

## Research Article

# The Role of Carotid Intima Media Thickness in Subclinical Hypothyroidism. A Systematic Review

Karagiannis AKA<sup>1\*</sup> and Nakouti T<sup>2</sup><sup>1</sup>Division of Endocrinology, Diabetes and Metabolism, Korgialeneio - Mpenakeio Hospital, Greece<sup>2</sup>Department of Internal Medicine, "Henry Dunant" Hospital Center, Greece**\*Corresponding author:** Karagiannis AKA, Division of Endocrinology, Diabetes and Metabolism, Korgialeneio - Mpenakeio Hospital, Ypolochagou Kabbatha 30, Athens, Greece**Received:** June 10, 2020; **Accepted:** July 08, 2020;**Published:** July 15, 2020**Abstract****Background:** Subclinical Hypothyroidism (SCH), defined as elevated serum Thyroid-Stimulating Hormone (TSH) in the presence of normal circulating free Thyroxine (FT4) and Triiodothyronine (T3). This entity has been associated with increased carotid Intima-Media Thickness (IMT) in recent studies, though this evidence is controversial in others.**Aim:** The aim of this study was to assess whether carotid IMT in patients with SCH differs or not from that one of euthyroid patients.**Methods:** We analytically searched Pubmed and Scope databases until May 2020 and also the bibliographies of key articles to identify studies that reported carotid IMT in patients with SCH in comparison with euthyroid subjects.**Results:** We identified 30 studies that met the eligibility criteria. Of these, 24 were prospective studies, 4 were randomized, 1 was observational and 1 was retrospective. SCH was statistically correlated with an increased IMT in 16 studies, whereas in 10 others there were not significant differences. One study provided indirect positive correlation of IMT with homocysteine levels in serum and not with thyroid function. Thyroxine administration/replacement was associated with a statistically reversed IMT in most studies.**Conclusions:** In most studies SCH is associated with an increased carotid IMT, which may be due to elevated Thyrotropin (TSH), dyslipidemia and hypertension, while thyroxine administration for restoration of euthyroidism seems to act beneficially in decreasing IMT.**Keywords:** Carotid Artery; Intima-Media Thickness; Subclinical Hypothyroidism; Ultrasound

## Abbreviations

TSH: Thyroid-Stimulating Hormone; SCH: Subclinical Hypothyroidism; Anti-TPO: Anti-Thyroid Peroxidase Antibodies; Anti-Tg: Antithyroglobulin Antibody; IMT: Intima-Media Thickness

## Introduction

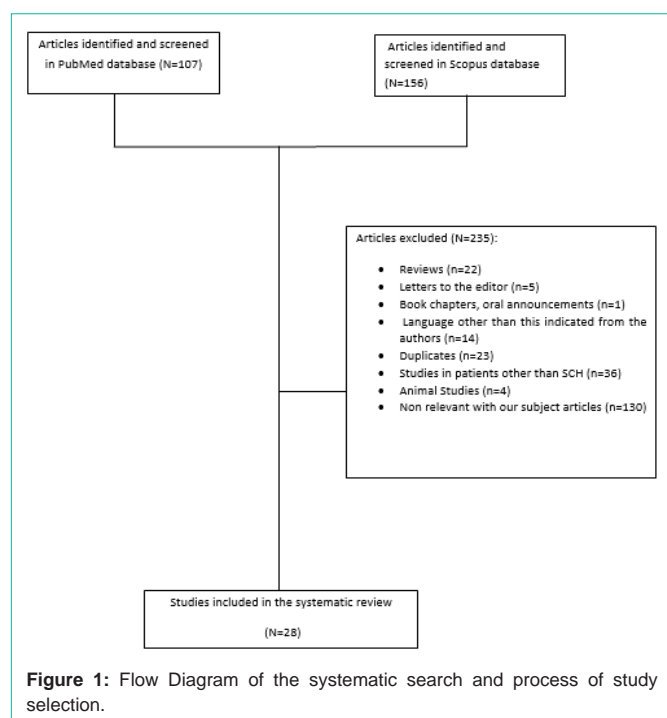
Clinical hypothyroidism is characterized by reduced secretion of thyroid hormones, and subclinical hypothyroidism is defined by high levels of Thyroid-Stimulating Hormone (TSH), while the concentration of thyroid hormones in the blood (total and free) is normal [1]. The frequency of hypothyroidism ranges between 0.5-1.5% in general population and is more prevalent in women older than 60 years in about 4% [2]. Subclinical Hypothyroidism (SCH) is more common and is found in about 10% of adults. Its prevalence is higher in women and in populations of iodine-deficient regions, and its frequency increases with age. The most common cause of subclinical hypothyroidism is autoimmune thyroiditis (Hashimoto thyroiditis). It is characterized by the presence of increased levels of anti-Thyroid Peroxidase Antibodies (anti-TPO) and/or antithyroglobulin antibody (anti-Tg) [3].

Both clinical and less subclinical hypothyroidism, can cause many symptoms. This entity can affect the skin, the respiratory system [4], the cardio-metabolic rhythm causing reduced basic metabolism

[3], the function of kidneys, the bowel motility [5], while anemia is observed in about 25% of the patients [3]. Hypothyroidism has also effect on nervous system both central and peripheral. It causes cognitive dysfunctions with inability of the patient to concentrate, while from peripheral nervous system, it is observed reduction and prolonged tendon reflexes and carpal tunnel syndrome too [3,6].

The Intima-Media Thickness (IMT) of carotids is a sign of preclinical atheromatosis and there are many studies which correlate increased IMT with increased cardiovascular danger [7,8]. Normal range for IMT is up to 0.9cm and when it reaches 1.4cm it is characterized as atheromatic plaque. According to many studies, IMT is due to the same reasons that lead to atheromatosis, like smoking, age, diabetes mellitus, increased blood pressure and dyslipidemia [8-10]. Nowadays, thanks to the widespread use of ultrasound, IMT can easily and reliably be calculated in every day clinical practice [11]. On the other hand, in many clinical and epidemiological studies, IMT is used as an indicator of preexisting atheromatosis, or its progression. Furthermore, it estimates the effect of the risk factors on the arterial wall, as well as the improvement after diet or medication [7,9].

Given that hypothyroidism affects many different systems accordingly to its severity, the aim of this study is to estimate the effect of subclinical hypothyroidism on the vessels as it is expressed by carotid IMT. Thus, we reviewed the literature till now to assess



whether carotid IMT in patients with SCH is different from that one in euthyroid patients and if so, whether it is reversed after thyroxine administration.

## Material and Methods

### Literature search

A search was conducted of all the available literature up to May 2020 using PubMed and Scopus databases. The following search term was used: (“Hypothyroidism” or “Thyroid Disease” or “subclinical hypothyroidism” or “subclinical thyroid dysfunction” or “thyroid-stimulating hormone”) and (“Intima Media Thickness” or “Carotid Wall Thickness” or “IMT” OR “Carotid Atherosclerosis”). Furthermore, the bibliographies of all the relevant articles were hand-searched in order to retrieve additional potentially eligible studies.

### Study selection

Any original article presenting data on patients with SCH and estimation of carotid IMT was evaluated. The studies referred to patients with clinical hypothyroidism or to pediatric patients were excluded.

Additionally, were excluded the similar older reviews, the duplicate studies, the studies on experimental animals, the letters to the editor, the book chapters, the oral announcements, and the articles in other language than English.

### Data extraction

The extracted data included the main characteristics of each study (first author’s name, year of publication, study design and period, country), the way carotid IMT was calculated, the number of patients in each group, and the presence of statistically significant differences between the control group and this one with SCH. Where applicable we included data when the two groups were matched for parameters like sex and age.

Additionally, data were collected from studies that was administered thyroxine in patients with SCH and explored the possibility this could reverse the increased carotid IMT.

## Results

Our research revealed 263 articles (107 from PubMed and 156 from Scopus). After applying the inclusion criteria, 233 articles were rejected as described in Figure 1. Totally, 30 articles were included in our review [12-39]. Twenty-four of them were prospective [12,14,17-27,29-39], 4 were randomized [13,16,40,41], 1 was observational [15], and 1 was retrospective [28].

Regarding the correlation between SCH and carotid IMT, we were estimated 25 studies in total [12-38]. Among them 20 [12,14,17,19,21-26,28,31-38] had this as primary endpoint, while to the rest 8, as secondary endpoint [13,15,16,18,20,27,29,30]. Only in 19 among 25 studies, group control was matched with the population of interest for factors like sex, age and body mass index [12-21,24,25,26,29,30,33,38]. As regards the way carotid IMT was calculated, in 23 of them [12-20,22-26,28-30,32-38] it was estimated in both carotid bifurcations and 10-20mm away of them, in 1 study only in right common carotid [21], while in another 2 was not mentioned [27,31] (Table 1).

Ten studies [13,16,18,20,27,33,37,39-41] were referred to the reverse of IMT after administration of thyroxine as primary endpoint. The dose of thyroxine was ranged from 0.75µg/Kg/d [38] to 100±30µg/d [39]. The period these studied were contacted was between 2 to 18.4 months (Table 2).

### Correlation between SCH and carotid IMT

Among the 25 studies which met the eligibility criteria, 17 of them [13,16-18,20,21,23,26,29-32,35-38] with 737 patients with SCH vs 514 patients of control group totally, showed significant difference ( $p$  value <0.05) regarding the increase of IMT. A cross sectional study with the highest population till now (528 patients with SCH vs 8095 euthyroid ones), showed also statistically significant increase of IMT [32].

Regarding the rest 10 studies, 7 [12,14,19,24,25,27,33] were case control studies with 209 patients with SCH versus 187 subjects of the control group and retrieved not significant difference of carotid IMT between the compared groups. Not significant difference was also found in 2 studies, one retrospective [28] and one observational [15], which included 287 patients with SCH vs 5385 euthyroid and 337 vs 3130 respectively.

Finally there was 1 study [22] which did not show direct correlation between carotid IMT and thyroid function, but indirectly due to increased levels of homocysteine.

### Reverse of carotid IMT after administration of thyroxine (L T4)

Only three out of ten studies which were reviewed [33,40,41], did not conclude in statistically reversed IMT. In one of those, 0.75µg/Kg/day were administered for 12 months [40], while the second one was randomized, the starting dose of thyroxine was either 50µg/day or 25µg/day to those with coronary heart disease or a body weight under 50kg and was administered for about 18.4 months [41]. The third study had shorter duration, 2 months, and the dose of thyroxine was 50µg/day [33]. In regards of the rest studies, thyroxine was replaced

**Table 1:** Characteristics of the included studies and the correlation of Subclinical Hypothyroidism and carotid IMT.

First Author Year	Study Design	Country	IMT calculation	Patients Number	Differences in IMT	Matching of different factors
[12]	Prospective (case control)	Turkey	Bilateral 10-20 mm from the bifurcation of common carotid artery	25 pts with SCH vs 23 control pts (TSH 8.85±6.86 vs 1.71±0.91)	Non statistically significant difference	Matching for smoking, hypertension and family history of cardiovascular disease
[13]	Randomized	Italy	Bilateral both to the bifurcation of CCA and some mm before this	45 pts with SCH vs 32 control group [TSH 6.31(3.65-15) vs 1.19 (0.34-2.50)]	P value <0.001* (0.75±0.13 for SCH vs 0.63±0.07 for euthyroid)	Matching for sex, age and BMI
[14]	Prospective (case control)	Portugal	Average measurements in both carotids	30 pts with SCH vs 27 controls (TSH 8.69±3.82 vs 1.53±0.75)	Non-statistically significant difference	Matching for sex
[15]	Observational	Japan	10mm from the carotid bifurcation	377 pts with SCH vs 3130 controls (TSH 8.32±11.42 vs 1.723±0.824)	Non-statistically significant difference	Matching for sex, age and BMI
[16]	Randomized	Turkey	10mm from carotid bifurcation and to internal carotid artery bilaterally	44 pts with SCH vs 20 controls (TSH 7.6 ± 4.2 vs 2.3 ±0.8)	P value <0.001* (0.66±0.16 for SCH vs 0.54±0.10 for euthyroid)	Matching for sex and age
[17]	Prospective (case control)	Italy	Average of 5 calculations in each side (left and right) for every 4-5mm from carotid bifurcation	41 pts with SCH vs 31 controls (TSH 8.8 ± 1.7 vs 1.9 ± 0.3) respectively	P value < 0.001*	Matching for sex and age
[18]	Prospective (case control)	Korea	20mm from carotid bifurcation bilaterally	36 pts with SCH vs 32 controls (TSH 12.32 ± 5.9 vs 1.6 ±0.6)	P value <0.05* (0.66±0.10 for SCH vs 0.57±0.08 for euthyroid)	Matching for sex, age and BMI
[19]	Prospective (case control)	Brazil	At carotid bifurcation bilaterally	21 pts with SCH vs 21 controls [TSH 8.3(4.3) vs 1.2(0.7) respectively]	Non statistically significant difference	Matching for BMI, age and atherosclerotic factors
[20]	Prospective (case control)	Turkey	10mm from carotid bifurcation bilaterally	38 pts with SCH vs 19 controls (TSH 11.26 ± 7.54 vs 1.48 ± 1.12)	P value 0.037* (0.64±0.13 for SCH vs 0.57±0.08 for euthyroid)	Matching for age
[21]	Prospective (case control)	Skopia	At right common carotid, where there was not atheromatic plaque	67 pts with SCH vs 30 controls (TSH 7.9 ± 3.6 vs 1.5 ±0.8)	P value 0.034* (0.61±0.1 for SCH vs 0.56±0.10 for euthyroid)	Matching for sex and age
[22]	Prospective (cross-sectional)	Turkey	Average of 2 calculations in each common carotid artery	16 pts with SCH vs 20 controls (TSH 6.91 ± 1.74 vs 1,39 ± 0,68 respectively)	Not direct correlation between SCH and IMT, but through increased homocystein levels	NR
[23]	Prospective (case control)	Poland	At common carotid artery (10mm internal of bifurcation), carotid bulb, and common femoral artery bilaterally	40 pts with SCH vs 15 controls (TSH 20.5 ± 6.4 vs 2.165 ± 0.8 respectively)	P value <0.01* in all the 3 calculations of IMT	NR
[24]	Prospective (case control)	Turkey	3 measurements 1mm one from each other in distance of 10mm from carotid bifurcation	33 pts with SCH vs 32 controls (TSH 9.37±3.91 vs 1.73±1.05 respectively)	Non statistically significant difference	Matching for sex and age
[25]	Prospective	Turkey	4 measurements beginning of the dilatation of the carotid bulb	32 pts with SCH vs 29 controls (TSH 12.5±8.6 vs 1.7±0.76 respectively)	Non statistically significant difference	Matching for age, gender and sex
[26]	Prospective (case control)	Turkey	3 measurements 1mm one from each other in distance of 10mm from carotid bifurcation	39 pts with SCH vs 29 controls (TSH 7.35 ± 4.03 vs 1.81 ± 0.98 respectively)	P value < 0.01* (0.65±0.13 for SCH vs 0.55±0.11 for euthyroid)	Matching for sex and age
[27]	Prospective	Turkey	NR	43 pts with SCH vs 30 controls (TSH 6.0 ± 1.4 vs 2.0 ± 0.3 respectively)	No statistically significant difference	NR
[28]	Retrospective	Italy	5 measurements 1 mm from each other, 15mm of the right carotid bifurcation	287 pts with SCH vs 5385 controls [TSH 5.09 (4.41-6.84) vs 1.59(1.06-2.20) respectively]	Non statistically significant difference	NR
[29]	Prospective	Turkey	Average of 3 measurements in each carotid	51 pts with SCH vs 43 controls (TSH 6.2 ± 1.3 vs 1.9 ± 0.8 respectively)	P value < 0.01* (0.74±0.3 for SCH vs 0.47±0.5 for euthyroid)	Matching for sex and age
[30]	Prospective	China	Average of 3 measurements in each carotid	10 pts with mild SCH vs 10 with significant SCH vs 10 controls (TSH 5.92±1.47 vs 12.98±3.23 vs 3.32±0.57)	P value >0.05 (0.82 ± 0.14 for mild SCH vs 0.75 ± 0.09 for euthyroid) P value < 0.05* (0.99 ± 0.32 for significant SCH vs 0.75 ± 0.09 for euthyroid)	Matching for sex and age
[31]	Prospective	Brazil	NR	29 pts with SCH vs 31 controls	P=0.048 maximum IMT higher in the SCH vs controls	NR

[32]	Prospective (cross sectional)	Brazil	10mm from carotid bifurcation	528 pts with SCH vs 8095 controls [TSH 5.12 (4.45-6.37) vs 1.53 (1.07-2.22) respectively]	P value 0.009*	NR
[33]	Prospective	Iran	Common carotid artery	25 pts with SCH vs 25 controls (TSH 7.19±1.29 vs 2.4 ±0.55 respectively)	Non statistically significant difference	Matching for age and sex
[34]	Prospective	Turkey	Average of 5 measurements in both carotids and 10mm from carotid bifurcation	35 pts with SCH vs 30 controls [TSH 7.2(5–19.1) vs 1.4(0.5–3.5) respectively]	P value 0.004* (0.63±0.10 for SCH vs 0.55±0.05 for euthyroid)	NR
[35]	Prospective	Italy	3 measurements at internal carotid and at 10mm from carotid bifurcation	22 pts with SCH vs 26 controls (TSH 6.52 ± 1.64 vs 1.99 ± 0.68 respectively)	P value 0.002* (0.96±0.22 for SCH vs 0.67±0.12 for euthyroid)	NR
[36]	Prospective	Egypt	4 measurements at the beginning of the dilatation of the carotid bulb	30 pts with SCH vs 40 controls (TSH 7.2±2.2 vs 3.2±0.48 respectively)	P value <0.001* (0.6±0.2 for SCH vs 0.45±0.07 for euthyroid)	Matching for age and sex
[37]	Prospective, case control	Turkey	Distal common carotid artery, 2cm proximal to the carotid bulb	160 pts with SCH vs 86 controls (TSH 7.71±4.08 vs 1.82±0.82 respectively)	P value 0.008* (0.55±0.13 for SCH vs 0.43±0.19 for euthyroid)	Matching for age, gender, BMI, waist circumference and blood pressure
[38]	Prospective	Turkey	3 different points 1 cm distal of the right and left anterior carotid artery	40 pts with SCH vs 40 controls (TSH 1.99±0.9 vs 2.12.±1.42 respectively)	P value 0.042 (0.5±0.27 for SCH vs 0.5±0.16 for euthyroid)	NR

**Abbreviations:** IMT: Intima-Media Thickness; pts: patients; CCA: Common Carotid Artery; SCH: Subclinical Hypothyroidism; TSH: Thyroid-Stimulating Hormone; BMI: Body Mass Index; NR: Not Reported

**Table 2:** Reverse of IMT after thyroxine replacement.

First Author Year	Study Design	Country	Dose of Thyroxine	Before replacement	After replacement	P Value
[13]	Randomized	Italy	Mean dose 70µg/day for 6 months after becoming euthyroid or after standardised of the dose of thyroxine	0.76±0.14	0.67±0.13	0.03*
[16]	Randomized	Turkey	100µg/day for 8 months	0.65±0.99	0.55±0.08	<0.001*
[39]	Prospective	Ireland	100±30µg/day for 18 months	0.82±0.2	0.71±0.2	0.046*
[18]	Prospective (case control)	Korea	67µg/day for 12 months	0.67±0.11	0.60±0.10	0.021*
[20]	Prospective (case control)	Turkey	101±27.46µg/d for about 6 months (4-8 months)	0.64±0.13	0.63±0.12	0.008*
[40]	Randomized	Brazil	0.75µg/kg/day for 12 months	Non statistically significant reverse		
[27]	Prospective	Turkey	NR, 6 months duration	3.4±0.7	2.3±0.5	0.007*
[31]	Prospective	Iran	50µg/day, 2 months duration	Non statistically significant reverse		
[41]	Randomized	Switzerland	Starting dose 25-50µg/day, about 18.4 months	Non statistically significant reverse		
[35]	Prospective	Turkey	Started with a dose of 25µg/day and measurement of TSH every 4 weeks for dose adjustment, 12 weeks after becoming euthyroid	0.55±0.13	0.44±0.17	0.03*

**Abbreviations:** IMT: Intima-Media Thickness; NR: Not Reported

for 6-18 months and revealed statistically reduced carotid IMT, p value <0.05 (Table 2).

## Discussion

In our study, we systematically reviewed the literature, in order to retrieve the possible correlation between SCH and carotid IMT.

The SCH is related with increased arterial blood pressure and dyslipidemia. In the metaanalysis by Gao et al, [42] were compared euthyroid with SCH patients, and the last ones had slightly increased IMT. Yao et al in a metaanalysis of 27 case control studies also concluded in the association of the SCH and arterial wall stiffness [43]. Similarly, although the total sample size was small, in the metaanalysis by Gong et al that included 1521 subjects, the SCH was positively associated with IMT compared to controls [44]. Lorenz et al, and Saif et al found a positive correlation of IMT with the risk of vascular complications such as endothelial dysfunction, myocardial infarction and stroke [8,36]. Moreover, in a study by Niknam et al the authors found a positive correlation between SCH and endothelial dysfunction which could be reversed by thyroxine replacement [33].

These evidences indicate the positive effect of SCH on cardiovascular events.

The correlation between SCH and atherosclerosis could be attributed to many mechanisms such as TSH levels per se, increased arterial blood pressure, dyslipidemia hyperglycemia, inflammation and coexistence of autoimmunity.

TSH levels per se might play a role in increased IMT in patients with SCH in a dual mechanism. In 2009 Zhang W et al., proved that TSH receptor was present on hepatocytes and the increased TSH levels could additionally increase a hepatic reductase, which is involved in the cholesterol synthesis [45]. This could implicate a mechanism of direct action of TSH on the liver that could lead to dyslipidemia [46]. On the other hand, TSH levels might have a direct role in atherosclerosis independently from other factors like age, hypertension or dyslipidemia [21]. In a study by Lambrinouadaki et al., the authors studied euthyroid postmenopausal women and found that the TSH levels could contribute to the vascular sclerosis [47]. The scientists concluded to the question if the upper normal levels of TSH should be reviewed.



Hypertension is another factor which can lead to increased IMT. In the recent bibliography hypertension has been correlated with IMT either as an independent factor [48], or in association with SCH [42,49]. A possible mechanism which connects hypothyroidism with hypertension, is the increased sodium and water reabsorption through the inappropriate secretion of antidiuretic hormone. This additionally to the increased permeability of the capillaries and the accumulation of proteins in the extracellular space contributes to increase of IMT and vascular sclerosis [50-52].

Dyslipidemia is one main cause of cardiovascular disease. While previous studies did not find any association of SCH with abnormalities in cholesterol levels [53] SCH seems to be statistically correlated with increased total cholesterol, LDL and triglycerides, but not with HDL levels [42,54]. In a study by Tan et al the increased triglycerides were found to be an independent factor that increased IMT [38]. Moreover, given that LDL is responsible for the development of the atheromatic plaque, SCH is in accordance with atheromatic disease especially in subjects over 40 years old as is indicated by the study of Monzani et al. [13]. According to the same study, it is remarkable that the administration of thyroxine not only improved the lipidemic profile but also led to the reverse of IMT, something that strengthens the relationship among dyslipidemia, atherosclerosis and SCH. However, Duman et al. concluded that the administration of statin therapy reduced both IMT and lipids levels. Instead of this, the replacement of thyroxine reduced IMT, but did not decrease the lipids levels [16]. This reverse of IMT had been proved by other studies too [18,37,39] included two metaanalysis by Zhao et al [55] and Aziz et al [56], respectively and enhances the correlation between SCH and IMT. However, in a metaanalysis by Swaid et al [57] the authors included 7 RCTs and they did not find any reverse in IMT after thyroxine administration. According to the authors this may happened because they included the paper of Blum et al, a study with significant weight, that found no difference in IMT and carotid atherosclerosis in older persons with SCH [41]. That might be due to multiple metabolic dysfunctions in the elderly that affect the formation of atheromatic plaque. According to Yazici et al., the restoration of thyroid dysfunction with thyroxine was associated statistically with reduction in both epicardial fat and IMT, resulting in a potential reduction of cardiovascular risk [27].

Regarding the metabolism of glucose and its correlation with SCH, the data are controversial. Maratou et al. reported the presence of insulin resistance in patients with SCH, while other studies ended up with totally different results [58,59]. In the meta analysis by Gao et al, only half of the studies included data regarding the glucose metabolism of the patients [42]. Furthermore, in a recent study the scientists found that patients with SCH had increased glycemic levels compared to euthyroid controls and the experiments in SCH mouse model revealed that the abnormal glucose metabolism, as well as insulin resistance, predominantly involve the IRE1 $\alpha$ /XBP-1 pathway [60].

Beside arterial blood pressure, dyslipidemia and TSH levels per se, also the mechanism of inflammation could explain the correlation between SCH and IMT. The patients with SCH have also increased hs-CRP [61]. However, in a study by Kebapcilar et al., even if there was not found significant differences in hs-CRP between euthyroidic patients and those with SCH, there was a significant reduce of IMT

after administration of thyroxine [20]. On the other hand, apelin and homocysteine seems to be two new players in vascular and cardiac disorder in patients with SCH. Yasar et al in a recent paper studied populations with and without SCH and found that patients with hypothyroidism had increased homocysteine and lower apelin levels that were reversed after thyroxine administration [37]. Apelin may trigger cardiovascular dysfunction via elevation of inflammatory markers such as IL-6 and TNF- $\alpha$  according to Tang R et al. [62]. Thus, the apelin system may indicate a new mediator in increasing IMT in patients with SCH, through inflammatory process.

Moreover, the incidence of atherosclerosis in subjects with thyroiditis Hashimoto was increased both in SCH [63], and euthyroid patients. This evidence possibly indicates that autoimmunity plays a role in worsening IMT causing carotid stenosis [19]. However, there were many studies in our review that did not show significant differences in IMT of control versus SCH subjects. This would probably happened because the group of patients with SCH had neither serious dyslipidemia nor significant autoimmunity [14]. According to the study of Cabral et al, despite there were not statistically differences of IMT in both control group and group of patients with SCH, the presence of autoimmunity by itself led to a possible increase of IMT in the patients with SCH and positive anti-TPO compared to those without increased antibodies [19].

As every study, our systematic review has some limitations. Firstly, our findings should be interpreted with caution since most of the included studies were prospective case control studies and there were only 4 randomized studies. Secondly, the integrity of the results could be affected, since there was heterogeneity between the studies, regarding the position of IMT calculation and the information given by the authors about the selection criteria of control and patient group. Finally the inherent weakness of each study to know how long ago the entity of SCH was installed and how long the negative impact on the vascular network preexisted, further increases the heterogeneity.

Accordingly to many studies, IMT could have clinical importance to be estimated in patients with SCH regularly. Additionally, in this review, 7 out of 10 studies showed a statistically reduce of IMT after the administration of thyroxine and 2 of them were randomized studies. However, more double blind randomized studies need to evaluate the efficacy of thyroxine administration in the decrease of carotid IMT and cardiovascular risk in patients with SCH.

## References

1. Sawin CT, Castelli WP, Hershman JM, Mc Namara P, Bacharach P. The aging thyroid. Thyroid deficiency in the Framingham Study. *Arch Intern Med.* 1985; 145: 1386-1388.
2. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf).* 1977; 7: 481-493.
3. Williams Textbook of Endocrinology, 12<sup>th</sup> Edition, Thyroid Section.
4. Arem R, Rokey R, Kiefe C, Escalante DA, Rodriguez A. Cardiac systolic and diastolic function at rest and exercise in subclinical hypothyroidism: effect of thyroid hormone therapy. *Thyroid.* 1996; 6: 397-402, 1996.
5. Ebert EC. The thyroid and the gut. *J Clin Gastroenterol.* 2010; 44: 402-406.
6. Longo D, Fauci A, Kasper D, Hauser S, Jameson L, Loscalzo J. Disorders of the thyroid gland. Harrison's principles of internal medicine. (18<sup>th</sup> ed.) New York: McGraw-Hill 201.

7. de Groot E, van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, et al. Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat Clin Pract Cardiovasc Med*. 2008; 5: 280-288.
8. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation*. 2007; 115: 459-467.
9. Masoura C, Pitsavos C, Aznaouridis K, Skoumas I, Vlachopoulos C, Stefanadis C. Arterial endothelial function and wall thickness in familial hypercholesterolemia and familial combined hyperlipidemia and the effect of statins. A systematic review and meta-analysis. *Atherosclerosis*. 2011; 214: 129-138.
10. Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. *Diabet Med*. 2006; 23: 609-616.
11. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation*. 1986; 74: 1399-1406.
12. Cikim AS, Oflaz H, Ozbey N, Cikim K, Umman S, Meric M, et al. Evaluation of endothelial function in subclinical hypothyroidism and subclinical hyperthyroidism. *Thyroid*. 2004; 14: 605-609.
13. Monzani F, Caraccio N, Kozàková M, Dardano A, Vittone F, Virdis A, et al. Effect of Levothyroxine Replacement on Lipid Profile and Intima-Media Thickness in Subclinical Hypothyroidism: A Double-Blind, Placebo Controlled Study. *J Clin Endocrinol Metab*. 2004; 89: 2099-2106.
14. Almeida CA, Teixeira PDF, Soares DV, Cabral MD, Costa SM, Salles EF, et al. Carotid Intima-Media Thickness as a Marker of Cardiovascular Risk in Patients With Subclinical Hypothyroidism. *Arq Bras Endocrinol Metab*. 2007; 51: 472-477.
15. Takashima N, Niwa Y, Mannami T, Tomoike H, Iwai N. Characterization of Subclinical Thyroid Dysfunction From Cardiovascular and Metabolic Viewpoints. The Suita Study. *Circ J*. 2007; 71: 191-195.
16. Duman D, Demirtunc R, Sahin S, Esertas K. The effects of simvastatin and levothyroxine on intima-media thickness of the carotid artery in female normolipemic patients with subclinical hypothyroidism: a prospective, randomized-controlled study. *J Cardiovasc Med (Hagerstown)*. 2007; 8: 1007-1011.
17. Franzoni F, Galetta F, Fallahi P, Tocchini L, Braccini L, Rossi M, et al. Carotid integrated backscatter analysis in patients with subclinical hypothyroidism. *Clin Endocrinol (Oxf)*. 2008; 68: 278-283.
18. Kim SK, Kim SH, Park KS, Park SW, Cho YW. Regression of the Increased Common Carotid Artery-intima Media Thickness in Subclinical Hypothyroidism after Thyroid Hormone Replacement. *Endocrine J*. 2009; 56: 753-758.
19. Cabral MD, Teixeira PF, Silva NA, Morais FF, Soares DV, Salles E, et al. Normal flow-mediated vasodilatation of the brachial artery and carotid artery intima-media thickness in subclinical hypothyroidism. *Braz J Med Biol Res*. 2009; 42: 426-432.
20. Kebapçılar L, Comlekci A, Tuncel P, Solak A, Secil M, Gencil O, et al. Effect of levothyroxine replacement therapy on paraoxonase-1 and carotid intima-media thickness in subclinical hypothyroidism. *Med Sci Monit*. 2010; 16: CR41-CR47.
21. Valentina VN, Marijan B, Chedo D, Branka K. Subclinical hypothyroidism and risk to carotid atherosclerosis. *Arq Bras Endocrinol Metabol*. 2011; 55: 475-480.
22. Gunduz M, Gunduz E, Kircelli F, Okur N, Ozkaya M. Role of Surrogate Markers of Atherosclerosis in Clinical and Subclinical Thyroidism. *Int J Endocrinol*. 2012; 109797.
23. Knapp M, Lisowska A, Sobkowicz B, Tycińska A, Sawicki R, Musiał WJ. Myocardial perfusion and intima-media thickness in patients with subclinical hypothyroidism. *Adv Med Sci*. 2013; 58: 44-49.
24. Asik M, Sahin S, Ozkul F, Anaforoglu I, Ayhan S, Karagol S, et al. Evaluation of epicardial fat tissue thickness in patients with Hashimoto thyroiditis. *Clin Endocrinol (Oxf)*. 2013; 79: 571-576.
25. Kilic ID, Tanriverdi H, Fenkci S, Akin F, Uslu S, Kaftan A. Noninvasive indicators of atherosclerosis in subclinical hypothyroidism. *Indian J Endocrinol Metab*. 2013; 17: 271-275.
26. Gunes F, Asik M, Temiz A, Vural A, Sen H, Binnetoglu E, et al. Serum H-FABP levels in patients with hypothyroidism. *Wien Klin Wochenschr*. 2014; 126: 727-733.
27. Yazıcı D, Özben B, Toprak A, Yavuz D, Aydın H, Tarçın Ö, et al. Effects of restoration of the euthyroid state on epicardial adipose tissue and carotid intima media thickness in subclinical hypothyroid patients. *Endocrine*. 2015; 48: 909-915.
28. Delitala AP, Filigheddu F, Orrù M, AlGhatrif M, Steri M, Pilia MG, et al. No evidence of association between subclinical thyroid disorders and common carotid intima medial thickness or atherosclerotic plaque. *Nutr Metab Cardiovasc Dis*. 2015; 25: 1104-1110.
29. Akbaba G, Berker D, Isık S, Tuna MM, Koparal S, Vural M, et al. Changes in the before and after thyroxine treatment levels of adipose tissue, leptin, and resistin in subclinical hypothyroid patients. *Wien Klin Wochenschr*. 2016; 128: 579-585.
30. Zha K, Zuo C, Wang A, Zhang B, Zhang Y, Wang B, et al. LDL in patients with subclinical hypothyroidism shows increased lipid peroxidation. *Lipids Health Dis*. 2015; 14: 95.
31. França M, Nogueira CR, Hueb JC, Mendes AL, Padovani CR, Ferreira da Silva Mazeto GM. Higher carotid Intima-Media Thickness in subclinical hypothyroidism associated with the metabolic syndrome. *Metab Syndr Relat Disord*. 2016; 14: 381-385.
32. Peixoto de Miranda ÉJ, Bittencourt MS, Pereira AC, Goulart AC, Santos IS, Lotufo PA, et al. Subclinical hypothyroidism is associated with higher carotid intima-media thickness in cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Nutr Metab Cardiovasc Dis*. 2016; 26: 915-921.
33. Niknam N, Khalili N, Khosravi E, Nourbakhsh M. Endothelial dysfunction in patients with subclinical hypothyroidism and the effects of treatment with levothyroxine. *Adv Biomed Res*. 2016; 16: 38.
34. Altay M, Karakoç MA, Çakır N, Demirtaş CY, Cerit ET, Aktürk M, et al. Serum Total Sialic Acid Level is Elevated in Hypothyroid Patients as an Atherosclerotic Risk Factor. *J Clin Lab Anal*. 2017; 31.
35. Carbotta G, Tartaglia F, Giuliani A, Carbotta S, Tromba L, Jacomelli I, et al. Cardiovascular risk in chronic autoimmune thyroiditis and subclinical hypothyroidism patients. A cluster analysis. *Int J Cardiol*. 2017; 230: 115-119.
36. Saif A, Mousa S, Assem M, Tharwat N, Abdelhamid A. Endothelial dysfunction and the risk of atherosclerosis in overt and subclinical hypothyroidism. *Endocr Connect*. 2018; 7: 1075-1080.
37. Yasar HY, Demirpence M, Colak A, Yurdakul L, Zeytinli M, Turkon H, et al. Serum irisin and apelin levels and markers of atherosclerosis in patients with subclinical hypothyroidism. *Arch Endocrinol Metab*. 2019; 63: 16-21.
38. Tan M, Korkmaz H, Aydın H, Doğuç DK. FABP4 levels in hypothyroidism and its relationship with subclinical atherosclerosis. *Turk J Med Sci*. 2019; 49: 1490-1497.
39. Adrees M, Gibney J, El-Saeity N, Boran G. Effects of 18 months of L-T4 replacement in women with subclinical hypothyroidism. *Clin Endocrinol (Oxf)*. 2009; 71: 298-303.
40. Cabral MD, Teixeira P, Soares D, Leite S, Salles E, Waisman M. Effects of thyroxine replacement on endothelial function and carotid artery intima-media thickness in female patients with mild subclinical hypothyroidism. *Clinics (Sao Paulo)*. 2011; 66: 1321-1328.
41. Blum MR, Gencer B, Adam L, Feller M, Collet TH, da Costa BR, et al. Impact of Thyroid Hormone Therapy on Atherosclerosis in the Elderly With Subclinical Hypothyroidism: A Randomized Trial. *J Clin Endocrinol Metab*. 2018; 103: 2988-2997.
42. Gao N, Zhang W, Zhang YZ, Yang Q, Chen SH. Carotid intima-media

- thickness in patients with subclinical hypothyroidism: A meta-analysis. *Atherosclerosis*. 2013; 227: 18-25.
43. Yao K, Zhao T, Zeng L, Yang J, Liu Y, He Q, et al. Non-invasive markers of cardiovascular risk in patients with subclinical hypothyroidism: A systematic review and meta-analysis of 27 case control studies. *Sci Rep*. 2018; 8: 4579.
44. Gong N, Gao C, Chen X, Fang Y, Tian L. Endothelial Function in Patients With Subclinical Hypothyroidism: A Meta-Analysis. *Horm Metab Res*. 2019; 51: 691-702.
45. Zhang W, Tian LM, Han Y, Ma HY, Wang LC, Guo J, et al. Presence of thyrotropin receptor in hepatocytes: not a case of illegitimate transcription. *J Cell Mol Med*. 2009; 13: 4636-4642.
46. Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, et al. A novel role for thyroid-stimulating hormone: up-regulation of hepatic 3-hydroxy-3-methylglutaryl-coenzyme a reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. *Hepatology*. 2010; 52: 1401-1409.
47. Lambrinouadaki I, Armeni E, Rizos D, Georgiopoulos G, Kazani M, Alexandrou A, et al. High normal thyroid-stimulating hormone is associated with arterial stiffness in healthy postmenopausal women. *J Hypertens*. 2012; 30: 592-599.
48. Wang JG, Staessen JA, Li Y, Van Bortel LM, Nawrot T, Fagard R, et al. Carotid intima-media thickness and antihypertensive treatment: a meta-analysis of randomized controlled trials. *Stroke*. 2006; 37: 1933-1940.
49. Cai Y, Ren Y, Shi J. Blood pressure levels in patients with subclinical thyroid dysfunction: a meta-analysis of cross-sectional data. *Hypertens Res*. 2011; 34: 1098-1105.
50. Gumieniak O, Perlstein TS, Hopkins PN, Brown NJ, Murphey LJ, Jeunemaitre X, et al. Thyroid function and blood pressure homeostasis in euthyroid subjects. *J Clin Endocrinol Metab*. 2004; 89: 3455-3461.
51. Marcisz C, Jonderko G, Kucharz EJ. Influence of short-time application of a low sodium diet on blood pressure in patients with hyperthyroidism or hypothyroidism during therapy. *Am J Hypertens*. 2001; 14: 995-1002.
52. Ojamaa K, Klemperer JD, Klein I. Acute effects of thyroid hormone on vascular smooth muscle. *Thyroid*. 1996; 6: 505-512.
53. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. *Ann Fam Med*. 2004; 2: 351-355.
54. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000; 160: 526-534.
55. Zhao T, Chen B, Zhou Y, Wang X, Zhang Y, Wang H, et al. Effect of Levothyroxine on the Progression of Carotid Intima-Media Thickness in Subclinical Hypothyroidism Patients: A Meta-Analysis. *BMJ Open*. 2017; 7: e016053.
56. Aziz M, Kandimalla Y, Machavarapu A, Saxena A, Das S, Younus A, et al. Effect of Thyroxin Treatment on Carotid Intima-Media Thickness (CIMT) Reduction in Patients With Subclinical Hypothyroidism (SCH): A Meta-Analysis of Clinical Trials. *J Atheroscler Thromb*. 2017; 24: 643-659.
57. Swaid B, Kheiri B, Sundus S, Shah Miran M, Haykal T, Zayed Y, et al. The Effect of Levothyroxine Treatment in Individuals with Subclinical Hypothyroidism on Surrogate Markers of Atherosclerosis: A Meta-Analysis of Randomized Controlled Trials. *J Community Hosp Intern Med Perspect*. 2019; 9: 305-309.
58. Maratou E, Hadjidakis DJ, Kollias A, Tsegka K, Peppas M, Alevizaki M, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *Eur J Endocrinol*. 2009; 160: 785-790.
59. Gjedde S, Gormsen LC, Rungby J, Nielsen S, Jørgensen JO, Pedersen SB, et al. Decreased lipid intermediate levels and lipid oxidation rates despite normal lipolysis in patients with hypothyroidism. *Thyroid*. 2010; 20: 843-849.
60. Xu C, Zhou L, Wu K, Li Y, Xu J, Jiang D, et al. Abnormal Glucose Metabolism and Insulin Resistance Are Induced via the IRE1 $\alpha$ /XBP-1 Pathway in Subclinical Hypothyroidism. *Front Endocrinol (Lausanne)*. 2019; 17: 303.
61. Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, et al. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. *Atherosclerosis*. 2003; 166: 379-386.
62. Tang R, Wang R, Ao X, Cheng X. Plasma level of apelin and carotid atherosclerosis in maintenance hemodialysis patients. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2017; 42: 617-622.
63. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med*. 2000; 132: 270-278.