International Journal of Medicine Research
ISSN: 2455-7404
www.medicinesjournal.com
Volume 3; Issue 1; January 2018; Page No. 69-71

Effect of levothyroxine on intimal medial thickness as marker of endothelial function in subclinical hypothyroidism

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Abstract
Background: Hypothyroidism is a risk factor in atherosclerotic cardiovascular diseases, but there is controversy in effect of subclinical hypothyroidism on cardiovascular diseases. Measuring intimal medial thickness by ultrasound is accepted method of detection of early atherosclerotic changes, which has been proven to be directly related to coronary artery disease.
Aims and Objectives: We aim to estimate the relation between subclinical hypothyroidism and endothelial dysfunction and the effects of levothyroxine therapy on it.
Materials and Methods: Fifty newly diagnosed subclinical hypothyroidism cases aged 18-65 years were taken from out and in patients Departments of medicine of Hamidia Hospital, Bhopal from December 2015 to December 2016. The clinical examination consisted of relevant medical history, physical examination measurement like height, weight, body mass index (BMI), and waist hip ratio, systolic and diastolic blood pressure. Blood sampling for measurement of hemoglobin, total leukocyte count (TLC), T3, T4, thyroid stimulating hormone (TSH) and lipid profile consisting of total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) was obtained. Carotid intima media thickness (CIMT) was measured before and after 6 months of levothyroxine therapy.
Results: Female preponderance was observed (80.39%) and most common age was 30-40 years (58.82%). CIMT in both of the right (Z=-3.923, p<0.001) and left carotid artery (Z=-3.31, p=0.001) have reduced significantly with levothyroxine replacement therapy. Weight (r=0.288,p=0.041), BMI (r=0.283, p=0.044), WHR (r=0.332, p=0.017) TSH (r=0.393, p=0.017) and LDL-C (r=0.409, p=0.003) had a positive correlation with CIMT-Right and WHR (r=0.285, p=0.043), TSH (r=0.357, p=0.039) and LDL-C (r=0.287, r=0.041) had the a positive correlation with CIMT-Left. In a multivariate regression model, only Waist Hip Ratio (p=0.012) and TSH (p=0.049) were found as significant predictor of change in CIMT in right carotid artery whereas only Waist Hip Ratio (p=0.011) were found as significant predictor of change in CIMT in left carotid artery.
Conclusion: Levothyroxine treatment does reduce the CIMT in patients with subclinical hypothyroidism and therefore improves markers associated with cardiovascular disease and decreases cardiovascular morbidity.

Keywords: CIMT, subclinical hypothyroidism, Carotid intima media thickness, endothelial dysfunction

Introduction

Although the association of atherosclerosis with overt hypothyroidism has been well established, there is still controversy about its association with subclinical hypothyroidism despite exclusive research [1]. However, considering relatively high prevalence of SCH even in asymptomatic population [2]. together with the fact that atherosclerosis being the leading cause of mortality in developed countries, the effect of SCH on atherosclerosis should be cleared. [3, 4].

Subclinical hypothyroidism (SCH) is a common condition affecting 4% to 20% of general population. SCH is defined as increased serum thyroid stimulating hormone in presence of normal circulatory T3 and T45 [4]. The strongest arguments for levothyroxine therapy in SCH are high risk of progression to overt hypothyroidism, possible improvement of quality of life, and possibility that SCH is a cardiovascular risk factor [4, 5].

CIMT is increasingly used as a surrogate marker for atherosclerosis and has a high positive predictor value for CAD [6]. Hence, present study was performed to evaluate relationship between SCH and endothelial function as well as effect of levothyroxine therapy on endothelial function in the form of CIMT in SCH.

Materials and Methods

A prospective study was performed on 50 newly diagnosed SCH cases who attended the Outpatient department or were admitted in Medicine Department, Hamidia Hospital, and Bhopal from December 2015 to December 2016.

Cases were selected according to a predefined inclusion and exclusion criteria. Eligible participants included for the study were aged between 18-65 years who have recently been diagnosed as SCH and never taken any treatment for the same. Cases who were chronic smokers or were obese or having hyperlipidemia or having other major medical disorders were excluded from the study.

The clinical examination consisted of relevant medical history, physical examination measurement like height,

weight, body mass index (BMI), and waist hip ratio, systolic and diastolic blood pressure. Blood sampling for measurement of hemoglobin, total leukocyte count (TLC), T3, T4, thyroid stimulating hormone (TSH) and lipid profile consisting of total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) was obtained.

Blood samples were collected after 8 hours of overnight fasting for determination of lipid profile and thyroid profile. Thyroid profile was measured by ELISA microplate reader. CIMT was measured by ultrasonography of both common carotid arteries using multifrequency probe by a radiologist. The reference point for measurement of CIMT was beginning of dilation of carotid bulb, with loss of parallel configuration of the near and far walls of common carotid artery. The mean CIMT of four measurements was calculated in each patient. CIMT was again measured in each patient after 6 months of levothyroxine therapy. Cutoff value for TSH to be called as subclinical hypothyroidism in this study was 5.5µIU /ml. For CIMT to be called as significant, value of 0.08cm is decided.

All the data was analyzed using IBM SPSS ver. 20 software. Frequency distribution and cross tabulation was used to prepare tables. The quantitative data expressed as mean ± standard deviations (SD) and qualitative data was expressed as percentages. The data was analyzed by using Wilcoxon signed ranks test. Significance level was set as $p<0.05$.

Results

Most common age group was30-40 years (58.82%) followed by41-50 year (17.64%). Most of the patients were female [41 (80.39%).

CIMT right before and after the therapy was 0.089±0.018 and 0.077± 0.011 respectively ($p<0.001$). CIMT left before and after the therapy was 0.106±0.026 and 0.075 ± 0.009 respectively ($p<0.001$). From Wilcoxon signed ranks test it was found that CIMT in both of the right ($Z=-3.923$, $p<0.001$) and left carotid artery ($Z=-3.31$, $p=0.001$) have reduced significantly with levothyroxine replacement therapy in SCH patients.

Table 1: Showing Baseline parameters among study population (n=51)

Parameters	Mean ±SD	Median	Range
Age (years)	38.25±9.31	37	20-60
Weight (kgs)	68.88±12.16	68	45-93
SBP (mmHg)	119.14±7.28	118	100-134
DBP (mmHg)	73.78±6.88	76	60-84
T3	1.72±0.66	1.80	0.67-3.69
T4	9.15±2.98	8.41	4.4-17.84
TSH	14.73±12.09	9.07	5.13-62.67
BMI (kg/m^2)	25.46±3.51	24.00	19.53-37.03
WHR	0.875±0.078	0.88	0.72-1.20
Hb	11.04±1.37	11.00	8.1-13.0
TLC	6623.53±1610.53	6400	3400-10300
TC (mg/dL)	175.16±44.11	176	113-343
TG (mg/dL)	140.43±65.72	130	45-369
HDL (mg/dL)	41.18±6.66	41	31-59
LDL (mg/dL)	96.62±30.71	97	39.60-240
VLDL (mg/dL)	29.40±16.90	27.80	9.0-114.4

Data is expressed as mean±SD, SBP; systolic blood pressure, DBP; diastolic blood pressure, TSH; thyroid stimulating hormone, WHR; waist hip ratio, Hb; hemoglobin, TLC; total leukocyte count, TC; total cholesterol, TG; triglyceride, HDL; high density lipoprotein, LDL; low density lipoprotein, VLDL; very low density lipoprotein

Weight ($r=0.288$, $p=0.041$), BMI ($r=0.283$, $p=0.044$), WHR ($r=0.332$, $p=0.017$) TSH ($r=0.393$, $p=0.017$) and LDL-C ($r=0.409$, $p=0.003$) does have a positive correlation with CIMT-Right as determined by Spearman's correlation test. WHR ($r=0.285$, $p=0.043$), TSH ($r=0.357$, $p=0.039$) and LDL-C ($r=0.287$, $r=0.041$) does have a positive correlation with CIMT-Leftas determined by Spearman's correlation test.

In a multivariate regression model, only Waist Hip Ratio ($p=0.012$) and TSH ($p=0.049$) were found as significant predictor of change in CIMT in right carotid artery. For every one unit increase in WHR, CIMT increased by 0.127 units (1.127-1.000) with a point estimate of 1.127 with 95% CI = 1.026-1.988. For every one unit increase in WHR, CIMT increased by 0.005 units (1.005-1.000) with a point estimate of 1.005 with 95% CI = 1.001-1.009. In a multivariate regression model, only Waist Hip Ratio ($p=0.011$) were found as significant predictor of change in CIMT in left carotid artery. For every one unit increase in WHR, CIMT increased by 0.350 units (1.327-2.374) with a point estimate of 1.127 with 95% CI = 1.026-1.988

Discussion

The study was conducted in Hamidia Hospital, Bhopal during a period of December 2016 to December 2017 on 50 cases of SCH. Cases between age 18-65 years were taken who were not receiving any treatment for the same. Chronic smokers, obese persons and those with hyperlipidemia were excluded. Mean CIMT of right carotid artery ($p<0.001$, $z=-3.923$) and left carotid artery ($p=0.001$,$z=-3.31$) reduced significantly with levothyroxine treatment. Using spearman's correlation it was found that BMI, WHR, TSH, LDL-C was positively correlated with CIMT right carotid artery while WHR, TSH,

LDL-C positively correlated with CIMT left carotid artery. WHR and TSH values were found as significant predictors of change in CIMT right carotid artery. In case of left carotid artery only WHR was found as significant predictor of change in CIMT.

Few studies have evaluated the relationship between SCH and endothelial dysfunction and the effect of levothyroxine treatment in endothelial function in SCH patients. Monzani *et al*. were the first to show association between CIMT and SCH [7]. In the study, CIMT was associated with age, TSH and LDL-C values, and CIMT improved with levothyroxine therapy. Kim *et al.* also found increased CIMT in SCH which regressed by levothyroxine therapy and this regression was associated with LDL-C levels [8]. Tian *et al.* showed that SCH is associated with preclinical vascular alteration, characterized by increased CIMT, which had been shown to be related to high sensitive CRP and TSH [9]. Taddei *et al.* showed in a group of subclinical hypothyroid patients that 6 months of euthyroidism by levothyroxine treatment increased acetylcholine induced vasodilation [10]. However, not all studies showed an association between TSH and CIMT. In a study by Chiche at al among a population of hyperlipidemic patients, investigators found that neither prevalence nor severity of carotid plaques nor CIMT were significantly different between hypothyroid patients and controls [11].

Small sample size was the main limitation in present study; a large randomized clinical trial is needed to strengthen the present study findings.

Conclusion

Levothyroxine therapy does reduce the CIMT in patients with SCH. CIMT is a useful marker of endothelial function and is directly related to coronary artery disease. Levothyroxine therapy reduces CIMT, thus improves markers associated with cardiovascular disease and decreases cardiovascular morbidity. Levothyroxine therapy does have a role in reducing cardiovascular risk in SCH patients.

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