



## Metabolic effects caused by sodium levothyroxine in subclinical hypothyroidism patients with low HDL

Bernardo F. Garcia<sup>b</sup>, Glauca L. da Veiga<sup>a,\*</sup>, Beatriz CA. Alves<sup>a</sup>, Flavia S. Gehrke<sup>c,d</sup>, Fernando Luiz A. Fonseca<sup>a,b</sup>

<sup>a</sup> Clinical Analysis Department, Faculdade de Medicina ABC, São Paulo, Brazil

<sup>b</sup> Pharmaceutical Sciences Department, Universidade Federal de São Paulo, São Paulo, Brazil

<sup>c</sup> Sciences of Health Department, Instituto de Assistência Médica ao Servidor Público Estadual de São Paulo, São Paulo, Brazil

<sup>d</sup> Pharmacy Department, Universidade Paulista, São Paulo, Brazil



### ARTICLE INFO

#### Keywords:

Subclinical hypothyroidism  
HDL cholesterol  
Sodium levothyroxine

### ABSTRACT

**Introduction:** Subclinical hypothyroidism (SH) is an autoimmune thyroid disorder characterized by elevated TSH with values of T3, T4, free T3 and free T4 within the reference range. High TSH levels are associated with lipid alteration.

**Method:** A total of 21 patients aged between 18 and 80 years were recruited. The sample was composed of 17 females and 4 males, all of whom had TSH values ranging from 5.0 to 9.9 (mIU/L) and normal free T4 levels. They were followed up for 26 months while undergoing sodium levothyroxine replacement therapy (12.5–25 mcg/day). Throughout this period, TSH, free T4 HDL, LDL, triglyceride, total cholesterol and glucose levels were evaluated.

**Results:** A significant improvement in HDL cholesterol levels was observed. There was also a decrease in fasting glucose. No significant changes were seen in triglyceride levels.

**Conclusion:** As observed throughout this study, SH patients with low HDL under therapy showed a significant increase in HDL levels after TSH levels were normalized. Therefore, it is quite clear that thyroid hormones affect lipid metabolism, and, as a result, metabolic syndrome components.

### 1. Introduction

Subclinical hypothyroidism (SH) is an autoimmune thyroid disorder characterized by elevated TSH with normal values of T3, T4, free T3 and free T4 (Pereira et al., 2015). The most common cause of SH is considered to be chronic autoimmune thyroiditis associated with the presence of anti-TPO (anti-thyroid peroxidase) antibodies (Javed and Sathyapalan, 2016). Patients with positive anti-Tg (thyroglobulin antibodies) antibodies are also at a higher risk of developing the disease (Pereira et al., 2015). Females are more prone to clinical hypothyroidism, and the presence of anti-thyroid antibodies as well as advanced age are strong risk factors for the disorder (Javed and Sathyapalan, 2016).

SH is a relatively common condition (Danese et al., 2000) that affects 4–20% of the general population (Pereira et al., 2015). Treatment starts with the administration of sodium levothyroxine to prevent the progression of symptoms (Danese et al., 2000; Baumgartner et al., 2014a). Subclinical thyroid failure can be present years before the onset

of clinical hypothyroidism (Danese et al., 2000; Garg and Vanderpump, 2013).

It is widely known that the treatment of SH with sodium levothyroxine has the potential to decrease the levels of lipids (Danese et al., 2000). Thus, dyslipidemia is a common feature in SH patients, especially in cases involving the increase of total cholesterol and LDL levels (Li et al., 2017). TSH values above the upper limit of the normal range are related to lipid profile alterations (Wanjia et al., 2012; Petrosyan, 2015). Moreover, with the increase of LDL levels and decrease of HDL levels, cardiovascular risk factors have constantly been evidenced (Pereira et al., 2015; LeFevre and U.S. Preventive Services Task Force, 2015).

The use of sodium levothyroxine aims to keep TSH levels within the limits of normality (Glivic et al., 2015). Some studies show that greater plasma concentrations of TSH predispose to higher levels of insulin resistance (Pereira et al., 2015; Waring et al., 2012). Abnormal metabolism of the thyroid hormone is an important cause of coronary atherosclerosis (Wanjia et al., 2012). Upon treating patients with high

\* Corresponding author.

E-mail addresses: [grlveiga@gmail.com](mailto:grlveiga@gmail.com) (G.L. da Veiga), [profferfonseca@gmail.com](mailto:profferfonseca@gmail.com) (F.L.A. Fonseca).

levels of TSH, the risk of cardiovascular disease tends to be reduced (Glivic et al., 2015; Pop-Radu and Gliga, 2013; Li et al., 2016).

Some studies report that patients with high cholesterol are more likely to develop SH (Pereira et al., 2015). Thyroid dysfunction is common among metabolic syndrome patients. Such patients are at a higher risk to develop SH (Chang et al., 2017; Khatiwada et al., 2016; Vyakaranam et al., 2014).

The current study aimed to recruit SH patients with low HDL, treat them with sodium levothyroxine, and evaluate if there was an increase in this cholesterol fraction.

## 2. Materials and methods

All participants in this study were seen at the Endocrinology Ambulatory Care Center, located in a municipality of São Paulo. This study was approved by the FMABC Ethics Committee (protocol number #721.828).

Inclusion criteria encompassed SH patients with low HDL. Cut-off values were established as follows: below 45 mg/dL for men and below 50 mg/dL for women.

Exclusion criteria were set as follows: individuals aged below 18 or above 80 years, SH patients on sodium levothyroxine, clinical hypothyroidism patients or those on hypolipidemic drugs.

The study ended up with 21 patients (17 women and 4 men) with TSH values ranging from 5.0 to 9.9 (mIU/L) and normal free T4 levels. They were followed up for 26 months while undergoing sodium levothyroxine replacement therapy (12.5–25 mcg/day). Throughout this period, TSH, free T4 HDL, LDL, triglyceride, total cholesterol and glucose levels were evaluated. All of the participants signed the Free and Informed Consent Form (FICF).

Qualitative variables were presented as absolute and relative frequencies. For quantitative variables with non-normal distribution (Shapiro-Wilk,  $p < 0.05$ ), median, confidence interval and 25 and 75 percentiles were used. Variables with normal distribution (Shapiro-Wilk,  $p > 0.05$ ) were described by mean, standard deviation and minimum-maximum values.

Since the pre- and post-moments of the markers presented normal distribution (Shapiro-Wilk,  $p > 0.05$ ), Student's *t*-test was applied in order to analyze the association between them (95% CI). All tests used a confidence interval of 95%. Stata 11.0 was used for statistical analysis.

## 3. Results

Table 1 shows the biochemical measures before and after the use of sodium levothyroxine within the period of 6 months.

To verify the effects on the studied biochemical parameters after the use of sodium levothyroxine, such parameters were evaluated before and after the treatment. Table 2 shows the means of the laboratory values before and after the use of sodium levothyroxine and the variation of the biological markers.

## 4. Discussion

The results found here show that there was a significant improvement in HDL cholesterol values. Furthermore, there was also a decrease in fasting glucose. Regarding triglyceride levels, no significant changes were observed.

Therefore, it has become quite clear that upon treating SH, there is an improvement in HDL levels and a resulting decrease in cardiovascular risk (Pereira et al., 2015). According to Pereira et al., in addition to SH there have been similar evidences of cardiovascular risk related to manifested hypothyroidism with lipid alterations (LDL increase, HDL decrease and increase in insulin resistance). Some studies concluded that there is an increased risk of metabolic syndrome in patients with slightly increased TSH levels.

The decrease in fasting glucose also supports the idea of decreasing

**Table 1**  
Characterization of biological markers.

Variable	n	%
Gender		
Male	4	19.1
Female	17	80.9
	<b>Mean (SD)</b>	<b>Minimum - Maximum</b>
Glucose		
Pre-treatment	93.2 (21.1)	63.0–154.0
Post-treatment	88.0 (20.8)	67.0–158.0
TGS		
Pre-treatment	165.6 (71.5)	76.0–335.0
Post-treatment	164.4 (60.5)	80.0–331.0
T-COL		
Pre-treatment	201.5 (42.1)	149.0–287.0
Post-treatment	212.2 (41.5)	152.0–285.0
LDL		
Pre-treatment	131.6 (33.6)	92.0–212.0
Post-treatment	136.8 (38.0)	83.0–210.0
HDL		
Pre-treatment	38.5 (6.4)	24.0–48.0
Post-treatment	42.0 (7.3)	26.0–56.0
TSH		
Pre-treatment	7.1 (1.4)	4.8–9.9
Post-treatment	5.0 (2.4)	1.8–13.3
Free T4		
Pre-treatment	1.1 (0.1)	0.8–1.5
Post-treatment	1.1 (0.2)	0.7–1.4
	<b>Median (95%CI)</b>	<b>p.25 - p.75</b>
Age	50.0 (39.4; 59.1)	39.0–60.0

SD: standard deviation; 95%CI: 95% confidence interval; p.25 - p.75: 25 and 75 percentiles; TGS: triglycerides, T-COL: total cholesterol; 04LDL: low density protein; HDL: high density protein TSH: thyroid-stimulating hormone; Free T4: free thyroxin concentration.

risk factors and the development of metabolic syndrome (Chang et al., 2017). Chang and coworkers, concluded that clinical and SH are significantly associated with the risk of the onset of metabolic syndrome.

SH is prevalent, and it is frequently associated with metabolic syndrome markers (Pereira et al., 2015). Thus, the current study documents the importance of the control of TSH levels through the observation of the relationship between these levels and the improvement or not of lipid values, especially HDL cholesterol.

The literature cites that higher TSH levels are related to a higher risk of developing insulin resistance followed by metabolic syndrome components (Pereira et al., 2015). This study highlighted the fact that the thyroid dysfunction known as SH is prevalent in the general population, and it is associated with some components of metabolic syndrome, such as low HDL cholesterol.

Therefore, treatment of SH is of utmost importance, and oral sodium levothyroxine is the medication of choice. Javed et al., pointed out that treatment of SH with sodium levothyroxine, rather than the use of T3 or the combination of T4 and T3, is the therapy of choice (Javed and Sathyapalan, 2016).

During the twenty-six month evaluation, when sodium levothyroxine replacement was conducted with the administration of a daily dose of 12.5–25 mcg and the resultant control of TSH within the reference range, it could be observed that there was a significant increase in HDL cholesterol levels as well as a decrease in fasting glucose levels.

It has been demonstrated, not only that patients with metabolic syndrome are more likely to develop subclinical thyroid dysfunction but also that triglyceride levels are higher and HDL cholesterol levels are lower in patients with SH (Khatiwada et al., 2016). In their study, Khatiwada and coworkers, revealed that the increase in TSH may be a predicting factor for metabolic syndrome.

Should a patient be treated for SH, it is advisable that the medical professional request TSH and free T4 tests within 2–3 months. The TSH

**Table 2**  
Association between the pre- and post-treatment of the biological markers.

Variables	Pre	Post	Delta	p <sup>a</sup>
	Mean (95%CI)			
Glucose	93.2 (81.0; 105.6)	88.0 (77.3; 98.7)	−10.5 (−25.9; 4.8)	0.157
TGS	165.6 (132.9; 198.0)	164.4 (136.9; 191.9)	−0.9 (−27.1; 25.1)	0.940
T-COL	201.5 (182.3; 220.5)	212.2 (193.3; 231.1)	10.8 (−7.3; 28.9)	0.227
LDL	131.6 (116.1; 146.8)	136.8 (119.5; 154.2)	5.2 (−7.8; 18.4)	0.411
HDL	38.5 (35.6; 41.3)	42.0 (38.7; 45.3)	3.6 (1.3; 5.7)	0.003
TSH	7.1 (6.4; 7.7)	5.0 (3.8; 6.2)	−2.1 (−2.9; −1.1)	< 0.001
Free T4	1.1 (1.0; 1.2)	1.1 (1.1; 1.1)	0.1 (−0.2; 0.2)	0.687

<sup>a</sup> Student's *t*-test. 95% CI: confidence interval of 95%.

reference value should be generally set between 0.4 and 2.5 mIU/I, and in case of elderly patients, between 1.0 and 5.0 mIU/I (Javed and Sathyapalan, 2016).

After thorough analysis of the results obtained from the 21 studied patients with SH and low HDL undergoing therapy with sodium levothyroxine throughout 26 months, the conclusion is that there was a significant increase in HDL levels after TSH was normalized. Such alterations show that there is a negative relationship between TSH and HDL; thus, it becomes quite clear that the thyroid hormone affects lipid metabolism and, as a result, metabolic syndrome components.

Interestingly, the sample studied was mostly composed of women, which corroborates recent studies that identified a higher prevalence of this pathology in female patients (Baumgartner et al., 2014b; Ding et al., 2018; A fact sheet from the off, 2015). Considering the literature data already mentioned, we emphasize that our sample was elaborated for convenience.

Many studies show greater correlation between subclinical hypothyroidism and metabolic syndrome components. Therefore, this clinical picture may be harmful to cardiovascular health.

## 5. Conclusion

Finally, it can be observed that the treatment of SH with oral sodium levothyroxine regarding HDL cholesterol and glucose is quite beneficial.

## Declarations of interest

None.

## References

- A Fact Sheet from the Office on Women's Health. [Cited 2017/10/10]. Available from: [http://motherjourney.com/uploads/3/5/3/1/35315324/owh\\_restaurants\\_solutions.pdf](http://motherjourney.com/uploads/3/5/3/1/35315324/owh_restaurants_solutions.pdf).
- Baumgartner, C., Blum, M.R., Rodondi, N., 2014 Dec 23a. Subclinical hypothyroidism: summary of evidence in 2014. *Swiss Med. Wkly.* 144, w14058.
- Baumgartner, C., Blum, M.R., Rodondi, N., 2014 Dec 23b. Subclinical hypothyroidism: summary of evidence in 2014. *Swiss Med. Wkly.* 144, w14058.
- Chang, C.H., Yeh, Y.C., Caffrey, J.L., Shih, S.R., Chuang, L.M., Tu, Y.K., 2017 Jul 28. Metabolic syndrome is associated with an increased incidence of subclinical

- hypothyroidism - a cohort study. *Sci. Rep.* 7 (1), 6754.
- Danese, M.D., Ladenson, P.W., Meinert, C.L., Powe, N.R., 2000 Sep. Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J. Clin. Endocrinol. Metab.* 85 (9), 2993–3001.
- Ding, X., Yang, L., Wang, J., Tang, R., Chen, Q., Pan, J., Yang, H., Chen, X., Chen, Z., Mu, L., 2018 Nov 27. Subclinical hypothyroidism in polycystic ovary syndrome: a systematic review and meta-analysis. *Front. Endocrinol. (Lausanne)* 9, 700.
- Garg, A., Vanderpump, M.P., 2013. Subclinical thyroid disease. *Br. Med. Bull.* 107, 101–116.
- Glivic, Z., Sudar, E., Tica, J., Jovanovic, A., Zafirovic, S., Tomasevic, R., Isenovic, E.R., 2015. Effects of levothyroxine replacement therapy on parameters of metabolic syndrome and atherosclerosis in hypothyroid patients: a prospective pilot study. *Int. J. Endocrinol.* 2015, 147070.
- Javed, Z., Sathyapalan, T., 2016 Feb. Levothyroxine treatment of mild subclinical hypothyroidism: a review of potential risks and benefits. *Ther. Adv. Endocrinol. Metab.* 7 (1), 12–23.
- Khawwaja, S., Sah, S.K., Kc, R., Baral, N., Lamsal, M., 2016 Feb 1. Thyroid dysfunction in metabolic syndrome patients and its relationship with components of metabolic syndrome. *Clin. Diabetes Endocrinol.* 2, 3.
- LeFevre, M.L., U.S. Preventive Services Task Force, 2015 May 5. Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* 162 (9), 641–650.
- Li, X., Meng, Z., Jia, Q., Ren, X., 2016 Oct. Effect of L-thyroxine treatment versus a placebo on serum lipid levels in patients with sub-clinical hypothyroidism. *Biomed. Rep.* 5 (4), 443–449.
- Li, X., Wang, Y., Guan, Q., Zhao, J., Gao, L., 2017 Jul. The lipid-lowering effect of levothyroxine in patients with subclinical hypothyroidism: a systematic review and meta-analysis of randomized controlled trials. *Clin. Endocrinol. (Oxf.)* 87 (1), 1–9.
- Pereira, T.A., Neves, C., Esteves, C., Carvalho, D., Delgado, L., Medina, J.L., 2015. Hipotiroidismo subclínico, tireoidite autoimune e fatores de risco cardiovascular. *Arq. Med.* 29 (3), 69–73 [online].
- Petrosyan, L., 2015 Feb 26. Relationship between high normal TSH levels and metabolic syndrome components in type 2 diabetic subjects with euthyroidism. *J. Clin. Transl. Endocrinol.* 2 (3), 110–113.
- Pop-Radu, C.C., Gliga, M., 2013. Lipoprotein(a) levels in thyroid disorders. *Acta Med. Marisiensis* 59 (2), 81–84.
- Vyakaranam, S., Vanaparthi, S., Nori, S., Palarapu, S., Bhongir, A.V., 2014 Sep. Study of insulin resistance in subclinical hypothyroidism. *Int. J. Health Sci. Res.* 4 (9), 147–153.
- Wanjia, X., Chenggang, W., Aihong, W., Xiaomei, Y., Jiajun, Z., Chunxiao, Y., Jin, X., Yinglong, H., Ling, G., 2012 Mar 27. A high normal TSH level is associated with an atherogenic lipid profile in euthyroid non-smokers with newly diagnosed asymptomatic coronary heart disease. *Lipids Health Dis.* 11, 44.
- Waring, A.C., Rodondi, N., Harrison, S., Kanaya, A.M., Simonsick, E.M., Miljkovic, I., Satterfield, S., Newman, A.B., Bauer, D.C., 2012 Jun. Health, ageing, and body composition (health ABC) study. Thyroid function and prevalent and incident metabolic syndrome in older adults: the health, ageing and body composition study. *Clin Endocrinol. (Oxf.)* 76 (6), 911–918.