ORIGINAL RESEARCH PAPER

Volume-6 | Issue-9 | September-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFECT OF HYPOTHYROIDISM AND ITS TREATMENT ON PROATHEROGENIC LIPID LEVELS.

Biochemistry

Dr. Sohil Takodara Assistant Professor, Department of Biochemistry, R.D.Gardi Medical College, Ujjain

Dr. Sagar Dholariya Assistant Professor, Department of Biochemistry, R.D.Gardi Medical College, Ujjain - Corresponding Author

Dr.Poornima Manjrekar Professor and Head, Department of Biochemistry, Kasturba Medical College,Mangalore.

Dr. Alap Christy Head Quality Assurance Metropolis,Mumbai

Dr. Ruby P Babu Biochemist and Quality Manager at Manipal Hospitals Bangalore

ABSTRACT

Overt hypothyroidism is associated with abnormalities of lipid metabolism, which may predispose to the development of atherosclerotic coronary artery disease. Therefore the aim of the study was to assess proatherogenic lipid levels in 30-45 years aged women with newly diagnosed hypothyroidism and compare the same with patients on Levothyroxine therapy and euthyroid control. The serum Lipoprotein(a)[Lp(a)],LDL cholesterol[LDL-C] and Oxidized LDL[Ox-LDL] levels were analyzed in three cohorts each of 25 divided into newly diagnosed cases of overt hypothyroidism, cases of hypothyroidism on Levothyroxine with doses within 100-200mcg/day for a period of at least 5 years and euthyroid women between the ages of 30-45 years in KMC Hospital, Mangalore, Karnataka, India. The results analysed using Statistical Package for Social Science version 20.0 are presented as Mean ± SD and compared by Kruskal –Wallis test and MANN-Whitney U test. Correlation analysis was done by Spearman's correlation coefficient test. The mean levels of Lipoprotein, Direct LDL and Ox-LDL were high in cases of newly diagnosed hypothyroidism. All three proatherogenic lipids were low in the treated group in comparison to newly diagnosed cases but the difference was significant only for LDL-C.Thyroid Stimulating Hormone levels were very well correlated with Lp(a) and Direct LDL. Dyslipidemia in patients with thyroid disease because of the effects of thyroid hormones in almost all steps of lipid metabolism, consisting of high levels of LDL cholesterol and Lp(a). High proatherogenic lipid levels particularly Lp(a) and LDL suggests risk of atherosclerosis in patients of hypothyroidism. In later stages of hypothyroidism the changes occur due to high lipids may not be reverted by levothyroxine therapy.

KEYWORDS

Hypothyroidism, Lipoproteins, Levothyroxine, Atherosclerosis

Introduction

The thyroid gland produces two hormones predominantly, thyroxine (T4) and triiodothyronine (T3).[1] Reduced production and action of thyroid hormones is the central feature of the clinical state termed hypothyroidism. Primary hypothyroidism is due to permanent loss or destruction of the thyroid, through processes such as autoimmune destruction or irradiation injury. Central or secondary hypothyroidism, due to insufficient stimulation of a normal gland, is the result of hypothalamic or pituitary disease or defects in the thyroid-stimulating hormone (TSH). Primary hypothyroidism which is the cause in more than 99% of the patients, there is a significant increase in basal serum TSH concentration. As hypothyroidism progresses, the serum TSH increases further, the serum free T4 falls, and finally at the most severe stage, serum T3 concentrations may become subnormal.[2] Thyroid hormones effects on lipid metabolism include: (a) enhanced utilization of lipid substrates (b) increase in the synthesis and mobilization of triglycerides stored in adipose tissue; (c) increase in the concentration of non esterified fatty acids (NEFA) and (d) increase of lipoprotein-lipase activity.[3] In hypothyroid patients the most frequent lipid abnormality is hypercholesterolemia mainly due to an increased concentration of low density lipoproteins (LDL).[4] Oxidized LDL is a modification of the LDL that occur when free redicals react with polyunsaturated fatty acids and induce lipid peroxidation. These modified lipid are proatherogenic and proinflammatory.[5] Overt hypothyroidism accompyning hypercholesterolemia, is widely recognized as a risk factor for atherosclerosis and cardiovascular disease. Apart from altered lipid profile patients of hypothyroidism has been associated with the elevated lipoprotein profile particularly a modified LDL that is Lipoprotein(a).[6]Treatment with Levothyroxine is often initiated for two reasons. First, therapy may prevent progression to the symptomatic stage of overt hypothyroidism, which otherwise occurs at a rate of about 5% per year in those with mild thyroid failure. Second, therapy may also reduce symptoms of thyroid hormone deficiency that have been shown to be present and reversible in about 25% of individuals with mild thyroid failure.[7] However, it has been less clear whether the therapy with Levothyroxine lowers the elevated lipid levels.[8] Therefore the aim of the study was to analyse the proatherogenic lipid levels[Direct LDL, Oxidised LDL and Lipoprotein(a)] in 30-45 years aged women in newly diagnosed hypothyroidism and compare the same with patients on Levothyroxine therapy and euthyroid control.

Materials and Methods

Case control study was done in which only women aged between 30-45 years were included on the basis of T3, T4 and TSH levels, present complains and history of treatment taken. From the KMC hospital, Ambedkar Circle and KMC hospital Attavar, 25 newly diagnosed hypothyroid women and 25 hypothyroid women on Levothyroxine therapy for atleast 5 years were included in the study with their consent. 25 euthyroid women were chosen from the general population as a control. Newly diagnosed cases of overt hypothyroidism, cases of hypothyroidism on Levothyroxine with doses within 100-200mcg/day for a period of at least 5 years and euthyroid women between the ages of 30-45 years were included in the study. Patients with history of diabetes, hypertension, ischemic heart disease , congestive cardiac failure, chronic renal failure were excluded. Pregnant women with known dylipidemic status and women on oral contraceptive pills and lipid lowering drugs were excluded.

Biochemical measurements: Serum was obtained from the blood, collected in a sterile vacutainer from each subject. The serum sample were taken for estimation of direct LDL-cholesterol, Oxidized LDL and Lipoprotein(a) at the Department of Biochemistry, Center for Basic Sciences, KMC Bejai.

Methods: The serum Lipoprotein(a), Direct LDL and Ox-LDL levels were analyzed by ECLIA, Enzymatic colorimetric assay and TBARS[9] methods respectively. The results analysed using Statistical Package for Social Science version 20.0 are presented as Mean ± SD and compared by Kruskal –Wallis test and MANN-Whitney U test. Correlation analysis was done by Spearman's correlation coefficient test. P-value <0.05 was considered as a significant.

Results:

The study included 75 women aged between 30-45 years, divided into

three groups on the basis of T_3 ,T_4,TSH levels, present complains and history of treatment taken.

Table-1. Comparison of variables among the groups.
The mean age and serum T4 were similar without any significant difference among the groups. But a significant

Variables	Euthyroid (group 1) N= 25	Newly diagnosed (group 2) N= 25	On Treatment (group 3) N= 25	P value
Lipoprotein(a) (mg/dl)	21.36±8.82	37.14±14.92	31.93±13.31	<0.001
Direct LDL(mg/dl)	95 ± 10.93	136.76 ± 30.16	119.56 ± 24.23	<0.001
Oxidized LDL(µmol/L)	7.99 ± 1.55	13.7 ± 3.68	11.89 ± 3.39	<0.001
Age(years)	38.08 ± 6.06	37.88 ± 5.82	40.4 ± 5.09	0.252
TSH(µIU/ml)	2.40 ± 0.85	11.96 ±13.18	3.93 ± 2.99	<0.001
T_3(ng/ml)	1.46 ± 0.52	1.19 ± 0.32	1.22 ± 0.33	0.01
T_4(µg/dl)	8.53 ± 2.0	7.28 ± 2.07	8.27 ± 2.3	0.07

difference in mean TSH and T_3 values were noted. The difference was also significant for LDL-C, Ox-LDL and Lp(a).

Table-2 Comparison of Lp(a), Direct LDL and Ox-LDL within the groups.

Parameters	Group-I	Group-II	Mean Difference Z	p-value
Lipoprotein(a)	Euthyroid	Newly Diagnosed	-4.357	<0.001
		On Treatment	-3.124	<0.001
	Newly Diagnosed	On Treatment	-1.620	0.105
Direct LDL	Euthyroid	Newly Diagnosed	-4.941	<0.001
		On Treatment	-4.058	<0.001
	Newly Diagnosed	On Treatment	-2.145	0.032
Oxidised -LDL	Euthyroid	Newly Diagnosed	-5.229	<0.001
		On Treatment	-4.385	<0.001
	Newly Diagnosed	On Treatment	-1.669	0.095

Z= MANN-Whitney U Test
The mean level of Lp(a), LDL-C and Ox-LDL were high in cases of newly diagnosed hypothyroidism and in the treated group in comparison to euthyroid group. Significant difference in mean LDL-C values was noted between Group-2 and Group-3. Though mean Lp(a) and Ox-LDL values were reduced in treated group in comparison but difference was not significant. (Fig.1-3)

Table-3 Correlation analysis between proatherogenic lipids with each other and with TSH among all the groups by Spearman's correlation coefficient test.

Category			LDL	Ox-LDL	TSH
Euthyroid	**Lp(a)**	r	-.281	.201	.222
		p	.174	.335	.285
	LDL	r		-.212	-.197
		p		.308	.346
	Ox-LDL	r			.189
		p			.365
Newly diagnosed	**Lp(a)**	r	.718**	.170	.739**
		p	<0.001	.416	<0.001
	LDL	r		.301	.725**
		p		.144	<0.001
	Ox-LDL	r			.295
		p			.152
On Treatment	**Lp(a)**	r	.047	-.127	-.246
		p	.825	.545	.235
	LDL	r		.029	-.054
		p		.891	.797
	Ox-LDL	r			.053
		p			.802

There was a significant linear correlation was found between TSH and Lp(a) [r=0.739] , TSH and LDL-C [r=0.725] and also between Lp(a) and LDL-C[0.718] in newly diagnosed hypothyroid group. However Ox-LDL levels were not correlating with TSH levels in the same group. In other groups correlation analysis was not significant statistically.

Fig.1 Comparison of mean values of Lp(a) among the groups.

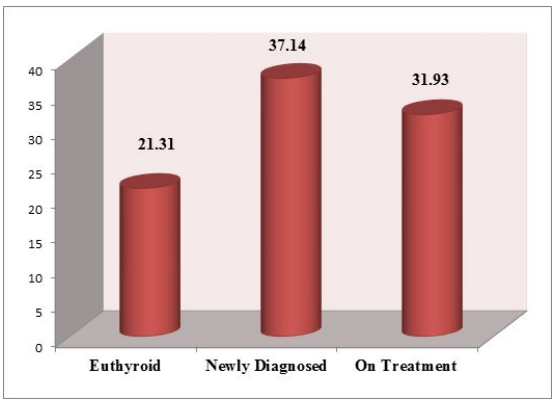


Fig.2 Comparison of mean values of Ox-LDL among the groups.

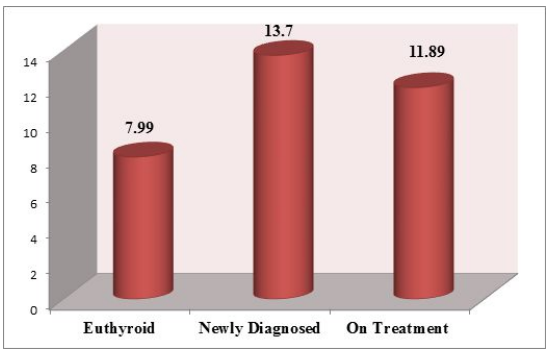
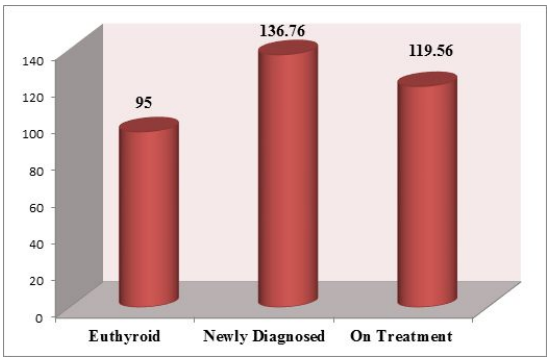


Fig.3 Comparison of mean values of Direct LDL among the groups.



Discussion
Dyslipidemia is a common finding in patients with thyroid disease because of the effects of thyroid hormones in almost all steps of lipid

metabolism, consisting of high levels of total and LDL cholesterol. [10] The result observed in our study was similar to that of studies by Tzotzas et al where high lipid levels were found in hypothyroid patient. [11] LDL cholesterol is an independent and modifiable CVD risk factor. Mora et al have found LDL-C, Apo B-100, Apo B-100/A1 ratio to be useful marker for CVD risk.[12]

Overt hypothyroidism is characterized by hypercholesterolemia and a marked increase in low-density lipoproteins and apolipoproteins. Whereas the prevalence of overt hypothyroidism in patients with hypercholesterolemia is estimated to be 1.3% to 2.8%, 90% of patients with hypothyroidism had hypercholesterolemia.[13]

Specifically, some studies have demonstrated that LDL is increased in subclinical hypothyroidism and is reversed with thyroid hormone replacement.[14] In this study it was found in Overt hypothyroidism cases. The reported mechanisms for the development of hypercholesterolemia in hypothyroidism include decreased fractional clearance of LDL by a reduced number of LDL receptors in the liver in addition to decreased receptor activity.[15]The catabolism of cholesterol into bile is mediated by the enzyme cholesterol 7-α hydroxylase. This liver-specific enzyme is negatively regulated by T3 and may contribute to the decreased catabolism and increased levels of serum cholesterol associated with hypothyroidism.[16]The increased serum lipid levels in subclinical hypothyroidism as well as in overt disease are potentially associated with increased cardiovascular risk.[17] If untreated, the dyslipidemia together with the diastolic hypertension associated with hypothyroidism may further predispose the patient to atherosclerosis.[18-20]

It's been proven that LDL cholesterol has a major role in formation of atheromatous plaque and along with it another modified lipid which Lp(a) which has been considered as an emerging risk factor for atherosclerosis.[21]Because of the evidence linking raised Lp(a) concentrations with the development of atherosclerosis,[22] attention has focused on serum Lp(a) levels in thyroid diseases. This lipoprotein is synthesized mainly in the liver and consists of a LDL particle bound to an apoprotein that is structurally similar to plasminogen. The relationship between overt hypothyroidism and Lp(a) levels and the effect of levothyroxine therapy are still controversial.[23] The findings of this study is high level of Lp(a) along with high LDL cholesterol suggesting risk of atherosclerosis in patients of hypothyroidism. A number of studies suggest a decrease of TC and LDL-C after levothyroxine substitution[24-26]whereas others report no significant changes[27,28].Lp(a) levels and their response to treatment have been evaluated previously.[29-31]All but one failed to demonstrate any significant changes in Lipoprotein(a) levels following levothyroxine substitution therapy. In this study Lipoprotein(a) level were high in Newly diagnosed cases and the levels reduced in on treatment group but the difference was not statistically significant. This suggests the predominance of genetic factors in Lp(a) metabolism, atleast in hypothyroidism, although thyroid hormones are proposed to play a role in Lipoprotein(a) metabolism.[30] The levothyroxine dose and length of the treatment period may be the reasons for this discrepancy between these two groups, and some previous studies, supporting this hypothesis, reported a dose-dependent effect of levothyroxine therapy on Lp(a) levels in clinically overt hypothyroidism. De Bruin et al [32] and Engler and Riesen et al[33] found that 25 µg levothyroxine therapy decreased the Lp(a) concentration by 55%, but higher doses of levothyroxine were associated with no change in Lp(a) levels. Also the effect of levothyroxine therapy on arterial stiffness has remained controversial. These studies supports the findings of the current study. Thus screening for proatherogenic lipids should be done as early as possible in hypothyroid patients preferably at subclinical stage since in the changes which occurs due to high lipids in later stages and with higher doses of levothyroxine may not be reverted.

Another aspect of the study was related to oxidative stress and hypothyroidism. In our study the Oxidised LDL levels were elevated in newly diagnosed hypothyroid patients. This finding was similar to the study done by Nanda et al[34]and Erdamar et al [35].Oxidized LDL (Ox-LDL) are known to promote atherogenesis through foam cell formation and inflammatory responses. The process involves receptor-mediated endocytosis of Ox-LDL which leads to lipid accumulation and vascular cell dysfunction including induction of apoptosis which represents major cause of plaque growth and rupture. The evaluation of the real effects of thyroid hormone on parameters of oxidative stress appears very difficult considering that thyroid hormone levels are influenced by diet, environmental factors, and reaction capacity to daily stress situations, in which cases, the parameters of oxidative stress are also modified.[35] For this reason, the effect of thyroid hormone on oxidative stress parameters in women is not clear and depends on different variables.

This study was conducted to know the proatherogenic lipid levels in Hypothyroidism patient and to know the effect of levothyroxine treatment on lipid levels. Main reason for that is because of influence of thyroid hormones on the expression of enzymes involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes in lipid levels, in thyroid disease. Dyslipidemia coexists with other metabolic abnormalities, including, hypertension, insulin resistance, oxidative stress, all of them being risk factors for cardiovascular disease. In addition, dyslipidemia induces insulin resistance and oxidative stress, via a vice- vicious cycle. The existing data support that there is an increased cardiovascular morbidity in patients with thyroid disease. However, more studies need to be done, especially prospective on larger no. of population, to elucidate the real significance of dyslipidemia or other metabolic changes to CVD morbidity and mortality in clinical thyroid disease.

References:

1) Jameson L, Weetman A. Disorders of the Thyroid Gland. In: Fauci A, Braunwald E, Kasper D, Hauser, Longo D, Loscalzo J, Stephen L, editors. Principles of Internal Medicine by Harrison's. 17th edition. volume-II. USA. Mcgraw-Hill; 2008. p. 2224-2233.
2) Brent G, Larsen P, Davies T. Hypothyroidism and Thyroiditis. In: Kronenberg H, Melmed S, Polonsky K, Larsen P, editors. Williams Textbook of Endocrinology. 11thedition. USA. Saunders Elsevier; 2008. p. 377-409.
3) Pucci E, Chiovato L, Pinchera A. Thyroid and Lipid Metabolism. International Journal of Obesity 2000; 24: 109-112.
4) Bhaskaran S, Kumar H, Nair V et al. Cochin 2004; Subclinical hypothyroidism: Indications for thyroxine therapy. Thyroid research & practice, Sep –Dec 2004.
5) Vol. 1 No-3, 10 –14 O'Brien T, Dinneenn SF, O' Brien P, Palumbo PJ. Hyperlipdemia in patients with primary and secondary hypothyroidism. Mayo Clin Proc 1993; 68: 860-866.
6) Sriver CR. Lipoprotein(a). In: Scrives CR, Beadet AL, Slyws, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. 8thedition. NewYork. Mcgraw-Hill; 2001.2753-2787.
7) Danese M, Ladenson P, Meinert C and Powe N. Effect of thyroxine therapy on serum lipoproteins in patient with mild thyroid failure: A quantitative review of literature. The Journal of Clinical Endocrinology & Metabolism 2000; 85: 2993-3001.
8) Hamano K, Inoue M, Increased risk of atherosclerosis estimated by pulse wave velocity in hypothyroidism and its reversal with appropriate thyroxine treatment. Endocr J 2005; 52: 95-101.
9) Heinrich W, Dietrich S. A simple specific method for precipitation of low density lipoproteins. Journal of Lipid Research 1983;24:904-909.
10) Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid 2000;10:665–679.
11) Tzotzas T, Krassas GE, Konstantinidis T & Bougoulia M. Changes in lipoprotein (a) levels in overt and subclinical hypothyroidism before and during treatment. Thyroid2000;10:803–808.
12) Mora S, Rifai N, Buring JE et al. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. Circulation 2008; 118:993-1001.
13) Duntas LH. Thyroid disease and lipids. Thyroid 2002; 12:287-293.
14) Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of thyroid hormone on cardiac function: the relative importance of heart rate, loading conditions, and myocardial contractility in the regulation of cardiac performance in human hyperthyroidism. J ClinEndocrinolMetab. 2002;87:968–974.
15) Evered DC, Ormston BJ, Smith PA, Hall R, Bird T. Grades of Hypothyroidism. BMJ. 1973;1:657–662.
16) Rush J, Danzi S, Klein I. Role of thyroid disease in the development of statin-induced myopathy.The Endocrinologist. 2006;16:279–285.
17) Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, Burckhardt D, Girard J, Weintraub BD. Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. Am J Med. 1992;92:631–642.
18) Drover VAB, Agellon LB. Regulation of the human cholesterol 7 alpha-hydroxylase gene (CYP7A1) by thyroid hormone in transgenic mice. Endocrinology. 2004;145:574–581.
19) Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 2000;132:270 –278.
20) Danzi S, Klein I. Thyroid hormone and the cardiovascular system. Minerva Endocrinologica. 2004;29:139–150.
21) Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: randomised, crossover trial.J ClinEndocrinol Metab.2007;92:1715–1723.
22) Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in subclinical hypothyroidism: response to replacement, a randomized placebocontrolled study.JClinEndocrinolMetab. 2002;87:1533–1538.
23) Law MR, Wald NJ et al. How much and how quickly does reduction in serum cholesterol concentration lower risk of ischemic heart disease? J Br Med 1994;308:367-373.
24) Arem M, Escalante DA, Arem N, Morrisett JD, Patsch W. Effect of l-thyroxine therapy on lipoprotein fractions in overt and subclinical hypothyroidism, with special reference to lipoprotein(a). Metabolism. 1995 ;44:1559–1563.
25) Yildirimkaya M, Ozata M, Yilmaz K, Kilinc C, Gundogan MA &Kutluay T. Lipoprotein (a) concentration in subclinical hypothyroidism before and after levo-thyroxine therapy. Endocrine Journal1996;43:731–736.
26) Miura S, Itaka M, Yoshimura H, Kitahama S, Fukasawa N, Kawakami Yet al.Disturbed lipid metabolism in patients with subclinical hypothyroidism: effect of L-thyroxine therapy. Internal Medicine1994;33:413–417.

27) Paoli M, Bellabarba G, Velazquez E, Mendoza S, Molina C, Wang P et al. Sex steroids, lipids and lipoprotein cholesterols in women with subclinical and overt hypothyroidism before and after L-thyroxine therapy. ClinicaChimica Acta 1998 ;275:81–91.
28) Diekman T, Lansberg PJ, Kastelein JJP & Wiersinga WM. Prevalence and correction of hypothyroidism in a large cohort of patients referred for dyslipidemia.Archives of Internal Medicine 1995;155:1490–1495.
29) Bostom AG, Cupples LA, Jenner J, Ordovas JM, Seman LJ, Wilson PW, Schaefer EJ, Castelli WP. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. JAMA. 1995; 276:544–548.
30) Romaldini JH, Biancalana MM, Figueiredon DI, Farah CS & Mathias PC. Effect ofL-thyroxine administration on antithyroid antibody levels, lipid profile and thyroid volume in patients with Hashimoto's thyroiditis. Thyroid1996;3:183–188.
31) Cooper DS, Halpern R, Wood LC, Levin AA & Ridgway EC. L-Thyroxine therapy in subclinical hypothyroidism. Annals of Internal Medicine 1984;10:118–124.
32) De Bruin TW, Van Barlingen H, Van LindeSibenius Trip M, VaVuurst De Vries AR, Akveld MJ, Erkelens DW. Lipoprotein (a) and apolipoprotein B plasma concentration in hypothyroid, euthyroid, and hyperthyroid subjects. J ClinEndocrinolMetab 1993;76:121-126.
33) Engler H, Riesen WF. Effect of thyroid function on concentration of lipoprotein(a). ClinChem 1993;39:2466-2469
34) Nanda N, Bobby Z, Hamide A, et al. Association between oxidative stress and coronary lipid risk factors in hypothyroid women is independent of body mass index. Metabolism 2007; 56: 1350-1355.
35) Erdamar H, Demirci H, Yaman H, et al.The effect of hypothyroidism, hyperthyroidism, and their treatment on parameters of oxidative stress and antioxidant status. ClinChem Lab Med 2008;46:1004-10.