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CARDIOVASCULAR RISK IN HASHIMOTO THYROIDITIS PATIENTS ACCORDING TO THEIR THYROID STATE: A CROSS-SECTIONAL STUDY

Riesgo cardiovasvular en pacientes con Tiroiditis de Hashimoto en dependencia de su estado tiroideo: un estudio transversal

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Abstract

Aims: To investigate the association between cardiovascular risk factors and cardiovascular risk score with the thyroid status of patients with Hashimoto's Thyroiditis.

Methods: Thirty-eight consenting adults with Hashimoto's Thyroiditis participated in this cross-sectional study. The cardiovascular risk factors considered included age, sex, blood pressure, body mass index, fast blood glucose, lipid profile, cardiovascular comorbidities, C reactive protein, and erythrocyte sedimentation rate. The Framingham CV risk score was performed. The sample was classified into euthyroid (n = 15), clinical hypothyroidism (n = 9), and subclinical hypothyroidism (n = 13), and included the presence of antithyroid antibodies. Fisher's exact test was used to determine the association between the variables studied.

Results: 100% of the sample were women; a mean age between 39-59 years old. The category with low risk was the largest (n = 30), equivalent to 78.9%; moderate risk, no patient was obtained; high risk (n = 8) constituted 21.1%. Statistical significance between age and CV risk

Resumen

Objetivo: investigar la asociación entre los factores de riesgo cardiovascular y el nivel de riesgo cardiovascular con el estado tiroideo de pacientes con Tiroiditis de Hashimoto.

Métodos y técnicas: treinta y ocho adultos con tiroiditis de Hashimoto participaron en este estudio descriptivo transversal. Los factores de riesgo cardiovascular considerados incluyeron edad, sexo, presión arterial, índice de masa corporal, glucemia, perfil lipídico, comorbilidades cardiovasculares, Proteína C Reactiva y Eritrosedimentación. Se utilizó la calculadora de riesgo cardiovascular de Framingham. La muestra se clasificó según el estado tiroideo en eutiroidismo (n = 15), hipotiroidismo clínico (n = 9) e hipotiroidismo subclínico (n = 13) e incluyó la presencia de anticuerpos antitiroideos. Se utilizó la prueba exacta de Fisher para determinar la asociación entre las variables estudiadas.

Resultados: el 100 % de la muestra fue de sexo femenino; con una edad media entre 39-59 años. La categoría con bajo riesgo fue la mayor muestra (n = 30), equivalente al 78,9 %; riesgo moderado, no se obtuvo ningún paciente; alto riesgo (n = 8) constituyó el 21,1 %. Se encontró significancia estadística entre la edad y el nivel de riesgo cardiovascular en pacientes con hipotiroidismo clínico (p < 1),

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score in patients with clinical hypothyroidism was found (p < 1), 95% CI. The glucose level in the subclinical hypothyroidism and clinical hypothyroidism had statistical significance. The presence of anti-Thyroglobulin (antiTg) was shown to be closely related to the level of CV risk in patients with subclinical hypothyroidism.

Conclusion: Age, glycemia, anti-Tg, history of DM, dyslipidemia, or cerebrovascular accidents have been linked to raising the risk of developing CVD in up to 10 years depending on their thyroid profile. No evidence of a direct relationship between CV risk score and thyroid state was found in the participants of this study.

Keywords: autoimmune thyroiditis; Hashimoto's disease; cardiovascular diseases; risk factor's.

IC 95 %. El nivel de glucosa en el hipotiroidismo subclínico y el hipotiroidismo clínico tuvo significancia estadística. Del mismo modo, se demostró que la presencia de antitiroglobulina (antiTg) está estrechamente relacionada con el nivel de riesgo cardiovascular en pacientes con hipotiroidismo subclínico.

Conclusión: la edad, la glucemia, los anti-Tg, el antecedente de diabetes mellitus, la dislipemia y haber padecido algún accidente cerebrovascular se ha relacionado con un aumento del riesgo de desarrollar un evento cardiovascular hasta en 10 años en función de su perfil tiroideo. No se encontró evidencia de una relación directa entre la puntuación de riesgo cardiovascular y el estado de la tiroides en los participantes de este estudio.

Palabras clave: tiroiditis autoinmune; enfermedad de Hashimoto; enfermedades cardiovasculares; factores de riesgo.

Introduction

Autoimmune Thyroiditis is defined as a disorder that affects the thyroid gland which results in an inflammatory process. Hashimoto's Thyroiditis (HT) is an autoimmune disease that is categorized as a type of systemic inflammatory affection.[1, 2] The incidence of this disease has increased as a result of lifestyle changes, bringing about serious health issues to the individuals that suffer from it. One of the most prominent issues is an increase in CV risk factors, promoting the appearance of diseases of this nature.

Cardiovascular Diseases (CVD) are one of the main causes of morbidity and mortality worldwide; according to WHO, in 10 years, CVD could be the cause of around 24 million deaths annually.[3] Over the last decades, the origin of plaques of atheromas on arteries has been identified as a consequence of pro-inflammatory disease cytokines. Although the pathophysiology of the formation of these lesions are not fully explained, there is increasing evidence especially on other autoimmune diseases like lupus erythematosus, rheumatoid arthritis, or antiphospholipid syndrome approving its existence.[4-6]

The hypothyroid state of Hashimoto's thyroiditis has been observed to increase the risk of atherosclerosis and other cardiovascular diseases.[7, 8] Other studies have reported an increased risk of approximately 20% for coronary heart disease on the subclinical hypothyroid state.[9] HT being an underdiagnosed disease, represent a fundamental element in the development of CV diseases; not only due to the low levels of thyroid hormones, which play a fundamental role in cardiovascular physiology but also because of circulating autoimmune antibodies and activation of the immune system, resulting in prolonged systemic inflammation.[10]

Most studies have focused on hypothyroidism or subclinical hypothyroidism in patients with no HT, associating it to be the presumed cause of diverse cardiovascular diseases. Few studies have specifically examined the cardiovascular risk score associated with patients with an autoimmune thyroid disease, which can potentially precipitate cardiovascular disease because of the progressive inflammation in addition to the thyroid state. For this reason, this study aims to determine the cardiovascular risk score in patients with Hashimoto's Thyroiditis according to their thyroid status.

Methods

This cross-sectional study recruited patients diagnosed with Hashimoto's Disease under routine care of the endocrinology outpatient at the health centers: Clínica Unión Médica del Norte and Hospital Metropolitano de Santiago (HOMS) in Santiago de los Caballeros, Dominican Republic from December 2019 to February 2020. The inclusion criteria for the study sample were: 1) 18-65 years of age; 2) assist endocrinology department of the before mentioned clinics; 3) newly diagnosed with HT; 4) if long term diagnosed, patient must be enlisted in the hospital database with the medical history on the first consultation; 5) necessary lab tests of *lipid profile, thyroid state, glycemia, C-Reactive Protein*, erythrocyte sedimentation rate, *thyroperoxidase antibodies (anti-tpo) and anti-thyroglobulin antibodies (anti-tg)* must be present in patient history plus the body mass index (BMI) and the Blood Pressure (BP). The exclusion criteria included: 1) a known history of cardiovascular disease before being diagnosed with HT; 2) diagnosis of another autoimmune disease. These were established to be able to diminish the confounding bias in this study. All subjects voluntarily participated in the research work obtaining written consent from each patient.

Patients were qualified to particular groups on the basis of the result of their last thyroid hormone state according to the parameter proposed by the American Thyroid Association (ATA). The diagnosis of Hashimoto's thyroiditis was stated on an elevated concentration of thyroid antibodies (aTPO and/or aTG) titer, and typical ultrasound. All included into the study were divided into three groups, according to their TSH levels: (I) those with euthyroidism [TSH (0.4 mU/L to 4.0 mU/L)] (II) those with subclinical hypothyroidism [TSH (4.0mU/L at 10.0mU/L)] (III) those with clinical hypothyroidism [TSH (+ 10.00mU/L)]. After all data collection, the tabulation and processing of these were carried out. Each patient was assigned an identification code with the intention of ensuring their confidentiality and preventing personal information from being leaked. All the information was organized in a database using Microsoft excel.

The study was approved by the Bioethics Committee of the Faculty of Health of the Pontificia Universidad Católica Madre y Maestra, Santiago campus, Dominican Republic, following the established rules of the Belmont Report, the Nuremberg Code, and the Declaration of Helsinki in order to ensure ethical compliance during each interaction with the participants.

Variables

The Body Mass Index (BMI), levels and variations of thyroid function (TSH, FT4, FT3), metabolic parameters including total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL), triglycerides, and fasting blood glucose were analyzed, in addition with inflammation data including anti-Tg, anti-TPO, C-Reactive Protein, and the Erythrocyte Sedimentation Rate. Also, the comorbidities of the patients that were considered: Diabetes Mellitus type 2 (DM2), dyslipidemia, cerebrovascular infarction (CVA), and hypertension. These were taken in labs of preference of the patient, and if the numerical value was not given in the necessary measure it was converted. Blood pressure was taken in the office by the medical doctor in charge with a sphygmomanometer either manual or digital. The diastolic and systolic blood pressures were measured with a mercury sphygmomanometer while the participant was sitting in a silent environment. In addition, the BMI was calculated by dividing weight in kilograms by height in meters squared. These parameters were taken by the doctors in the first appointment. Framingham's risk score was calculated utilizing the app Qx calculate.

Statistical Methods

Qualitative variables were presented as percentages or proportions. The analysis was focused on the distribution of the groups according to their thyroid status; euthyroid, clinical hypothyroid, and subclinical hypothyroid. Also, the level of cardiovascular risk was categorized into three groups: low risk, moderate risk, and high risk, applying the Framingham cardiovascular risk score. The sociodemographic variables were

analyzed using frequencies and percentages, maintaining a univariate analysis. The interpretation of the BMI, metabolic parameters, inflammation data and the comorbidities were determined following a bivariate analysis, depending on the thyroid state and the cardiovascular risk score. These variables were analyzed using the Fisher's exact test with a 95% confidence interval (CI). P values of <0.05 were considered statistically significant. The analysis was performed using the SPSS statistical data analysis program (SPSS Statistics version 17.0.0).

Results

This cross-sectional study consisted of 38 subjects diagnosed with Hashimoto's thyroiditis. The 100% of the sample were women, with a mean age of 39-59 years (65.8%). Table 1 shows the demographic data. There was no statistical significance between cardiovascular risk and thyroid state. Fifteen individuals (39.5%) were categorized as euthyroid [TSH (0.4 mU/L to 4.0 mU/L)] where 33.3% of these had a high cardiovascular risk score based on the Framingham risk score. The second group, with a subclinical hypothyroid state [TSH (4.0mU/L to 10.0mU/L)], consisted of ten individuals (26.3%) where 15.4% had high cardiovascular risk scores. The third group, based on the hypothyroid patients [TSH (+10.00mU/L)] had thirteen subjects (34.2%) and 10% had a high cardiovascular risk score. Table 2 shows the bivariate analysis of the thyroid state and the cardiovascular risk.

Approximately half of the studied group (47.4%) consisted of overweight or obese individuals. There was no statistical significance between age and BMI within thyroid groups, except in the clinical hypothyroid group which showed statistical significance. Total cholesterol, triglycerides, LDH-C, and LDL-D were not significant in the studied groups. Glucose levels had statistical significance with all groups except the ones with euthyroidism, where most individuals had normal glucose levels. Table 3 shows the bivariate analysis between the BMI and the metabolic parameters depending on the thyroid state and the cardiovascular risk.

CRP and Erythrocyte sedimentation rate (ESR) did not have statistical significance for any group. The euthyroid and subclinical hypothyroid groups with elevated levels of CRP had a greater cardiovascular risk score, 20% and 33%, respectively. Similarly, 40% of patients with elevated ESR also had high cardiovascular risk. On the other hand, the relationship between anti-TPO could not be valued. Anti- Tg had significant values for the subclinical group. Table 4 shows the analysis between the inflammation data depending on the thyroid state and the cardiovascular risk.

Lastly, 100% of patients who suffered from DM2 had high cardiovascular risk scored with statistical significance p values in euthyroid and subclinical hypothyroid groups, ($p = 0.001$) and ($p = 0.015$), respectively. History of dyslipidemia in patients of the clinical hypothyroidism group had clinical statistical significance in this study ($p = 0.032$).

Discussion

The results of this study back up the hypothesis that there are existing cardiovascular parameters that can be associated with a high cardiovascular risk on the Framingham risk score in patients with systemic inflammatory diseases. On that note, it must be taken into consideration that the presence of high levels of inflammatory variables promote an accelerated development of cardiovascular diseases, specifically in the formation of atherosclerosis. The ongoing inflammatory activity of Hashimoto's thyroiditis can precipitate endothelial damage.[11, 12] Our study sample had a mean age between 39-59 years, out of which women make up 100%. In regard to the metabolic panel, 47.4% of the participants had a BMI between 18.5-24.9kg/m^2 that represents the "optimal weight" group, most having optimal metabolic profiles and little to no alterations in their inflammatory profiles; 31.6% we found to possess elevated levels of CRP

and 36.8% had high levels of ESR. Both anti-TPO and anti-Tg were present in 100% and 92.1%, respectively, taking into consideration that such markers are diagnostic for HT.[13] Regarding the total group, we found that 13.2% had DM, 10.5% suffered from dyslipidemia, 5.3% had hypertension and 2.6% had been affected by a CVA, the rest had no known comorbidities. The Framingham cardiovascular risk score was used on all the participants, 78.9% obtained a low-risk score, while 21.1% obtained a high-risk score. After dividing the participants according to their thyroid state, it could be observed that there was a greater percentage of high-risk patients in the euthyroid group.

As mentioned before, the entirety of the sample were women, this possibly being due to the fact that women are usually the ones who assist to endocrinologic consults since women are the gender with the highest risk to suffer from HT.[14] Similar results were seen in a study that included 1,165 participants, 90.8% of which were women, and found that there was a statistical relationship between cardiovascular risk and HT.[15] Age is another important parameter taken into consideration in this study for cardiovascular risk which has statistical significance (p-value <0.05) in the subclinical hypothyroidism group. Many studies corroborate our findings, one where it was concluded that older age groups between 60-80 years had a higher risk.[16-18] These results suggest that there could be a direct relationship between these 2 variables.

Among the anthropometric variables, no statistical significance was obtained between BMI and thyroid status. This was also seen in a cohort study who searched for the relationship between sub-clinical hypothyroidism and cardiovascular risk where they did not find a relationship between these variables in their study, given the circumstance that a normal BMI does not measure abdominal fat, this being a compartment that is closely associated with cardiometabolic abnormalities.[19-21]

Furthermore, Total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) showed no significant difference between the three groups. These results differ from those found by Atta[22] where the cholesterol profile showed statistically significant higher levels in hypothyroid subjects. The discrepancy between the results could be due to the fact that the patients were receiving treatment for their disease and thyroid levels controlled. Regarding DM2, a significant association with cardiovascular risk in the euthyroid and subclinical hypothyroid group was found in our study ($p < 0.05$). This was also seen in a study conducted by Kantanaka[23] who used the participants' risk score and found statistical significance between these two variables when compared with thyroid state.

Our results demonstrated that in the group of individuals with subclinical hypothyroidism and clinical hypothyroidism, blood glucose had a statistically significant relationship with the cardiovascular risk, p-value < 0.05 for both groups. We also found a negative association between levels of glucose in the blood and the euthyroid individuals with their cardiovascular risk. This is in accordance with several previous studies.[24, 25]

C-reactive protein (CRP), a low-grade inflammation marker, has been considered as a cardiovascular risk factor and associated with atherosclerosis. Fonseca et al. observed that high levels of CRP affect the cardiovascular system, acting as an effective cardiovascular risk marker.[26] According to the inflammatory profile in these samples, we did not find a statistical significance between CRP and the cardiovascular risk level depending on the thyroid state. But it was observed that the individuals with subclinical euthyroid and hypothyroid groups that had high levels of CRP obtained a high risk on the Framingham scale. Our results are in accordance with Christ-Crain et al. They found that CRP levels increase with the progression of thyroid dysfunction even though there was no significant relationship between thyroid hormones and CRP levels.[27] However, it is noted that CRP is not included as a variable in the Framingham cardiovascular risk

score calculator, although its presence shows to be a relevant factor in terms of cardiovascular risk according to the literature.[28]

The presence of anti-TPO antibodies is an important marker used for the diagnosis of HT, which is why it was present in our entire sample (100%), causing the p-value to be non-evaluable, however, 33.3% of the euthyroid subjects, 15.4% of the subclinical hypothyroid individuals and 10% of the clinical hypothyroid group had high cardiovascular risk. Liu et al.[29] observed that high levels of anti-TPO directly increased PCR; therefore, it had the potential to be used as a marker of chronic inflammation, resulting in pathologies such as atherosclerosis.[30] The erythrocyte sedimentation rate (ESR) was found to be elevated in 36.8% of the sample. The group of patients with subclinical hypothyroidism had the most individuals with high levels of ESR, though no significant relationship was found between cardiovascular risk depending on thyroid status and this variable. Like PCR, it is not included in the Framingham cardiovascular risk score calculator. There are studies that portray ESR as a factor used to predict cardiovascular risk. Gupta et al., in order to determine the role of inflammatory markers in people with autoimmune thyroid disease, found that inflammatory markers like ESR were increased in patients with subclinical hypothyroidism compared to a control group.[31] Therefore, these were considered factors that, if not controlled, could increase cardiovascular risk.

This study had some limitations that can be worked on by future researchers. First, there was a high rejection rate of participation in the study by the health care professionals, which acts as a factor that makes data collection difficult. Second, the small number of patients diagnosed with Hashimoto thyroiditis attending the consultations, and the inclusion and exclusion criteria used, further limited the number of participants. Finally, the length of data collection greatly affected the results. It was observed that the group with the highest cardiovascular risk score was the euthyroid group, this being, for the most part, due to the variables that are included in the Framingham risk score, where patients with comorbidities such as diabetes mellitus and dyslipidemia or cerebrovascular accident history had a dramatic increase in risk. Therefore, we hereby recommend a prospective study where the T-test analysis is used to measure if there's a significant difference between groups.

Conclusion

This study corroborates that age, blood glucose level, the presence of anti-Tg, and having a history of Diabetes Mellitus type 2, dyslipidemia, or cerebrovascular infarction are factors associated with the development of cardiovascular diseases in 10 years depending on their thyroid profile. This investigation can help or encourage other research groups to further disseminate the topic of autoimmune diseases, specifically Hashimoto's thyroiditis, in relation to cardiovascular diseases, in order to obtain more information for their prevention treatment. This study provides useful and new information on Hashimoto's thyroiditis and cardiovascular diseases, hopefully motivating future investigations on this topic and the elaboration of health guidelines for the prevention of CV diseases in patients with HT.

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Author contribution

GK, RE, CY contributed to the conception of the work. GK, RE, CY performed the statistical analysis and interpretation of the data. GK, RE, CY wrote the manuscript and contributed to the design of the clinical study. All authors critically revised the first draft and the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting interest

The authors declare that there is no conflict of interest.

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