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Original Research Article

Assessment of carotid intima-media thickness in hypothyroidism and the effect of thyroid replacement therapy

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ABSTRACT

Background: Carotid artery intima-media thickness (CAIMT) measurement in hypothyroidism will help assess the progression of atherosclerosis and timely intervention may prevent vascular complications.
Methods: This study included 30 clinical hypothyroid (CH), 30 subclinical hypothyroid (SCH) and 30 euthyroid. As per procedure, informed consent was taken from the patients in prescribed formats before their participation in the study. Patients were divided into 3 groups of CHs, SCH and Controls after obtaining the thyroid function test values. CAIMT on the right side was measured in the three groups for comparison. Other parameters included age, sex, height, weight, body mass index (BMI), total cholesterol and triglycerides. After 4 months of levothyroxine therapy, CAIMT, total cholesterol and triglycerides were reassessed.
Results: The CAIMT was increased in CH and SCH group when compared to euthyroid individuals. The mean CAIMT in CH group was 0.60±0.009cm, in SCH group it was 0.055±0.010 cm and in controls it was 0.047±0.006 cm. After 4 months of levothyroxine therapy, there was no change observed in the mean CAIMT values.
Conclusions: CAIMT levels were increased in CH and SCH group when compared to euthyroid group. There was no regression of CAIMT after 4 months of levothyroxine therapy.

Keywords: Carotid artery intima-media thickness, Clinical hypothyroidism, Subclinical hypothyroidism

INTRODUCTION

Carotid artery intima-media thickness (CAIMT) is a generally acknowledged measure of subclinical atherosclerotic alterations. It is used to estimate vascular function in clinical analyses to assess the efficacy of interventions that reduce atherosclerosis and related diseases.[1] This parameter has been listed in the European guidelines for prevention of cardiovascular diseases, and 0.9 mm is the threshold value for CAIMT. Advancement of atherosclerosis is indicated when the value of CAIMT is over the threshold.[2] Several risk factors for atherosclerotic cardiovascular disease have been recognized, including endothelial dysfunction, hyperhomocysteinemia, elevated C-reactive protein (CRP) levels, and insulin resistance. The effect of hypothyroidism on vascular risk factors for atherosclerosis has been investigated in many studies.

Variations in flow-mediated, endothelium-dependent vasodilatation, which occurs early in atherogenesis, have been noted in patients with hypothyroidism. It is tentative whether it can be attributed to a direct effect of thyroid hormone deficiency or facilitated through the elevated cholesterol levels induced by hypothyroidism.[3] Prompt treatment must be initiated for all patients with a TSH value of >10µIU/L.[4]

Hypothyroidism has been associated with atherosclerosis, which in turn may lead to cardiovascular events. Subclinical hypothyroidism in our country is generally undiagnosed and if diagnosed, patients discontinue treatment and lose follow up due to the lack of physical symptoms in most. In this study, we have assessed the CAIMT of hypothyroid patients (clinical and subclinical) and compared it with euthyroid individuals to have a better understanding of association of atherosclerotic changes that tend to occur in these patients.

METHODS

This research study was conducted in the Department of General Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry, a tertiary health care centre. The samples were collected during the period of 18 months from January 2016 to June 2017. The study was initiated with 30 clinical hypothyroid, 30 subclinical hypothyroid patients and 30 euthyroid individuals equally distributed in both genders.

Inclusion criteria

- Age: 18-65 years.
- Thyroid hormone dysfunction assessed by laboratory findings.
- Newly diagnosed hypothyroid patients.
- Euthyroid individuals

Exclusion criteria

- Diabetes
- Hypertension
- TSH < 10 µIU/ml
- Previous h/o CAD.
- Patients already on thyroid replacement therapy.
- Renal Failure.
- Malignancies
- Patients on lipid lowering drugs.
- Smokers.

Brief explanation of the procedure

Patients were divided into 3 groups

- Group 1 - Subclinical Hypothyroidism (SCH) containing 30 patients. [Elevated TSH (10 – 20 µIU/ml) but FreeT4 and FreeT3 within normal ranges]
- Group 2 - Clinical Hypothyroidism (CH) containing 30 patients. [Elevated TSH, Low FreeT4 and FreeT3]
- Group 3 - Euthyroid individuals (Control) containing 30 patients. [Normal TSH, FreeT4 and FreeT3].

Age, sex, height, weight, thyroid profile, total cholesterol, triglycerides and CAIMT were measured and recorded in all patients fulfilling the inclusion criteria. Subjects were age and sex matched. Hypothyroid patients were started on levothyroxine therapy. They were followed up at the end of 4 months to reassess their thyroid profile, lipid status and CAIMT. The data was documented accordingly. Normal individuals were explained about the benefits of the investigations and after obtaining their consent thyroid profile, lipid profile, and carotid intima media thickness were measured and recorded.

CAIMT was measured with Mindray DC-8 ultrasound equipment using the linear transducer of 7 MHz frequency. The subject was placed in supine position with his/her neck in extension and rolled contra-laterally by about 45º. The intima-media thickness was taken on the far wall, 10 mm proximal to the right common carotid bulb. IMT was evaluated as the distance between the lumen intima and the media-adventitia interface.[5] A single radiologist manually measured the IMT and he was blinded to the identity of the subjects.

Venous blood samples were drawn between 7 am and 8 am after an overnight fast. Thyroid function test was done by chemiluminescent immunometric assay. The normal values for TSH according to our lab were 0.3 – 4.20 µIU/ml, for FT4: 0.93 – 1.76 ng/dl, and FT3: 2.0 – 4.4 pg/ml.

Total cholesterol was estimated using an enzymatic method (cholesterol oxidase and peroxidase method) and triglyceride was measured using glycerol-3-phosho oxidase (GPO) method.

Thyroid function was evaluated considering three categories: clinical hypothyroidism, subclinical hypothyroidism and euthyroid. The collected data were compared using One way ANOVA test.

Nonparametric tests (Wilcoxon signed rank test and Kruskal-Wallis test) were used for univariate analysis of triglyceride values.

The review parameters were compared between the two groups (clinical and subclinical hypothyroidism) using the Paired t-test.

$p < 0.05$ was considered statistically significant.

RESULTS

A total of 90 patients were taken for this study. They were divided into three groups of subclinical, clinical and euthyroid, with each group containing 30 participants

with mean age of 33.90±10.69, 35.53±9.95 and 37.93±9.78 years respectively. p value was 0.307 (Table 1). Among all the 3 groups, the percentage of male subjects were 6.7% and the percentage of female subjects were 93.3%. (Table 2). The mean BMI was 24.66±4.13, 27.07±4.89 and 22.86±3.01 kg/m2 in SCH, CH and euthyroid group respectively (Table 3).

Table 1: Mean age of study subjects.

	Mean (in years)	Standard Deviation	p value *
Subclinical (n=30)	33.90	10.69	
Clinical (n=30)	35.53	9.95	0.307
Euthyroid (n=30)	37.93	9.78	

*One way ANOVA test

Table 2: Gender distribution of study subjects.

	Subclinical		Clinical		Euthyroid		Total	
	N	%	N	%	N	%	N	%
Male	2	{6.7}	2	{6.7}	2	{6.7}	6	{6.7}
Female	28	{93.3}	28	{93.3}	28	{93.3}	84	{93.3}
Total	30	{100.0}	30	{100.0}	30	{100.0}	90	{100.0}

Fisher's exact p value=1

Table 3: Mean body mass index (BMI) of the study participants (N=90).

	Mean	Standard Deviation	P value *
Subclinical (n=30)	24.66	4.13	
Clinical (n=30)	27.07	4.89	0.006
Euthyroid (n=30)	22.86	3.01	

*One way ANOVA test

In our study, we found that the mean TSH level for the SCH group was 15.58±3.13µIU/ml, for CH 66.487±34.815µIU/ml and for euthyroid it was 2.47±1.25µIU/ml. In the SCH group the mean FT3 level was 2.35±0.69pg/ml while in the CH group it was 1.61±0.58pg/ml and in euthyroid group the mean was 2.35±0.38pg/ml. The mean FT4 in the SCH group was 1.23 ± 0.33 ng/dl, which was within the normal limits. While in the CH group it was 0.82 ± 0.49 ng/dl which is lower than the SCH group. In the euthyroid group, mean FT4 was 1.77 ± 0.23 ng/dl. The p value in all the three groups was < 0.0001 (Table 4).

Table 4: Mean TSH, FT3 and FT4 of study participants.

	TSH		FT3		FT4	
	Mean (µIU/ml)	SD	Mean (pg/ml)	SD	Mean (ng/dl)	SD
Subclinical (n = 30)	15.58	3.13	2.35	0.69	1.23	0.33
Clinical (n = 30)	66.48	34.81	1.61	0.58	0.82	0.49
Euthyroid (n = 30)	2.47	1.253	2.35	0.38	1.77	0.23
p Value*	<0.0001		<0.0001		<0.0001	

*One way ANOVA

Total cholesterol values in the SCH group ranged from 172 to 237 mg/dl. The mean was 201.43 ± 18.26 mg/dl. In the CH group the values ranged from 182 to 352 mg/dl and the mean was 233.27 ± 42.49 mg/dl. The mean in euthyroid group was 154.57 ± 25.23 mg/dl.

The p value was < 0.0001 which was statistically significant. Kruskal Wallis test was used to calculate the median triglyceride values because the variation in triglyceride levels mandated the use of a non-parametric method. In the CH group, the lowest triglyceride range varied among patients from 63 mg/dl to as high as 1533 mg/dl. The calculated median triglycride was 129 mg/dl. In the SCH group the lowest value we obtained was 92 mg/dl and the highest was 347 mg/dl. The calculated median was 207mg/dl. 17 study participants had TG > 200 mg/dl. Median triglyceride of euthyroid subjects were 102.5 mg/dl. There was a significant difference

observed in the triglyceride levels between the 3 groups with a p value < 0.0001 (Table 5).

The mean CAIMT on the right side was estimated for all the three groups. In the SCH group the mean was 0.55 ± 0.1mm and in the CH group it was 0.60 ± 0.09mm. Although within the normal range CAIMT was increased in the SCH and CH group when compared with euthyroid controls with a mean CAIMT of 0.47 ± 0.06 mm. The p value was < 0.0001 which was statistically significant. The mean CAIMT was more in the CH group when compared with the SCH group (Table 6).

Table 5: Mean total cholesterol and median triglyceride levels of study participants.

	Total cholesterol		Triglyceride	
	Mean (mg/dl)	**SD**	**Median (mg/dl)**	**Inter quartile range**
Subclinical (n = 30)	201.43	18.26	207	184.5-232
Clinical (n = 30)	233.27	42.49	129	101.5-164
Euthyroid (n = 30)	154.57	25.23	102.5	90-126.5
p Value	<0.0001*		<0.0001#	

*One way ANOVA test, #Kruskal Wallis test

Table 6: Mean CAIMT of the study participants.

	Mean (mm)	Standard Deviation	p value *
Subclinical (n=30)	0.55	0.10	<0.0001
Clinical (n=30)	0.60	0.09	
Euthyroid (n=30)	0.47	0.06	

*One way ANOVA test

Comparison of parameters after 4 months of levothyroxine among subclinical and clinical study participants

After 4 months of levothyroxine therapy, the mean levels of TSH was estimated in both clinical and subclinical hypothyroidism groups. In the subclinical group, the mean TSH levels reduced to 2.92 µIU/ml from 15.58 µIU/ml. In the clinical group, the mean TSH levels reduced from 66.49 µIU/ml to 13.58 µIU/ml (Table 7).

The mean FT3 levels were calculated in both subclinical and clinical hypothyroisim group after 4 months of levothyroxine therapy. In the SCH group the mean FT3 was within the normal range 2.35 pg/ml and there was not any significant difference after levothyroxine therapy, with a mean of 2.39 pg/ml. In the CH group the mean FT3 was on the lower side with a value of 1.61 pg/ml, improved to 2.26 pg/ml after 4 months of levothyroxine therapy with a p value of < 0.0001 and showed statistical significance (Table 7).

Table 7: Comparison of TFT values - baseline and after 4 months of levothyroxine.

	Subclinical (n = 30)	Clinical (n = 30)
Mean TSH Baseline ± SD (µIU/ml)	15.58 ± 3.13	66.49 ± 34.82
Mean TSH after 4 months ± SD (µIU/ml)	2.92 ± 1.60	13.58 ± 12.30
p Value*	<0.0001	<0.0001
Mean FT3 Baseline ± SD (pg/ml)	2.35 ± 0.69	1.61 ± 0.58
Mean FT3 after 4 months ± SD (pg/ml)	2.39 ± 0.36	2.26 ± 0.39
p Value*	0.7333	<0.0001
Mean FT4 Baseline ± SD (ng/dl)	1.23 ± 0.33	0.82 ± 0.49
Mean FT4 after 4 months ± SD (ng/dl)	1.70 ± 0.30	1.65 ± 0.34
p Value*	<0.0001	<0.0001

*Paired samples t test

The mean FT4 levels were calculated in both SCH and CH group after 4 months of levothyroxine therapy. In the SCH group the mean FT4 although within the normal range of 1.23 ng/dl, there was improvement after levothyroxine therapy, with a mean of 1.70 ng/dl. The p value in SCH group was 0.7333 which was not statistically significant. In the CH group the mean FT4 was on the lower side with a value of 0.82 ng/dl, which improved to 1.65 ng/dl after 4 months of levothyroxine therapy. The p value was < 0.0001 which was statistically significant (Table 7).

Mean total cholesterol (TC) levels were estimated in SCH and the CH group after 4 months of levothyroxine therapy. In the SCH group, the mean TC reduced from 201.43 mg/dl to 145.73 mg/dl. In the CH group, the mean TC reduced from 233.27 mg/dl to 162.97 mg/dl. The calculated p value was <0.0001 in both the groups, which was statistically significant (Table 8).

In the SCH group, the mean TG reduced from 205.90 mg/dl to 103.70 mg/dl, with a p value of < 0.0001 which showed statistical significance. In the CH group, the mean TG reduced from 197.53 mg/dl to 114.40 mg/dl. The p value was calculated using Wilcoxon signed rank test and was found to be 0.001 (Table 8).

The mean CAIMT, measured on the right side, in the SCH group before initiating levothyroxine therapy was 0.55 ± 0.1 mm. After 4 months of levothyroxine therapy the mean CAIMT had the same value of 0.55 ± 0.1 mm. (p value 0.3256) In the CH group the mean CAIMT, measured on the right side, was 0.60 ± 0.09 mm before initiating on levothyroxine therapy. The mean CAIMT was 0.61 ± 0.08 mm after 4 months of levothyroxine therapy. (p value 0.0960) (Table 9).

Table 8: Comparison of TC and TG levels after 4 months of levothyroxine.

	Subclinical (n = 30)	Clinical (n = 30)
Mean Total Cholesterol – Baseline ± SD (mg/dl)	201.43 ± 18.26	233.27 ± 42.49
Mean Total Cholesterol after 4 months ± SD (mg/dl)	145.73 ± 23.04	162.97 ± 24.71
p Value	<0.0001	<0.0001
Mean Triglyceride – Baseline ± SD (mg/dl)	205.90 ± 51.31	197.53 ± 265.48
Mean Triglyceride after 4 months ± SD (mg/dl)	103.70 ± 23.83	114.40 ± 38.90
p Value	<0.0001*	0.001#

*Paired samples t test #Wilcoxon signed rank test

Table 9: Comparison of CAIMT levels after 4 months of levothyroxine.

	Subclinical (n = 30)	Clinical (n = 30)
Mean CAIMT – Baseline ± SD (in mm)	0.55 ± 0.1	0.60 ± 0.09
Mean CAIMT After 4 months ± SD (in mm)	0.55 ± 0.1	0.61 ± 0.08
p Value*	0.3256	0.0960

*Paired samples t test

DISCUSSION

The mean age in subclinical (SCH) and clinical hypothyroidism (CH) were 33.90 ± 10.69 and 35.53 ± 9.95 years respectively. Since the subjects were age matched, to avoid age related atherosclerosis to influence CAIMT, there was no significant variation among the three groups. In the euthyroid group the mean age was 37.93 ± 9.78 years. p value was 0.307. In a study done by Unnikrishnan et al, the mean age of hypothyroid subjects were 46 ± 14.68 years which is in sharp contrast to our study, as the subjects were age matched.[6]

Among the three groups, the percentage of male subjects in SCH and CH were 6.7% and the percentage of female subjects were 93.3%. The subjects were sex matched to avoid significant variation among the three groups. Studies have shown that atherosclerotic changes develop 7 to 10 years later in women than in men.[7]

Mean BMI was 24.66 ± 4.13, 27.07±4.89 and 22.86±3.01 kg/m^2 in SCH, CH and euthyroid group respectively. In the SCH and CH group BMI was higher when compared with euthyroid group. This shows the role thyroid hormone plays in obesity. In a study done by Aziz KM clinical hypothyroid patients had a higher BMI when compared with SCH group (32.2±7.44 versus 29.4±5.7).[8] The p value was 0.006 which was statistically significant.

Since management of patients with a serum TSH level of less than 10 µIU/ml is controversial, in our study, we had selected patients with TSH > 10µIU/ml.[9] The mean TSH level for the SCH was 15.585±3.135 µIU/ml, for CH 66.487±34.815 µIU/ml and for euthyroid controls, it was 2.477±1.253 µIU/ml. Presently, the approach is routine levothyroxine therapy for patients with a serum TSH of more than 10.0 µIU/ml.[10] Levothyroxine was initiated at a dose of 0.5µg/kg and 1.6 µg/kg for subclinical and clinical cases respectively.

After 4 months of levothyroxine therapy, on reassessing the patients, FT3 improved in the CH group from mean 1.61 ± 0.58 pg/ml to 2.26±0.39 pg/ml. In the SCH group, the FT3 levels were in the normal range during the starting phase the mean almost remained the same after 4 months.

FT4 levels the CH group improved from mean of 0.82±0.49 ng/dl to 1.65±0.34 ng/dl (P < 0.0001) after 4 months of therapy. The mean FT4 level was in the normal range (1.23±0.33 ng/dl) in the SCH group at the

start of levothyroxine therapy and the levels improved after 4 months (1.70±0.30 ng/dl).

In our study, the mean TC values in the SCH group was calculated to be 201.43±18.26 mg/dl which when reviewed after 4 months of levothyroxine therapy reduced to 145.73±23.04 mg/dl (P < 0.0001). A meta-analysis by Liu et al suggested that the serum total cholesterol, levels were significantly increased in patients with subclinical hypothyroidism when compared with euthyroid individuals.[11]

According to a study conducted in Delhi by Asranna et al the mean total cholesterol levels were significantly higher in patients with SCH (173.72 mg/dl) which reduced after 3 months of levothyroxine treatment (161.86 mg/dl).[12] In another study of dyslipidemia in an Indian population of 100 patients with SCH and 52 euthyroid controls, total cholesterol in the age group of 40-50 years were significantly elevated.[13]

In CH group the mean TC of 233.27±42.49 mg/dl reduced to 162.97±24.7 mg/dl. This finding was in conjunction with a study conducted by Pearce et al.[14] where mean TC was elevated in the study participants (284±52 mg/dl). Substitution therapy with levothyroxine significantly improves lipid metabolism abnormalities. Dyslipidemia is usually corrected within a period of 4-6 weeks of thyroxin replacement therapy.[15]

The mean triglyceride level in the CH group was 197.53±265.48 mg/dl which reduced after 4 months of levothyroxine therapy to 114.40±38.90 mg/dl. Similarly, in the SCH group the mean TG was 205.90±51.31 mg/dl which reduced to 103.70±23.83 mg/dl.

This finding does not correlate with a study done in Punjab by Singh et al.[16] where the mean TG was 157±42.39 mg/dl. The elevated TG levels in clinical hypothyroidism may be attributed to a decline the lipoprotein lipase activity, which impairs the clearance of TG-rich lipoproteins.[15,17] There are many previous reports on the effect of thyroxine treatment on serum TG and HDL levels and they all conclude that thyroxine substitution has no effect on TG and HDL levels.[18] In this study we see a significant reduction in triglyceride levels after 4 months of levothyroxine therapy.

The mean CAIMT on the right side was calculated for all the three groups. In the SCH group the mean was 0.55±0.10 mm, and in the CH group, it was 0.60±0.09 mm. Although within the normal range, CAIMT was increased in the SCH and CH group when compared with euthyroid group with a mean CAIMT of 0.47±0.06 mm. A similar finding was observed according to a study conducted in India by Karoli et al where the mean CAIMT obtained in SCH was 0.6±0.1 mm, in CH it was 0.7 ± 0.14 mm and in euthyroid it was 0.5±0.08 mm.[19]

These values do correspond to the findings of this study giving a better insight into the theory of increased CAIMT in hypothyroid patients. Gao et al. in a meta-analysis found that SCH was associated with an increased carotid IMT, which may be due to elevated TSH and dyslipidemia.[20] Whether the increase in CAIMT can be attributed to hypothyroidism alone is controversial as most patients with deranged thyroid function tend to have dyslipidemia. The results of a multi-ethnic study of atherosclerosis show a positive association between CAIMT progression and stroke. Cakal et al have similarly established higher CAIMT in primary hypothyroid patients.[21,22]

Their study has also found a positive correlation between lipids, CAIMT, and TSH levels and have concluded that CAIMT is an objective sign of accelerated atherosclerosis in patients with primary hypothyroidism. In contrast to these studies, Delitala et al in their study concluded that thyroid hormone was not associated with carotid artery plaque or increased CAIMT.[23] Likewise, Jorde et al also arrived at a conclusion that CAIMT and serum TSH levels were not related and rather CAIMT was increased in patients taking levothyroxine.[24]

On reviewing the subjects of this study after 4 months of levothyroxine therapy, the CAIMT was reassessed. The mean CAIMT did not change and had the same value of 0.55±0.1 mm (p = 0.3256) and 0.61±0.08 mm (p = 0.0960) in the SCH and CH group respectively. In a study done by Nagasaki et al the basal CAIMT was significantly higher in hypothyroid patients (0.63±0.018 mm) than in control subjects (0.55±0.02 mm, p <0.005).[25] After 1 year of euthyroidism, 34 out of 35 patients showed a significant decrease of CCA IMT, to 0.55±0.015 mm (p <0.0001), a level comparable to euthyroid controls.

The changes in CAIMT could not be appreciated in this study as the duration of treatment was too short to improve CAIMT. The rate of progression of IMT in the common carotid artery is approximately 0.01 mm/year.[2] The regression of CAIMT observed by Zhao et al. was after more than 6 months of levothyroxine therapy.[2]

Limitations of the study

- Thyroid peroxidase levels were not assessed.
- The sample size was rather small.
- The time period to assess the regression of CAIMT was not sufficient. Other studies have used a period of 6 months to 1 year.

CONCLUSION

Hypothyroidism does contribute to an increase in the carotid artery intima-media thickness. The CAIMT was more in the clinical group when compared with subclinical group. After 4 months of levothyroxine

therapy, there was no regression observed in either the clinical or the subclinical group.

It was also observed that the total cholesterol and triglyceride levels were elevated in both clinical and subclinical group. After 4 months of levothyroxine therapy, a considerable reduction was seen in both total cholesterol and triglyceride levels.

Hence, we can conclude that a 4 month period is inadequate to assess the progression and effect of levothyroxine over the changes in CAIMT and that levothyroxine therapy has a beneficial effect in reducing total cholesterol and triglyceride levels.

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