,386
	TABAC/NUN(1)	1,885	,747	6,373	1	,012	6,583	1,524	28,436
	LIBID_REG	1,269	,523	5,877	1	,015	3,556	1,275	9,919
	Constante	-3,639	,760	22,904	1	,000	,026		
Paso 5[e]	ETI_FAM_REG(1)	1,219	,529	5,312	1	,021	3,384	1,200	9,542
	PAI_REG(1)	2,381	,974	5,977	1	,014	10,811	1,603	72,901
	TABAC/NUN(1)	1,938	,753	6,618	1	,010	6,942	1,586	30,378
	CAFÉ_>4(1)	1,329	,634	4,394	1	,036	3,776	1,090	13,075
	LIBID_REG	1,322	,531	6,194	1	,013	3,753	1,324	10,633
	Constante	-3,820	,777	24,195	1	,000	,022		

a. Variables especificadas en el paso 1: LIBID_REG.

b. Variables especificadas en el paso 2: TABAC/NUN.

c. Variables especificadas en el paso 3: PAI_REG.

d. Variables especificadas en el paso 4: ETI_FAM_REG.

e. Variables especificadas en el paso 5: CAFÉ_>4.

Supplementary table 7.

Las variables no están en la ecuación[a]

			Puntuación	gl	Sig.
Paso 1	Variables	DEPRES_REG	,235	1	,628
		EAI_FAM__REG(1)	,832	1	,362
		ETI_FAM_REG(1)	3,607	1	,058
		PAI_REG(1)	4,186	1	,041
		ABOR-<10SEM_REG(1)	2,012	1	,156
		ABOR->10 SEM_REG(1)	3,666	1	,056
		IRREG-MENS_REG	3,325	1	,068
		TABAC/NUN(1)	4,702	1	,030
		TABAC/EX(1)	1,203	1	,273
		FUMA_ACT__REG(1)	3,678	1	,055
		CAFÉ_>4(1)	4,025	1	,045
		VIV-CULT(1)	,812	1	,367
		TRAB-LEÑ_REG(1)	1,631	1	,202
		FATI_REG	,195	1	,659
		AUM-PESO_REG	1,279	1	,258
		FRIO_REG	,072	1	,789
		PIEL_REG	,009	1	,923
		ALOPE_REG	,605	1	,437
		CONSTIP_REG	1,417	1	,234
		REFLEJ_REG	,012	1	,914
		DIPLO_REG	2,393	1	,122
		INFERTI_REG	1,481	1	,224
		Vitamina D-Suf(1)	1,606	1	,205
		vitd_ins_def	1,606	1	,205
Paso 2	Variables	DEPRES_REG	,551	1	,458
		EAI_FAM__REG(1)	,852	1	,356
		ETI_FAM_REG(1)	5,746	1	,017
		PAI_REG(1)	7,489	1	,006
		ABOR-<10SEM_REG(1)	1,801	1	,180
		ABOR->10 SEM_REG(1)	3,261	1	,071
		IRREG-MENS_REG	3,699	1	,054

		TABAC/EX(1)	1,716	1	,190
		FUMA_ACT__REG(1)	1,716	1	,190
		CAFÉ_>4(1)	4,116	1	,042
		VIV-CULT(1)	,588	1	,443
		TRAB-LEÑ_REG(1)	1,016	1	,314
		FATI_REG	,000	1	,983
		AUM-PESO_REG	1,376	1	,241
		FRIO_REG	,001	1	,976
		PIEL_REG	,000	1	,996
		ALOPE_REG	,571	1	,450
		CONSTIP_REG	,948	1	,330
		REFLEJ_REG	,058	1	,809
		DIPLO_REG	1,626	1	,202
		INFERTI_REG	1,671	1	,196
		Vitamina D-Suf(1)	1,758	1	,185
		vitd_ins_def	1,758	1	,185
Paso 3	Variables	DEPRES_REG	,024	1	,877
		EAI_FAM__REG(1)	,961	1	,327
		ETI_FAM_REG(1)	5,701	1	,017
		ABOR-<10SEM_REG(1)	1,467	1	,226
		ABOR->10 SEM_REG(1)	2,973	1	,085
		IRREG-MENS_REG	3,344	1	,067
		TABAC/EX(1)	1,126	1	,289
		FUMA_ACT__REG(1)	1,126	1	,289
		CAFÉ_>4(1)	4,830	1	,028
		VIV-CULT(1)	,881	1	,348
		TRAB-LEÑ_REG(1)	1,224	1	,269
		FATI_REG	,006	1	,940
		AUM-PESO_REG	,851	1	,356
		FRIO_REG	,005	1	,942
		PIEL_REG	,232	1	,630
		ALOPE_REG	,767	1	,381
		CONSTIP_REG	1,605	1	,205
		REFLEJ_REG	,112	1	,738
		DIPLO_REG	1,990	1	,158

		INFERTI_REG	1,579	1	,209
		Vitamina D-Suf(1)	2,190	1	,139
		vitd_ins_def	2,190	1	,139
Paso 4	Variables	DEPRES_REG	,004	1	,949
		EAI_FAM__REG(1)	1,171	1	,279
		ABOR-<10SEM_REG(1)	2,035	1	,154
		ABOR->10 SEM_REG(1)	3,423	1	,064
		IRREG-MENS_REG	2,714	1	,099
		TABAC/EX(1)	1,155	1	,282
		FUMA_ACT__REG(1)	1,155	1	,282
		CAFÉ_>4(1)	4,857	1	,028
		VIV-CULT(1)	,706	1	,401
		TRAB-LEÑ_REG(1)	1,227	1	,268
		FATI_REG	,130	1	,718
		AUM-PESO_REG	,581	1	,446
		FRIO_REG	,000	1	,990
		PIEL_REG	,229	1	,632
		ALOPE_REG	,855	1	,355
		CONSTIP_REG	2,128	1	,145
		REFLEJ_REG	,159	1	,690
		DIPLO_REG	2,496	1	,114
		INFERTI_REG	1,354	1	,245
		Vitamina D-Suf(1)	1,855	1	,173
		vitd_ins_def	1,855	1	,173
Paso 5	Variables	DEPRES_REG	,129	1	,720
		EAI_FAM__REG(1)	,934	1	,334
		ABOR-<10SEM_REG(1)	2,088	1	,148
		ABOR->10 SEM_REG(1)	3,589	1	,058
		IRREG-MENS_REG	3,217	1	,073
		TABAC/EX(1)	1,176	1	,278
		FUMA_ACT__REG(1)	1,176	1	,278
		VIV-CULT(1)	,417	1	,519
		TRAB-LEÑ_REG(1)	,745	1	,388
		FATI_REG	,493	1	,482
		AUM-PESO_REG	,276	1	,599

	FRIO_REG	,016	1	,899
	PIEL_REG	,238	1	,626
	ALOPE_REG	,932	1	,334
	CONSTIP_REG	2,601	1	,107
	REFLEJ_REG	,276	1	,599
	DIPLO_REG	2,494	1	,114
	INFERTI_REG	1,225	1	,268
	Vitamina D-Suf(1)	2,173	1	,140
	vitd_ins_def	2,173	1	,140

a. Los chi-cuadrados residuales no se calculan debido a redundancias.

Supplementary table 8.

Resumen de procesamiento de casos

COD	N válido (por lista)
Positivo[a]	46
Negativo	252
Perdidos	2

Los valores más grandes de las variables de resultado de prueba indican una prueba mayor para un estado real positivo.

a. El estado real positivo es 1.

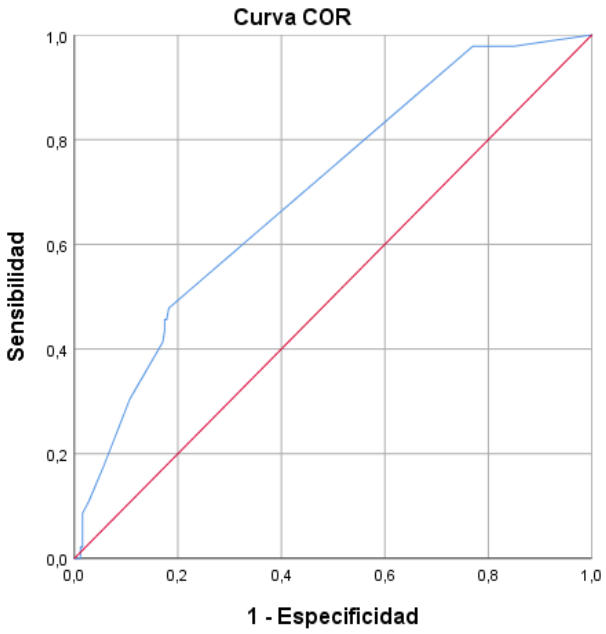
Supplementary figure 1.

Área bajo la curva

Variables de resultado de prueba: Probabilidad pronosticada

Área
,700

Las variables de resultado de prueba: Probabilidad pronosticada tienen, como mínimo, un empate entre el grupo de estado real positivo y el grupo de estado real negativo. Las estadísticas podrían estar sesgadas.



Los segmentos de diagonal se generan mediante empates.

12.6. APPENDIX 6

Supplementary table 1.

Pruebas ómnibus de coeficientes de modelo

		Chi-cuadrado	gl	Sig.
Paso 1	Paso	8,417	1	,004
	Bloque	8,417	1	,004
	Modelo	8,417	1	,004
Paso 2	Paso	4,928	1	,026
	Bloque	13,345	2	,001
	Modelo	13,345	2	,001
Paso 3	Paso	5,172	1	,023
	Bloque	18,517	3	,000
	Modelo	18,517	3	,000
Paso 4	Paso	5,870	1	,015
	Bloque	24,387	4	,000
	Modelo	24,387	4	,000
Paso 5	Paso	4,495	1	,034
	Bloque	28,882	5	,000
	Modelo	28,882	5	,000
Paso 6	Paso	3,525	1	,060
	Bloque	32,407	6	,000
	Modelo	32,407	6	,000

Supplementary table 2.

Resumen del modelo

Paso	Logaritmo de la verosimilitud -2	R cuadrado de Cox y Snell	R cuadrado de Nagelkerke
1	182,994[a]	,037	,064
2	178,066[a]	,057	,100
3	172,894[a]	,079	,138
4	167,024[a]	,102	,179
5	162,529[b]	,120	,210
6	159,004[b]	,134	,234

a. La estimación ha terminado en el número de iteración 5 porque las estimaciones de parámetro han cambiado en menos de ,001.

b. La estimación ha terminado en el número de iteración 6 porque las estimaciones de parámetro han cambiado en menos de ,001.

Supplementary table 3.

Prueba de Hosmer y Lemeshow

Paso	Chi-cuadrado	gl	Sig.
1	,000	0	.
2	,000	0	.
3	,090	1	,765
4	,093	2	,955
5	,875	3	,832
6	1,911	3	,591

Supplementary table 4.

Tabla de contingencia para la prueba de Hosmer y Lemeshow

		anti-TPO = 0		anti-TPO = 1		
		Observado	Esperado	Observado	Esperado	Total
Paso 1	1	177	177,000	25	25,000	202
	2	15	15,000	9	9,000	24
Paso 2	1	176	176,000	23	23,000	199
	2	16	16,000	11	11,000	27
Paso 3	1	160	160,539	18	17,461	178
	2	16	15,461	5	5,539	21
	3	16	16,000	11	11,000	27
Paso 4	1	30	30,042	1	,958	31
	2	130	130,614	17	16,386	147
	3	21	20,441	6	6,559	27
	4	11	10,903	10	10,097	21
Paso 5	1	29	29,310	1	,690	30
	2	6	6,295	1	,705	7
	3	129	129,797	16	15,203	145
	4	17	15,419	5	6,581	22
	5	11	11,179	11	10,821	22
Paso 6	1	27	27,472	1	,528	28
	2	8	7,353	0	,647	8
	3	122	123,150	14	12,850	136
	4	23	21,216	6	7,784	29
	5	12	12,809	13	12,191	25

Supplementary table 5.

Tabla de clasificación[a]

			Pronosticado		
			anti-TPO		Porcentaje
	Observado		0	1	correcto
Paso 1	anti-TPO	0	192	0	100,0
		1	34	0	,0
	Porcentaje global				85,0
Paso 2	anti-TPO	0	191	1	99,5
		1	32	2	5,9
	Porcentaje global				85,4
Paso 3	anti-TPO	0	190	2	99,0
		1	29	5	14,7
	Porcentaje global				86,3
Paso 4	anti-TPO	0	192	0	100,0
		1	30	4	11,8
	Porcentaje global				86,7
Paso 5	anti-TPO	0	191	1	99,5
		1	28	6	17,6
	Porcentaje global				87,2
Paso 6	anti-TPO	0	190	2	99,0
		1	27	7	20,6
	Porcentaje global				87,2

a. El valor de corte es ,500

Supplementary table 6.

Variables en la ecuación

		B	Error estándar	Wald	gl	Sig.	Exp(B)	95% C.I. para EXP(B) Inferior	Superior
Paso 1[a]	LIBID_REG(1)	1,446	,473	9,364	1	,002	4,248	1,682	10,728
	Constante	-1,957	,214	83,920	1	,000	,141		
Paso 2[b]	LIBID_REG(1)	1,524	,476	10,237	1	,001	4,591	1,805	11,680
	SS-A/Ro52_REG(1)	2,728	1,245	4,804	1	,028	15,304	1,335	175,495
	Constante	-2,035	,222	84,239	1	,000	,131		
Paso 3[c]	ETI_FAM_REG(1)	1,192	,499	5,709	1	,017	3,293	1,239	8,756
	LIBID_REG(1)	1,496	,487	9,423	1	,002	4,466	1,718	11,610
	SS-A/Ro52_REG(1)	2,912	1,249	5,431	1	,020	18,388	1,589	212,819
	Constante	-2,219	,247	80,733	1	,000	,109		
Paso 4[d]	ETI_FAM_REG(1)	1,435	,523	7,528	1	,006	4,198	1,507	11,698
	TABAC/NUN(1)	1,370	,634	4,668	1	,031	3,936	1,136	13,640
	LIBID_REG(1)	1,716	,512	11,218	1	,001	5,560	2,037	15,172
	SS-A/Ro52_REG(1)	3,285	1,332	6,080	1	,014	26,701	1,962	363,462
	Constante	-3,446	,652	27,960	1	,000	,032		
Paso 5[e]	ETI_FAM_REG(1)	1,561	,532	8,622	1	,003	4,762	1,680	13,498
	TABAC/NUN(1)	1,605	,673	5,682	1	,017	4,979	1,330	18,636
	LIBID_REG(1)	1,717	,519	10,950	1	,001	5,570	2,014	15,405
	SS-A/Ro52_REG(1)	3,451	1,364	6,400	1	,011	31,546	2,176	457,363
	Ku(1)	2,485	1,113	4,981	1	,026	12,000	1,354	106,378
	Constante	-3,750	,703	28,457	1	,000	,024		

Paso 6[f]	ETI_FAM_REG(1)	1,588	,538	8,713	1	,003	4,894	1,705	14,049
	TABAC/NUN(1)	1,691	,693	5,966	1	,015	5,428	1,397	21,090
	CAFÉ_>4(1)	1,292	,652	3,933	1	,047	3,641	1,015	13,055
	LIBID_REG(1)	1,737	,529	10,772	1	,001	5,680	2,013	16,028
	SS-A/Ro52_REG(1)	3,604	1,381	6,812	1	,009	36,729	2,453	549,874
	Ku(1)	2,326	1,167	3,974	1	,046	10,235	1,040	100,734
	Constante	-3,952	,733	29,050	1	,000	,019		

a. Variables especificadas en el paso 1: LIBID_REG.

b. Variables especificadas en el paso 2: SS-A/Ro52_REG.

c. Variables especificadas en el paso 3: ETI_FAM_REG.

d. Variables especificadas en el paso 4: TABAC/NUN.

e. Variables especificadas en el paso 5: Ku.

f. Variables especificadas en el paso 6: CAFÉ_>4.

Supplementary table 7.

Las variables no están en la ecuación[a]

			Puntuación	gl	Sig.
Paso 1	Variables	HTA_REG(1)	1,559	1	,212
		DEPRES_REG(1)	1,559	1	,212
		EAI_FAM__REG(1)	,923	1	,337
		ETI_FAM_REG(1)	5,393	1	,020
		ABOR->10 SEM_REG(1)	3,182	1	,074
		TABAC/NUN(1)	3,141	1	,076
		TABAC_1_5_REG(1)	2,713	1	,100
		TABAC_>15__REG(1)	1,739	1	,187
		TABAC/EX(1)	1,346	1	,246
		FUMA_ACT__REG(1)	1,477	1	,224
		CAFÉ_>4(1)	3,989	1	,046
		VIV-CULT(1)	1,690	1	,194
		TRAB-LEÑ_REG(1)	,914	1	,339
		PER-PESO(1)	,004	1	,950
		CALOR(1)	,419	1	,517
		PIEL_REG(1)	,001	1	,979
		CONSTIP_REG(1)	2,004	1	,157
		TEMBL(1)	,017	1	,896
		PALPIT(1)	,412	1	,521
		DIPLO_REG(1)	3,027	1	,082
		INFERTI_REG(1)	1,311	1	,252
		Vitamina D-Insu(1)	2,048	1	,152
		SS-A/Ro52_REG(1)	8,277	1	,004
		Ku(1)	2,883	1	,089
Paso 2	Variables	HTA_REG(1)	1,642	1	,200
		DEPRES_REG(1)	1,642	1	,200
		EAI_FAM__REG(1)	1,737	1	,187
		ETI_FAM_REG(1)	6,141	1	,013
		ABOR->10 SEM_REG(1)	3,035	1	,081
		TABAC/NUN(1)	3,628	1	,057
		TABAC_1_5_REG(1)	2,555	1	,110

		TABAC_>15__REG(1)	1,739	1	,187
		TABAC/EX(1)	1,888	1	,169
		FUMA_ACT__REG(1)	1,323	1	,250
		CAFÉ_>4(1)	4,515	1	,034
		VIV-CULT(1)	2,080	1	,149
		TRAB-LEÑ_REG(1)	,929	1	,335
		PER-PESO(1)	,096	1	,756
		CALOR(1)	,138	1	,710
		PIEL_REG(1)	,041	1	,839
		CONSTIP_REG(1)	2,244	1	,134
		TEMBL(1)	,002	1	,962
		PALPIT(1)	,245	1	,621
		DIPLO_REG(1)	2,006	1	,157
		INFERTI_REG(1)	1,256	1	,262
		Vitamina D-Insu(1)	,955	1	,328
		Ku(1)	3,103	1	,078
Paso 3	Variables	HTA_REG(1)	1,259	1	,262
		DEPRES_REG(1)	1,259	1	,262
		EAI_FAM__REG(1)	1,800	1	,180
		ABOR->10 SEM_REG(1)	3,359	1	,067
		TABAC/NUN(1)	5,027	1	,025
		TABAC_1_5_REG(1)	3,295	1	,069
		TABAC_>15__REG(1)	2,151	1	,142
		TABAC/EX(1)	2,611	1	,106
		FUMA_ACT__REG(1)	1,738	1	,187
		CAFÉ_>4(1)	4,490	1	,034
		VIV-CULT(1)	1,999	1	,157
		TRAB-LEÑ_REG(1)	1,114	1	,291
		PER-PESO(1)	,145	1	,703
		CALOR(1)	,000	1	,988
		PIEL_REG(1)	,035	1	,852
		CONSTIP_REG(1)	3,272	1	,070
		TEMBL(1)	,517	1	,472
		PALPIT(1)	,104	1	,747
		DIPLO_REG(1)	2,537	1	,111

		INFERTI_REG(1)	1,045	1	,307
		Vitamina D-Insu(1)	1,446	1	,229
		Ku(1)	4,039	1	,044
Paso 4	Variables	HTA_REG(1)	,662	1	,416
		DEPRES_REG(1)	2,806	1	,094
		EAI_FAM__REG(1)	1,500	1	,221
		ABOR->10 SEM_REG(1)	3,195	1	,074
		TABAC_1_5_REG(1)	1,454	1	,228
		TABAC_>15__REG(1)	5,988	1	,014
		TABAC/EX(1)	,031	1	,861
		FUMA_ACT__REG(1)	,031	1	,861
		CAFÉ_>4(1)	5,514	1	,019
		VIV-CULT(1)	1,493	1	,222
		TRAB-LEÑ_REG(1)	,438	1	,508
		PER-PESO(1)	,069	1	,793
		CALOR(1)	,104	1	,747
		PIEL_REG(1)	,019	1	,890
		CONSTIP_REG(1)	2,412	1	,120
		TEMBL(1)	,029	1	,865
		PALPIT(1)	,066	1	,797
		DIPLO_REG(1)	1,411	1	,235
		INFERTI_REG(1)	1,227	1	,268
		Vitamina D-Insu(1)	1,190	1	,275
		Ku(1)	7,420	1	,006
Paso 5	Variables	HTA_REG(1)	,724	1	,395
		DEPRES_REG(1)	1,190	1	,275
		EAI_FAM__REG(1)	1,338	1	,247
		ABOR->10 SEM_REG(1)	3,052	1	,081
		TABAC_1_5_REG(1)	1,571	1	,210
		TABAC_>15__REG(1)	,931	1	,335
		TABAC/EX(1)	,607	1	,436
		FUMA_ACT__REG(1)	,607	1	,436
		CAFÉ_>4(1)	4,252	1	,039
		VIV-CULT(1)	1,820	1	,177
		TRAB-LEÑ_REG(1)	,757	1	,384

		PER-PESO(1)	,021	1	,884
		CALOR(1)	,021	1	,885
		PIEL_REG(1)	,033	1	,855
		CONSTIP_REG(1)	1,790	1	,181
		TEMBL(1)	,002	1	,961
		PALPIT(1)	,177	1	,674
		DIPLO_REG(1)	1,695	1	,193
		INFERTI_REG(1)	1,147	1	,284
		Vitamina D-Insu(1)	,675	1	,411
Paso 6	Variables	HTA_REG(1)	,885	1	,347
		DEPRES_REG(1)	,414	1	,520
		EAI_FAM__REG(1)	1,106	1	,293
		ABOR->10 SEM_REG(1)	3,115	1	,078
		TABAC_1_5_REG(1)	1,414	1	,234
		TABAC_>15__REG(1)	,345	1	,557
		TABAC/EX(1)	,896	1	,344
		FUMA_ACT__REG(1)	,896	1	,344
		VIV-CULT(1)	1,358	1	,244
		TRAB-LEÑ_REG(1)	,458	1	,499
		PER-PESO(1)	,010	1	,920
		CALOR(1)	,042	1	,838
		PIEL_REG(1)	,063	1	,801
		CONSTIP_REG(1)	2,093	1	,148
		TEMBL(1)	,003	1	,954
		PALPIT(1)	,102	1	,750
		DIPLO_REG(1)	1,718	1	,190
		INFERTI_REG(1)	1,039	1	,308
		Vitamina D-Insu(1)	,560	1	,454

a. Los chi-cuadrados residuales no se calculan debido a redundancias.

Supplementary table 8.

Resumen de procesamiento de casos

anti-TPO	N válido (por lista)
Positivo[a]	40
Negativo	258
Perdidos	2

Los valores más grandes de las variables de resultado de prueba indican una prueba mayor para un estado real positivo.

a. El estado real positivo es 1.

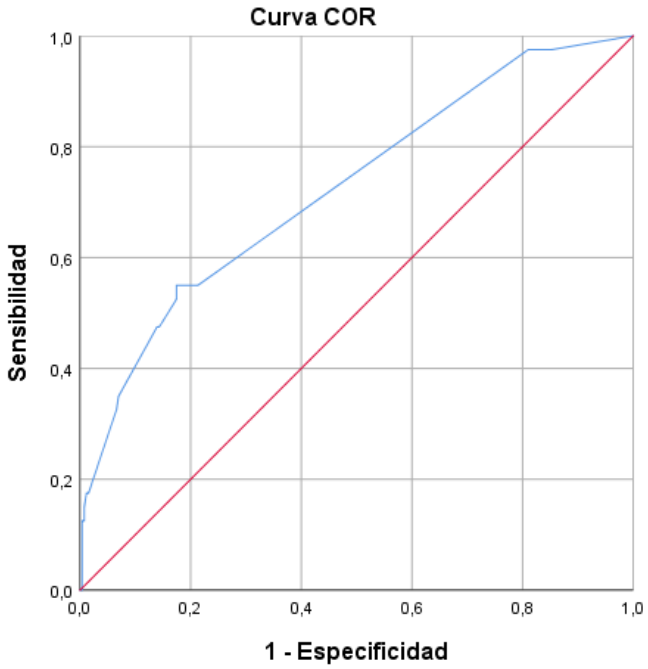
Supplementary figure 1.

Área bajo la curva

Variables de resultado de prueba: Probabilidad pronosticada

Área
,725

Las variables de resultado de prueba: Probabilidad pronosticada tienen, como mínimo, un empate entre el grupo de estado real positivo y el grupo de estado real negativo. Las estadísticas podrían estar sesgadas.



Supplementary table 9.

Pruebas ómnibus de coeficientes de modelo

		Chi-cuadrado	gl	Sig.
Paso 1	Paso	3,340	1	,068
	Bloque	3,340	1	,068
	Modelo	3,340	1	,068
Paso 2	Paso	4,086	1	,043
	Bloque	7,426	2	,024
	Modelo	7,426	2	,024
Paso 3	Paso	2,916	1	,088
	Bloque	10,342	3	,016
	Modelo	10,342	3	,016
Paso 4	Paso	2,093	1	,148
	Bloque	12,435	4	,014
	Modelo	12,435	4	,014

Supplementary table 10.

Resumen del modelo

Paso	Logaritmo de la verosimilitud -2	R cuadrado de Cox y Snell	R cuadrado de Nagelkerke
1	83,276[a]	,016	,047
2	79,191[a]	,034	,103
3	76,275[a]	,047	,142
4	74,181[a]	,057	,170

a. La estimación ha terminado en el número de iteración 6 porque las estimaciones de parámetro han cambiado en menos de ,001.

Supplementary table 11.

Prueba de Hosmer y Lemeshow

Paso	Chi-cuadrado	gl	Sig.
1	,000	0	.
2	,000	0	.
3	,000	0	.
4	,000	0	.

Supplementary table 12.

Tabla de contingencia para la prueba de Hosmer y Lemeshow

		anti-TG = 0		anti-TG = 1		
		Observado	Esperado	Observado	Esperado	Total
Paso 1	1	202	202,000	11	11,000	213
Paso 2	1	202	202,000	11	11,000	213
Paso 3	1	193	193,000	7	7,000	200
	2	9	9,000	4	4,000	13
Paso 4	1	189	189,000	6	6,000	195
	2	13	13,000	5	5,000	18

Supplementary table 13.

Tabla de clasificación[a]

			Pronosticado		
			anti-TG		Porcentaje
	Observado		0	1	correcto
Paso 1	anti-TG	0	201	1	99,5
		1	10	1	9,1
	Porcentaje global				94,8
Paso 2	anti-TG	0	201	1	99,5
		1	10	1	9,1
	Porcentaje global				94,8
Paso 3	anti-TG	0	201	1	99,5
		1	10	1	9,1
	Porcentaje global				94,8
Paso 4	anti-TG	0	201	1	99,5
		1	10	1	9,1
	Porcentaje global				94,8

a. El valor de corte es ,500

Supplementary table 14.

Variables en la ecuación

		B	Error estándar	Wald	gl	Sig.	Exp(B)	95% C.I. para EXP(B) Inferior	Superior
Paso 1[a]	CENP-B(1)	3,001	1,451	4,278	1	,039	20,100	1,170	345,275
	Constante	-3,001	,324	85,776	1	,000	,050		
Paso 2[b]	ETNIA_REG_A(1)	2,095	,893	5,508	1	,019	8,125	1,413	46,734
	CENP-B(1)	3,194	1,459	4,788	1	,029	24,375	1,395	425,863
	Constante	-3,194	,361	78,375	1	,000	,041		
Paso 3[c]	ETNIA_REG_A(1)	2,218	,903	6,039	1	,014	9,190	1,567	53,907
	SS-A/Ro52_REG(1)	2,624	1,284	4,177	1	,041	13,786	1,114	170,674
	CENP-B(1)	3,317	1,466	5,121	1	,024	27,571	1,559	487,524
	Constante	-3,317	,385	74,312	1	,000	,036		
Paso 4[d]	ETNIA_REG_A(1)	2,351	,916	6,593	1	,010	10,500	1,745	63,196
	B2GP1 IgG_REG(1)	2,064	1,192	2,995	1	,084	7,875	,761	81,522
	SS-A/Ro52_REG(1)	2,757	1,293	4,546	1	,033	15,750	1,249	198,573
	CENP-B(1)	3,450	1,474	5,480	1	,019	31,500	1,753	565,945
	Constante	-3,450	,415	69,217	1	,000	,032		

a. Variables especificadas en el paso 1: CENP-B.

b. Variables especificadas en el paso 2: ETNIA_REG_A.

c. Variables especificadas en el paso 3: SS-A/Ro52_REG.

d. Variables especificadas en el paso 4: B2GP1 IgG_REG.

Supplementary table 15.

Las variables no están en la ecuación

			Puntuación	gl	Sig.
Paso 1	Variables	ETNIA/M(1)	4,645	1	,031
		ETNIA_REG_A(1)	7,561	1	,006
		CANC (1)	5,511	1	,019
		ABOR-<10SEM_REG(1)	,371	1	,543
		IRREG-MENS_REG(1)	3,645	1	,056
		ANTI-HORM(1)	3,268	1	,071
		TABAC/NUN(1)	1,352	1	,245
		CAFÉ/1(1)	1,620	1	,203
		TOMA-CAFÉ(1)	1,347	1	,246
		PESTIC _REG(1)	,151	1	,697
		ALOPE_REG(1)	2,499	1	,114
		Vitamina D-Suf(1)	2,471	1	,116
		Vitamina D-Insu(1)	1,420	1	,233
		B2GP1 IgG_REG(1)	2,642	1	,104
		SS-A/Ro52_REG(1)	5,511	1	,019
	Estadísticos globales		32,169	15	,006
Paso 2	Variables	ETNIA/M(1)	,125	1	,724
		CANC (1)	1,885	1	,170
		ABOR-<10SEM_REG(1)	,490	1	,484
		IRREG-MENS_REG(1)	3,107	1	,078
		ANTI-HORM(1)	1,745	1	,186
		TABAC/NUN(1)	,963	1	,326
		CAFÉ/1(1)	1,433	1	,231
		TOMA-CAFÉ(1)	1,117	1	,291
		PESTIC _REG(1)	,125	1	,724
		ALOPE_REG(1)	1,883	1	,170
		Vitamina D-Suf(1)	3,629	1	,057
		Vitamina D-Insu(1)	,880	1	,348
		B2GP1 IgG_REG(1)	3,492	1	,062
		SS-A/Ro52_REG(1)	6,949	1	,008
	Estadísticos globales		24,679	14	,038

Paso 3	Variables	ETNIA/M(1)	,110	1	,740
		CANC (1)	2,002	1	,157
		ABOR-<10SEM_REG(1)	,762	1	,383
		IRREG-MENS_REG(1)	2,651	1	,103
		ANTI-HORM(1)	1,169	1	,280
		TABAC/NUN(1)	1,171	1	,279
		CAFÉ/1(1)	1,196	1	,274
		TOMA-CAFÉ(1)	,989	1	,320
		PESTIC _REG(1)	,110	1	,740
		ALOPE_REG(1)	2,026	1	,155
		Vitamina D-Suf(1)	3,545	1	,060
		Vitamina D-Insu(1)	,257	1	,612
		B2GP1 IgG_REG(1)	4,134	1	,042
	Estadísticos globales		19,269	13	,115
Paso 4	Variables	ETNIA/M(1)	,097	1	,756
		CANC (1)	2,125	1	,145
		ABOR-<10SEM_REG(1)	,744	1	,389
		IRREG-MENS_REG(1)	2,790	1	,095
		ANTI-HORM(1)	1,700	1	,192
		TABAC/NUN(1)	,968	1	,325
		CAFÉ/1(1)	1,612	1	,204
		TOMA-CAFÉ(1)	,869	1	,351
		PESTIC _REG(1)	,097	1	,756
		ALOPE_REG(1)	2,257	1	,133
		Vitamina D-Suf(1)	3,742	1	,053
		Vitamina D-Insu(1)	,305	1	,581
	Estadísticos globales		15,393	12	,221

Supplementary table 16.

Resumen de procesamiento de casos

anti-TG	N válido (por lista)
Positivo[a]	12
Negativo	280
Perdidos	8

Los valores más grandes de las variables de resultado de prueba indican una prueba mayor para un estado real positivo.

a. El estado real positivo es 1.

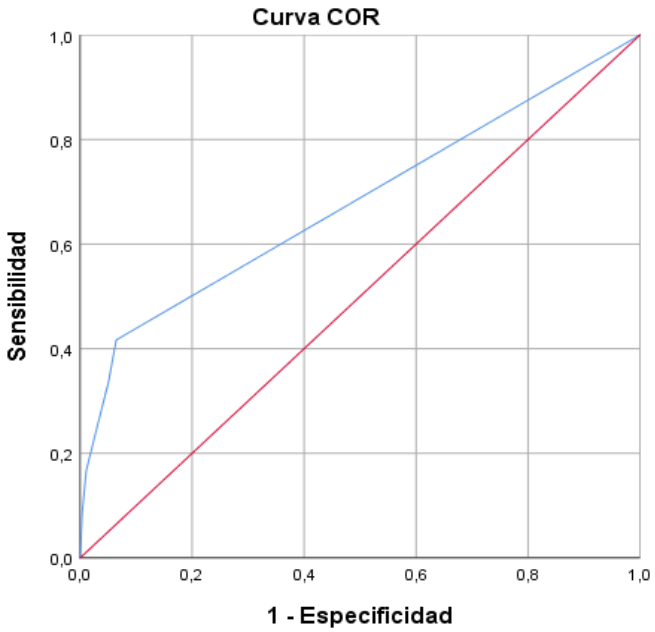
Supplementary figure 2.

Área bajo la curva

Variables de resultado de prueba: Probabilidad pronosticada

Área
,679

Las variables de resultado de prueba: Probabilidad pronosticada tienen, como mínimo, un empate entre el grupo de estado real positivo y el grupo de estado real negativo. Las estadísticas podrían estar sesgadas.



Los segmentos de diagonal se generan mediante empates.