Journal of Advances in Medicine and Medical Research

27(9): 1-9, 2018; Article no.JAMMR.44329
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Interrelationship of High Sensitive C Reactive Protein and Thyroperoxidase Antibody Levels with Dyslipedemia in Subclinical Hypothyroidism and Overt Hypothyroidism

Anindya Dasgupta[1] and Suparna Roy[1*]

[1]Department of Biochemistry, Calcutta National Medical College and Hospital, Kolkata, India.

Authors' contributions

This work was carried out in collaboration between both authors. Authors AD and SR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AD managed the analyses of the study. Author SR managed the literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/44329
Editor(s):
(1) Dr. Mohamed Essa, Department of Food Science and Nutrition, Sultan Qaboos University, Oman.
(2) Dr. Chan-Min Liu, School of Life Science, Xuzhou Normal University, Xuzhou City, China.
Reviewers:
(1) Uma Kaimal Saikia, Gauhati Medical College, India.
(2) Jorge Pacheco Rosado, Escuela Nacional de Ciencias Biológicas, IPN, México.
Complete Peer review History: http://www.sciencedomain.org/review-history/26694

Original Research Article

Received 25 July 2018
Accepted 09 October 2018
Published 19 October 2018

ABSTRACT

Background and Aims: Antibodies against thyroperoxidase (TPO-Ab) and cholesterol levels are raised in overt hypothyroidism (OH) along with an increase of hsCRP, an early indicator of low grade inflammation. However, hypercholesterolemia and dyslipedemia has been found inconsistently in subclinical hypothyroidism (SCH) in different regions. The present study aimed at elucidating the relative importance of hsCRP and TPO-Ab with altered lipid parameters in both SCH and OH patients in this Region.
Study Design: Hospital-based case control study.
Methodology: Lipid parameters and hsCRP were measured in and TPO-Abs positive 35 OH and 35 SCH patients and 30 control subjects. Serum TSH, free T4, TPO-Ab, hsCRP levels and lipid parameters were measured by ELISA and standard photometric assays respectively. Post hoc ANOVA, bivariate correlation and multiple linear regression assays were used for analysing the

**Corresponding author: E-mail: drsuparnaray.ray@gmail.com;*

differences between mean values, strength of association between study variables and dependence of LDL cholesterol(LDLc) on hsCRP and TPO-Ab levels.

Results: Mean LDLcandHDLc were significantly increased and decreased respectively in both OH (146 ± 11.4; 29.5 ± 4.6); and SCH (132.4 ± 8.4; 37.6 ± 4.1) when compared with the control groups (90.8 ± 8.1; 44.4 ± 7.7) in graded manner (P < 0.001 between all groups).A similar rise in hsCRP levels (1.14 ± .32 in control, 2.22 ± .40 in SCH and 3.5 ± 1.0 in OH; P < 0.001 between all groups) was observed. Elevation in TPO-Ab levels in OH and SCH groups were significant only in comparison with the control groups (21.2 ± 5.5 in control, 44.8 ± 15 in SCH and 52.4 ± 16.7 in OH group; P < 0.001 against control group for both SCH and OH, but .07 between SCH and OH groups). LDLc was directly correlated with both TPO-Ab and hsCRPlevels in both groups. However, hsCRP levels showed better predictor effect on LDLc levels in both groups (β = .484 and .498; P = .002 and .003 for the OH and SCH respectively) in comparison to TPO-Ab (β = .281 and .200; P = .059 and .206 for the OH and SCH respectively).

Conclusion: Our findings specify the contributory roles of a low grade inflammatory state on altered LDLc metabolism that culminates in atherosclerosis in early thyroid diseases. It is also evident that hsCRP is a better indicator of it compared to TPO-Ab in even TPO-Ab positive hypothyroid patients. As in the OH group, hsCRP measurement in SCH can also help in initiating restrictive measures to minimise its further progression in OH conditions.

Keywords: Thyroperoxidase antibody (TPO); hsCRP; subclinical hypothyroidism; overt hypothyroidism; LDL cholesterol.

1. INTRODUCTION

Subclinical hypothyroidism (SCH) as well as its overt (OH) form, has been associated with significant risks for dyslipedemia and the consequent cardiovascular risks from it [1]. Studies from different parts of the world have suggested a prevalence of about 3 to 8% for the SCH [2-5]. On the other hand, antibodies against thyroperoxidase(TPO-Ab) enzyme are found in almost 80 percent and 50 percent in OH and SCH respectively [6]. Presence of these antibodies in Hashimoto's thyroiditis potentiates development of thyroid lymphoma and papillary carcinoma of thyroid [7]. Its presence in clinically euthyroid pregnant women has been found to be associated with repeated miscarriages in early pregnant stages which is promptly reverted to normalcy with thyroid hormone replacement [8]. Although, some studies reported no association of cholesterol levels with TSH in Hashimoto's thyroid disorder [9], recently TPO-Abs have been found to be associated with dyslipidemia in OH as well as in SCH groups making it as a potential cardiovascular risk factor [10,11]. Furthermore, the high sensitive C reactive protein (hsCRP), an independent risk factor for cardiovascular diseases as per Framingham risk score [12], has also been reported to be elevated at an early stage of hypothyroidism in several studies [13,14].However, this association has not been found to be significant in other places [15,16]. Hence, other than the immunological importance, presence of TPO antibodies and increased C reactive proteins herald special mention regarding their potential association with dyslipedemia and cardiovascular complications in hypothyroid patients. However, this association has been debated much and lacks significance congruence among different population groups.In our country hypothyroidism, both in its overt and subclinical form, constitute a major cause of morbidity among different age groups including pregnant mothers and the newborns [17,18].This potential association is important clinically as it needs to be investigated in both SCH and OH patients for formulating an appropriate management schedule at the earliest.

Keeping these factors in mind we hypothesised that dyslipedemia and so the cardiovascular risk factors should be associated with an increased TPO-Ab and hsCRP in the hypothyroid patients in our study group. Hence, the present study has been designed accordingly to assess this relationship in both groups of SCH and OH patients in this region with an aim to ascertain the potential relationship between TSH fT4 and lipid profile with TPO-Ab and hsCRP levels in both SCH and OH patients.

2. MATERIALS AND METHODS

The methodology for the present hospital based cross sectional study was designed to assess and compare the relationship between TSH, fT4 and lipid profile parameters with that of the

hsCRP and TPO levels in SCH and OH patients.

2.1 Selection of Study Subjects

The cases were selected from the thyroid clinic of our tertiary care hospital. Both male & female subjects between age group 20 to 60 years were selected for assessing the serum levels of free T4 (fT4), TSH, LDLc, HDLc, triglyceride (TG), total cholesterol (TC), antibodies against thyroperoxidase (TPO-Ab) and hsCRP. Following exclusion criteria were considered for final selection of the case group.

Exclusion criteria for cases: Pregnant women were excluded to avoid the altered immunological status during pregnancy. Patients with any other metabolic disorders or any chronic illness were also excluded from the study by proper history taking and supportive investigations. History of smoking alcohol drug addiction or patients suffering from any malignant disorders were excluded from the study.

Following the inclusion and exclusion criteria, the maximum number of possible cases was selected using the method of convenience within the stipulated study period of one year starting from June 2016 to June 2017 in our tertiary care medical college and hospital. 30age and sex matched normal subjects having no history of any metabolic disorders, inflammatory or any other co-morbid condition that could cause an increase in hsCRP or alter thyroid function status, and without any addiction, history were selected as control group for this study.

2.2 Ethical Consideration

The study strictly adhered to the Helsinki declaration for human studies 1975, revised in 2000. The study was undertaken after getting the approval from the institutional ethical committee.

2.3 Analysis of Biochemical Parameters

Immunological assays were performed using ELISA kits from Accubind, USA for the TSH, fT4, TPO-Ab and hsCRP. Lipid parameters like TC, LDLc, HDLc and TG levels were measured using standard colorimetric reagent kits from ERBA, Transasia, USAin fully automated biochemical analyzer from XL 600, ERBA, Transasia USA. Coefficient of variation for each test remained below 10% throughout the study period.

2.4 Statistical Analysis

Data obtained were analysed for normal distribution using Kolmogrov Smirnov analysis .For normally distribute parameters comparison between their mean values were performed using independent t test and post hoc ANOVA with Bonferroni's correction as needed. The degree of association within the study variables were analysed by multiple correlations and regression analysis as applicable. All statistical analyses were done by SPSS software version 20. P- value less than 0.05 were taken as statistically significant for a 95% confidence interval for the present study.

3. RESULTS ANALYSIS

We subdivided the case group into SCH and OH patients based on serum fT4 levels, as follows: (1) SCH group: elevated TSH (>6.16 μIU/mL), but total fT4 within the reference range (0.8 to 2 ng/dL); (2) OH group: elevated TSH (>6.16 μIU/mL) and fT4 below the lower limit of the reference range (0.8 ng/dL).Accordingly 35 patients were classified as OH and 35 were classified as SCH.

First, we performed the ANOVA tests to elicit the significance of difference between the mean values of OH, SCH and control groups. In Table 1A simple one way ANOVA showed that there was a significant difference ($P < 0.05$ for all parameters) between the OH, SCH and control population. To obtain the significance of difference between the individual groups post hoc ANOVA was done with Bonferroni correction to avoid the biasness in the P value assessment due to repeated comparisons. Results showed that difference between all individual parameters were statistically significant between the three groups separately except that for the fT4 where no significant difference were found between the control and SCH group.

When the data were analysed for the strength of association between different parameters in the OH group (Table 2), it was found that that hsCRP and TPO antibodies were directly associated with the TSH and LDLc values while showing inverse relationships with the fT4 values. In addition, hsCRP showed a negative association with HDLc and positive correlation with the TG level.

Table 1A. Simple one way ANOVA to show the significance of difference between the mean values of study parameters between groups and within groups as a whole

ANOVA					
		Sum of squares	**Mean square**	**F**	**Sig.(P value)**
TSH	Between groups	3497.358	1748.679	295.680	<.001
	Within groups	573.668	5.914		
	Total	4071.027			
fT4	Between groups	13.648	6.824	147.227	<.001
	Within groups	4.496	.046		
	Total	18.145			
TPO-Ab	Between groups	16675.429	8337.715	45.107	<.001
	Within groups	17929.881	184.844		
	Total	34605.310			
hsCRP	Between groups	85.555	42.778	91.973	<.001
	Within groups	45.116	.465		
	Total	130.671			
LDL	Between groups	52604.954	26302.477	289.572	<.001
	Within groups	8810.730	90.832		
	Total	61415.684			
HDL	Between groups	3609.234	1804.617	57.529	<.001
	Within groups	3042.793	31.369		
	Total	6652.027			
TGL	Between groups	36954.133	18477.066	104.978	<.001
	Within groups	17072.819	176.008		
	Total	54026.952			
VLDL	Between groups	1478.165	739.083	104.978	<.001
	Within groups	682.913	7.040		
	Total	2161.078			
TC	Between groups	44796.206	22398.103	202.380	<.001
	Within groups	10735.306	110.673		
	Total	55531.512			

Similar analysis in the Table 3 showed that the TPO Abs and hsCRP levels were significantly associated with TSH and LDLc values in the SCH group without showing any association with the fT4 values. Positive association of both TPO-Ab and hsCRP were also observed with the LDLcvalues. hsCRP showed a negative association with HDLc and positive association TG levels also.

Multiple linear regression analysis in the Table 4 and 5 revealed that as in the case of OH group, LDLc levels in the SCH patients were also significantly dependent on the hsCRP values only.

4. DISCUSSION

In the present study, significantly elevated levels of TPO-Ab and hsCRP in both SCH and OH groups (Table 1A and 1B) were significantly associated with raised LDL cholesterol level (Table 2 and 3). Several studies have strongly suggested that elevated TPO-Ab and TSH signify poorer prognosis for SCH patients and overall poor outcome for hypothyroid patients leading to early thyroid failure [19,20] and its impending complexities like dyslipedemia, atherosclerosis and cardiovascular morbidity. High cholesterol level and low HDLc values have been found to be major confounding factors for hypothyroid patients. In SCH increased cholesterol levels has been found to be associated with rising tires of serum TSH values [21]. Some studies reported changes in both triglyceride and LDLc levels in SCH [22,23] whereas others reported changes in LDLc only that reverts back to normal with levothyroxine therapy [24]. In our study, both LDLc and triglyceride levels were found to be significantly directly associated with TSH levels in SCH and OH groups (Tables 2 and 3). However, when their association with the fT4 levels were analysed, LDLconly showed significant increase in both SCH and OH groups (Table 2 and 3). High LDLc levels in SCH have been so far attributed to reduced LDL receptor sensitivity due to altered adipokine status in SCH along with a decreased turnover of cholesterol ester transfer protein mediated conversion of LDL to HDL due to compromised T3 function [25].

Table 1B. Post hoc ANOVA with Bonferroni correction to show the significance of difference between the mean values of study parameters between each individual group separately (n for OH, SCH and control group = 35, 35 and 30 respectively, Total N = 100)

Dependent variable	(I) Grouping	(J) Grouping	Sig.
TSH (mIU/l)	CONT	SCH	<.001
(Mean±S.D)	(3.01 ± 1.10)	OH	<.001
	SCH	CONT	<.001
	(8.9 ± 1.6)	OH	<.001
	OH	CONT	<.001
	(17.5 ± 3.6)	SCH	<.001
fT4 (ng/dl)	.CONT	SCH	.632
(Mean±S.D)	(1.31 ± .19)	OH	<.001
	SCH	CONT	.632
	(1.25 ± .28)	OH	<.001
	OH	CONT	<.001
	(.50 ± .15)	SCH	<.001
TPO-Ab (IU/ml)	CONT	SCH	<.001
(Mean±S.D)	(21.2 ± 5.5)	OH	<.001
	SCH	CONT	<.001
	(44.8 ± 15)	OH	.070
	OH	CONT	<.001
	(52.4 ± 16.7)	SCH	.070
hsCRP (mg/l)	CONT	SCH	<.001
(Mean±S.D)	(1.14 ± .32)	OH	<.001
	SCH	CONT	<.001
	(2.22 ± .40)	OH	<.001
	OH	CONT	<.001
	(3.5 ± 1.0)	SCH	<.001
LDLc (mg/dl)	CONT	SCH	<.001
(Mean±S.D)	(90.8 ± 8.1)	OH	<.001
	SCH	CONT	<.001
	(132.4 ± 8.4)	OH	<.001
	OH	CONT	<.001
	(146 ± 11.4)	SCH	<.001
HDLc (mg/dl)	CONT	SCH	<.001
(Mean±S.D)	(44.4 ± 7.7)	OH	<.001
	SCH	CONT	<.001
	(37.6 ± 4.1)	OH	<.001
	OH	CONT	<.001
	(29.5 ± 4.6)	SCH	<.001
TG (mg/dl)	CONT	SCH	<.001
(Mean±S.D)	(115 ± 12.7)	OH	<.001
	SCH	CONT	<.001
	(145.5 ± 13.7)	OH	<.001
	OH	CONT	<.001
	(162.4 ± 13.2)	SCH	<.001
TC	CONT	SCH	<.001
(Mean±S.D)	(158.2 ± 8.1)	OH	<.001
	SCH	CONT	.000
	(199.2 ± 10.1)	OH	.002
	OH	CONT	.000
	(208.1 ± 12.5)	SCH	.002

hsCRP is an established marker of low grade inflammation responsible for atherosclerotic changes and several studies have confirmed its elevation in the early phases of SCH [26,27] while some studies reporting no such association [15]. In the present study significant increase in the hsCRP levels has been found in the SCH group in comparison the control subjects that was further increased in the OH state (post hoc ANOVA, Table 1B). This graded increase was most likely due to elevated levels of inflammatory states as reflected by a direct correlation between the TPO-Ab and hsCRP levels in both groups (Table 2 for OH and Table 3 for SCH).

Furthermore, both TPO-Ab and hsCRP were directly related with the serum LDLc levels in both SCH and OH patients indicating their individual contributory roles in hyper-cholesterolemia induced atherosclerosis. However, when we further explored their combined effects on the LDLc levels in both groups by multiple linear regression analysis (Table 4 for OH and Table 5 for the SCH group), it was revealed that serum hsCRP played a more determining predictive role in the elevation of LDLc levels in both groups.

Table 2. Bivariate Pearson's correlation analysis showing the strength of association between different study parameters in OH group N=35

		TSH	fT4	TPOAb	hsCRP	LDLc	HDLc	TG	TC
TSH	Pearson correlation	1	-.679**	.424*	.462**	.466**	-.558**	.328	.098
	Sig. (2-tailed)		.<001	.011	.005	.005	.000	.049	.574
fT4	Pearson correlation	-.679**	1	-.486**	-.360*	-.354*	.363*	-.243	.023
	Sig. (2-tailed)	.<001		.003	.034	.037	.032	.159	.897
TPOAb	Pearson correlation	.424*	-.486**	1	.379*	.358*	-.017	.065	.038
	Sig. (2-tailed)	.011	.003		.025	.035	.921	.710	.829
hsCRP	Pearson correlation	.462**	-.360*	.379*	1	.529*	-.368*	.096	.370*
	Sig. (2-tailed)	.005	.034	.025		.001	.029	.584	.029
LDLc	Pearson correlation	.466**	-.354*	.358*	.529*	1	-.317	.235	.563**
	Sig. (2-tailed)	.005	.037	.035	.001		.064	.174	.<001
HDLc	Pearson correlation	-.558**	.363*	-.017	-.368*	-.317	1	-.089	-.071
	Sig. (2-tailed)	.000	.032	.921	.029	.064		.610	.684
TG	Pearson correlation	.328	-.243	.065	.096	.235	-.089	1	.241
	Sig. (2-tailed)	.054	.159	.710	.584	.174	.610		.164
TC	Pearson correlation	.098	.023	.038	.370*	.563**	-.071	.241	1
	Sig. (2-tailed)	.574	.897	.829	.029	.<001	.684	.164	

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

Table 3. Bivariate Pearson's correlation analysis showing the strength of association between different study parameters in SCH group

		TSH	fT4	TPO-Ab	hsCRP	LDLc	HDLc	TG	TC
TSH	Pearson correlation	1	-.655**	.427*	.466**	.604**	-.271	.470**	.539**
	Sig. (2-tailed)		.000	.010	.005	.000	.115	.004	.001
	N	35	35	35	35	35	35	35	35
fT4	Pearson correlation	-.655**	1	-.180	-.295	-.458**	.052	-.210	-.468**
	Sig. (2-tailed)	.000		.302	.085	.006	.765	.226	.005
	N	35	35	35	35	35	35	35	35
TPO-Ab	Pearson correlation	.427*	-.180	1	.430**	.414*	-.268	.216	.219
	Sig. (2-tailed)	.010	.302		.010	.013	.120	.212	.207
	N	35	35	35	35	35	35	35	35
hsCRP	Pearson correlation	.466**	-.295	.430**	1	.584**	-.069	.442**	.524**
	Sig. (2-tailed)	.005	.085	.010		.000	.693	.008	.001
	N	35	35	35	35	35	35	35	35
LDL	Pearson correlation	.604**	-.458**	.414*	.584**	1	-.294	.469**	.806**
	Sig. (2-tailed)	.000	.006	.013	.000		.087	.005	.000
	N	35	35	35	35	35	35	35	35
HDL	Pearson correlation	-.271	.052	-.268	-.069	-.294	1	.014	.232
	Sig. (2-tailed)	.115	.765	.120	.693	.087		.935	.180
	N	35	35	35	35	35	35	35	35
TG	Pearson correlation	.470**	-.210	.216	.442**	.469**	.014	1	.647**
	Sig. (2-tailed)	.004	.226	.212	.008	.005	.935		.000
	N	35	35	35	35	35	35	35	35
TC	Pearson correlation	.539**	-.468**	.219	.524**	.806**	.232	.647**	1
	Sig. (2-tailed)	.001	.005	.207	.001	.000	.180	.000	
	N	35	35	35	35	35	35	35	35

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

Table 4. Multiple linear regression analysis showing the predictive values of TPO antibodies and hsCRP on LDL cholesterol levels in overt hypothyroid (OH) patients

Coefficients[a]						
Model		Unstandardised coefficients		Standardised coefficients	t	Sig.
		B	Std. error	Beta		
1	(Constant)	116.005	7.590		15.283	.000
	TPOAb	.227	.116	.281	1.957	.059
	hsCRP	5.342	1.583	.484	3.374	.002

a. Dependent Variable: LDLc

p value significant at P<0.05for 95% confidence interval

Table 5. Multiple linear regression analysis showing the predictive values of TPO antibodies and hsCRP on LDL cholesterol levels in subclinical hypothyroid patients

Coefficients[a]						
Model		Unstandardised coefficients		Standardised coefficients	t	Sig.
		B	Std. error	Beta		
1	(Constant)	104.379	6.634		15.735	.000
	TPO Ab	.113	.088	.200	1.290	.206
	hsCRP	10.366	3.227	.498	3.212	.003*

a. Dependent Variable: LDLc

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

Apart from being a result of direct inflammatory effect, increase in hsCRP in the SCH group has been found to be attributable to high TSH levels itself that increases the peroxidation of existing LDLc particles [28] along with increasing LDLc levels in blood by increasing insulin resistance and its adverse effects on fat depots [29]. Although, we did not assess these factors in the present study, we can opine from these previous observations that dependence of LDLc levels on hsCRP observed in our present study is multifactorial and hence is a strong indicator of hypercholesterolemia and resultant cardiovascular complications in both SCH and OH hypothyroid patients.

5. CONCLUSION

Our combined results of bivariate correlation and multiple linear regression analyses indicate that in spite of graded elevation in TPO-Ab levels along with an increase in TSH and LDLc values in both SCH and OH groups, serum hsCRP levels have better predictive value for LDLc elevation in comparison to TPO-Ab when considered together in both groups. These findings reiterate the contributory roles of a low grade inflammatory state on altered LDLc metabolism that culminates in atherosclerosis in early thyroid diseases. We also showed that hsCRP is a better indicator of it compared to TPO-Ab in even TPO-Ab positive hypothyroid patients.We propose that as in overt hypothyroidism, hsCRP measurement can predict early atherosclerotic changes in subclinical hypothyroidism significantly and help in initiating restrictive measures to minimise its further progression in overt hypothyroid conditions.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

The study adhered strictly to the Helsinki Declaration for human studies. The study was approved by the Institutional Ethical Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Saric MS, Jurasic MJ, Sovic S, Kranjcec B, Glivetic T, Demarin V. Dyslipidemia in subclinical hypothyroidism requires assessment of small dense low density lipoprotein cholesterol (sdLDL-C). Rom J Intern Med; 2017.
2. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid

antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2): 489-99.
3. Riniker M, Tieche M, Lupi GA, Grob P, Studer H, Burgi H. Prevalence of various degrees of hypothyroidism among patients of a general medical department. Clin Endocrinol (Oxf). 1981;14(1):69-74.
4. Herrmann J. Prevalence of hypothyroidism in the elderly in Germany. A pilot study. J Endocrinol Invest. 1981;4(3):327-30.
5. Kostoglou-Athanassiou I, Ntalles K. Hypothyroidism - new aspects of an old disease. Hippokratia. 2010;14(2):82-7.
6. Jayashankar CA, et al. Int J Res Med Sci. 2015;3(12):3564-3566.
7. Maitra A. The endocrine system. In: Kumar V, Abbas AK, Aster JC, editors. Robbins and cotran pathologic basis of disease. 9th ed. Philadelphia: Elsevier Saunders; 2014; II:1082–105.
8. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. Indian J Endocrinol Metab. 2011;15(Suppl 2):S78-81.
9. Hariharan S, Padhi S, Sahoo J, Sarangi R. Dyslipidemia in hypothyroid subjects with Hashimoto's thyroiditis. International Journal of Medical Science and Public Health. 2015;4(9):1-3.
10. Srivastava VK, Singh H. Association of thyroid peroxidase antibody and dyslipidemia in subclinical hypothyroidism. J Family Med Prim Care. 2017;6(1):63-68.
11. Monzani F, Caraccio N, Kozà kowà M, Dardano A, Vittone F, Virdis A, et al. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: A double-blind, placebo- controlled study. J Clin Endocrinol Metab. 2004;89:2099–106.
12. Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: The cardiovascular health study. Circulation. 2005;112(1):25-31.
13. Roy S, Banerjee U, Dasgupta A. Effect of sub clinical hypothyroidism on C-reactive protein and ischemia modified albumin. Mymensingh Med J. 2015;24(2):379-84.
14. Sharma R, Sharma TK, Kaushik GG, Sharma S, Vardey SK, Sinha M. Subclinical hypothyroidism and its association with cardiovascular risk factors. Clin Lab. 2011;57(9-10):719-24.
15. Toruner F, Altinova AE, Karakoc A, Yetkin I, Ayvaz G, Cakir N, et al. Risk factors for cardiovascular disease in patients with subclinical hypothyroidism. Adv Ther. 2008;25(5):430-7.
16. Park YJ, Lee EJ, Lee YJ, Choi SH, Park JH, Lee SB, et al. Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects. Arch Gerontol Geriatr. 2010;50(3):e68-73.
17. Mir SA, Masoodi SR, Shafi S, Hameed I, Dar MA, Bashir MI, et al. Efficacy and safety of Vitamin D supplementation during pregnancy: A randomized trial of two different levels of dosing on maternal and neonatal Vitamin D outcome. Indian J Endocrinol Metab. 2016;20(3):337-42.
18. Kaur G, Thakur K, Kataria S, Singh TR, Chavan BS, Atwal R. Current and future perspective of newborn screening: An Indian scenario. J Pediatr Endocrinol Metab. 2016;29(1):5-13.
19. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. JAMA. 1987;258(2):209-13.
20. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, et al. Prospective study of the spontaneous course of sub-clinical hypothyroidism: Prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab. 2002; 87(7):3221-6.
21. Nair SN, Kumar H, Raveendran M, Menon VU. Subclinical hypothyroidism and cardiac risk: Lessons from a south Indian population study. Indian J Endocrinol Metab. 2018;22(2):217-22.
22. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The colorado thyroid disease prevalence study. Arch Intern Med. 2000; 160(4):526-34.
23. Lee MW, Shin DY, Kim KJ, Hwang S, Lee EJ. The biochemical prognostic factors of subclinical hypothyroidism. Endocrinol Metab (Seoul). 2014;29(2):154-62.
24. Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in subclinical hypothyroidism: Response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab. 2002;87(4):1533-8.

25. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. Open Cardiovasc Med J. 2011;5: 76-84.
26. Tuzcu A, Bahceci M, Gokalp D, Tuzun Y, Gunes K. Subclinical hypothyroidism may be associated with elevated high-sensitive C-reactive protein (low grade inflammation) and fasting hyperinsulinemia. Endocr J. 2005;52(1):89-94.
27. Sharma R, Sharma TK, Kaushik GG, Sharma S, Vardey SK, Sinha M. Subclinical hypothyroidism and its association with cardiovascular risk factors. Clin Lab 2011;57:719-24.
28. Zha K, Zuo C, Wang A, Zhang B, Zhang Y, Wang B, et al. LDL in patients with subclinical hypothyroidism shows increased lipid peroxidation. Lipids Health Dis. 2015;14:95.
29. Peixoto de Miranda EJ, Bittencourt MS, Santos IS, Lotufo PA, Bensenor IM. Thyroid function and high-sensitivity C-reactive protein in cross-sectional results from the Brazilian longitudinal study of adult health (ELSA-Brasil): Effect of Adiposity and Insulin Resistance. Eur Thyroid J. 2016;5(4):240-6.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/26694