INTERRELATIONSHIP OF THE PRO-INFLAMMATORY MARKER HSCRP WITH DYSLIPIDEMIC CHANGES: A COMPARATIVE STUDY BETWEEN SUBCLINICAL AND OVERT HYPOTHYROIDISM

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ABSTRACT

CONTEXT

Sustained hypercholesterolemia with low-grade inflammation makes hypothyroid patients more prone for cardiovascular disorders. Recently, these risks are also becoming evident in Subclinical Hypothyroidism (SH).

AIMS, SETTINGS AND DESIGN

We made an effort to evaluate the interaction of hsCRP with dyslipidemic changes and their contributions as cardiovascular risk factors in both Subclinical (SH) and Overt Hypothyroidism (OH) patients in a hospital based, case control study consisting of 30 OH, 34 SH and 34 properly matched control subjects within a span of one year.

METHODS

Changes on serum hsCRP, TSH and fT4 levels were assessed by ELISA. Total serum Cholesterol (TC), LDL Cholesterol (LDLc), HDL Cholesterol (HDLc) and triglyceride (TG) were measured by standard pre-validated photometric tests as applicable.

STATISTICAL ANALYSIS

Data obtained were compared for difference between mean values by one way and post hoc ANOVA. Predictive values of individual lipid parameters on the rise of hsCRP were evaluated in both OH and SH groups by multivariate linear regression analysis. SPSS software, version 17 for Windows was used for all statistical analyses. For all analyses, P value was considered significant at a level of $P < 0.05$ for 95% confidence interval.

RESULTS

Post hoc ANOVA showed that mean values of hsCRP, TG, TC and LDLc were increased most in the OH group followed by that in the SH with a significant difference between two groups ($p < 0.001$). In contrast, fT4 and HDLc showed decreased levels in both SH and OH groups, also with a significant difference between themselves. Results of multiple linear regression analysis revealed that LDLc ($\beta = 0.653$, $P < 0.001$ for SH and $\beta = 0.326$, $P = 0.030$ for OH) and fT4 ($\beta = -0.241$, $P = 0.044$ for SH and $\beta = -0.444$, $P = 0.046$ for OH) were most important positive and negative predictors respectively for changes in the hsCRP levels.

CONCLUSIONS

A low-grade inflammation starts in early stages of hypothyroidism, which is directly dependent on serum thyroxine and inversely dependent on LDLc. We conclude that there is a possible link between the development of low-grade inflammation and LDLc in the SH state that is more potentiated as the disease progresses to OH.

KEYWORDS

High Sensitive C Reactive Protein; Hypercholesterolemia; LDL Cholesterol; Overt Hypothyroidism; Pro-Inflammatory State; Subclinical Hypothyroidism.

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INTRODUCTION

Hypothyroidism is one of the commonest endocrine disorders throughout the world with a prevalence of 2-15% in USA and Europe.[1] In India it is reported to be the second commonest endocrine disorder after diabetes mellitus.[2] Primary hypothyroidism is manifested as either Overt Hypothyroidism (OH) or Subclinical Hypothyroidism (SH).

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OH is defined as an elevated serum TSH with decreased thyroxine level, whereas SH the milder spectrum of the disease is defined as elevated serum TSH with blood thyroxine within the normal reference interval. SH, sometimes known as the compensated hypothyroidism also has a substantial prevalence of 4-10.[3] percent among general population and about 7–10 percent among the elderly.[4] The clinical importance of SH is revealed by an explicit association of this disease with poor left ventricular function and increased arterial stiffness.[5,6] Furthermore, the Rotterdam study has provided significant evidence of arterial atherosclerosis and myocardial infarction in elderly women with SH.

Deranged blood lipid profile is a characteristic feature in established hypothyroidism. Regarding changes in lipid profile in SH, variable results have been reported with conflicting reports involving both normal.[7] and elevated levels.[8,9] for

LDL cholesterol fraction (LDLc). Furthermore, the significant increase in its levels has been reported to be normalized in SH patients after thyroxine therapy.[9] Indicating a direct link between the LDLc metabolism and circulating levels of thyroxine. Results in Norway and Australia reported significant association between lipid profile with SH, whereas the Suita study did not find any such observations.[10] Recent studies including some based on a large sample size of 60000 patients have also indicated a significantly elevated levels of TC and LDLc in the SH patients compared to the control subjects. Some of the studies also found substantial decrease in the TG level after replacement therapy with thyroxine in SH patients.[11]

All these observations suggest that in spite of inconsistent results, SH patients may be in a state of mild thyroid failure and hence are more liable to suffer from atherosclerotic and cardiovascular diseases than the normal population.[12,13] However, due to inconsistency in these observations in different studies undertaken in different geographical regions, further investigation are needed to reach a more conclusive opinion and a comprehensive understanding of the interplay of metabolic events in SH for a better understanding of its clinical outcome.

In addition to a sustained hyperlipidemia, the prevalence of a state of low-grade inflammation potentiates the cardiovascular risks for hypothyroid patients. Till date, variable results are available regarding changes in the hsCRP levels in the SH patients. Some studies have reported significant rise in this marker of low-grade inflammation in the SH group.[14,15] while other did not find any such change.[16] However, recent studies have not only described a raised hsCRP level in SH patients compared to healthy controls.[17] but also reported its normalization after appropriate replacement therapy with thyroxine.[18,19] Furthermore, a link between hyperlipidemia and changes in hsCRP has been cued in hypothyroid cases that has not been yet explored much in the SH group.

Keeping these factors in mind and the potential risk of simultaneous increase in hsCRP and atherogenic lipids for cardiovascular disorders, we hypothesized that the low-grade inflammatory marker hsCRP might be elevated in SH as well as in the OH patients and this increase might be dependent on the circulating thyroxine levels along with some particular lipid fraction like TG, LDL or HDL. Accordingly, the present study was designed to test this hypothesis.

MATERIAL AND METHODS

Study Design and Settings

The present study was conducted in the Department of Biochemistry of a Tertiary Care Medical College and Hospital, West Bengal, India. It was a case control non-interventional study that spanned a period of one year from February 2013 to January 2014.

Selection of Cases and Controls

Sixty four cases aged between 20 to 40 years were selected on convenience basis from the thyroid clinic of the Biochemistry Department during the stipulated study period.

Inclusion Criteria

We planned to segregate the case group into OH and SH based on the result of serum fT4 level as follows:

i) SH group with raised TSH, but fT4 within reference range (0.8–2.0ng/dL) and ii) OH group with raised TSH and fT4 below the reference range (<0.8ng/dL). Cases were selected between the age group of 20–40 yrs by the method of convenience with no male-female discretion. 34 healthy control subjects matched for age and sex were selected from the same population group belonging to similar socioeconomic and nutritional status.

Exclusion Criteria

Patients having history of chronic alcohol ingestion, smoking, drug addiction, any malignant disorder, chronic inflammatory diseases and any other metabolic or endocrinological disorders were excluded. Same exclusion criteria were followed for selection of the control subjects.

Ethical Guidelines

Informed consents were obtained from both the cases and control groups as per protocol. Institutional ethical clearance was obtained before start of the study. Total study adhered to the guidelines of the ICMR's Ethical guidelines for biomedical research on human participants, (2006) and the Helsinki Declaration 1975, revised in 2000.

METHODOLOGY

1. Serum TSH and fT4 were estimated by competitive and non-competitive ELISA respectively by the reagent kits obtained from AccuBind, USA. The coefficient of variation (CV) were found to be 6 percent and 8 percent for the TSH and fT4 respectively.
2. Serum hsCRP was measured by immunoturbidimetric method obtained from ERBA, Transasia. CV for this assay was 5 percent for this assay.
3. Serum lipids were estimated by standard photometric techniques with the autoanalyzer, XL 600 from ERBA, Transasia. Cholesterol was estimated by the CHOD-PAP method, whereas the LDLc and HDLc were measured by direct methods. All reagents were obtained from ERBA, Transasia. The CV for these assays remained within 6 percent throughout the assay process.

Statistical Analysis

Data were analysed for the significance of difference between the mean values by post hoc ANOVA between the OH, SH and control groups. Dependence and predictive values of the study parameters in the case group were analysed with the help of multiple linear regression study. For all studies, the P value was considered to be significant at a level of 0.05 or less with a confidence interval of 95%. All relevant statistical analysis were performed by using SPSS software for Windows, version 17.

RESULTS

Difference between the mean values of study parameters:

The Table 1 shows the results of one way ANOVA performed on OH, SH and normal control subjects. From the p values ($p<0.001$ for all parameters), it is evident that the overall difference between these three groups was significant. However, to ascertain the degree of difference between the individual of OH, SH and control groups post hoc ANOVA with Bonferroni correction was performed and the results are shown in the Table 2.

In Table 2, the post hoc ANOVA revealed the significance of difference between the individual groups separately while Bonferroni correction compensated for the multiple comparisons. Mean values of serum TSH, TG, TC, LDLc and hsCRP showed significant increase ($p < 0.001$) in the OH groups compared to SH groups, that in turn showed a significant higher values than the control subjects ($p < 0.001$). On the other hand, values of fT4 and HDLc showed significant trend in opposite direction showing marked reduction in their values ($p < 0.001$), most in the OH group followed by that in the SH and the normal controls.

Results for age and BMI matching are shown in Table 3. In table III post hoc ANOVA revealed that there was no significant difference between the age and BMI distribution indicating that all three groups were matched for age and body weight. Chi square test indicated that these three groups were also sex matched ($\chi 2 = 0.09$, $p = 0.95$, data not shown in Table).

The degree of dependence of hsCRP on the thyroid parameters and the lipid profile in the SH groups is shown in the Table 4. FT4 value showed a strong negative predictive effect on the hsCRP with the TSH exhibiting an opposite effect. Similarly, the predictive value of LDL is found to be significantly positive on the increase of the hsCRP. No such effects from the HDLc and TG were observed.

Table 5 shows the degree of dependence of hsCRP on thyroid parameters and lipid profile in the OH group. Among the thyroid parameters, fT4 value is found to have a strong negative predictive value on the hsCRP without any such effect from the TSH. The predictive value of LDLc is found to be significantly positive on the increase on hsCRP. No such effects from the HDLc and TG were observed on hsCRP.

		Sum of Squares	df	Mean Square	F	Sig. (P value)
TSH (μIU/mL)	Between Groups	7694.824	2	3847.412	131.547	.P < 0.001
	Within Groups	2807.744	96	29.247		
	Total	**10502.568**	**98**			
fT4 (ng/dL)	Between Groups	19.414	2	9.707	130.448	P < 0.001
	Within Groups	7.144	96	.074		
	Total	**26.558**	**98**			
HSCRP (mg/L)	Between Groups	464.152	2	232.076	49.008	P < 0.001
	Within Groups	454.608	96	4.736		
	Total	**918.761**	**98**			
TC (mg/dL)	Between Groups	67950.815	2	33975.408	45.723	P < 0.001
	Within Groups	71334.356	96	743.066		
	Total	**139285.172**	**98**			
TG (mg/dL)	Between Groups	175966.174	2	87983.087	66.194	P < 0.001
	Within Groups	127599.482	96	1329.161		
	Total	**303565.657**	**98**			
LDL (mg/dL)	Between Groups	44399.149	2	22199.574	34.692	P < 0.001
	Within Groups	61430.597	96	639.902		
	Total	**105829.745**	**98**			
HDL (mg/dL)	Between Groups	1910.975	2	955.488	17.758	P < 0.001
	Within Groups	5165.252	96	53.805		
	Total	**7076.227**	**98**			

Table 1: One way ANOVA showing the differences between study parameters among 3 groups

*P value is considered significant at $P < 0.05$ for 95% confidence interval.

Dependent Variable	(I) VAR00009	(J) VAR00009	Mean Difference (I-J)	Std. Error	Sig.
TSH (μIU/mL)	1.00	2.00	9.38339*	1.35467	P < 0.001
		3.00	21.66019*	1.34557	P < 0.001
	2.00	1.00	-9.38339*	1.35467	P < 0.001
		3.00	12.27680*	1.30225	P < 0.001
	3.00	1.00	-21.66019*	1.34557	P < 0.001
		2.00	-12.27680*	1.30225	P < 0.001
fT4 (ng/dL)	1.00	2.00	-.82378*	.06833	P < 0.001
		3.00	-1.05410*	.06787	P < 0.001
	2.00	1.00	.82378*	.06833	P < 0.001
		3.00	-.23031*	.06569	P < 0.001
	3.00	1.00	1.05410*	.06787	P < 0.001
		2.00	.23031*	.06569	P < 0.001
HSCRP (mg/L)	1.00	2.00	1.87451*	.54510	P < 0.001
		3.00	5.24305*	.54143	P < 0.001
	2.00	1.00	-1.87451*	.54510	P < 0.001
		3.00	3.36854*	.52400	P < 0.001
	3.00	1.00	-5.24305*	.54143	P < 0.001
		2.00	-3.36854*	.52400	P < 0.001
TC (mg/dL)	1.00	2.00	35.07059*	6.82816	P < 0.001
		3.00	64.85714*	6.78228	P < 0.001
	2.00	1.00	-35.07059*	6.82816	P < 0.001
		3.00	29.78655*	6.56394	P < 0.001
	3.00	1.00	-64.85714*	6.78228	P < 0.001
		2.00	-29.78655*	6.56394	P < 0.001
TG (mg/dL)	1.00	2.00	42.94118*	9.13227	P < 0.001
		3.00	103.30000*	9.07091	P < 0.001
	2.00	1.00	-42.94118*	9.13227	P < 0.001
		3.00	60.35882*	8.77890	P < 0.001
	3.00	1.00	-103.30000*	9.07091	P < 0.001
		2.00	-60.35882*	8.77890	P < 0.001
LDL (mg/dL)	1.00	2.00	26.93922*	6.33646	P < 0.001
		3.00	52.40476*	6.29388	P < 0.001
	2.00	1.00	-26.93922*	6.33646	P < 0.001
		3.00	25.46555*	6.09127	P < 0.001
	3.00	1.00	-52.40476*	6.29388	P < 0.001
		2.00	-25.46555*	6.09127	P < 0.001
HDL (mg/dL)	1.00	2.00	-4.58137*	1.83738	P = 0.043
		3.00	-10.78095*	1.82504	P < 0.001
	2.00	1.00	4.58137*	1.83738	P = 0.043
		3.00	-6.19958*	1.76629	P = 0.002
	3.00	1.00	10.78095*	1.82504	P < 0.001
		2.00	6.19958*	1.76629	P = 0.002

Table 2: Multiple Comparisons between the biochemical parameters using post hoc ANOVA with Bonferroni correction

*P value is considered significant at P < 0.05 for 95% confidence interval.

Dependent Variable	(I) VAR00010	(J) VAR00010	Mean Difference (I-J)	Std. Error	Sig.
BMI	1.00	2.00	-.45686	.54070	P=1.000
		3.00	-.53333	.53707	P=0.970
	2.00	1.00	.45686	.54070	P= 1.000
		3.00	-.07647	.51978	P=1.000
	3.00	1.00	.53333	.53707	P=0.970
		2.00	.07647	.51978	P=1.000
AGE (Years)	1.00	2.00	-1.74118	1.63612	P=0.870
		3.00	1.22857	1.62513	P=1.000
	2.00	1.00	1.74118	1.63612	P=0.870
		3.00	2.96975	1.57281	P=0.186
	3.00	1.00	-1.22857	1.62513	P=1.000
		2.00	-2.96975	1.57281	P=0.186

Table 3: Multiple Comparisons between the anthropometric parameters using post hoc ANOVA with Bonferroni correction

*P value is considered significant at P < 0.05 for 95% confidence interval.

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-6.904	5.141		-1.343	P = 0.190
	TSH	0.179	0.072	0.245	2.494	P = 0.019
	FT4	-3.110	1.473	-0.241	-2.111	P = 0.044
	TG	0.000	0.009	-0.003	-0.031	P = 0.975
	LDL	0.129	0.017	0.653	7.520	P < 0.001
	HDL	0.007	0.048	0.014	0.145	P = 0.885
a. Dependent Variable hsCRP (SH)						

Table 4: Multiple linear regression showing the dependence of hsCRP on the thyroid and lipid parameters in SH patients

*P value is considered significant at P <0.05 for 95% confidence interval.

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	4.166	6.470		0.644	P = 0.526
	TSH	0.058	0.109	0.111	0.534	P = 0.598
	fT4	-9.393	4.456	-0.444	-2.108	P = 0.046
	TG	0.013	0.018	0.115	0.754	P = 0.458
	LDL	0.053	0.023	0.326	2.314	P = 0.030
	HDL	-0.025	0.058	-0.036	-0.437	P=0.666
a. Dependent Variable: hsCRP(OH)						

Table 5: Multiple linear regression showing the dependence of hsCRP on the thyroid and lipid parameters in OH patients

*P value is considered significant at P <0.05 for 95% confidence interval.

DISCUSSION

In the present study, although we observed significant elevations in TSH in both OH and SH groups compared to the control subjects, the increase was more in the OH group than found in the SH patients. Similar trends were observed for TC, LDL and TG levels while an opposite change was found for fT4 and HDL among these groups (Post hoc ANOVA, table II). These observations indicated clearly that along with OH, SH patients showed altered biochemical parameters albeit lower than found in their OH counterparts. However, as these changes in the SH group were significantly higher than that found in the normal control subjects, these patients are supposed to face significant consequences of altered metabolic status due to a mild thyroid failure characteristic of the SH.

Elevated atherogenic lipids, i.e. TC, LDL and TG along with a reduced cardioprotective lipoprotein HDL level render SH patients more prone to serious complications like premature atherosclerotic incidences and cardiovascular attacks compared to the normal population. Our findings and interpretations keep in track with the earlier as well as the recent observations that a mild thyroid failure does occur in SH state and that is sufficient to pose significant atherosclerotic and cardiovascular threat in these patients.[12,17] although, some degree of variable association of lipid profile with SH has been attributed to differences in genetic background and body weight distribution among individuals.[10] These factors are not supposed to play critical role in our study group as the OH, SH and control groups were all matched for their age and body weights.

However, we did not study any genetic profile in these patients in the present study and keep it for further research. Although several studies have reported changes in apolipoproteins in hypothyroid patients, conventional lipid risk factors and CRP have been reported to be better markers for cardiovascular risks.[20] In hypothyroidism, several low-grade immunological markers have been found to be increased that include hsCRP.[21] anti-TPO, anti-TG antibodies, etc. This low-grade inflammation has been found to play a significant role in sympathovagal imbalance that is one of the major contributing factors leading to cardiovascular abnormalities. Sympathovagal imbalance has been found to be one of the major contributing factors for increases in lipid parameters like TC, TG and LDLc in hypothyroid disorders.[22]

In SH, studies have reported changes in TC and LDL levels to be so significant that they remained unaltered even after correction for the age and gender.[13,23] In our study, the multiple linear regression analysis (Table IV and V) also revealed LDLc to be the most important predictor for the rise in hsCRP level in both SH and OH groups. Increases in low-grade inflammatory markers have been already reported in previous studies like elevation in hsCRP and CD40 ligands in SH.[18] But in addition to the dyslipidemic changes and increased hsCRP levels found in hypothyroid patients, the findings of our study further suggests that the rise in hsCRP levels is dependent on the extent of increase in LDLc in blood that renders these patients more vulnerable to the cardiovascular risks from the combined effects of dyslipidemia and a low-grade inflammatory state.

In our study, hsCRP levels were found to be dependent on both TSH and fT4 in SH groups, while on only fT4 in the OH group (Table IV and V). Changes in the hsCRP levels were reported to be associated with serum TSH in a graded manner in SH patients in some previous studies.[24] These observations along with the findings in our study clearly indicate that serum TSH levels have a significant predictive role on hsCRP in SH patients. As a compensatory increase in serum TSH in SH makes an effort to maintain the compromised thyroxine levels within normal reference range, elevated levels of TSH in blood

are sustained to maintain the normal thyroxine levels in serum. However, as the patients progress to OH, the compensatory mechanism of TSH elevation is subdued and serum levels of thyroxine starts falling down. This partially explains the observation in our study that although, hsCRP is dependent on both fT4 and TSH in SH patients, it is dependent only on fT4 in OH cases.

In conclusion, findings of the present study indicate that a pro-inflammatory or a low-grade inflammatory state prevails even in the early stages of mild thyroid failure, i.e. the SH state and furthermore this elevation shows a graded response along with the decrease in thyroxine level and increase in blood LDLc fraction through the course of the disease. Although, some studies have negated the need of replacement therapy at the SH stage, others have advocated that therapy with thyroxine has been found to provide significant improvement of these biochemical parameters in SH patients that has been found to cause significant improvement in carotid arterial intimal thickness.[4] subclinical inflammation.[25] and hemostatic defects.[26] Keeping these factors in mind and the significant dependence of the hsCRP on fT4 and LDLc in a graded manner we suggest identification of SH at an earliest possible stage followed by appropriate replacement therapy as needed.

However, our observations and interpretations need to be judged in the context of inherent limitations of the case control non-interventional studies, limited sample size and lack of genetic evidences that may affect the population variation. In addition to above conclusions we thus propose the need for further research considering larger sample sizes in different cohorts involving both biochemical and genetic factors.

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