Hypothyroidism Induced Lipid Peroxidation and Coronary Hazard in Lucknow

Sankha Simlai¹, Pradeep Kumar², Tapan Kumar Mohapatra³, Preeti Sharma⁴

¹, ², ³, ⁴ Department of Biochemistry, Santosh Medical College and Hospital, Ghaziabad, Uttar Pradesh, India.

ABSTRACT

BACKGROUND
Dyslipidaemia is a common trait in subclinical (S.H.T.) and overt (O.H.T.) hypothyroidism and had been comprehensively studied; the association of dyslipidaemia, peroxidation of lipids, and coronary lipid risk factors have not been well-thought-out in sub-clinical and clinical hypothyroidism in contrast to controls. The intent of our study was to estimate lipid profile, coronary lipid risk factors, lipid peroxidation index, and malondialdehyde (M.D.A.). Our intention is also to determine their associations with TSH, thyroid hormone (FT3, FT4), and B.M.I. in hypothyroid patients.

METHODS
This is a case control study conducted among 176 OHT patients, 176 SHT patients, and 176 healthy controls from OPD of the medical college.

RESULTS
It was observed that all lipid parameters were higher in O.H.T. patients when measured against controls (p < 0.05). Similarly, the parameters were also high in the S.H.T patients group compared to euthyroid controls (p < 0.05). HDL-C was low in both hypothyroid groups when evaluated against controls (p < 0.05). Coronary lipid risk factors and levels of serum M.D.A. were also seen to be high in both hypothyroid patient groups (p < 0.05). FT3 and FT4 were correlated with TC (p = < 0.05) and (p < 0.05) respectively and with non-HDL-C (p < 0.05) and correspondingly (r = - 0.34, p < 0.05) in OHT subjects. TC (p < 0.05), LDL-C (p < 0.05), Non-HDL-C (p < 0.05), LDL-C / HDL-C (p < 0.05) and MDA (p < 0.01) were correlated with TSH. After nullification with B.M.I., M.D.A.’s relation to LDL-C / HDL-C along with TC / HDL-C ratios constantly continued although similarity between M.D.A. and LDL-C had been lost. If the function of M.D.A. was cancelled, B.M.I. correlations with T.G., T.C., and VLDL-C remained constant along with the correlation with atherogenic lipid factors and atherogenic index (A.I.) whereas the B.M.I. and LDL-C link had been lost. No associations were observed in patients with S.H.T however.

CONCLUSIONS
Dyslipidaemia, coronary lipid risk factors, and peroxidation of lipids were more distinct in overt hypothyroids than in the sub-clinical group.

KEYWORDS
Atherogenic Risk, Dyslipidaemia, Lipid Peroxidation, Thyroid Hormone
BACKGROUND

Thyroid hormones have noteworthy effect on the synthesis, metabolism, as well as mobilization of lipids. They control B.M.I. by altering the mitochondrial oxygen consumption, producing free radicals. Thus, alteration in thyroid hormones influences lipid parameters and free radical generation leading to oxidative stress (SOX) and dyslipidaemia. The most common abnormality in hypothyroidism is Dyslipidaemia. Oxidative stress is the outcome of increased free radical production or impaired antioxidant system or both. Circulating malondialdehyde (M.D.A.) judged as an indicator to assess Oxidative stress. Increased M.D.A. level is a sign of increased peroxidation of lipids in hypothyroidism. There is inadequate knowledge of SOX and increased peroxidation of lipids in SHT and O.H.T patients.

Both O.H.T. and S.H.T. patients had been accounted for cardiovascular (CV) risk in hypothyroidism. Studies have suggested dyslipidaemia increases the peroxidation of lipids which may lead to atherosclerosis. Moreover increase in weight and B.M.I. had been frequently stated in hypothyroidism which are potential risk factors for atherosclerosis. It has been demonstrated that peroxidation of lipid is involved in coronary artery disease (CAD). Likewise, cardiac lipid risk factors, along with cardiac index (A.I.) were used to assess the risk of atherosclerosis. Though chances of atherosclerosis risk is overall acknowledged in O.H.T., but the association of increased risk of CAD in S.H.T is disputed. Alternatively, the existence of SOX in hypothyroid has been barely accounted, therefore, in our study, we intended to estimate the lipid parameters and M.D.A. Atherosclerotic risk has been assessed by various Cardiac lipid risk factors in S.H.T. patients along with O.H.T. hypothyroids when compared with healthy euthyroid controls. Our focus was also to establish the link between dyslipidaemia, cardiac lipid risk factors, peroxidation of lipids, and B.M.I. with proper correlation in both hypothyroid patient groups.

METHODS

The study was conducted from October 2016 to December 2018. 176 OHT patients and 176 SHT patients were recruited from O.P.D. and I.P.D. department of Endocrinology from G.C.R.G. Hospital and Medical College, Lucknow, Uttar Pradesh, India. Alongside 176 euthyroid were also enrolled for the study. Anthropometric data and Biochemical Parameters were tabulated. Clinical hypothyroidism was characterized by elevated levels of TSH (> 15 mU / L), along with reduced levels of FT4 (< 55 µg / L). On the other side, SHT status was confirmed by high level of TSH (5 - 15 mU / L) along with normal or slightly high FT4 levels (55 – 135 µg / L). Smokers, alcoholics, diabetics, hypertensives, hepatic / renal disease patients, inflammatory diseases, pregnant / postmenopausal women, other endocrine diseases, lipid-lowering drug users, and recipients of vitamin / antioxidant supplement were excluded from enrollment. The study was approved by the research and ethics committee of the medical college. Fasting samples of blood were collected, centrifuged, and stored until further analysis. Thyroid hormones like triiodothyronine (FT3) and thyroxine (FT4) were estimated by radioimmunoassay kits (R.I.A. kits). Measurement of TSH was done using immunoradiometric assay kits. For lipid parameters like TC and TG, enzymatic methods were used using commercial kits. LDL-C kits were obtained from local suppliers. LDL-C and VLDL was measured using the Friedwald formula. As for Cardiac lipid risk factors TC-HDL-C was utilized for measuring non-HDL-C. Ratios of T.C. / HDL along with TG / HDL and LDL-C / HDL were taken to assess the risk factors for heart lipids. Log of TG / HDL-C was used to test the atherogenic index. Lipid peroxidation was measured by calculating M.D.A by T.B.A.R.S. method. The estimations were performed semiautoanlyser (Meril) and spectrophotometer estimation.

Statistical Analysis

All data was expressed as mean ± S.D. Collected data was coded & entered in M.S. Excel Sheet. Any disparity among groups was calculated by student independent sample t-test, between groups. To understand the associations between parameters, Pearson correlation analysis before nullification of influencing factors and also after nullification of influencing factors was performed. Significance in statistical calculation was considered as per the value of p < 0.05. All analytical procedures were done on S.P.S.S. 23 for Windows.

RESULTS

The general characteristics and biochemical parameters are revealed in (Table 1). B.M.I. was high in both hypothyroid groups when evaluated against controls, but there was hardly any notable dissimilarity among hypothyroid patients and the controls. A noteworthy increase was seen in lipids of OHT patients when contrasted with SHT subjects and euthyroids. In the S.H.T. group also lipids were seen to be markedly higher in comparison with controls. HDL-C level was however markedly low in both hypothyroid groups, predominantly on O.H.T. than S.H.T when evaluated against control group. All cardiac lipid risk factors and Atherogenic Index were markedly high in both hypothyroid group patients, higher elevation was seen in the O.H.T. group than in S.H.T against euthyroid group. M.D.A was high in both hypothyroid groups predominantly over clinical hypothyroids when evaluated against euthyroids. We found a marked positive relationship among FT3 and T.C. and a negative connection among FT4 and T.C. and non-HDL-C in clinical hypothyroidism groups (Table 2). TSH had positive relationship with T.C. along with LDL-C and coronary lipids such as non-HDL-C along with the ratio of LDL-C / HDL-C. There was no link between FT3, FT4, or TSH with either lipid parameters or cardiac lipid risk factors in S.H.T. patients. We found that M.D.A correlates with TSH in the O.H.T. group but not in the S.H.T. group.
The plasma M.D.A. had a marked positive correlation with ratios of T.C. or LDL / HDL ratio, along with LDL-C in O.H.T. cases. These correlations of M.D.A. was however lost for LDL-C but remained marked for ratios of T.C. or LDL / HDL-C ratios even after statistically canceling out the effect of B.M.I. using partial correlation analysis (Table 3). There was a marked positive correlation of B.M.I. with all lipid variables other than HDL-C. These correlations remained marked for all lipid variables except LDL-C after correcting for M.D.A. using partial correlation analysis (Table 4). We found no marked correlations of M.D.A. with any lipid variables in S.H.T. patients either before or after nullification with B.M.I. (Table 3). There were also no marked correlations of B.M.I. with any lipid variables in S.H.T. patients either before or after nullification with M.D.A. (Table 4).

Independent Student t-test was carried out on data interpretation. n* p < 0.01 if testing SHT with euthyroids, # p < 0.01 if testing OHT with controls, + p < 0.05 if testing OHT with SHT.

**DISCUSSION**

In our study hyperlipidaemia and OHT link was portrayed by elevated lipids and decreased HDL-C levels in hypothyroidism against controls. These findings are alike with others who studied O.H.T. patients.2,9,10 Apart from the diminished activity of HMG-CoA reductase, reduced oxidative metabolism,24 decreased cholesterol clearance,2,22,23 and delayed removal of LDL3 have been proposed as masked mechanisms leading to high cholesterol levels in O.H.T. Low expression of LDL receptor causes a low LDL particle clearance leading to LDL accumulation and increased LDL-C and T.C levels.2,24 Hypertriglyceridemia in hypothyroidism is caused by decreased lipoprotein lipase activity and decreased triglyceride-rich lipoproteins clearance25. It has been acknowledged before that the removal of both endogenous and exogenous T.G. is reduced answering for hypertriglyceridemia in hypothyroidism.26 In addition, hyperlipidaemia in hypothyroidism is also accounted for reduced thyroid hormones, i.e., lower lipolysis regulation,24 low triglyceride lipase in the liver,22 and the impaired lipoprotein lipase activity leading to a slower rate of VLDL catabolism.26 Hypothyroidism has been previously reported with lower levels of HDL-C in both OHT20 and SHT patients.25,26 Hence in support of this, our present study showed markedly decreased HDL-C levels in both OHT and SHT compared to controls explaining several proteins coding genes required for the metabolism of HDL, regulated by the thyroid31, Apolipoprotein (A-I) has been found to be lower in hypothyroidism affecting HDL metabolism.31 In addition, decreased HDL-C is also associated with obesity32 and hypertriglyceridemia33 in hypothyroidism. Due to decreased activities of cholesteryl ester transport protein34 and hepatic lipase35, the catabolism of HDL particles is reduced leading to a normal or high level of HDL-C. Differences in various reports may be due of environmental factors or influence of genes affecting the metabolism of HDL-apolipoproteins A-I,
because of which HDL levels may be high, low, or unchanged.36 Our study shows LDL-C levels to be notably high in SHT group than controls and was concordant with a few previous studies.5,6 On the contrary, no alteration in LDL-C levels in SHT has been stated in previous studies attributable to the difference in TSH levels in other studies. High TSH levels in hypothyroidism may augment fat mobilization with consequential dyslipidaemia.38 In our study, a marked increase in some lipids like T.G., T.C. along with LDL-C and VLDL-C in OHT was seen when they are compared against SHT subjects suggesting a different measure of dyslipidaemia in different stages and severity of hypothyroidism. Much lower fT3, fT4 level, and excess TSH levels may contribute to pronounced dyslipidaemia in OHT and SHT. This supports our finding of the correlations of T.C. with fT3, fT4 along with LDL-C and TSH in OHT patients (Table 2). Both O.H.T. and S.H.T. patients are stated to associate with myocardial and cardiovascular (CV) risk10 The various fractions of lipid and apolipoproteins29 along with the values of non-HDL-C are vigilant indicators of Cardiovascular vulnerability. The atherogenic index, a substitute of small size LDL had emerged as a major cardiac risk causing factor.40 In our present study, all lipid risk factors were markedly high in hypothyroidism predominantly in the O.H.T. group than S.H.T. indicating increased CV risk in OHT than SHT and controls. (Table 1). This may be because of low thyroid hormone, excess TSH level, and distinct dyslipidaemia compared to the S.H.T. group. Added to this, pronounced correlation of fT3, fT4 with non-HDL and TSH with non-HDL-C as well as LDL-C / HDL-C was identified in OHT subjects (Table 2). It is clear that peroxidation of lipid was involved in the development of atherosclerosis12 and has been well-thought-out as a potential CV risk factor.15 Dyslipidaemia, on the other hand, has been stated to increase peroxidation of lipids11 and so we evaluated the lipid peroxidation marker, M.D.A. and also determined its association with lipid parameters in hypothyroidism.

We found that M.D.A. was high in both hypothyroids suggesting an increased peroxidation of lipids compared to controls. Many studies, although has controversial reports41,42 Some even stated no change in peroxidation of lipid in hypothyroidism against controls. Our finding of increased peroxidation is concordant with many previous studies on OHT7,9,45 and S.H.T.9,10 There are multifactorial reasons for increased peroxidation of lipid and oxidative stress in hypothyroidism. In quite a lot of studies, this has been reasoned with decreased levels of thyroid hormones,6 excess of TSH levels,7 dyslipidaemia,47 accumulation of reducing equivalents48 and decreased clearance of oxidants.47 We also found high M.D.A. level in hypothyroidism, which may be because of variation in thyroid hormone, TSH level, and extent of dyslipidaemia between stages of the disease. The significance in the correlation of M.D.A. with TSH (Figure 1) and LDL-C (Table 3) observed in O.H.T. patients were in supports of this perception. In the S.H.T. group, M.D.A. had a positive association with TSH (Fig 2) but was not significant, maybe because of less high TSH level in SHT compared to the O.H.T group. Besides, diminished or damage antioxidant defence system stated in hypothyroidism might also have contributed to increased peroxidation of lipid increasing M.D.A. levels.

Although in our present study, we have excluded smokers, alcoholics, hypertensives and obesity, still B.M.I. is acknowledged to affect dyslipidaemia and oxidative stress.48 Since dyslipidaemia, increased peroxidation of lipid, and increased B.M.I. are frequently linked with hypothyroidism, we have studied the association of M.D.A. with lipid parameters and all atherogenic lipid risk factors after cancelling out the consequence of B.M.I. It was recorded that M.D.A. was linked with LDL-C and along with LDL / HDL and TC/ HDL-C ratios in O.H.T. patients. (Table 3). This association of M.D.A. remained prominent even after nullification with B.M.I., suggestive of an independent association of lipid peroxidation marker with atherogenic lipid risk factors. We also studied the association of B.M.I. with lipid parameters and atherogenic lipid risk factors before and after nullifying the effect of M.D.A in the O.H.T group (Table 4). We observed B.M.I. had marked associations with all lipids except LDL-C and with all lipid risk factors except LDL-C / HDL-C. Moreover, all these associations remained marked after cancelling out the role of M.D.A. This clearly suggests that increased B.M.I. is separately associated with increased atherogenic lipid risk factors. However, in S.H.T. patients, M.D.A. showed no associations with any lipid parameters either before or after nullification with B.M.I. (Table 3), and also there was no association of B.M.I. with lipid parameters before and after nullification with M.D.A. (Table 4). This scrutiny may be due to a lesser change in lipid variables and B.M.I. in the S.H.T. group compared to the O.H.T. group. We also did not find any noteworthy association of B.M.I. with M.D.A in O.H.T. and S.H.T patients. However reduction in calorie usage leads to obesity and ultimately leading to errors in lipid metabolism has been previously reported. Our findings hence indicated that both augmented B.M.I. and high MDA are separately associated with high levels of atherogenic lipid risk factors in hypothyroidism.

**CONCLUSIONS**

Dyslipidaemia, peroxidation of lipid and atherogenic lipid risk factors were prominently high in O.H.T. than S.H.T. patients compared to controls. Low thyroid hormones and excess TSH in circulation may lead to manifold coronary risks like dyslipidaemia, higher B.M.I., and increased peroxidation of lipid. This up to date study supports the evidence of increased peroxidation of lipid in hypothyroidism. Seeing that both dyslipidaemia and peroxidation of lipids contribute to atherosclerotic risk, antioxidant supplementation along with routine thyroxine therapy might be an important preventive step towards the development of future cardiovascular risk in O.H.T. and S.H.T. patients.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.

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