

CAROTID INTIMA-MEDIA THICKNESS (C-IMT) IN HYPOTHYROIDISM- EARLY ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS

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ABSTRACT

BACKGROUND

The present study entitled "Carotid Intima Media Thickness in Hypothyroidism" was conducted in the department of General medicine, A.V.B.R.H and J.N.M.C, Sawangi, Meghe, Wardha. C-IMT was measured by recording ultrasonographic images of both the left and right common carotid artery with a 7-MHz linear array transducer. Patients were examined in the supine position, with the head turned 45° from the side during the scanning procedure.

The aim of the study is to evaluate carotid intima media thickness (C-IMT) in hypothyroidism.

MATERIALS AND METHODS

The study included 100 cases of newly detected hypothyroidism not on thyroid replacement therapy, and 50 matched healthy controls. Body mass index (BMI), thyroid profile, lipids, blood pressure and the mean of C-IMT were determined.

RESULTS

Mean values of C-IMT, triglycerides, and total cholesterol were significantly high in hypothyroidism group versus controls. Carotid intima-media thickness was significantly increased in SCH and overt hypothyroidism group as compared to controls ($p < 0.001$). On comparing all independent variables like BMI, lipids and blood pressure with dependent variable C-IMT, statistically significant difference was found with FT4 ($p=0.024$), TSH ($p=0.041$) and with HDL ($p=0.021$).

CONCLUSION

In overt and subclinical hypothyroidism groups, values of diastolic blood pressure (DBP), triglycerides (TG), low density lipoprotein (LDL) were deranged. All these may contribute to atherosclerosis and an increase in C-IMT, causing potential risk for future cardiovascular disease, stroke. So, hypothyroidism group having deranged lipid profile and other risk factors like obesity should be screened for atherosclerosis by measuring C-IMT. This group can be targeted for primary prevention of coronary artery diseases (CAD) and its early management like lipid lowering agents apart from being treated for hypothyroidism.

KEYWORDS

Hypothyroidism, Subclinical, Dyslipidaemia, Arterial Hypertension, Triglyceride, Primary Prevention.

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BACKGROUND

Diseases of thyroid gland are most common endocrinal disorders after diabetes. India contributes to a large quantity of thyroid disorders. Recent statistics show that 300 million people in the world are suffering from thyroid disorders and among them about 42 million people reside in India.¹ Thyroid hormone has significant effect on cardiovascular system and lipid profile. As cardiovascular system is abundant in thyroid hormone receptors and is one of the important sites of action for thyroid hormones, it is relatively sensitive to changes in the levels of thyroid hormones.² The effect of hypothyroidism on vascular and haemostatic risk

factors for atherosclerosis has also been investigated in few studies.³ In spite of advances in hindering with medical care of illness, atherosclerotic diseases remain a leading cause of death with a worth considering clinical and economic burden worldwide. And so the identification of additional modifiable risk factors for atherosclerosis has significance.⁴

Overt hypothyroidism leads to increase in cholesterol levels especially LDL (low density lipoprotein) and TG (triglyceride). Both these factors have vast recognized effect on vessel wall and as a risk factor for atherosclerosis and cardiovascular disease. Association of atherosclerosis with overt hypothyroidism has been well existed for long and is a well-known fact.⁵ Subclinical hypothyroidism (Sch) is a mutual condition affecting 4%-20% of the all over population.⁶

Coronary endothelium dysfunction precedes atherosclerosis has been linked to adverse cardiovascular events, and may account for some of the increased risk in patients with hypothyroidism. A study concluded that hypothyroidism in women is associated with microvascular endothelial dysfunction, even after adjusting for confounders, and may explain some of the increased risk of cardiovascular disease in these patients.⁷

Atherosclerosis is a clinical condition that eventually leads to various complications like coronary artery disease (CAD), stroke, increase in blood pressure. The carotid intima media thickness (C-IMT) measurement directly correlates with atherosclerosis.^{8,9} In clinical studies, the C-IMT measurement parallels the significance of traditional cardiovascular risk factors,¹⁰ thus highlighting the utility and consistency of using noninvasive measurements to assess risk factors based on vessel wall biology. Accordingly, the clinical application of C-IMT represents a powerful, noninvasive surrogate marker of atherosclerosis, providing a meaningful end point measurement for clinical trials.¹¹ Many epidemiological studies and clinical trials proved that carotid intima media thickness is an indicator of subclinical atherosclerosis along with coronary atherosclerosis. Increase in C-IMT is associated with subclinical atherosclerosis. Hypothyroidism is a known condition for causing atherosclerosis.¹² This study was conducted with an aim to assess C-IMT in case of hypothyroidism.

Aim of the Study

To evaluate C-IMT in hypothyroidism.

Objectives

1. To compare the lipid profile in Sch and overt hypothyroidism
2. To estimate C-IMT in overt hypothyroidism
3. To estimate C-IMT in subclinical hypothyroidism
4. To compare C-IMT in both groups with normal subjects
5. To correlate BMI, blood pressure, lipid profile with C-IMT in hypothyroidism

MATERIALS AND METHODS

The present study entitled "Carotid intima media thickness in hypothyroidism" was conducted in the department of

General medicine, A.V.B.R.H and J.N.M.C, Sawangi Meghe, Wardha. It is 1200 bedded tertiary care center and teaching hospital. The study was carried out over a period of 24 months from September 2016 to September 2018.

Study Design

- Cross sectional study with control group.

Sample Size

Sample size formula with designed error of margin:

$$N = Z \alpha / 2 \times p (1-p) / d^2$$

Where, $Z \alpha / 2$ is level of significance at 5%=1.96

P = Sample size is calculated based on prevalence of hypothyroidism is around 9.1%=0.091 (prevalence is given from 4% to 20% in different studies.)

D = desired error of margin = 6%=0.06

So, $N = (1.96 \times 1.96 \times 0.091 \times (1-0.091)) / 0.06 \times 0.06 = 88.27$.

So, the final sample size in this study was 100 cases of hypothyroidism.

Inclusion Criteria

Patients with clinical features suggestive of hypothyroidism and diagnosis made as per report of thyroid profile.

Exclusion Criteria

1. Patients who were on thyroid replacement therapy.
2. Patients on antithyroid drugs (Carbimazole, methimazole, propylthiouracil).
3. DM (Diabetes mellitus).
4. CAD (Coronary artery disease).
5. Critically ill patients.
6. CKD (chronic kidney disease).

Blood Pressure

Blood pressure was measured twice on the right arm supine position and in sitting position with a mercury sphygmomanometer with a standard sized cuff after a resting period of five minutes in a sitting position.

Palpatory method was carried out prior to the auscultatory method for determination of systolic blood pressure. Both systolic and diastolic blood pressure were recorded in mmHg.

Blood pressure will be cross checked 2 times.

In the case of hypertension ($\geq 140/90$ mmHg), the measurement was repeated after 5 minutes.

Anthropometric Measurements

Weight in kilograms was recorded with subjects standing motionless on the standard weighing machine, without shoes or any heavy accessory. Height in centimeters was measured with patients standing without foot wear, against a wall mounted scale with the head positioned erect so that the top of the external auditory meatus was in level with the lower level of the bony cavity of orbit. BMI was calculated by using formula – weight in kilograms / (height in meter)². Obesity and overweight were determined by Asian criteria.¹³

Laboratory Investigations

Fasting Lipid Profile-

Blood samples were collected by venepuncture in the morning after an overnight fast of about 8 hours. Serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined by using a photometric method (Abbott diagnostics C16000 chemistry analyser).

Calculation of the value of low-density lipoprotein cholesterol (LDL-C) was performed using the Friedewald formula.¹⁴

Thyroid Profile

Morning fasting sample, after fasting for 8 hours at 6 am was withdrawn and sent for thyroid function test. FT3, FT4, TSH were tested. Tests were done by immunoassay system by CENTAUR CP named equipment by SIEMEN'S company in central laboratory of the hospital.

Values were interpreted according to laboratory values of FT3, FT4, TSH. Normal range of thyroid profile-FT3- 2.3-4.2 pg/ml, FT4- 0.89-1.76 ng/dl, TSH- 0.25-5 μ IU/ml

After data collection appropriate statistical test will be applied for interpretation of data.

Colour Doppler of Neck

C-IMT was measured by recording ultrasonographic images of both the left and right common carotid artery with a 7-MHz linear array transducer. Patients were examined in the supine position, with the head turned 45° from the side during the scanning procedure. The reference point for the measurement of C-IMT was the beginning of the dilatation of the carotid bulb, with loss of the parallel configuration of the near and far walls of the common carotid artery. An R-wave-triggered optimal longitudinal image of the far wall

was frozen. On this image, the sonographer traced the leading edges corresponding to the transition zones between lumen-intima and media-adventitia over a length of 1 cm proximal to the reference point at its thickest point, not including plaques. The mean c- IMT of the four measurements was calculated in each patient. Values more than 0.5 mm of mean values are considered to be towards higher value like if mean is 7.6 mm of both sides then it is taken as 8 mm and values less than 0.5 mm of mean are taken towards lower value like carotid intima media thickness is 6.4 mm then that is taken as 6 mm.

All examinations and measurement were performed by same examiner to exclude examiners bias.

Statistical Analysis

Statistical analysis was done by using descriptive and inferential statistics using one-way ANOVA, multiple comparison: Tukey test and multiple regression analysis and software used in the analysis were SPSS 22.0 version and Graph Pad Prism 6.0 version and $p < 0.05$ is considered as level of significance. In this study, comparison of each parameter in all three groups was done by descriptive statistics. One-way ANOVA test was used to see source of variation between groups and within groups. Multiple comparison: TUKEY TEST was done to compare individual group with another group. Chi square test (χ^2) was used to test association of different study variables with the study group. Z-test (standard normal deviation) was used to test the significant difference between groups. t – test was used to compare means. Odds ratio and 95% confidence intervals were calculated to find out risk factor. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics	Subclinical		Overt Hypothyroidism		Control		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age (yrs.)	38.04	13.71	39.76	14.57	47.38	15.39	0.35 (NS)
BMI (kg/m ²)	26.62	2.69	26.00	2.14	24.26	1.56	0.003 (S)
FT3 (pg/ml)	3.05	0.53	1.26	0.40	3.04	0.49	0.0001 (S)
FT4 (ng/dl)	1.29	0.36	0.89	0.32	1.11	0.23	0.0001 (S)
TSH (μ IU/ml)	8.80	5.16	34.24	10.50	3.60	0.65	0.0001 (S)
TC (mg%)	185.42	24.91	205.40	20.43	45.96	3.99	0.001 (ns)
TG (mg%)	151.12	25.78	182.24	38.15	133.58	13.14	0.0001 (S)
HDL (mg%)	51.69	4.42	44.04	5.59	45.96	3.99	0.0001 (S)
LDL (mg%)	116.37	22.58	135.92	12.71	23.68	4.88	0.0001 (S)
VLDL (mg%)	17.32	6.31	26.32	10.51	23.68	4.88	0.001 (ns)
SBP (mmHg)	123.56	10.18	125.12	13.56	119.94	9.86	0.356 (ns)
DBP (mmHg)	80.84	14.03	88.96	13.68	72.00	12.68	0.0001 (S)
CIMT (mm)	0.825	0.272	0.836	0.267	0.503	0.090	0.0001 (S)

Table 1. Baseline Characteristics of Cases and Control Group

	Unstandardized Coefficients		Standardized Coefficients	t	p-Value
	B	Std. Error	Beta		
CIMT	-0.419	0.553			
Age(yrs.)	0.000	0.002	-0.012	0.104	0.918, NS
BMI	0.011	0.011	0.124	1.050	0.298, NS
FT3	0.006	0.061	0.012	0.097	0.923, NS
FT4	-0.193	0.084	-0.259	2.307	0.024, S
TSH	0.014	0.007	0.270	2.091	0.041, S
TG	0.000	0.001	0.014	0.100	0.920, NS
HDL	0.013	0.005	0.267	2.366	0.021, S
LDL	-0.0002	0.001	0.000	0.000	1.000, NS
VLDL	0.000	0.005	-0.003	0.024	0.981, NS
SBP	0.004	0.005	0.145	0.851	0.398, NS
DBP	0.001	0.003	0.050	0.294	0.770, NS

Table 2. Multiple Regression Analysis for CIMT in Subclinical Hypothyroidism

On comparing all independent variables like BMI, lipid profile and blood pressure with dependent variable C-IMT, statistically significant difference was found with FT4 ($p=0.024$), TSH($p=0.041$) and with HDL($p=0.021$) whereas with other variables it shows no significant difference.

DISCUSSION

It is a well-known fact that the patients with hypothyroidism have an increased risk of atherosclerosis. Carotid intima media thickness is an indicator subclinical atherosclerosis. So the present study was carried out to correlate carotid intima media thickness with hypothyroidism and lipid profile. In this study, mean age in subclinical hypothyroidism (Sch) was $38.04 \text{ years} \pm 13.71$, in overt hypothyroid group it was $39.76 \text{ years} \pm 14.57$ and $47.38 \text{ years} \pm 15.39$ in control group. In our study, male to female ratio in cases was 1:12.5 Thus, it can be interpreted that the hypothyroidism population had more females than males.

The mean of BMI of cases was $26.62 \pm 2.69 \text{ kg/m}^2$ and in controls it was $24.26 \pm 1.56 \text{ kg/m}^2$. A similar study carried out by Yeqing Gu et al;¹⁵ found that BMI of cases was in range of $25.0\text{--}25.3 \text{ kg/m}^2$ and BMI in control group was found to be 23.3 to 25.1 kg/m^2 . Frank M. Bengel et al¹⁶ found that, in cases of hypothyroidism BMI ranges between $25.54 \pm 2.18 \text{ kg/m}^2$. Another study carried out by Harikumar K et al;¹⁷ concluded that obesity and hypothyroidism often co-exist. The data suggests that a greater number of hypothyroidism populations were overweight or obese as compared to controls.

In our study FT3 level was significantly reduced in cases of overt hypothyroidism, but no significant difference is found in control and subclinical group. Study carried out by Ismail DoguKilic et al; mean of FT3 levels in subclinical hypothyroid was 2.45 ± 0.59 , and in control group it was 2.58 ± 0.58 .

On comparing mean FT4 in three groups, a study carried out by Ismail DoguKilic et al; FT4 levels in cases were 1.04 ± 0.41 and in normal individuals it was 1.09 ± 0.20 , which was not significant in controls and subclinical group. In our study, statistically significant difference was found between control and overt hypothyroidism group ($p=0.013$, s) and no significant difference was found in control and subclinical group ($p=0.008$, ns) and significant difference

was found between overt hypothyroidism and subclinical group ($p=0.0001$, s).

In this study the mean of TSH level among three groups was significantly variable. ($F=31.55$, $p\text{-value}=0.0001$ s). Study carried out by Krstevska B and Velkoska et al,¹⁸ TSH in cases was $7.9 \text{ mU/l} \pm 3.6 \text{ mU/l}$ and in control group it was $5.1 \text{ mU/l} \pm 0.8$ ($p < 0.0001$ s). On comparing mean TSH in three groups, it was found that between control and overt hypothyroidism groups significant difference was found ($p=0.0001$, s). And also, in control and subclinical groups significant difference was found ($p=0.0001$, s) and significant difference was found between overt hypothyroidism and subclinical groups ($p=0.0001$, s).

In our study mean DBP levels in control group was $72 \text{ mmHg} \pm 12.68$, in overt hypothyroidism group mean DBP in patient was $88.84 \text{ mmHg} \pm 13.68$ and in patients of Sch, it was $80.84 \text{ mmHg} \pm 14.03$. Study carried out by Paulo H. N. Harada et al¹⁹ the mean of Systolic blood pressure in control group was 125 mmHg and in cases it was 126 mmHg (<0.001 (NS)), Mean of diastolic blood pressure in DBP in controls was 77 mmHg and in cases it was 92 mmHg . diastolic pressure (mmHg). Krstevska B and Velkoska et al¹⁸ they have found that, systolic blood pressure in systolic pressure (mmHg) $128 \text{ mmHg} \pm 20$, 7 121 , $8 \text{ mmHg} \pm 16$, 5 0 , 11 Diastolic blood in cases were 81 , $66 \text{ mmHg} \pm 12.3$ and in control group it was 78 , $6 \text{ mmHg} \pm 9.1$ which was significant.

Hypothyroidism is a recognized cause of secondary hypertension. Studies on the prevalence of hypertension in hypothyroidism have demonstrated elevated blood pressure values. The possible factors for the elevated diastolic blood pressure may be an increased peripheral vascular resistance and low cardiac output. The hypothyroid patients have significant volume changes, initiating a volume- dependent, low plasma renin activity mechanism which further contribute to hypertension.²⁰ In another study carried out by Tienlens E et al; concluded that hypothyroidism causes aortic stiffness and hypertension (usually diastolic) and

thyroid hormone therapy decreases aortic stiffness, promoting decreased blood pressure in about 50% of these patients.²¹

On comparing mean HDL, VLDL and Tg levels, all were significantly increased in hypothyroidism and Sch group as compared to controls.

Yeqing Gu et al, found that increase in TG and LDL levels were increased as compared to euthyroid population along with decrease in HDL levels. Changhwan Seo et al;²² have compared lipid profile in patients of hypothyroidism on thyroid replacement therapy and pts of hypothyroidism who are not on therapy. They have found that there is definite dyslipidaemia in the group who were not on therapy. (i.e. increase in TG and LDL.)

Mean C-IMT levels in control group was 0.503 mm $\pm$ 0.090, in overt group mean C-IMT in patient was 0.836 mm $\pm$ 0.267 and in subclinical group it was 0.825 mm $\pm$ 0.272. Significant difference was found between control and overt hypothyroidism group ($p=0.0001$, s) and in control and subclinical group ($p=0.0001$ s) and no significant difference was found between overt hypothyroidism and subclinical group ($p=0.979$ ns).

Similarly, Takamura N et al²³ found that C-IMT is independently associated with thyroid function and increased cardiovascular risk in subjects with low thyroid function. Jayanta Paul et al;²⁴ also found that there is increased C-IMT in hypothyroid patients and hence they are prone to cardiovascular events. Monzani F et al²⁵ were the first to show increase in C-IMT in hypothyroidism. As hypothyroidism has effects on endothelium of arteries and C-IMT directly correlates to subclinical atherosclerotic changes involved in thickening of arterial walls. Kim SK et al;²⁶ also showed relationship between hypothyroidism and C-IMT. Varun Vijayan et al;²⁷ study concluded the same.

Peixoto et al;²⁸ conducted cross-sectional analysis of the Brazilian longitudinal study of adult health. Study included 8623 individuals out of which 8095 were euthyroid and 528 were hypothyroid cases. It was observed that Sch is associated with IMT as continuous variable ($p=0.36$) and IMT is $>75^{\text{th}}$ percentile. Gao N et al;²⁹ in a meta-analysis demonstrated higher carotid IMT level in pts with Sch compared with euthyroids. Edip U et al;³⁰ study included 38 children diagnosed with Sch and a control group comprising 38 healthy, euthyroid children. In the patient group, C-IMT was also significantly higher compared to the control group ($p=0.001$).

CONCLUSION

This cross-sectional study was aimed to evaluate C-IMT as a noninvasive tool to detect atherosclerotic vessel involvement in hypothyroidism. Study concluded that, C-IMT is increased in both overt and subclinical hypothyroidism group as compared to control group. This study found that majority of cases of hypothyroidism was overweight and obese. In overt and subclinical hypothyroidism group, values of DBP, TG and LDL were increased. HDL was decreased. All these may affect C-IMT. So patients of hyperthyroidism having deranged lipid profile and other risk factors like obesity

should be screened for atherosclerosis by measuring C-IMT. These groups can be targeted for primary prevention of CAD and its early management like lipid profile lowering agents apart from being treated for hypothyroidism.

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