

Effect of the normalization of TSH and free T4 on lipid profile in a pediatric population with primary hypothyroidism

Efecto de la normalización de TSH y T4 libre sobre el perfil lipídico en población pediátrica con hipotiroidismo primario

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What do we know about the subject matter of this study?

Primary hypothyroidism is associated with increased cardiovascular risk and dyslipidemia. In the adult population, treatment with levothyroxine has shown an improvement in cardiometabolic parameters, including the lipid profile, although there is little data on the pediatric population.

What does this study contribute to what is already known?

In children with hypothyroidism, there is an association between TSH, FT4, and lipid profile. Normalizing the thyroid profile allows a reduction of cholesterol, triglycerides, and LDL-C. Persistent post-treatment dyslipidemia is associated with obesity, overweight, and pre-treatment dyslipidemia.

Abstract

Hypothyroidism has been associated with dyslipidemia. Its treatment with levothyroxine has shown a positive effect on the lipid profile in adults, however, there is a lack of data on the pediatric population. **Objective:** to evaluate the effect of the thyroid profile normalization on the lipid profile in children with primary hypothyroidism. **Patients and Method:** Retrospective study in children aged from 6 to 16 years, with diagnosis of primary hypothyroidism due to Hashimoto's thyroiditis, in treatment with levothyroxine, and who had an evaluation of serum lipids before and during their treatment. The lipid profile was evaluated in 2 stages: the first one referred to as "before levothyroxine treatment" (at the diagnosis of primary hypothyroidism) and the second one referred to as "thyroid profile normalization" (when normalization of Thyroid-stimulating hormone [TSH] and free T4 [FT4] was achieved during levothyroxine treatment). Sociodemographic and anthropometric data were recorded. The lipid profile evaluation consisted of the serum determination of total cholesterol (TC), high-density cholesterol (HDL-C), and TG. The phenotype of dyslipidemias was determined according to the Fredrickson's classification. **Results:** 72 patients were included (61% women; age

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11.5 ± 2.9 years), out of which 58.3% (n = 42) presented pre-treatment dyslipidemia. In hypothyroid state, it was evident the correlation of TSH with TC (r = 0.36; p = 0.002), LDL-C (r = 0.46; p = 0.01), and HDL-C (r = -0.33; p = 0.004). The thyroid profile normalization showed the reduction of TC [184 mg/dL (IQR 92-322) vs 147 mg/dL (IQR 92-283); p = 0.05], LDL-C [99 mg/dL (IQR 44-232) vs 82 mg/dL (IQR 41-168); p = 0.02], TG [113 mg/dL (IQR 50-483) vs 88 mg/dL (IQR 16-343); p = 0.03], and the frequency of dyslipidemia [58.3% vs 22.2%; p = 0.001], as well as the TC correction with TG (r = 0.35; p = 0.02) and LDL-C (r = 0.88; p = 0.01). Persistent dyslipidemia was associated with obesity (r = 0.27; p = 0.02), overweight (r = 0.58; p = 0.001), and pre-treatment dyslipidemia (r = 0.53; p = 0.001). **Conclusions:** There is an association between TSH, TC, LDL-C, and HDL-C in hypothyroidism. When the thyroid profile was normalized, there was a reduction of TC, TG, LDL-C, and dyslipidemia frequency. Persistent dyslipidemia was associated with obesity, overweight, and pre-treatment dyslipidemia.

Introduction

Thyroid hormones play a fundamental role in lipid homeostasis by regulating the activity of receptors, enzymes, and transfer proteins involved in lipoprotein metabolism¹. In children and adolescents, Hashimoto's thyroiditis is the most frequent cause of primary acquired hypothyroidism, which is more prevalent during puberty onset and infrequent before age 3 years.

Hashimoto's thyroiditis is more prevalent in females (3-4:1 ratio) and may be associated with other autoimmune diseases, Down syndrome, or Turner syndrome. It has a wide spectrum of presentation, ranging from an asymptomatic state to myxedema coma². In patients with primary hypothyroidism due to Hashimoto's thyroiditis, there is evidence of an increase in pro-atherogenic markers, dyslipidemia, and cardiovascular risk³.

Lipid metabolism alterations caused by hypothyroidism are due to thyroid hormone deficiency. Among the related pathophysiological mechanisms are a decreased expression of HMG-CoA reductase⁴, reduced cell surface LDL-C receptors⁵, increased intestinal cholesterol absorption⁶, reverse cholesterol transport alterations⁷⁻⁹, alterations in the formation and fecal excretion of bile acids¹⁰, and decreased lipoprotein lipase activity⁸.

Levothyroxine replacement therapy has shown an improvement in cardiometabolic parameters, including lipid profile. Most of the studies have been conducted in the adult population, with few studies in the pediatric one, and even fewer in the Latino population¹¹⁻¹⁴.

The objective of our study was to evaluate the effect of normalization of thyroid-stimulating hormone (TSH) and free T4 (FT4) on the lipid profile and its alterations in a pediatric population with primary hypothyroidism due to Hashimoto's thyroiditis treated

with levothyroxine, as well as to determine the association between TSH, FT4, BMI, and lipid profile before treatment with levothyroxine and normalization of the thyroid profile.

Patients and Method

Retrospective study in children with primary hypothyroidism seen at the Hospital de Pediatría, Centro Médico Nacional Siglo XXI, IMSS, Mexico City, from January 2011 to June 2017. The study was reviewed and approved by the Local Health Research and Ethics Committee of the Hospital de Pediatría, Centro Médico Nacional Siglo XXI, IMSS. Data were obtained through the review of medical records.

We included girls and boys aged between 6 and 16 years, diagnosed with primary hypothyroidism due to Hashimoto's thyroiditis, treated with levothyroxine, and with biochemical evaluation of serum lipids before and during their medical follow-up. Primary hypothyroidism due to Hashimoto's thyroiditis was defined as deficient thyroid hormone production caused by antibody-mediated thyroid dysfunction, biochemically diagnosed by low serum FT4 concentrations (reference value 0.93-1.7 ng/dL), increased TSH (reference value 0.27-4.2 µIU/mL), and the presence of anti-TPO antibodies ≥ 9.0 IU/mL and/or anti-thyroglobulin antibodies ≥ 4.0 IU/mL. We excluded patients with diabetes mellitus, primary dyslipidemia, nephrotic syndrome, congenital, secondary to procedures, central or subclinical hypothyroidism, glucocorticoid use, non-autoimmune thyroid disease, neoplasms, renal, hepatic, or another chronic degenerative disease, inadequate adherence to levothyroxine treatment, malabsorption syndrome, or those who failed to achieve normalization of TSH and FT4.

Normalization of TSH and FT4 was defined as achievement in TSH concentrations between 0.27

and 4.2 $\mu\text{IU/mL}$ and FT4 between 0.9 and 1.7 ng/dL , measured by electrochemiluminescence immunoassay (ECLIA, Cobas, Roche Diagnostics®).

The administered dose of levothyroxine was 4 to 5 $\mu\text{g/kg/day}$ in patients between 6 and 12 years of age, 2 to 3 $\mu\text{g/kg/day}$ in those older than 12 years with incomplete development or puberty, and 1.6 $\mu\text{g/kg/day}$ in those older than 12 years with complete development and puberty.

For study purposes, two-time points were established: the first one referred to as “before levothyroxine treatment” (at diagnosis of primary hypothyroidism) and the second one referred to as “at normalization of the thyroid profile” (when normalization of TSH and FT4 was achieved during levothyroxine treatment).

Sociodemographic and anthropometric data were collected (age, sex, Tanner stage, weight, height, Z-score for weight and height, and BMI), determining overweight a BMI between the 85th-94th percentile and obesity a BMI at the 95th percentile or higher¹⁵.

The lipid profile was evaluated determining serum concentrations of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG), after a 12-hour fast, by colorimetric assay (Cobas Lipid Panel, Roche Diagnostics®), before treatment with levothyroxine and normalization of the thyroid profile. Low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald formula ($\text{LDL} = \text{TC} - [\text{TG}/5] - \text{HDL-Cholesterol}$), as long as TG concentrations were below 400 mg/dL ¹⁶. According to the National Cholesterol Education Program (NCEP), hypertriglyceridemia was defined as TG concentrations $> 100 \text{ mg/dL}$ in children under 9 years of age and $\text{TG} > 130 \text{ mg/dL}$ between 10 and 19 years of age, hypercholesterolemia as TC concentrations $\geq 200 \text{ mg/dL}$, increase in LDL as LDL-C concentrations $\geq 130 \text{ mg/dL}$, and low HDL as HDL-C concentrations $< 40 \text{ mg/dL}$ ¹⁷. The phenotype of lipid profile alterations (dyslipidemia) was characterized according to the Fredrickson classification¹⁸.

Statistical analysis

Qualitative variables were described in frequencies and proportions. Quantitative variables were described as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Normality was determined with the Shapiro-Wilks test. The Chi-square test was used to compare qualitative variables, as well as the Wilcoxon and Mann-Whitney U tests for the quantitative ones, and Spearman's correlation coefficient was used to establish associations between variables. A < 0.05 p-value was considered statistically significant. SPSSv.13 and GraphPad Prism software were used as statistical tools.

Results

Patients

72 patients were included with a mean age of 11.5 ± 2.9 years, and 61% ($n = 44$) of them were female. According to Tanner stage, 68% ($n = 49$) were pubescent [stage II: 18% ($n = 13$); stage III: 14% ($n = 10$), and stage IV: 14% ($n = 10$)]. Regarding nutritional status, 4.2% ($n = 3$) were underweight, 43% ($n = 31$) normal weight, 25% ($n = 18$) overweight, and 27.8% ($n = 20$) obese. Before levothyroxine treatment, they present TSH concentrations of 29.8 $\mu\text{IU/mL}$ (IQR 16.7-69.8), and FT4 of 0.55 ng/dL (IQR 0.35-0.69).

Lipid profile alterations and phenotype characterization in patients with primary hypothyroidism

Before the levothyroxine treatment, lipid profile components showed the following concentrations: TC 184 mg/dL (IQR 92-322), LDL-C 99 mg/dL (IQR 44-232), HDL-C 48 mg/dL (IQR 22-80), and TG 113 mg/dL (IQR 50-483). Dyslipidemia was present in 58.3% ($n = 42$) of the patients. 43% ($n = 31$) presented hypercholesterolemia, hypertriglyceridemia in 36% ($n = 26$), increased LDL in 50% ($n = 36$), and low HDL in 12.5% ($n = 9$). According to the Fredrickson classification, phenotype IIa was observed in 22.2% ($n = 16$), phenotype IIb in 18% ($n = 13$), and phenotype V in 8.1% ($n = 13$) (Table 1).

Effect of TSH and FT4 normalization on lipid profile and its alterations

Upon normalization of the thyroid profile, there were TSH concentrations of 1.4 $\mu\text{IU/mL}$ (IQR 0.8-2.8) and FT4 of 1.4 ng/dL (IQR 1.2-1.6). Normalization of the thyroid profile took 12 weeks (IQR 10-13). In lipid profile, there were statistically significant differences in concentrations of TC [184 mg/dL (IQR 92-283) vs 147 mg/dL (IQR 92-220); $p = 0.05$], LDL-C [99 mg/dL (IQR 44-150) vs 82 mg/dL (IQR 41-168); $p = 0.02$], and TG [113 mg/dL (IQR 50-382) vs 88 mg/dL (IQR 16-243); $p = 0.03$]. There was no difference in HDL-C concentrations [48 mg/dL (IQR 22-80) vs 47 mg/dL (IQR 24-75); $p = 0.45$] (Figure 1). There was a 65% reduction in the dyslipidemia frequency ($p = 0.001$), a 42% in hypercholesterolemia ($p = 0.03$), and a 65% in hypertriglyceridemia ($p = 0.001$). 22.2% ($n = 16$) of the patients persisted with lipid profile alterations, highlighting hypercholesterolemia in 25% ($n = 18$), hypertriglyceridemia in 12.5% ($n = 9$), and increased LDL-C in 25% ($n = 18$), as well as a higher frequency of low HDL [12.5% ($n = 9$) vs 26.3% ($n = 19$); $p = 0.03$] (Figure 2). According to the Fredrickson classification, there was a reduction in the frequency of phenotype IIa and IIb during levothyroxine treatment (Table 1).

Association between TSH, FT4, BMI, and lipid profile before treatment with levothyroxine and thyroid profile normalization

When evaluating the association between TSH, FT4, and lipid profile before levothyroxine treatment, TSH concentrations had a positive correlation with age ($r = 0.39$; $p = 0.001$), TC ($r = 0.36$; $p = 0.002$), and LDL-C ($r = 0.46$; $p = 0.01$), and a negative one with HDL-C ($r = -0.33$; $p = 0.004$) and FT4 ($r = -0.45$; $p = 0.001$). FT4 concentration showed a positive correlation with HDL-C ($r = 0.28$; $p = 0.02$), and a negative one with LDL-C ($r = -0.28$; $p = 0.02$) and TSH ($r = -0.45$; $p = 0.001$). There was no correlation between TSH or FT4 with BMI and TG. When evaluating the association between BMI and lipid profile, there was a positive correlation between BMI and TG ($r = 0.39$; $p = 0.001$), with no evidence of correlation with HDL-C, TC, or LDL-C.

Upon normalization of the thyroid profile, there was no association between TSH and lipid profile parameters. Post-treatment TC concentrations cor-

related with pre-treatment TC ($r = 0.40$; $p = 0.001$) and pre-treatment LDL-C ($r = 0.34$; $p = 0.004$), as well as with LDL-C ($r = 0.88$; $p = 0.01$) and TG ($r = 0.35$; $p = 0.02$) when achieving thyroid profile normalization. In the case of HDL-C, concentrations correlated negatively with FT4 ($r = -0.27$; $p = 0.02$), BMI ($r = -0.42$; $p = 0.001$), and TG ($r = -0.38$; $p = 0.01$), and TG concentrations showed a positive correlation with BMI ($r = 0.47$; $p = 0.001$) and pre-treatment TG ($r = 0.50$; $p = 0.001$). There was no correlation of BMI with TSH, TC or LDL-C. The persistence of dyslipidemia upon TSH and FT4 normalization was associated with obesity ($r = 0.27$; $p = 0.02$), overweight ($r = 0.58$; $p = 0.001$), and pre-treatment dyslipidemia ($r = 0.53$; $p = 0.001$).

Given the frequency of overweight and obesity, along with the association of TG and HDL-C with BMI, the characteristics of the lipid and thyroid profile were compared between patients with and without obesity/overweight. Before levothyroxine treatment, there were no statistically significant differences in the

Table 1. Dyslipidemia phenotype according to the Fredrickson classification before levothyroxine treatment and at normalization of thyroid profile

Dyslipidemia	Before levothyroxine treatment; n (%)	At normalization of thyroid profile; n (%)	p=
Type I	0	0	
Type IIa	16 (22.2)	4 (5.6)	0.01
Type IIb	13 (18)	2 (2.8)	0.01
Type III	0	0	-
Type IV	0	0	-
Type V	13 (18.1)	10 (16.6)	0.82

Dyslipidemia type: Fredrickson DS, Lees RS. A system for phenotyping hyperlipoproteinemia. *Circulation* 1965;31:321-7. doi: 10.1161/01.cir.31.3.321.

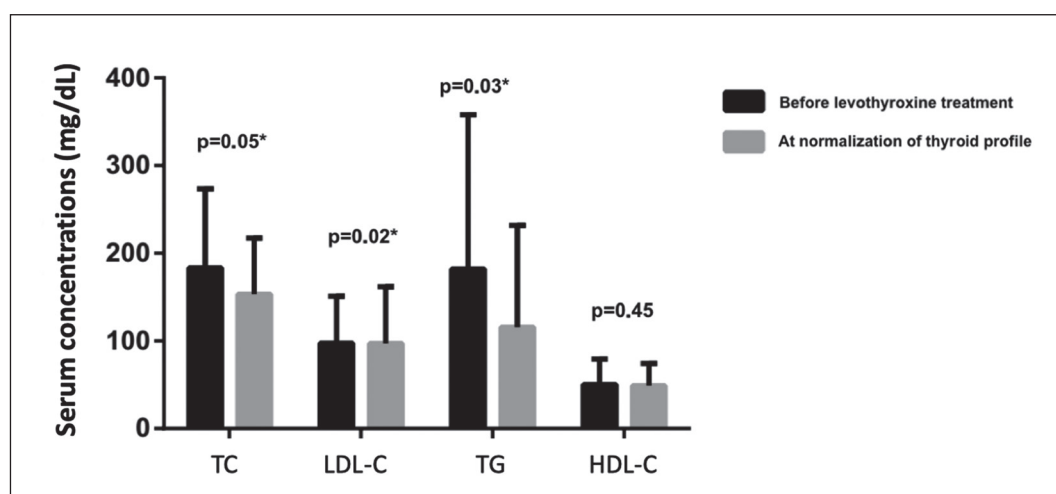


Figure 1. Parameters of Lipid profile before levothyroxine treatment and at normalization of thyroid profile. *statistical significance.

concentrations of TSH, FT4, TC, LDL-C, HDL-C, and TG; however, upon normalization of the thyroid profile, higher concentrations of TG and lower concentrations of HDL-C were observed in obese/overweight patients, with no differences for the rest of the variables (Table 2).

Discussion

In this study, we report the effect of TSH and FT4 normalization on the lipid profile and its alterations in pediatric patients with primary hypothyroidism treated with levothyroxine, as well as the association of TSH and FT4 with TC, LDL-C, and HDL-C concentrations before treatment.

Alterations in lipoprotein metabolism have been reported in up to 52% of adults with primary hypothyroidism¹¹. In children and adolescents with hypothyroidism, although serum concentrations alterations of TC, TG, LDL-C, VLDL-C, and HDL-C have been described, a frequency of dyslipidemia has not been determined, even in patients with subclinical hypothyroidism¹⁹. In our series, the frequency evidenced was higher than 50%, similar to that reported in the non-pediatric population. In hypothyroidism, dyslipidemia phenotypes II and IV have been described¹⁸. In our study, using the Fredrickson classification, we found a predominance of the phenotype IIa (increased LDL-C, normal TG, and VLDL, TC/TG ratio > 1.5) and IIb (increased LDL-C, TG, and VLDL)¹⁸, highlighting a mixed dyslipidemia component.

The effects of hypothyroidism on lipoprotein metabolism are related to the decrease in thyroid hormones⁴⁻¹⁰. In children and adolescents without thyroid disease, a positive association between TSH and non-HDL cholesterol has been observed²⁰.

In specific groups, such as obese patients, the association of TSH, lipid profile, and BMI has been evaluated. In patients with obesity without a diagnosis of hypothyroidism, a positive association of TSH with TC and LDL-C was observed, with no evidence of association between TSH and BMI²¹. In a study that included obese patients, both with subclinical hypothyroidism and without thyroid alteration, there was a positive association between TSH and TC, TG and BMI, and a negative one between FT4 and TC²². In our study, during hypothyroidism, we observed the positive association of TSH with TC and LDL-C and of FT4 with HDL, as well as the negative association of TSH with HDL-C and of FT4 with LDL-C, without corroborating an association between TSH and BMI. We did not find an association between TG and TSH or FT4, in contrast to the rest of the lipid profile components. With these data, we demonstrate the relationship between thyroid and lipid profile parameters in pediatric patients with hypothyroidism.

Several studies have shown improvement in the lipid profile after treatment with levothyroxine both in adults¹¹⁻¹⁴ and in the pediatric population²³. In adults with autoimmune hypothyroidism, the reduction of TG, apolipoprotein B (apoB), and atherogenic index of plasma (AIP) after treatment with levothyroxine has been demonstrated¹¹. In adults with post-surgical hypothyroidism, treatment with levothyroxine showed a reduction in TC, TG, LDL-C, apolipoprotein A-I, and apoB levels¹².

In a systematic review, Danese et al. reported decreased TC and LDL-C levels after levothyroxine treatment, with inconclusive results for HDL-C and TG¹³. In patients with subclinical hypothyroidism, post-treatment reduction of TC and LDL-C has also been described¹⁴. Cerbone et al. observed in children with subclinical hypothyroidism, increased AIP and TG/HDL-C ratio, hyperhomocysteinemia, and decrea-

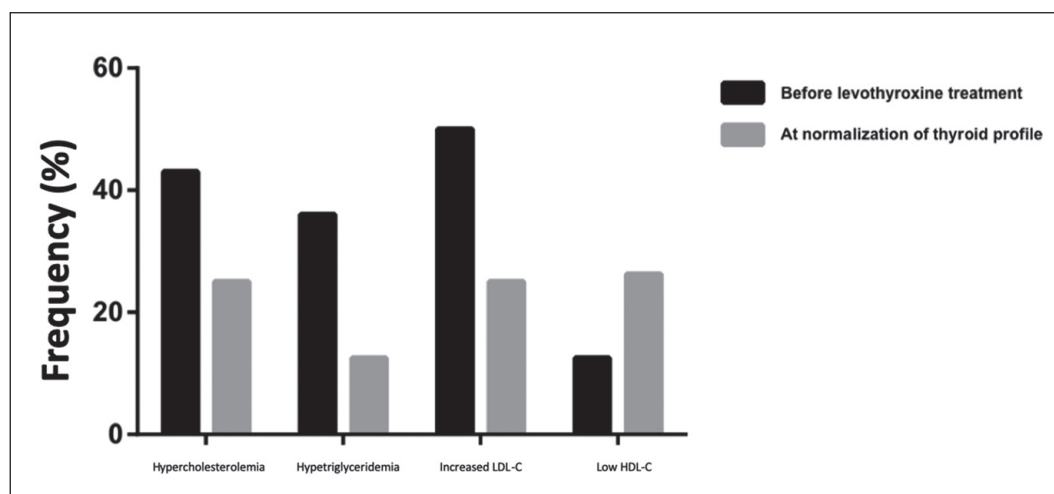


Figure 2. Frequency of dyslipidemia before levothyroxine treatment and at normalization of thyroid profile.

Table 2. Characteristics of lipid profile, TSH and FT4 in patients with and without overweight/obesity

	Without overweight/obesity	With overweight/obesity	p
Before levothyroxine treatment			
Total Cholesterol (mg/dL)	200 (157-222)	169 (144-210)	0.18
LDL-C (mg/dL)	124 (89-141)	95 (74-144)	0.31
HDL-C (mg/dL)	50 (44-60)	45 (41-53)	0.07
Triglycerides (mg/dL)	96 (78-189)	114 (83-176)	0.55
TSH (μIU/mL)	38,8 (18,5-77)	21,2 (12-47)	0.14
FT4 (ng/dL)	0,6 (0,4-0,7)	0,49 (0,3-0,6)	0.20
At normalization of thyroid profile			
Total Cholesterol (mg/dL)	154 (126-175)	144 (128-170)	0.5
LDL-C (mg/dL)	82 (66-96)	82 (63-105)	0.88
HDL-C (mg/dL)	50 (45-56)	42 (39-49)	0.006
Triglycerides (mg/dL)	74 (61-112)	112 (65-162)	0.02
TSH (μIU/mL)	1,0 (0,6-2)	1,3 (0,9-2,12)	0.06
FT4 (ng/dL)	1,4 (1,2-1,6)	1,3 (1,2-1,6)	0.99

Quantitative variables were reported in median and interquartile range. LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TSH: thyroid-stimulating hormone, FT4: Free thyroxine.

sed HDL-C²⁴. When evaluating the effect of levothyroxine in this group of patients, there was a decrease in waist-to-height ratio, TG/HDL-C ratio, and AIP, as well as an increase in HDL-C²³. In another study performed in children with subclinical hypothyroidism, there were no changes in the lipid profile when euthyroidism was achieved²⁵.

In our study, we observed an improvement in TC, TG, and LDL-C concentrations upon normalization of the thyroid profile, in line with the findings reported in the adult population. Likewise, we observed a decrease in the frequency of dyslipidemia. It should be noted that more than 20% of patients persisted with dyslipidemia, predominantly elevated LDL and low HDL, despite the changes evidenced in the lipid profile after normalization of TSH and FT4. With euthyroidism, we corroborated the association of TC with TG, pre-treatment TC, and LDL-C pre- and post-treatment; TG with BMI; HDL-C with BMI, and the persistence of dyslipidemia with obesity, overweight, and pre-treatment dyslipidemia.

These findings demonstrate that, despite the thyroid profile normalization, there are other factors associated with persistent dyslipidemia in this group of patients, such as alterations in nutritional status (overweight and obesity) and pre-treatment dyslipidemia, where timely therapeutic intervention is important in addition to treatment with levothyroxine.

It is worth mentioning the frequency of overweight [25% (n = 18)] and obesity [27.8% (n = 20)] found in our study, which is higher than that reported in the pediatric population according to the National Health Survey in Mexico (overweight 18.4% and

obesity 19.5% in population between 5 and 11 years; overweight 24.7% and obesity 15% between 12 and 19 years)²⁶. Although we did not find differences in the characteristics of the pre-treatment lipid profile, we observed higher TG and lower HDL-C concentrations in patients with obesity/overweight to euthyroidism, which, along with the correlation demonstrated between BMI, TG, and HDL, reflects the role of obesity and overweight in persistent dyslipidemia.

The limitations of the study include its retrospective design, the lack of biochemical determinations of lipoprotein fractions and sub-fractions, cardiovascular risk markers, and the lack of control of variables such as diet and physical activity. Among the strengths, we highlight that this is one of the first studies to evaluate the effect of TSH and FT4 normalization on the lipid profile in a pediatric population from a Latin American country with a high prevalence of cardiometabolic diseases. We consider further prospective studies to evaluate the effect of euthyroidism on the lipid profile and other markers of cardiovascular risk.

In conclusion, secondary dyslipidemia is present in more than half of the pediatric patients with primary hypothyroidism due to Hashimoto's thyroiditis, and there is an association between TSH, FT4, and lipid profile. Upon thyroid profile normalization, there is a reduction in TC, TG, and LDL-C concentrations, as well as in the frequency of dyslipidemia. Persistent dyslipidemia despite the achievement of euthyroidism is associated with obesity, overweight, and dyslipidemia during hypothyroidism, highlighting the importance of timely intervention of these factors together with treatment with levothyroxine.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients

and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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