Latent autoimmune thyroid disease

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A B S T R A C T

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

Methods: 300 euthyroid subjects, chosen by stratified sampling from an inception cohort of 1335 individuals, were included. Thyroid function was evaluated by measuring the serum levels of TSH (0.3–4.5 μIU/mL) and FT4 (5.2–12.7 μg/dL). Anti-peroxidase (TPOAbs), anti-thyroglobulin (TgAbs), and anti-TSH receptor (TrAbs) antibodies were evaluated with 23 additional autoantibodies as well as vitamin D (VitD) levels. The analysis included sociodemographic, clinical, and environmental characteristics. Data were analyzed by bivariate and multivariate tests.

Results: Thyroid autoimmunity was observed in 15.3% of the subjects (TPOAbs 11.3% and TgAbs 2.0%). In six individuals, both autoantibodies were positive. TrAbs were not detected in any individual. Familial thyroid disease (β = 3.4, 95% CI: 1.2–9.5, P = 0.021), the presence of other autoimmune diseases (β = 10.8, 95% CI: 1.6–72.9, P = 0.014) VitD insufficiency (P = 0.030), never smoke (β = 6.9, 95% CI: 1.6–30.4, P = 0.010), drinking more than 4 cups of coffee (β = 3.8, 95% CI: 1.1–13.1, P = 0.036), and a higher number of years exposed to wood smoke (P = 0.04) were associated with thyroid autoimmunity. In the case of TPOAbs, familial thyroid disease (β = 4.9, 95% CI: 1.7–14.0, P = 0.003), never smoke (β = 5.7, 95% CI: 1.4–21.0, P = 0.002), and drinking more than 4 cups of coffee (β = 3.6, 95% CI: 1.1–13.1, P = 0.047) were associated with their positivity. In addition, the presence of anti-SS-A/Ro52 (β = 36.7, 95% CI: 2.5–549.9, P = 0.009) and anti-Ku antibodies (β = 10.2, 95% CI: 1.1–100.7, P = 0.046) was also associated with TPOAbs. The presence of African ancestry (β = 10.5, 95% CI: 1.7–63.2, P = 0.01), anti-SS-A/Ro52 (β = 15.8, 95% CI: 1.2–198.6, P = 0.03), and anti-GENP-B antibodies (β = 31.2, 95% CI: 1.8–565.9, P = 0.02) were associated with TgAbs.

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

1. Introduction

Hypothyroidism is an endocrine disease characterized by the presence of elevated serum levels of Thyroid-Stimulating Hormone (TSH) and low levels of free thyroxine (FT4). This disorder is described in up to 10% of the population and its etiology originates mainly from autoimmunity, particularly Hashimoto Thyroiditis (HT) [1]. One of the main clinical challenges relies on the absence of specific symptoms, therefore many individuals are affected for this 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].

Hyperthyroidism, in turn, is the opposite of hypothyroidism. In this case, the levels of TSH secreted by adenohypophysis are suppressed due to the high secretion of FT4 by the thyroid gland [5]. Its prevalence varies between 0.8% in Europe [6], to 1.3% in the United States [7]. Unlike hypothyroidism, the prevalence of asymptomatic patients is low. Therefore, the symptoms are clearly defined at the beginning of the disease. Excess of thyroid hormone produces a wide variety of symptoms such as fatigue, sweating, tremor, anxiety, disturbed sleep, palpitations,
weight loss, and heat intolerance [5]. The main nosology of hyperthyroidism is autoimmunity being Graves’ disease (GD) the most important cause [5].

The prevalence of autoimmune thyroid disease (AITD) is around 5% [8], and the prevalence of thyroid autoantibodies in healthy subjects may be even higher [9]. This data is relevant, since the presence of thyroid autoantibodies could be a predictive tool of thyroid failure in genetically predisposed subjects, and in those individuals exposed to some environmental agents. In view of the high prevalence of AITD, many studies have sought to determine the prevalence of thyroid autoimmunity before the thyroid disease becomes overt by documenting the presence of thyroid autoantibodies in euthyroid individuals [7,10–15]. The reports from these studies ranged from the NHANES III study with a prevalence of 11.3% and 10.4% for anti-peroxidase antibodies (TPOAbs) and anti-thyroglobulin antibodies (TgAbs) respectively, to a prevalence of 13.1% in the Danish population. This is significant considering the importance of the thyroid autoantibodies as predictors of AITD [16,17]. The Whickham study reported a 2.1 risk per year in euthyroid subjects with TPOAbs of developing AITD [16].

Detection of risk factors for hypo- or hyperthyroidism allows the introduction of new approaches for primary prevention strategies. However, the risk factors influencing the appearance of thyroid autoimmunity are not fully understood. Therefore, given the high prevalence of AITD in areas with iodine sufficiency and the risk of comorbidity including polyautoimmunity (PolyA), the identification of thyroid autoimmunity in the general population becomes of high interest [2–4, 18–21]. Several studies have shown female: male ratios between 2:1 to 3:1 [7,11] and an age-associated increase in thyroid autoantibodies [22]. Genetic factors play also a role. A first approach to investigate their presence could be evaluated by analyzing the family history of AITD and other autoimmune diseases (ADs) [21]. Concerning environmental factors (i.e., autoimmune ecology), iodine, infections, vitamin D (vitD) deficiency, stress, drugs, and tobacco have been widely described in AITD [23]. In the current study we aimed to investigate the prevalence of thyroid autoantibodies in euthyroid individuals and the factors associated with latent thyroid autoimmunity in such individuals.

2. Methods

2.1. Population

Three hundred euthyroid Colombian individuals belonging to different socioeconomic strata as well as level of education and occupation participated in this study. The sample size was obtained by randomized stratified sampling of a population of 1335 individuals paired by age and gender using Epidat®, version 4.1. A confidence level of 95%, a power of 80%, and an estimated 11% prevalence of autoantibodies in euthyroid patients was obtained with a minimum sample size of 300 subjects (Fig. 1) [7]. None of the participants was on levothyroxine treatment, were under 18, presented undefined thyroid disease, history of hypothyroidism/hyperthyroidism, previous thyroid disease during pregnancy, had thyroid surgery nor history of thyroid cancer.
2.2. Sociodemographic and clinical factors

Sociodemographic information such as age, gender, ethnicity, socioeconomic stratum, and place of birth was obtained as previously described [20,24]. Additionally, subjects were asked about clinical antecedents such as contraceptive methods, comorbidities, obstetric, surgical, and pharmacological antecedents. Furthermore, habits such as consumption of coffee and tobacco, occupational and home exposures to toxic agents were also recorded [20,24] as were symptoms related to thyroid dysfunction and the presence of hyperthyroidism [1,5]. The clinical evaluation and data collection were done at the CREA between July and November of 2017. The clinical evaluation included the assessment of weight, height, abdominal perimeter, blood pressure, and reflex assessment.

2.3. Laboratory measurements

The thyroid function was evaluated by measuring TSH and FT4 serum levels. In addition, vitamin D levels, TPOAbs, TgAbs, and anti-TSH receptor antibodies (TRAbs) were detected as markers for thyroid autoimmunity. Furthermore, a panel of 23 autoantibodies were evaluated. TSH, FT4, and vitamin D levels were measured by electroquimiluminescence using the following thresholds: TSH (0.3–4.5 μIU/mL), FT4 (5.2–12.7 μU/dL), and vitamin D, a level above 30 ng/mL was considered to be sufficient; below 30 ng/mL, insufficiency; and below 20 ng/mL, deficiency [25].

TPOAbs, TgAbs, rheumatoid factor (RF) IgM, the anti-citrullinated protein antibodies (ACPA) IgG, the anti-cardiolipin antibodies (ACA) IgG, the anti-beta 2-glycoprotein (β2GP1) antibodies IgM and IgG were measured using indirect ELISA (Inova Diagnostics, Inc. San Diego, CA, USA), while TRAbs were measured with competitive ELISA (Eagle Biosciences, Nashua, NH, USA). The remaining 17 autoantibodies were evaluated by immunoblot assay (double-stranded DNA (dsDNA), nucleosomes, histones, SmD1, proliferating cell nuclear antigen (PCNA), P0, Anti-Sjögren’s syndrome type A (SS-A/Ro60), SS-A/Ro52, Anti-Sjögren’s syndrome type B (SS-B/La), centromere autoantigen B (CENP-B), Sc170, U1-snRNP, Anti-mitochondrial M2 antibody (AMA M2), Jo-1, PM-Scl, Mi-2, Ku) using IMTEC ANA-LIA Maxx from Human diagnostics, Magdelburg Germany. Latent autoimmunity was defined as presence of autoantibodies without fulfillment of international classification criteria [26].

2.4. Statistical analysis

Categorical variables were analyzed by frequencies, and quantitative continuous variables were expressed as mean and standard deviations (SD) and in the median and interquartile ranges (IQR) [27]. To assess associations between outcomes of interest and other variables, the χ2, Kruskal-Wallis and Mann–Whitney U test were used. Binary Logistic regression analysis was done. Shortly, TPOAbs and TgAbs were included as dependent variables, while those variables with biological plausibility were selected as independent variables. Obtained models were tested for goodness of fit by Hosmer–Lemeshow test, and their discrimination capacity were considered relevant if c-statistic was higher than 0.7. The significance level of the study was set to 0.05. Statistical analyses were done in SPSS statistics version 2.4.

3. Results

The sociodemographic, clinical, and thyroid variables are shown in Tables 1 and 2. The group of subjects mainly consists of women and young people. Thyroid autoimmunity was observed in 15.3% of the cases, TPOAbs in 11.3%, and TgAbs in 2%. Both autoantibodies were described in six individuals. TRAbs were not detected in any individual. Table 3 shows habits and environmental factors. Unlike tobacco consumption, which was low, coffee consumption was very important in this population. Organic solvents were the main toxin they have been exposed throughout life, followed by using of hair dyes and exposure to wood smoke. With respect to exposure at work or home, the main working or housing areas in which these individuals were exposed to toxins were farms followed by airports and laundries. Immunological data are described in Table 4. RF, ACA IgM, and β2GP1 IgM were the most prevalent autoantibodies in these subjects. In addition, an interesting percentage of familial autoimmunity and the presence of other ADs was found.
Table 3
Environmental characteristics.

| Characteristics                  | n – 300 (%) |
|----------------------------------|-------------|
| **Habits**                       |             |
| Never smoke                      | 232 (77.3)  |
| Former smoker                    | 44 (14.7)   |
| Active smoker                    | 24 (8.0)    |
| 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) |
| Less than 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             | 19/296 (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 (9.0)    |
| Factories                        | 13 (4.3)    |
| Garbage deposits                 | 10 (3.3)    |

Table 4
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)    |
| j2GP1 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)     |
| j2GP1 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)     |
| Nucleosomes                      | 1 (0.3)     |

RF: Rheumatoid factor, ACA: Anti-cardiolipin antibodies, j2GP1: Beta 2-glycoprotein 1 antibodies, SS-B/La: Anti-Sjögren’s syndrome type B antibodies, SS-A/Ro: Anti-Sjögren’s syndrome type A antibodies, ACPA: Anti-citrullinated protein antibodies, dsDNA: Anti-double stranded DNA antibodies, PCNA: Anti-proliferating cell nuclear antigen antibodies, Sm: Anti-Smith antibodies, RNP: Anti-ribonucleoprotein antibodies, CENP-B: Anti-centromere antibody subunit B.

The bivariate analysis showed an association between thyroid autoantibodies and familial thyroid disease (OR: 2.2, 95% CI: 1.1–5.0, P = 0.04), and low libido (OR: 2.3 95% CI: 1.1–5.2, P = 0.04). Furthermore, regarding environmental and biological factors, never smoke (OR: 2.7 95% CI: 1.1–7.1, P = 0.04), vitD insufficiency (P = 0.03), and a greater number of years of exposure to wood smoke (P = 0.04) were associated with the presence of thyroid autoimmunity.

In a further analysis, TPOAbs and TgAbs were studied separately. Familial thyroid disease (OR: 2.8 95% CI: 1.2–6.2, P = 0.01), never smoke (OR: 2.9 95% CI: 1.1–8.6, P = 0.04), and low libido (OR: 2.9 95% CI: 1.3–6.5, P = 0.009) were associated with anti-TPO positivity. Moreover, an association between TSH levels and TPOAbs was observed (Fig. 2). An association of TgAbs with the presence of menstrual irregularity (OR: 0.3 95% CI: 0.08–0.9, P = 0.022) and SS-A/Ro52 (OR: 13 95% CI: 1.1–154, P = 0.009) was observed. No association between TSH levels and TgAbs was seen despite a suggestive trend (Fig. 3).

The multivariate analysis included a logistic regression with the presence of thyroid autoantibodies as dependent variable. In this analysis, the history of familial thyroid disease, the presence of other ADs, never smoke, drinking more than 4 cups of coffee per day, and low libido were significantly associated with the presence of thyroid autoimmunity (Table 5).

Multivariate analysis using TPOAbs as the dependent variable shows that the presence of familial thyroid disease, never smoke, drinking more than 4 cups of coffee per day, and low libido were associated with anti-TPO positivity. In addition, the presence of anti–SS-A/Ro52 and anti–Ku antibodies was associated with the presence of TPOAbs (Table 6). The multivariate analysis using the TgAbs as a dependent variable showed that African ethnicity, anti–SS-A/Ro52, and anti-CENP-B antibodies were associated with TgAbs positivity (Table 7).

4. Discussion

Environmental factors (i.e., autoimmune ecology) that impair the immune response and give rise to the recognition of thyroid self-antigens in susceptible individuals is pivotal to the development of AITD. This causes an autoimmune response which eventually culminates in overt disease. All these steps are immersed in the natural history of the disease as it goes through a series of states from the pre-pathogenic phase, which

Fig. 2. There was a significant association between TSH levels and TPOAbs levels. An increase in TSH levels in same proportion to TPOAbs levels was observed.

Fig. 3. Although there was not statistically significant association between the TSH levels and levels of TgAbs, a trend in the influences of these autoantibodies on TSH levels was observed.
is asymptomatic, to the pathogenic period, characterized by the presence of symptoms [28]. Considering the current evidence, this study sought to confirm the role of some factors which had previously been studied in relation to the presence of thyroid autoantibodies as well as to find new ones that might contribute to the understanding of latent AITD.

The evaluation of these autoantibodies is relevant because they represent the highest risk of developing AITD [7,16]. An annual risk of 2.1% per year of developing hypothyroidism in the presence of thyroid autoantibodies has been documented [7]. Spite of diverse heritability, factors associated with thyroid autoantibodies has been documented [7]. Although African ethnicity was only observed in 4.5%, it can act as a risk factor for developing thyroid autoimmunity, particularly, TgAbs. These results are different from other studies, where some components of tobacco such as the alkaloids – nicotine and anatabine – exhibit an immunomodulatory effect. Nicotine is widely known for its anti-inflammatory effects [38]. This mechanism is mediated by the link between nicotine and its receptor. The link is expressed not only centrally and peripherally in pre-ganglionic fibers and neuromuscular synapses, but also in immune cells such as macrophages, dendritic cells, and CD4+ T-cells. The expression of the nicotinic receptor in these immune cells has been studied as a therapeutic target in order to enhance its anti-inflammatory effect [39].

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. However, it is not associated with the toxicity and addiction rates shown with nicotine. Also, it has a longer plasma half-life [40,41]. The first studies of anatabine were done on murine models and showed that the mice exposed to this alkaloid had a lower incidence and severity of thyroiditis (RR 0.59, 95% CI 0.36–0.95) [42]. This study showed a reduction in the immune response mediated by thyroid autoantibodies (i.e., TgAbs) and a control of the macrophage production of inducible nitric oxide synthase and cyclooxygenase 2 [42]. The previous results were confirmed in clinical trial in which anatabine decreased thyroid autoimmunity [43].

In addition, the presence of cyanide in cigarette smoke and metabolized to thiocyanate could be associated with a mild immunomodulatory response given the interference of thiocyanate in the transportation and uptake of iodine [37,44]. Therefore, the preparation of screening strategies for the population is necessary in order to evaluate the presence of thyroid autoantibodies in patients at risk of developing AITD, and who have recently abandoned tobacco.

The relationship between vitD levels and autoimmunity is widely known since low levels are associated with the risk of developing ADs, and once the AD is overt, the low levels of vitD have been associated with disease activity [45]. The results of our study confirm the association between low levels of VitD and thyroid autoimmunity [46,47].

### Table 5
Factors associated 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 |

### Table 6
Factors associated 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 |

### Table 7
Factors associated with TgAbs.

| Characteristic                  | β     | 95% CI   | P     |
|-------------------------------|-------|----------|-------|
| African ancestry              | 10.500| 1.745    | 63.196| 0.010 |
| β2GPI 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 |

### Table 8
Prevalence of thyroid autoantibodies.

| Publication date | Geographic location  | Number of cases | Female prevalence n (%) | Male prevalence n (%) | Ref |
|------------------|----------------------|-----------------|-------------------------|----------------------|-----|
| 1990             | United Kingdom       | 698             | –                       | 124 (17.8)           | –   |
| 1993             | Japan                | 1134            | 2896                    | 133 (11.7)           | 167 (5.7) | [13] |
| 1995             | United Kingdom       | 942             | 762                     | 248 (26.4)           | 67 (8.8) | [11] |
| 2000             | Norway               | 582             | 369                     | 81 (13.9)           | 10 (2.8) | [14] |
| 2002             | United States        | 8619            | 7914                    | 1258 (13.6)          | 633 (8.0) | [7] |
| 2003             | Germany              | 455             | 840                     | 117 (25.8)           | 120 (14.4) | [10] |
| 2010             | Netherlands          | 1216            | 1178                    | 144 (11.9)           | 56 (4.8) | [30] |
the prevalence of individuals with vitamin D insufficiency should be considered a public health problem and not exclusively a matter of ADs [48]. Despite the extensive study of environmental factors associated withAITD, the effect of coffee has been poorly studied. The results of this study showed an association between the presence of thyroid autoimmunity and coffee consumption, especially for those consuming more than 4 cups per day. With respect to these results, it could be presumed that the consumption of this amount of coffee may encourage the release of thyroglobulin as previously described [49] thus triggering an autoimmune response against this antigen. However, this is controversial since in other reports the effect of caffeine was protective [50]. This study documented a strong association between the presence of familial autoimmune disease and PolyA and the presence of thyroid autoantibodies. These are validated by different studies that have reported a heritability between 0.54 and 0.66 for the presence of thyroid autoantibodies [51].

5. Conclusions
The prevalence and associated factors of latent thyroid autoimmunity were determined in a sample of Colombian population. The results from the present study will facilitate the implementation of screening strategies in order to provide timely diagnosis and treatment. For now, there is still a lack of genetic studies that proffer in the genetic cause of AITD. The study of exposures evaluated in this study was carried out through a questionnaire. In that sense, it is necessary to study this type of exposition through the analysis of exposures.

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Conflict of interest
None.

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