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A cross-sectional study on incidence of dyslipidemia in patients of subclinical and overt hypothyroidism

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ABSTRACT

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Keywords:

INTRODUCTION

The thyroid gland produces two related hormones, thyroxine (T4) and triiodothyroxine (T3). Acting through nuclear receptors, these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adults(1) .Hypothyroidism is common, affecting over 1% of the general population and about 5% of individuals over age 60 years(2).

Hypothyroidism is a state that results from decreased production of thyroid hormones by the gland or rarely from their decreased action at tissue level. It is broadly classified into:

1 Congenital

2 Acquired: Primar , Secondary, Tertiary.

The division into primary and secondary is based on the site of dysfunction .By far the commonest cause of hypothyroidism is failure of the thyroid gland itself ,known as primary hypothyroidism .In adults the commonest cause of primary hypothyroidism is auto-immune induced failure[1] .

Lipoproteins are macromolecule complexes containing hydrophobic plasma lipids, particularly cholesterol and triglycerides in plasma(3). Derangement of one or many of the lipoproteins (dyslipidemia) can result from over-production or lack of clearance of the lipoprotein particles,or may be related to other defects in the lipoproteins or metabolic enzymes deficiencies.

A primary dyslipidemia (e.g familial hypercholesterolemia) refers to a genetic defects in the lipid metabolism that causes abnormal lipid levels .A secondary dyslipidemia may be due to various causes; environmental factors (diet rich in saturated fat or sedentary life style),disease (type II diabetes,hypothyroidism,obstructive jaundice etc) and medications (thiazide diuretics,progestins,anabolic steroids etc).

Hypothyroidism is an important and treatable cause of secondary dyslipidemia. Latter is an important risk factors for the development of coronary artery disease and peripheral vascular disease.

A relationship between hypothyroidism, lipid disorders, and coronary artery disease was first suggested in the 1960s(4).Thyroid disease is being increasingly diagnosed with greater awareness and is

one of the chronic non-communicable disease affecting women more though male population is not spared of the aliment .It is estimated that about 200million people are at the risk of iodine deficiency in our country[1].It has been found that a 2-fold change in free thyroxine will lead to 100-fold change in TSH. Even slight decrease in T4 level with in the normal range will lead to increase in serum TSH above the normal range. So, measurement of serum TSH is the important test for diagnosis of mild thyroid failure when the peripheral thyroid hormone levels are within normal laboratory range[5].

Thyroid dysfunction has a great impact on lipid as well as a number of other cardiovascular risk factors .Hypothyroidism is relatively common and is associated with unfavourable effects on lipids. It regulates a wide array of metabolic parameters. Indeed, even with the normal range of thyroid stimulating hormones (TSH) values, a linear increase in total cholesterol (TC), low density lipoprotein (LDL) and a linear decrease in high density lipoprotein cholesterol (HDL-C) level has been observed[6].

Overt hypothyroidism is associated with abnormalities of lipid metabolism, which may predispose to the development of atherosclerotic coronary artery disease[12]. Subclinical hypothyroidism (SH), defined as the clinical state of elevated serum thyrotropin (TSH) levels, with normal level of throxine (T4) and triiodothyroxine (T3) is more common disorder than overt hypothyroidism with a prevelance of 1.4-7.8% in older population and even greater percentiles among women[7,8].

In thyroid diseas, dyslipidemia and the coexisting metabolic abnormalities ,in combination with thyroid hormones induced hemodynamic alteration explain the high risk of cardiovascular disease[9,10]. Lipid and glucose metabolism are among the many physiological process that are regulated by thyroid hormones. Infact there is a strong link between thyroid hormone disorder and number of wide spread metabolic abnormalities[11]. Hence biochemical screening for thyroid dysfunction is critical in all dyslipidemic patients, as well as in all patients with unexplained improvement or worsening of their lipid profiles.

The association between thyroid hormones and dyslipidemia has been well established[12]. However, as Hippocrates once said".....the medical art is long lived, the moment deceptive, the experience illusory, and the right judgement difficult" [13], a revaluation of the effect of thyroid hormones replacement on lipids in patients of hypothyroidism seems justified in the light of a plead of new data presented in recent years.

AIMS AND OBJECTIVES

1. To ascess the association of subclinical hypothyroidism/overt hypothyroidism and lipid profile.
2. To find the importance of Low density lipoprotein cholesterol/ High density lipoprotein cholesterol (LDL-C/HDL-C) ratio rather than measurement of individual lipid profile parameters in bringing to light the dyslipidemic state associated with subclinical/overt hypothyroidism.

MATERIALS AND METHODS

A Cross sectional study was conducted on 100 cases presenting randomly to tertiary care Hospital in North India from all departments, OPDs and IPDs during the period from May 2014 to May 2015 .Approval of the study protocol was obtained from scientific and ethical committee of the institute and informed written consent was taken from all the patients after explaining the purpose of the study to them.

SAMPLE SIZE

Hundred freshly detected hypothyroid adult patients (age more than 18 years) satisfying inclusion and exclusion criteria were studied .Patients were divided into two groups. Group I consisted of 40 patients with overt hypothyroidism. Group II consisted of 60 patients with sub-clinical hypothyroidism. None were receiving any medications with known influence on lipid metabolism. No dietary restrictions were imposed during treatment.

CONTROL

Fifty healthy individuals with no history of any illness or on any medication known to affect lipid profile were taken as healthy controls. The age distribution of this reference group was not different from that of the patient with hypothyroidism.

STUDY TYPE

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This was a cross sectional study and was conducted between the period of May 2014 to May 2015

DATA ANALYSIS

Statistical tools used for the study was percentage, mean standard deviation (SD). Comparison of the quantitative variables was done using Chi square test and for qualitative variables Student test was used. Other statistical tests were used as appropriate. For all statistical tests, a ´p´ value of less than 0.05 was taken.

INCLUSION CRITERIA

1. Age more than 18 years
2. Symptoms and signs suggestive of hypothyroidism and biochemically confirmed hypothyroid.

EXCLUSION CRITERIA

Being a prospective study , cases of hypothyroidism coming to hospital for follow up, where diagnosis has already been established would not be included in the study.

Following category of hypothyroid patients will not be included in the study.

1. Cases of congenital , secondary and tertiary hypothyroidism
2. Patients undergoing treatment for dyslipidemia.
3. Cases of primary hypothyroidism with associated co-morbid conditions , known to affect the lipid profile e.g uncontrolled diabetes mellitus (HbA1c >9), renal, hepatic or vascular disease , alcoholism.
4. State of pregnancy and lactation.
5. Post menopausal female patients receiving hormone replacement therapy.
6. Patients on drugs known to affect lipid profile (Diuretics, β-blockers, statins, oral contraceptives and estrogen preprations, retinoids, interferons etc.)
7. Patients with immunologic and autoimmune disorders.

Gender Eligibility for this clinical trial; both

Minimum age of this clinical trial; 18 years

Maximum age of this clinical trial; 80 years

STUDY DESIGN

THYROID HORMONE ESTIMATION

Primary hypothyroidism was suspected after detailed history taking and clinical examination .To confirm hypothyroid status biochemically, following method was adopted:

After an overnight fast of minimum 10hrs, venous blood was drawn from the forearm and transfused to a sterile tube. After clotting the blood was centrifuged at room temperature for 20min at 4000 rpm.The seum so obtained was given a separate identification number and stored at -30^0c until analyzed .The readings were taken with instrument Mini vidas.

The laboratory evaluation of thyroid function was done by estimation of serum T3,T4 and TSH levels, using Chemilumiscence assay method.

Normal values for thyroid hormones taken for the study are given in Table 7:

THYROID HORMONES	NORMAL VALUES
T3	0.9-2.6ng/ml
T4	5.5-13.5µg/dl
TSH	0.3-6.5µIU/ml

Overt hypothyroidism was defined by subnormal serum T3 and T4 with raised TSH levels. Subclinical hypothyroidism was defined by the association of normal serum T3 and T4 with raised serum TSH levels.

LIPID PROFILE

For lipid profile estimation, which included total cholesterol(TC), high-density lipoprotein cholesterol(HDL-C), low-density lipoprotein cholesterol(LDL-C),very low-density lipoprotein cholesterol(VLDL-C), triglycerides(TG), and LDL/HDL ratio ,following method was adopted:

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After an overnight fast of minimum 10hrs, venous blood was drawn from the forearm and transferred to a tube containing sodium ethylenediamine tetraacetate (EDTA). Plasma was separated after centrifuging the sample at 400 rpm(1800×g) for 10min.

Vitro chemistry products CHOL slides quantitatively measures cholesterol (CHOL) concentration in serum and plasma using vitros 250/350/950 and 5, 1 FS chemistry system and the VITROS 5600 integrated system.

Test type	Vitros system	Incubation time	Temperature	Wavelength	Reaction sample volume
Colorimeteric	5600, 5, 1 FS, 950, 250/350	5 min	370c	540nm	5.5µl

Table 7: showing the method of cholesterol estimation using colorimeteric method

HDL-C was determined in the same manner using wave length of 670nm and Triglyceride with a wave length of 540nm.

LDL-C was calculated using Friedewald´s method:

LDL-C=TC-(HDL-C+VLDL).

VLDL-C was measured by following method:

VLDL-C=Triglycerides/2.2 for S.I unit (mmol/l).

The normal values for lipid profile taken for the study were as per Table 8

LIPID PARAMETERS	NORMAL VALUES
Total Cholesterol	130-250mg/dl
HDL-C	20-80mg/dl
LDL-C	Upto 170mg/dl
VLDL-C	10-30mg/dl
Triglycerides	30-160mg/dl
HDL/LDL Cholesterol	2.5-3.5

OBSERVATIONS AND RESULTS:

In this study, 100 patients with established hypothyroidism (subclinical/overt) were screened.Out of 100 patients 40 had overt hypothyroidism (26.67%)indicated as group I and remaining 60 patients had subclinical hypothyroidism (40.00%) indicated as group II whileas 50 patients were taken as healthy controls(33.33%). : In our study ,the mean age of patients in group I, group II and control were 42.53±12.3 , 42.35±12.16 and 41.28±10.78 years respectively (overall p value of <0.853). Thus both cases and control had similar mean ages . Overt hypothyroid group (I) consisted of 9 Males (22.50%) and 31 females (77.50%), while subclinical hypothyroid group (II) consisted of 11 males (18.33%) and 49 females (81.67%).It confirms the well-known predominance in females as compared to males (p-value <0.001). Control group consisted of 26 Males (52.00%) and 24 females (48.00%) of different age groups. Mean height of patients in group I, group II and controls were 159.0±6.74 cms, 157.52±4.66cms and 156.64±5.41 cms respectively which were similar across the groups. The mean weight of patients in group I,

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group II, and controls were 64.83±7.91 kg , 64.22±5.81 kg, and 59.64±6.24(p- value <0.001). Thus patients in both group I, group II had statistically significant high values as compared to control, however on comparing group I with group II, no significant difference in weight was observed (p=0.659). Mean BMI of patients in group I , group II and control was 25.68±3.07, 25.94±2.33, 24.20±2.47 respectively(overall p-value 0.001).On comparing, it was observed that both group I and group II patients had statistically significant high mean BMI values as compared to controls (group I vs cntrl P=0.013, group II vs cntrl p= <0.001). Thus although mean BMI values were high in group I, they didnot reach statistically significant levels. Mean systolic blood pressure of patients in group I , group II and control was 135.33±14.11, 128.83±8.73 and 120.00±3.02 mm of hg respectively (overall P-value <0.001). On comparing group I and group II with control, patients had statistically significant high systolic BP as compared to control (group I vs cntrl P =<0.001 and group II vs cntrl <0.001). Similarly diastolic BP in group I, group II and control was 81.88±10.11, 83.93±8.03 and 74.04±8.21 respectively (overall P-value <0.001). Statistically significant values were observed when both groups were compared with control (group I vs control P= <0.001, group II vs control <0.001). This signifies higher values of both systolic and diastolic BP in both groups as compared to control.

LIPID PROFILE: Average means values of lipid fractions in overt and subclinical hypothyroid patients is shown below:

Mean triglyceride value in both overt (160.25±59.98) and subclinical hypothyroid group (163.17±73.30) were significantly higher than control (group I vs control <0.001, group II vs control

Mean total cholesterol values in both hypothyroid group(group I 248.70±61.33, group II 219.98±57.00) were high as compared to control and were statistically significant (group I vs control P < 0.001, group II vs control <0.001).

Mean HDL-C values in both hypothyroid group were (group I 31.88±7.88, group II 34.57±10.14 and control 30.08±3.41) and was not statistically significant (overall P-value <0.012).

Mean LDL-C values in both hypothyroid group were (group I 186.14±60.87, group II 151.21±49.20) higher than control (114.28±34.44) and were statistically significant (group I vs cntrl <0.001 and group II vs control < 0.001).

Mean VLDL-C values in both hypothyroid groups were also high and statistically significant (group I vs control <0.001 , group II vs control < 0.001).

Similarly mean LDL/HDL ratio in both groups (group I 6.31±2.76, group II 4.60±1.78) and control (3.85±1.21) was higher and stastically significant (overall P-value <0.001).

Hence both groups had increased mean plasma concentration of triglycerides, total cholesterol, LDL-C, VLDL-C and LDL/HDL ratio. Plasma HDL-C was normal in both hypothyroid groups.

DISCUSSION

Hypothyroidism is a graded phenomenon with different level of severity showing a wide inter-individual range of clinical and biochemical presentations. With its protean manifestations hypothyroidism affects virtually every system. Primary hypothyroidism is an important reversible cause of secondary dyslipidemia overt hypothyroid group : We evaluated the total cholesterol values in overtly hypothyroid patients and found it to be significantly raised. Similar findings have been reported by others[18,19]. We also observed that raised values of low-density lipoprotein cholesterol parallel the raise in total cholesterol values. Similar association is seen in other studies . Raised LDL-C has been attributed to impared LDL-C catabolism secondary to a reduced number of LDL receptors[20] . Also , Lithell et al and Valdermarsson et al in their study suggest that cause of LDL elevation result from the action of thyroid hormones on the activities of lipoprotein lipase and hepatic lipase , the key enzyme involved in the metabolism of plasma lipoprotein[21,22]. Thyroid hormones appear to stimulate LDL receptor thus increasing its catabolism . Various studies have confirmed stimulation of LDL receptors both in vitro[22,23]) and in vivo[24] . Thus our study confirms that in overt hypothyroidism there is marked increase in total cholesterol and LDL-C values.

In the present study , we found no change in HDL-levels in primary overt hypothyroid patients .This

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finding contrasts with raised or even decreased levels mentioned in various studies[25,26-27], but are consistent with recent studies[8,28,29]). While reduced hepatic lipase activity tends to raise HDL-C in overtly hypothyroid patients, the co-existing reduced LPL activity exerts an opposite effect by decreasing the transfer of cholesterol from very low density lipoprotein with the net result that HDL-C remains normal in these patients. Our study, therefore supports the concept that HDL-C remain normal in hypothyroidism . The plasma triglyceride (TG) concentration and VLDL-C in present study was raised in overt group similar raised triglyceride and VLDL values in overt hypothyroidism has been reported[30,31].

Subclinical hypothyroidism:

We evaluated values of total cholesterol in subclinical hypothyroidism and found it to be significantly raised. In year 2000, Colorado study showed that sub-clinical hypothyroid patient had high level of serum cholesterol than euthyroid individuals[32]. However another study in the same year in Austria, involving the largest subclinical hypothyroid patients showed no increased basal serum cholesterol concentrations compared to normal subjects[33]. Recent double blind , placebo-controlled trial (basal thyroid study) showed conclusively that cholesterol values were increased in subclinical hypothyroidism. Thus our study supports the view that total cholesterol values are increased in these patients, and thus display a more atherogenic lipid profile as compared with healthy individuals . Raised low density and very low density lipoprotein cholesterol values were also seen in our patients.

High- density lipoprotein cholesterol values were within normal range . This is in contrast to studies showing increase or decrease in HDL-C values then controls[34]. However, in a recent meta-analysis involving 13 studies have shown no effect on HDL-C concentration[35]). Thus our study support the finding that HDL-C values remain normal in patients of subclinical hypothyroidism.

Similarly, we found raised triglyceride levels in patients of subclinical hypothyroidism. Similar association was found in other studies[36].

It has been found 1-unit increase in the LDL-C/HDL-C ratio is associated with a 75% increase in the risk of MI[38]. Many studies have found that the LDL-C/HDL-C ratio is more efficient tool to moniter the effect of lipid lowering therapies.

Our study has revealed a significant P-value of < 0.001 between the two group and also TC and LDL-C are significant . Our study is similar to the study done by B.U Althaus , J.J staub et al[32] which has shown a significant LDL-C/HDL-C ratio , but they have observed no significant value for HDL-C and LDL-C .

Lastly our study has shown a significant difference in systolic and diastolic blood pressure between subclinical/overt hypothyroid and euthyroid controls. These result are in contrast with the study done by A.EL Sabeth Hak et al[33] which has shown no difference for blood pressure between the two groups.

But the study done by Rafael Luboshitzky et al has not shown any significant difference for systolic blood pressure but has shown a significant difference for diastolic blood pressure when compared with control[41].Other studies have revealed ,that thyroid failure is strongly assisociated with arterial hypertension via sympathetic and adrenal activation [30].This clearly indicated that increased in bp attributes to the increased risk for cardiovascular disease in both subclinical/overt hypothyroidism.

To conclude, in our present study ,we found that both overt and subclincal hypothyroid patients exhibited a more atherogenic lipid profile compared with healthy individual.

SUMMARY:

In this prospective study, lipid profile of hundred patients of primary hypothyroidism were evaluated and followed up in medicine department of a tertiary care hospital in North India for a period of 1 year. Primary hypothyroidism was suspected after history taking and clinical examination and confirmed biochemically. Based on their thyroid levels, two groups of fourty overt cases and sixty subclinical cases were made and compared. Well matched fifty healthy adults were taken as control.

The commonest age group of hypothyroidism observed in our study was 40-50 years with female preponderance.

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Lipid profiles of both subclincal/overt hypothyroid group consisting of total cholesterol (TC) , triglycerides(TG),high density lipoprotein-cholesterol(HDL-C), low density lipoprotein-cholesterol(LDL-C),very low density lipoprotein-cholesterol(VLDL-C), and LDL-C/HDL-C ratio was estimated.

In both the groups ,high levels of triglycerides,total cholesterol,low density cholesterol and very low density lipoprotein cholesterol and LDL-C/HDL-C ratio were observed. High –density lipoprotein cholesterol remained unchanged.

CONCLUSION:

1. Derranged lipid profile is seen in primary hypothyroid patients.
2. Primary hypothyroidism is more common in 40-60 years of age groups.
3. Preponderance of primary hypothyroidism in females
4. Subclinical hypothyroidism is more common than overt.
5. Significant increase in systolic and diastolic bp was seen in both subclincal/overt groups.
6. LDL-C/HDL –C ratio was raised in both subclinical and overt hypothyroid groups.

BIBLIOGRAPHY

1. Harrison´s Principals in Internal Medicine (Endocrine Disorders) 18th Edition .
2. Current Medical Diagnosis and treatment 2013 Edition; 1105-1134.
3. Kim DW, Jung SL, Back JH et al. The prevalence and features of thyroid pyramidal lobe, accessory thyroid , and ectopic thyroid as assessed by computed tomography: a multi center study. Thyroid 2013 Jan; 23(1):84-91.
4. Current Medical Diagnosis and treatment 2013 Edition; 1105-1134.
5. Bastenic PA, Vanhaelst L , Nerve P. Coronary – artery disease in hypothyroidism . Lancet 1967; 2:1221.
6. Fatourechi V. Subclinical Hypothyroidism : An update for primary care physicians . Mayoclin proc 2009 : 84(1) : 65-71.
7. Asvold BO , Vattern L J, Nilsen TI , et al .The association between TSH within the refrence range and serum lipid concentrations in a population-based study . The HUNT study. Eur J. Endocrinol . 2007 ; 1561 : 181-186.
8. Tunbridge WMG , Evered DC , Hall R , et al. Lipid profiles and cardiovascular disease in the Wiekham areas with particular refrence to thyroid failure . Clinical Endocrinology 1997; 7: 495-508.
9. Samuels MH . Subclinical thyroid disease in the elderly . Thyroid 1998; 9 : 803-813.
10. Cooper DS , Subclinical thyroid disease : a clinician´s perpective . Annals of Internal Medicine 1998; 129:135-138.
11. Biondi B , Kahaly GJ .Cardiovascular involment in patients with different causes of hyperthyroidism. Nature Reviews Endocrinology . 2010; 6(8); 431-443.
12. Klein I, Ojamaa K. Thyroid hormones and the cardiovascular system. The New England Journal of Medicine 2001; 344(7): 501-509.
13. Crunkhorn S, Patti ME. Links between thyroid hormones action, oxidative metabolism, and diabetes risk. Thyroid 2008; 18:227-237.
14. Kutty KM, Brgant DG , Farid NR . Serum lipids in hypothyroidism- a reevaluation . J Clin Endocrinol Metab 1978; 46:55-56.
15. Hippocrates complete works. General Medicine Kaktos . The Greeks. 93: 222-223.
16. Keating Jr, Parkin T.G, Selby J.B et al . Treatment of heart disease associated with myxedema .Progress in Cardiovascular disease 1961, 3, 364-381.
17. Vanhaelst L, Neve D, Chailly P et al. Coronary artery disease in hypothyroidism .Observation in Clinical Myxedema . Lancet II,1967, 800-802.
18. Steinberg, A.D . Myxedema and coronary artery disease; A comparative autopsy study. Annals of Internal medicine 1968, 68, 338-344.
19. Bastenie , P.A, Vanhaelst L, Goldstein J. Asymptomatic autoimmune thyroiditis and coronary heart disease . Lancet,1977, 155-158.
20. Santi A, Duart MMF, Moreslo RN et al. Association between thyroid hormone, lipid and oxidative stress ,biomarkers in overt hypothyroidism clinical chemistry and

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Laboratory Medicine.2010, 48(11):1635-1639.
21. Nanda N, Booby Z, Haimde A: Association of thyroid stimulating hormones and coronary lipid risk factors with lipid peroidation in hypothyroidism . Clinical Chemistry and laboratory medicine 2008,.46(5): 674-679.
22. Fonnei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis .Evidence from short –term hypothyroidism in human . J Clin Endocrinol Metab, 2002; 87: 1996-2000.
23. National Cholesterol Education Program .Second report of the expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel II) Circulation 1994,.89:1333-1445.
24. Pazos F,Alvarez JJ, Prat JR, et al. Long term thyroid replacement therapy and levels of lipoprotein (a) and other lipoproteins, 1995. J Clin Endocrin and Metab; 80: 562-566.
25. Thompson GR, Soutar AK, Spengel FA, et al. Defects of receptor mediated low density lipoprotein catabolism in homozygous familial hyper-cholesterolemia and hypothyroidism in vivo.Proc Natl Acad Sci USA 1981, 78:2591-2595.
26. Chait A, Bierman EL, Albers JJ. Regulatory role of triiodothyronin in the degradation of low density lipoprotein by cultured human skin fibroblast. J Clin Endocrinol Metab 1979, 48: 887-889.
27. Staels B, Van Tol A, Chan L, Will H, Verhoeven G, Auwerx J. Alterations in thyroid status modulate apolipoprotein, hepatic triglyceride lipase , and low density lipoprotein receptors in rats. Endocrinology.1990, 127:1144-1152.
28. Pikary AE, Hershman JM,Parlow AF. A sensitive and precise radioimmunoassay for human thyroid stimulating hormone. J Clin Endocrinol Metsb 1975;41:676-684.
29. Canaris GJ, Manowitz NR, Mayor G, Ridway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000,160:526-534.
30. Vierhapper H, Nardi A, Grosser P, Raber W, Gess A. The Colorado throid disease prevalence study. Arch Intern Med.2000, 160:526-534.
31. Meier C, Staub JJ, Roth CB, et al . TSH controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: A double blind , placebo controlled trail(Basel Thyroid study) J Clin Endocrinol Metab 2001, 86:10;4860-4866.
32. Caron P, Calazel C, Parra HJ, Hoff M and Louvet JP. Decreased HDL cholesterol in subclinical hypothyroidism : the effect of L-thyroxine therapy. Clinical Endocrinology . 1990;33:519-523.

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