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*Original Research Article*

# Positive Correlation Found Between HDL and TSH in Hyperthyroidism

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## ABSTRACT

**Background:** Hyperthyroidism produces oxidative stress and dyslipidemia. We planned to measure serum ceruloplasmin and superoxide dismutase which are known antioxidants and lipid profile in hyperthyroid patients.
**Materials and methods:** 41 hyperthyroid patients and 32 control subjects were taken for the study. Study subjects were taken according to the inclusion and exclusion criteria after taking permission from the institutional ethics committee. Serum T4, TSH, ceruloplasmin, superoxide dismutase, and lipid profile were estimated. T4 and TSH were estimated by ELISA whereas ceruloplasmin, superoxide dismutase and lipid profile were estimated by autoanalyser.
**Results**: Significant decrease of serum TSH ($P<0.0001$), serum HDL ($P<0.0001$) whereas Significant increase of serum ceruloplasmin ($p<0.0001$), and superoxide dismutase ($p<0.0001$) were found in hyperthyroids when compared to controls. Furthermore we observed positive correlation between serum TSH and serum HDL($r=0.9642$, $p<0.05$).
**Conclusion:** Hyperthyroidism demands antioxidants to prevent the deterioration of the condition. It also requires correction of HDL level to prevent cardiovascular complications.

***Key words:*** HDL, TSH, Hyperthyroidism.

## INTRODUCTION

Commonest endocrine disorders of world are the thyroid diseases. Population study estimated about 108 million people in India are suffering from endocrine and metabolic diseases of which thyroid abnormalities contribute about 42 million. [(1)] Hyperthyroidism may results from generalised thyroid gland overactivity or due to some other causes. [(2)] However clinical, physiological and biochemical alterations occur when tissues are exposed to increased concentrations of thyroid hormones. [(3)] Different studies also supported that functional abnormalities of hyperthyroidism virtually affects many organ systems. [(4)]

An epidemiological study in Cochin has shown that subclinical and overt hyperthyroidism was present in 1.6% and 1.3% of subjects in community. [(5)] In another hospital based study at Pondicherry, 0.6% and 1.2% of female subjects were observed as hyperthyroids. [(6)]

In hyperthyroidism, due to increased tissue oxygen utilization, erythrocytes take part in oxygen distribution is more exposed to this molecule. This may results in increased rates of hemoglobin oxidation and methemoglobin production that may in turn, leads to an increment in production of superoxide radicals and alterations in antioxidant defense status. [(7)] Acceleration

of the basal metabolic rate and the energy metabolism of tissues in several

Mammalian species represent one of the major functions of thyroid hormones. Accumulating evidence has suggested that the hypermetabolic state in hyperthyroidism is associated with increases in free radical production and lipid peroxide levels. Also, the response of the antioxidant system to hyperthyroidism is unclear. [8] Several studies [9-11] have been performed to assess the levels of antioxidant enzymes in specific organs of experimental animals with hyperthyroidism. The data regarding the blood levels of antioxidant enzymes in untreated hyperthyroidism is limited and contrasting in the literature. [12]

Under physiological conditions, ROS generation is controlled by a large number of anti-free radical systems which act as protective mechanisms. These systems consist of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, as well as non-enzymatic antioxidants, among which the most important are vitamins C and E, carotenoids, glutathione and uric acid. [13] The disturbance of the pro-oxidant / antioxidant balance resulting from the increased production of ROS inactivation of detoxification systems or excessive consumption of antioxidants is a causative factor in the oxidative damage of cellular structures and molecules, such as lipids, proteins and nucleic acids. [14,15]

Serum ceruloplasmin is an enzymatic protein belonging to the circulating system of antioxidative protection and also playing a role in the cell-mediated immunity. [16]

In metabolism of lipids, thyroid hormones induce the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Moreover, triiodothyronine ($T_3$) upregulates LDL receptors by controlling the LDL receptor gene activation. This $T_3$-mediated gene activation is done by the direct binding of $T_3$ to specific thyroid hormone responsive elements (TREs). [17] Furthermore, $T_3$ controls the sterol regulatory element-binding protein-2 (SREBP-2), which in turn regulates LDL receptor's gene expression. [18] $T_3$ has also been associated with protecting LDL from oxidation. [19]

Thyroid hormones can influence HDL metabolism by increasing cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from $HDL_2$ to the very low density lipoproteins (VLDL) and TGs to the opposite direction. [20] In addition, thyroid hormones stimulate the lipoprotein lipase (LPL), which catabolizes the TG-rich lipoproteins, and the hepatic lipase (HL), which hydrolyzes $HDL_2$ to $HDL_3$ and contributes to the conversion of intermediate-density lipoproteins (IDL) to LDL and in turn LDL to small dense LDL (sdLDL). [21,22] Another effect of $T_3$ is the up-regulation of apolipoprotein AV (ApoAV), which plays a major role in TG regulation. [23] Indeed, increased levels of ApoAV have been associated with decreased levels of TGs. Proposed mechanisms for this effect include the decrease of hepatic VLDL-TG production and the increase of plasma LPL levels and activity, resulting in increase of lipoprotein remnant generation due to enhanced LPL-mediated lipolysis of VLDL-TG. Moreover, a greater clearance of lipoprotein core remnants, caused by increased hepatic uptake due to an enhanced affinity for the LDL receptor, has also been ascribed to ApoAV. [24]

Kung WC et al found thyroid hormones modulate the lipoprotein status. [25]

Following the above considerations, we have estimated lipid profile, SOD and ceruloplasmin in hyperthyroid patients, and tried to find any correlations exist between them.

## MATERIALS AND METHODS

***Study design:*** Cross sectional, observational study without any type of intervention.

***Duration of study:*** The duration of study was 6 months (1.7.2013 to 31.12.2013).

***Selection of cases and controls:*** A total of 41 hyperthyroid (16 males and 25 females, aged 30 to 60 years) patients were selected for the study. Written informed consent was taken from them. 32 age and sex matched controls were also selected, with consent, from apparently healthy persons who were not suffering from any diseases.

***Inclusion criteria:*** Selection was done according to method of convenience. All patients, for estimation of thyroid status (T4 and TSH), are according to the advice of physicians and Surgeons of different departments of the institution.

***Exclusion criteria:***

a) Patients suffering from any other endocrine disorders like diabetes mellitus.

b) Any other disease which may cause abnormal lipid profile, ceruloplasmin or SOD levels.

c) Antenatal mothers and psychiatry patients.

d) Smokers and tobacco chewers.

e) Patients taking antithyroid drugs and normal thyroid status.

***Ethical Clearance:*** *Before* commencement of the work, Ethical Clearance was obtained from the Institutional Ethics Committee, according to the Helsinki Declaration. Written informed consent was taken from cases and control subjects.

***Methods for analysis of test parameters:*** The assessment of cases and controls was done under 3 headings, history, clinical examination, and biochemical assay. For biochemical assay, 5 ml of blood from the subjects was collected aseptically using standard protocols. The serum was separated by centrifugation (3000 rpm for 5 min) immediately and analysis was done. Estimation of T4 was done by Competitive ELISA. [26] (Aspen Laboratories Pvt Ltd ). Estimation of TSH was done by Sandwich Elisa. [27] (Aspen Laboratories Pvt Ltd) Serum ceruloplasmin is measured by Ravin`s method. [28] Serum SOD is measured by Kakkars method [29] Serum total cholesterol (TC) by CHOD/ PAP method [30] (Crest Biosystems), triglyceride (TG) by GPO/PAP method [31] (Crest Biosystems) (S) LDL by Direct method [32] (Erba Lachema, diagnostics). (S) HDL by PEG/CHOD-PAP method [33] (Crest Biosystems).

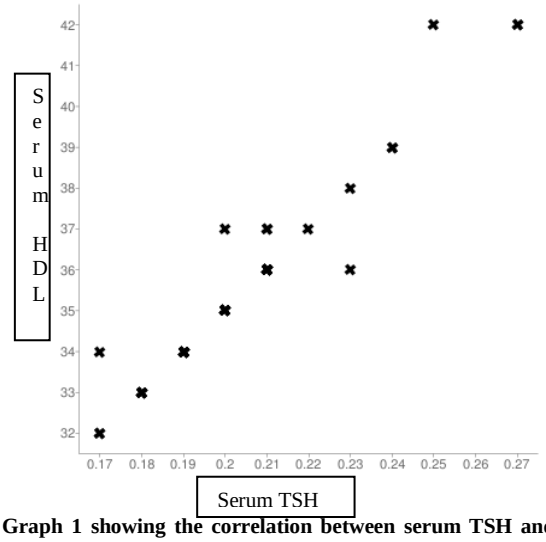
***Statistical Analysis:*** The values of all measured parameters were grouped and tabulated. The data were expressed as mean ± standard deviation. The Student t test was used for evaluation of the significance of difference in means of different groups. Pearson correlation was applied to test for association between the parameters where p value is significant between the control and case groups, p value less < 0.05 was considered as statistically significant.

## RESULTS

**Table 1: showing mean, standard deviation, significance and standard error of mean(case group) of the selected parameters of control and case groups.**

| Parameters | Controls(n=32) (mean±SD) | Cases(n=41) (mean±SD) | SEM | P value |
|---|---|---|---|---|
| T4 | 5.9±1.10 | 21.12±6.8 | 1.06 | P<0.0001* |
| TSH | 2.9±0.37 | 0.2±0.02 | 0.0031 | P<0.0001* |
| Ceruloplasmin | 31.9±3.08 | 50.48±3.67 | 0.57 | P<0.0001* |
| SOD | 3.78±1.37 | 6.96±1.35 | 0.21 | P<0.0001* |
| Total Cholesterol | 166.2±1.41 | 169.3±1.44 | 0.22 | p>0.05(NS) |
| Trigleceride | 142.4±1.35 | 139.3±1.78 | 0.27 | p>0.05(NS) |
| HDL | 47.9±1.40 | 35.5±2.39 | 0.37 | P<0.05* |
| LDL | 76.3±1.67 | 78.4±1.78 | 0.27 | p>0.05(NS) |

P value *Indicates significance. NS means not significant.




**Graph 1 showing the correlation between serum TSH and serum HDL.**

Results of our study have clearly shown that (Table 1) the serum T4, ceruloplasmin and SOD are significantly high( $p<0.0001$ ) , whereas serum TSH and HDL cholesterol are significantly low( $p<0.0001$) in hyperthyroid patients in comparison to controls. No significant alteration was observed in serum cholesterol, triglyceride and LDL levels among disease group and controls. Graph 1 has shown the positive correlation between serum TSH and serum HDL ($r=0.9642$, $p<0.05$).

## DISCUSSION

Present study has shown that, the antioxidants namely ceruloplasmin and SOD are significantly increased in hyperthyroid patients. Our study is in agreement with some previous studies. [16,34,35] Konstantions G [35] showed that hyperthyroidism increases lipid peroxidation. This finding is in agreement with previous reports indicating that the hypermetabolic state in hyperthyroidism is associated with increases in free radical production and lipid peroxide levels [36,37] Their study provides evidence that hyperthyroidism is associated with oxidative stress on DNA.

Serum ceruloplasmin levels were significantly higher in the hyperthyroid animals reflecting a greater oxidant stress. Ceruloplasmin is a copper-binding protein with well-documented antioxidant properties. Recent report revealed its capacity to promote vasculopathic effects that include lipid oxidation, negation of nitric oxide bioactivity and endothelial cell apoptosis. [38] Through these effects, elevated circulating ceruloplasmin levels have been associated with an increased risk for cardiovascular disease. [39]

We found significant increase of SOD in hyperthyroid patients. Our study corroborates with the study of Dave BN et al. [12] Experimental investigations of ROS-scavenging enzymes in erythrocytes of several species showed SOD may be constitutively present only at low levels but highly inducible under oxidative stress while GPx is normally abundant and less inducible. [39]

Similar observations were made for erythrocyte enzymes in Graves' disease patients [40] revealing significant induction of SOD activity. We didn't observe any correlation of ceruloplasmin and sod with TSH. In our study we also analyses lipid profile. We didn't observe any significant alteration of (S) total cholesterol, triglyceride, and LDLc, but observed decreased HDLc concentration in hyperthyroid patients. Our study is in agreement with the findings of Rizos CV et al, [17] they explained despite the increased activity of the HMG-CoA reductase, levels of TC, LDL-C, ApoB and Lp(a) tend to decrease in patients with clinical or subclinical hyperthyroidism. This is due to increased LDL receptor gene expression resulting in enhanced LDL receptor-mediated catabolism of LDL particles. [41,42] Triglyceride levels also remain unchanged observed by them. We found a positive correlation between (S) HDL and TSH in hyperthyroidism. ($r= 0.9642$, $p<0.05$)

A decrease in HDL-C levels is also observed in hyperthyroidism, due to increased CETP-mediated transfer of cholesteryl esters from HDL to VLDL and

increased HL-mediated catabolism of HDL2. [41,42] According to the statement of Kung WC et al, [25] since hyperthyroidism is associated with decreased HDLc but increased Apo A1 concentration, which needs verification of determination of HDL2 and HDL3 concentrations in these patients. Altered lipoprotein composition together with decreased cholesterol ester transfer activity has been observed in hypothyroidism. Change in cholesterol/cholesteryl ester molar ratio in HDL was inversely related to that of cholesterol ester transfer activity during treatment of hypothyroidism which accounts for higher HDL and free cholesterol/cholesteryl ester ratio in hypothyroid state. This finding supports their observation of decreased HDLc in hyperthyroid patients.

In agreement with the following observations, we found a positive correlation between serum TSH and serum HDL. Now we can hypothesize that with decrease of TSH in hyperthyroidism, serum HDL also decreases. Excess thyroid hormone modulates lipid profile particularly HDLc.

From the results of our study, we can predict that due to increased circulating ceruloplasmin and decreased HDL levels, there is more chance of cardiovascular disease (CVD) in hyperthyroidism.

## CONCLUSION

Hyperthyroidism increases oxidative stress. Thyroid hormone also influences lipid profile. We measured serum ceruloplasmin and SOD as antioxidants in hyperthyroid patients as well as lipid profile. Our results have shown that the antioxidants are significantly increased in them reflecting oxidative stress. Serum HDLc is significantly decreased reflecting the influence of excess thyroid hormone over lipoprotein metabolism. The only positive correlation found between(S) TSH and (HDL).

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