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Original Article

High free triiodothyronine and free-triiodothyronine-to-free-thyroxine ratio levels are associated with metabolic syndrome in a euthyroid population

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ABSTRACT

Aims: To determine the association between free triiodothyronine (FT3), free thyroxine (FT4) and free-triiodothyronine-to-free-thyroxine ratio (FT3/FT4) levels and Metabolic Syndrome (MetS).
Materials and methods: We carried out an analytical cross-sectional study in euthyroid adults of both sexes, who attended the outpatient service of a private clinic in Lima-Peru during the 2014–2016 period. Participants were divided into tertiles (low, intermediate and high) according to their FT3, FT4, and FT3/FT4 ratio values. MetS was defined when three or more metabolic criteria were met by the participants. ROC curves were constructed, and Youden's Index were used to identify the optimal cut-points of each thyroid marker. We elaborated crude/adjusted Poisson regression models to evaluate the association between the thyroid markers and the presence of MetS. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95% CI).
Results: We analyzed 245 participants, the average age was 38.5 ± 10.3 years, 29.8% were males, and the prevalence of MetS was 31%. In the adjusted Poisson regression models, the prevalence of MetS was higher among the high FT3 tertile compared to the low tertile (aPR = 2.01; 95% CI: 1.22–3.34). The prevalence of MetS was higher among the intermediate FT3/FT4 ratio tertile and the high FT3/FT4 ratio tertile compared to the low tertile, (aPR = 1.78; 95% CI: 1.02–3.10) and (aPR = 2.80; 95% CI: 1.67–4.72); respectively. The highest areas under the curve (AUC) were found for FT3 and FT3/FT4 ratio with areas of 0.654 (95% CI: 0.58–0.73) and 0.649 (95% CI: 0.57–0.72); respectively.
Conclusion: Elevated levels of FT3 and FT3/FT4 ratio were associated with MetS in a euthyroid population.
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1. Introduction

Metabolic syndrome (MetS) has become one of the greatest public health challenges in the world [1]. MetS is considered to be the pathology with the fastest growing incidence [2], in addition to being important due to the risk of Morbidity and cardiovascular mortality [3,4]. The prevalence of MetS is increasing worldwide; it is estimated that 20–25% of the world's adult population suffers from this disease [5]; this rise could be due to several factors such as the aging of the population, increase in life expectancy, sedentary lifestyle and inadequate nutrition [6]. Studies performed in Latin American populations showed a high prevalence of MetS, ranging from 12.3% to 42.7%, depending on the clinical diagnosis criteria used and the characteristics of the populations studied [7].

A set of related physiological, biochemical, clinical and metabolic factors define the MetS [8,9]. Other authors consider

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it as the set of visceral obesity, dyslipidemia, hyperglycemia and high blood pressure [1]. These factors will increase the risk of acquiring pathologies such as type 2 diabetes mellitus (T2DM), cardiovascular diseases, among others; thus increasing the risk of mortality of the patient [10]. Visceral obesity is considered the most common and most important manifestation for the diagnosis of MetS; this marker would lead to insulin resistance (IR), high blood pressure and dyslipidemias; being all risk factors for developing MetS [11].

Recently multiple cross-sectional studies have reported that elevated thyroid hormone levels are associated with MetS, even in euthyroid individuals [12–24]. Serum levels of thyroid stimulating hormone (TSH) within the reference ranges have been reported to be positively associated with MetS components [18–23]. Also, low levels of free thyroxine (FT4) are related to MetS parameters [12–17]; whereas high levels of free triiodothyronine (FT3) and free-triiodothyronine-to-free-thyroxine (FT3/FT4) ratio are associated with MetS components [14,17,24]. Besides, the therapeutic role in the management of MetS and related disorders that these hormones could have had been described [25]. However, not many studies have evaluated the association of thyroid parameters (FT3, FT4 and FT3/FT4 ratio) and MetS in euthyroid Latin American populations. Therefore, the objective of this study was to determine the association between thyroid hormone levels (FT3, FT4 and FT3/FT4 ratio) and the presence of MetS in a Hispanic euthyroid population.

2. Methods

2.1. Study design and population

An analytical cross-sectional study carried out in euthyroid adults of both sexes who attended the outpatient service of a private clinic in Lima-Peru.

2.2. Sample type and analysis unit

A non-probabilistic sampling was performed; the sample consisted of all patients who participated in the outpatient service of the private clinic between January 2014 and December 2016 and met the eligibility criteria of the study. The statistical power calculated for the associations among FT3 and FT3/FT4 ratio tertiles was 99%.

2.3. Procedures

We reviewed the medical records of the patients treated during the study period and collected all the data of interest. The laboratory values were only collected if the patient laboratory tests were performed with a maximum of 30 days after they were attended in the outpatient service of the private clinic. All participants had a minimum fasting period of eight hours for laboratory tests, according to the protocols established by the individual medical center.

2.4. Eligibility criteria

Participants included were aged ≥18 with no medical background of hypothyroidism, subclinical hypothyroidism or hyperthyroidism.

We excluded participants aged ≥60, with thyroid hormones values outside the following ranges: FT3: 2.3–4.2 pg/mL, FT4: 0.89–1.76 ng/dL, TSH: 0.40–5.0 μU/mL [26]; and pregnant women.

2.5. Variables definition

2.5.1. Exposures

Participants who met the eligibility criteria were categorized in tertiles according to their FT3, FT4 or FT3/FT4 ratio values respectively.

2.5.2. Outcomes: metabolic syndrome

We assessed the prevalence of MetS according to the International Diabetes Federation (IDF), the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria [9], the American College of Endocrinology position statement [27] and a previous study [26]. MetS was defined when three or more of the following criteria were met: [1] Body mass index (BMI) ≥25 kg/m^2 [2] fasting glucose levels ≥100 mg/dL or participants were on antidiabetic treatment; [3] triglycerides levels ≥150 mg/dL; [4] high-density lipoprotein (HDL) cholesterol levels <40 mg/dL in men and <50 mg/dL in women and [5] blood pressure (BP) ≥130/85 mmHg or participants were on antihypertensive treatment.

2.5.3. Other variables

The following variables were also included in the analysis: age (years), sex, waist-to-hip ratio, HbA1c percentage, body fat percentage, fasting insulin, postprandial blood glucose, Homeostasis Model Assessment (HOMA-IR), TSH.

2.6. Statistical analysis

We used STATA v14.0 (StataCorp, TX, USA) for our analysis. Descriptive results for numeric variables were presented as means with standard deviation (SD) or medians with interquartile range (IQR), depending on their distributions; otherwise, we expressed the qualitative variables as numbers with percentages. The study population characteristics according to the FT3, FT4 or FT3/FT4 ratio tertiles were compared using one-way analysis of variance (ANOVA) or Kruskal Wallis test for continuous variables and using the Chi-square test for categorical variables.

Two generalized linear models (crude and adjusted) from Poisson family with robust standard errors were constructed to assess the association between FT3, FT4 or FT3/FT4 ratio tertiles with MetS respectively. The reported association measure was the prevalence ratio (PR) with their respective 95% confidence intervals (95% CI). The adjusted model included the following confounding variables: age and sex; and the reported association measure was the adjusted prevalence ratio (aPR) with their respective 95% CI.

Finally, receiver operating characteristic (ROC) curves were constructed to compare the sensitivity and specificity of the various thyroid markers, calculating the areas under the curve (AUC) and their 95% CI by the bootstrap proceeding with 1000 repetitions [28–30]. We used the Youden's Index, which is defined as the sum of sensitivity and specificity by subtracting the unit. Thus, this index allows identifying the cut-point corresponding to a better balance of sensitivity/specificity. We considered optimal cut-points for those who had a higher Youden's rating [28].

2.7. Ethical considerations

The data was collected by two researchers from the private clinic to study epidemiological surveillance. For this study, participant information was delivered in a Microsoft Excel 2010 file with no biological identifiers, maintaining the confidentiality of the information.

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