

CHANGES IN TSH AND LIPID LEVELS AFTER COMMENCING TREATMENT FOR HYPOTHYROIDISM

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ABSTRACT

OBJECTIVE: The significance of dyslipidemia in subclinical hypothyroidism (SCH) and the effect of thyroid substitution on lipids remain controversial. The present study aimed to assess the association of SCH with lipid abnormalities and to quantify the effect of L-thyroxin therapy on serum lipid profiles. This work will also suggest new strategy for treatment of hypothyroidism. **DESIGN:** Serum lipid parameters of 50 patients with SCH and 100 euthyroid controls were evaluated in a cross-sectional study. **RESULTS:** The levels of patients of SCH were compared with levels observed in 100 normal persons. The overall observed Mean \pm SEM of T3, T4, TSH levels before treatment were: 2.06 ± 0.12 nmol/L, 88.8 ± 6.53 nmol/L 40 ± 7 μ IU/ml. Cholesterol, triglycerides, HDL and LDL levels were 208.5 ± 7.98 mg/dl, 154.7 ± 16.9 mg/dl, 26.73 ± 3.3 mg/dl and 137.5 ± 7.75 mg/dl respectively. After treatment with thyroxin 100 μ g of daily dose the Mean \pm SEM of T3, T4, and TSH were 2.14 ± 0.09 nmol/L, 116.8 ± 7.8 nmol/L and 12.37 ± 3.37 μ IU/ml. Lipid profile levels after treatment were 174.6 ± 10.5 mg/dl, 161.3 ± 22.9 mg/dl, 20 ± 1.99 mg/dl and 125.5 ± 9.8 mg/dl respectively. Overall comparison of hormone and lipid levels in patients of SCH. with those in normal persons showed that T3 and T4 were within normal range although T4 levels were significantly high compared to normal persons ($P < 0.05$). TSH was significantly high in SCH. ($P < 0.001$) when compared with normal controls. Cholesterol, HDL and LDL levels were significantly raised in SCH patients ($P < 0.001$ & $P < 0.05$ respectively) whereas triglyceride values were not significantly different from normal persons ($P > 0.05$). T3 remained almost unaffected after one month of thyroxin replacement therapy; T4 levels showed an increase in level but remained within the normal range. Whereas TSH values were significantly reduced ($P < 0.05$) reached close to the upper normal limit. Data of hormones and lipid levels obtained after two months of therapy was similar to that observed after one month therapy however, there was a steady decrease in TSH levels ($P < 0.001$). After three months of thyroxin replacement therapy, T3 levels again remained unaffected ($P > 0.05$), T4 levels were seemed stabilized and within normal range whereas TSH values were at upper border of normal range. During the follow up the levels of lipid profile shows same order i.e. there is no significant change in triglyceride, HDL and LDL but total cholesterol levels were significantly decreased. **CONCLUSION:** We concluded that thyroxin replacement therapy (100 μ g thyroxin daily dose) affects T4, TSH and cholesterol levels. T4 is increased relative to pretreatment values but remains within normal limits. TSH is reduced gradually as the treatment proceeds. Cholesterol levels decrease significantly in most of cases with the duration of treatment. However other lipids remain almost unaffected after three months of thyroxin replacement therapy.

Key Words: Subclinical hypothyroidism, Dyslipidemia, euthyroid, thyroxin.

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Introduction

There are many studies, which have linked treatment of hypothyroid or hyperthyroid disease with the serum levels of T3, T4, TSH and lipids (Cholesterol, LDL, triglycerides). Most of the work is converged over subclinical hypothyroidism (SCH). The potential benefits and risks of therapy for subclinical hypothyroidism have been debated for two decades. The possible advantages of treating subclinical hypothyroidism generally fall into three categories. First, progression to overt hypothyroidism, with its attendant morbidity, would be prevented by thyroxin therapy. Second, thyroxin therapy may improve the serum lipid profile and thereby potentially decrease the risk of death from cardiovascular causes. Finally, treatment may reverse the symptoms of mild hypothyroidism, including psychiatric and cognitive abnormalities.¹ Thyroid substitution treatment in patients with hypercholesterolemia and subclinical hypothyroidism decreases total plasma cholesterol by 0.4 mmol/l, but plasma levels remain elevated in most patients.² In some studies the cholesterol levels remain unaffected with thyroxin therapy with a thyroxin dose of 25 µg/day for two months.³⁻⁵

Lipid metabolism is highly dependent on various non-thyroid factors that are often not well defined or standardized in reported studies. These factors include a variety of dietary compounds, body mass index, sex, alcohol intake, drugs, hormones and particular genetic effects such as hypercholesterolemia. All studies on sub clinical hypothyroidism have been performed with rather small groups of patients and have low statistical power to unmask confounding variables. A particular problem not considered in earlier studies is the strong influence of smoking on lipid metabolism, which is detected only in hypothyroidism, in sub clinical and overt state, but not in euthyroid control. These lipid increasing factors could aggravate hypercholesterolemia, potentiating the effect of mild hypothyroidism.^{4,6}

The effects of subclinical hypothyroidism on serum lipid levels remain controversial. Some cross-sectional studies have demonstrated that serum levels of total cholesterol and LDL cholesterol are higher in patients with sub clinical hypothyroidism than in euthyroid controls.

A number of studies suggest a decrease of total cho-

lesterol and LDL-C after L-thyroxin-substitution, whereas other suggests no significant change occur after L-thyroxin therapy.

A recent meta-analysis of the effect of therapy for subclinical hypothyroidism on serum lipid levels demonstrated a mean reduction in the total cholesterol level of 7.9 mg per deciliter (0.2 mmol per liter) and in the LDL cholesterol level of 10 mg per deciliter (0.26 mmol per liter). Changes in high-density lipoprotein (HDL) cholesterol were heterogeneous among the studies and were not statistically significant. Patients with higher cholesterol levels (»240 mg per deciliter 6.21 mmol per liter]) and patients with subclinical hypothyroidism as a result of inadequately treated overt hypothyroidism had greater reductions in cholesterol levels.

In patients with newly diagnosed subclinical hypothyroidism whose total cholesterol level was less than 240 mg per deciliter, the mean reduction in total cholesterol was only 0.7 mg per deciliter (0.02 mmol per liter), which was not statistically significant. Some studies have suggested that patients whose serum thyrotropin level is less than 10 mu per liter may have no reduction in cholesterol levels with thyroxin replacement, but the meta-analysis did not directly address this issue.⁷⁻⁸ So it appears that the degree of change depends upon two parameters: the initial levels of cholesterol and the degree of dysfunction.^{5,9} Two randomized, placebo-controlled studies recently demonstrated that in the SCH serum LDL cholesterol levels are specifically and reversibly increased to an extent that may translate in to a sizeable cardiovascular risk.¹⁰⁻¹¹

An increase in secretion of thyroid-stimulating hormone (TSH) is the earliest biochemical sign of impending thyroid failure. The decrease in free thyroxin (FT4) below a critical individual value (set point) produces an increase in TSH by a negative feedback mechanism. TSH increases in an exponential manner in comparison with the decrease in FT4; a decrease in FT4 by a factor of 2 leads to an increase in TSH by a factor of about 100.

Materials and Methods

Subjects

A total of 50 cases of subclinical hypothyroidism were included in this study. The patients were exa-

mined and diagnosed at MINAR. The diagnosis was based on clinical assessment, hormone tests and thyroid scan. The patients were registered and kept under constant follow up. Repeat estimations of T₃, T₄ and TSH at different intervals during the course of treatment were recorded on a separate Performa. One hundred age and sex matched control euthyroid subjects were studied for comparing lipid profile of the hypothyroid patients. Serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured. The information thus recorded was statistically analysed at the end to find the pattern of variations of thyroid related hormones and lipids. The duration of study was six months.

Diagnostic Criteria

All patients were interviewed and examined for symptoms and signs of subclinical hypothyroidism. Patients were asked about appetite, weight gain, excessive sleep, weakness, cold intolerance, change in quality of voice and constipation. Patients were examined to assess the dry, thickened skin and delayed relaxation of ankle jerk. Patients were asked about history of anti-thyroid drugs intake or radioiodine (I-131) therapy for thyrotoxicosis or intake of thyroxine for previously diagnosed hypothyroidism.

Patient Samples

Each patient was requested to give at least two samples, one immediately after final diagnosis and the other after completion of the treatment. 5 cc venous bloods were collected from each person and allowed to clot. The coagulated blood was centrifuged to separate serum. The serum was stored at -20°C until Radioimmunoassay (RIA) for diagnosing subclinical hypothyroidism was carried out; results were interpreted in the light of clinical history. Analysis of initial samples showed that all samples have both T₃ and T₄ in subclinical hypothyroid range and patients who were diagnosed as hypothyroidism, their preserved samples were used to measure serum TC, TG, and HDL-C, LDL-C levels were calculated using Friedewald's formula.^{12,14}

TC and triglyceride levels in serum were measured by using Trinder method. RANDOX. HDL-C levels in serum were measured using CHOD-PAP method.

Magnetizable solid phase radioimmunoassays were applied to estimate T₃ and T₄ levels. The TSH levels were measured using magnetizable solid phase IRMA method. The internal and external quality control of these systems was first evaluated before application to this study. The assay sensitivities as calculated from 2SD of zero standards were: T₃ = 0.01 nmol/l and T₄ = 2.5 nmol/l, TSH = 0.1 µIU/ml. Working ranges of the assays were fairly wide to cover all clinical regions.

Normal Values

Normal values were derived at our laboratory. For this purpose serum T₃, T₄ and TSH levels were estimated in a total of 714 normal volunteers (males: 274, females: 439) aged between 10 to 66 years. Observed overall reference ranges were: T₃: 0.8-3.2 nmol/l, T₄: 52-175 nmol/l and TSH: 0.4-4 µIU/ml

Statistical Analysis

Mean and standard deviation were calculated for all variables. Difference between means and standard error of the difference was used to find out probability of any significant change/disagreement. Student's T test (paired t-test) was applied for comparison of values of our subgroup before, during and after completion of treatment.

Results and Discussion

The main emphasis of this study is to find out the effect of duration of treatment on TSH levels and lipid profile in subclinical hypothyroid patients.

In Multan and surrounding areas the prevalence of hypothyroidism seems to be more pronounced than hyperthyroidism. The own constituted laboratory values of TSH, T₃ and T₄ are 0.4-4 µIU/L, 0.8-3.2 nmol/L and 52-175 nmol/l respectively. The reference values reported for cholesterol, triglycerides, HDL and LDL are 200mg/dl, 150mg/dl and <150mg/dl respectively. The values observed in normal persons of this study are shown in (Tab. 1). These values are in close agreement with reference values provided on kits.

Mean ± (SEM) levels of thyroid hormones and lipids observed in normal persons and patients with subclinical hypothyroid before having any treatment

T3(nmol/L)	1.1-2.9
T4(nmol/L)	58-174
TSH(μ IU/L)	0.4-3.9
Total Cholesterol(mg/dl)	149-193
Triglycerides(mg/dl)	138-165
HDL(mg/dl)	48-63
LDL(mg/dl)	95-152

Table 1 Normal range of thyroid hormone and lipid profile obtained from normal persons (n=100)

of hypothyroidism are shown in (Tab.2). These values of thyroid hormones shown in table clearly indicates that there is no significant difference of T3 in control group and subclinical hypothyroid patients where as

S.No.	Controls (normal)	Patients	P value
T3(nmol/L)	2.012 \pm 0.03	2.06 \pm 0.12	P > 0.05 \neq
T4(nmol/L)	108.90 \pm 2.56	88.8 \pm 6.53	P < 0.05*
TSH(μ IU/L)	1.3 \pm 0.88	40.3 \pm 7.15	P < 0.001**
Total Cholesterol(mg/dl)	171 \pm 7.24	208 \pm 7.98	P < 0.05*
Triglycerides (mg/dl)	188 \pm 11.6	154.7 \pm 16.9	P > 0.05 \neq
HDL(mg/dl)	49.7 \pm 1.3	26.75 \pm 3.3	P < 0.001**
LDL(mg/dl)	99 \pm 12	137.5 \pm 7.75	P < 0.05*

Table 2: Mean \pm SEM of Thyroid hormones and lipid profile levels observed in normal persons (n=100) and patients (n=50) with subclinical hypothyroidism. (before treatment)

other parameters; T4 and TSH are significantly high in subclinical hypothyroid patients. In these cases total cholesterol, HDL and LDL are significantly high in subclinical hypothyroid patients but triglyceride is non significant Hypothyroidism is a graded phenomenon, extending from mild thyroid failure to severe overt hypothyroidism. Subclinical hypothyroidism may presents with different grades of severity.¹³ Our data was in close agreement with data represented by Caraccio and his colleagues.¹⁰ They reported that subclinical hypothyroidism patients had higher baseline lipid levels when compared with 27 euthyroid controls.

Mean \pm SEM of thyroid hormones and lipid profile levels observed in follow-up patients of one month treatment with subclinical hypothyroidism (before and after treatment) are represented in (Tab. 3). This indicates that after one month treatment there is no

S.No.	Before Treatment	After one month treatment	After two month treatment	After three month treatment			
	Values	P value	Values	P value			
T3(nmol/L)	2.3 \pm 0.18	2.1 \pm 0.14	P>0.05 \neq	2.25 \pm 0.15	P>0.05 \neq	2.02 \pm 0.2	P>0.05 \neq
T4(nmol/L)	88 \pm 9.93	125.5 \pm 12	P<0.05*	129.7 \pm 19	P<0.05*	124 \pm 9.40	P<0.05*
TSH(μ IU/L)	30 \pm 10.8	17.7 \pm 3.8	P<0.05*	8.76 \pm 8.4	P<0.001**	6.2 \pm 3	P<0.001**
Total Cholesterol (mg/dl)	209 \pm 13	153.8 \pm 9.2	P<0.05*	163.7 \pm 17	P<0.05*	142 \pm 20	P<0.05*
Triglycerides(mg/dl)	175.8 \pm 29	164.6 \pm 27	P>0.05 \neq	166.7 \pm 21	P>0.05 \neq	141 \pm 16	P>0.05 \neq
HDL(mg/dl)	22 \pm 1.9	26.4 \pm 3	P>0.05 \neq	25.9 \pm 4	P>0.05 \neq	30.8 \pm 4	P>0.05 \neq
LDL(mg/dl)	152.9 \pm 10	145 \pm 8	P>0.05 \neq	121.6 \pm 11	P>0.05 \neq	133.2 \pm 18	P>0.05 \neq

*Statistically Significant

**Statistically highly Significant

\neq Statistically Non- Significant

Table 3: Mean \pm SEM of Thyroid hormones and lipid profile levels observed in follow-up patients of one, two and three month treatment with subclinical hypothyroidism(before and after treatment) (n=22)

effect of therapy on T3, but was significant effect on T4 and TSH. In case of lipid profile Triglycerides HDL and LDL shows no significant change, whereas total cholesterol decreases significantly after one month of thyroxin treatment. After two and three months follow up, effect of therapy on thyroid hormones and lipid profile found same trend as after one month follow up.

Our results are in close agreement with the results of Milionis and his colleagues. They conclude that after three months follow-up treatment in patients who received L-thyroxin replacement therapy, a significant decrease of TSH levels was observed after treatment, accompanied by a significant increase in T4 levels. L-thyroxin resulted in a non-significant reduction in total and LDL-C levels. However L-thyroxin replacement therapy was associated with a significant reduction in HDL-C concentration.¹⁴

Overall values of lipid profile before and after treatment in subclinical hypothyroid patients shows that total cholesterol, triglycerides, and HDL and LDL values are (P < 0.05), (P > 0.05), (P > 0.05) and (P > 0.05) respectively. The change of total cholesterol, triglycerides, and HDL and LDL shows same trend as in one month, two months and three months follow up patients.

The Mean \pm SEM of thyroid hormones and lipid profiles before and after treatment observed in sub

clinically hypothyroid patients represented in (Tab. 3) are also put in (Graphs 1-7).

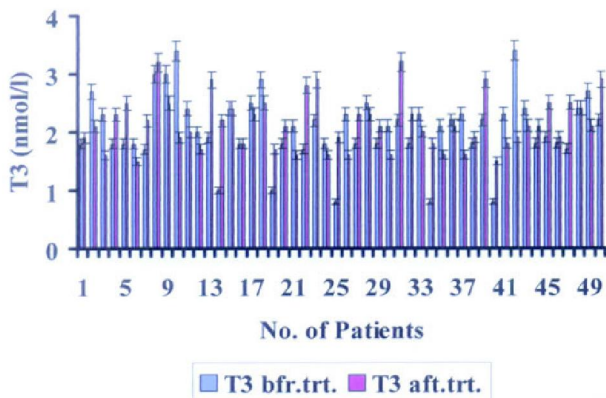


Figure 1: T3 levels (before and after treatment) in Subclinical hypothyroid patients. (n=50)

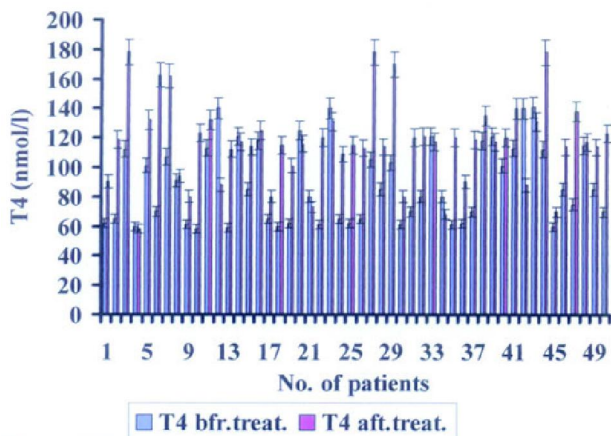


Figure 2: T4 levels (before and after treatment) in Subclinical hypothyroid patients. (n=50)

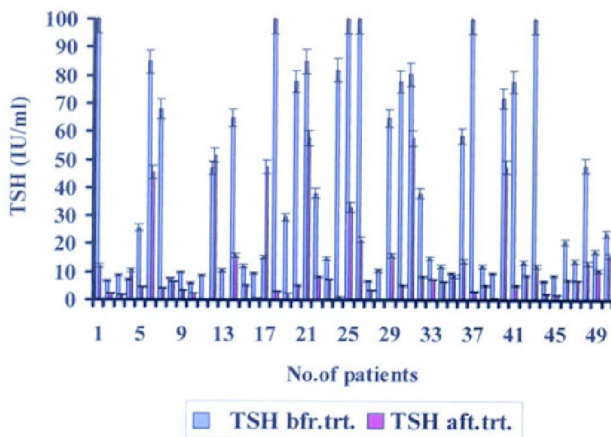


Figure 3: TSH levels (before and after treatment) in Subclinical hypothyroid patients. (n=50)

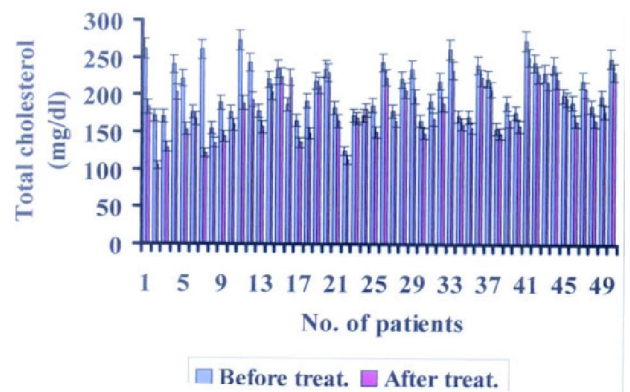


Figure 4: Cholesterol levels (before and after treatment) in Subclinical hypothyroid patients. (n=50)

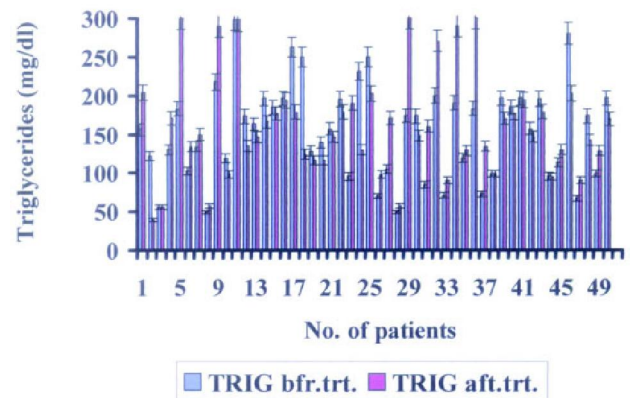


Figure 5: Triglycerides levels (before and after treatment) in Subclinical hypothyroid patients. (n=50)

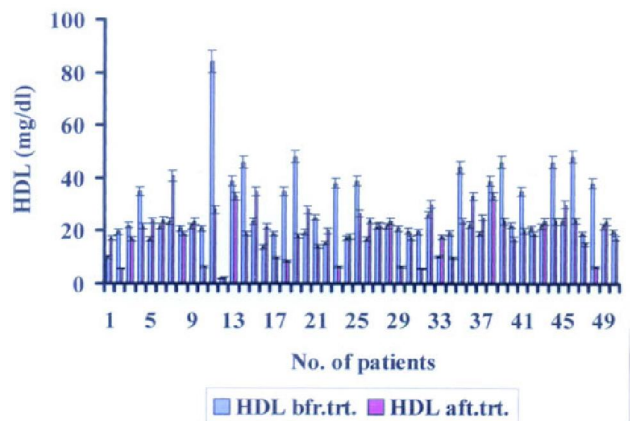


Figure 6: HDL levels (before and after treatment) in Subclinical hypothyroid patients. (n=50)

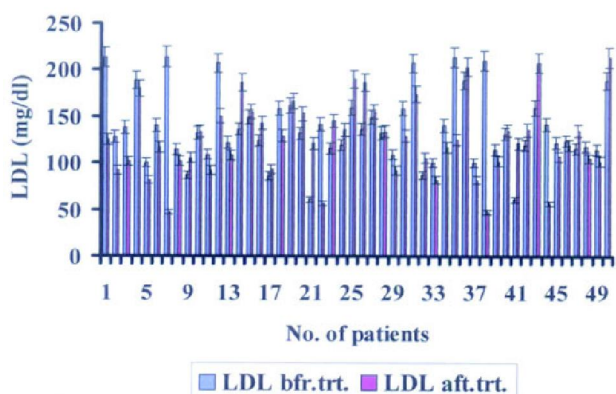


Figure 7: LDL levels (before and after treatment) in Subclinical hypothyroid patients. (n=50)

Recommendations for further work:

It is recommended that:

- Duration of treatment must be increased.
- Dose of thyroxin suggested by doctor must be followed strictly.
- Patients which are already taking cardiovascular/lipid lowering drugs must be monitored and diagnosed carefully.
- The effect of other hormonal levels specifically those affecting lipids mobilization e.g. Estrogen should also be observed during therapy.

References

1. Elder J MA, O'Reilly DS, Packard CJ, Series JJ, Shepherd J. The relationship between serum cholesterol and serum thyrotropin, thyroxine and triiodothyronine concentrations in suspected hypothyroidism. *Ann Clin Biochem* 1990; **27**: 110-3.
2. Bea C. Tanis RGJWAaHMS. *Clinical Endocrinology* June 1996; **44(6)**: 643.
3. DS. C. Subclinical hypothyroidism *Advnces in Endocrinology and Metabolism*. 1991; **2**: 77-88.
4. JJ. S. Minimal thyroid failure: effects on lipid metabolism and peripheral target tissues. Invited commentary. *European Journal of Endocrinology*. 1998; **(138)**: 137-8.
5. Tanis BC WRaSA. Effect of thyroid substitution on hypercholesterolaemia in patients insubclinical hypothyroidism:a reanalysis of intervention studies. *Clinical Endocrinology*. 1996; **44**: 643-9.
6. Muller B ZH, Huber P,Ratcliffe JG and Saub JJ. Impaired action of thyroid hormone associated with smoking in women with hypothyroidism. *New England Journal of Medicine* 1995; **(333)**: 964-9.
7. Cooper DS HR, Wood LC, Levin AA, Ridgway EC. L-thyroxine therapy in subclinical hypothyroidism: a double-blind, placebo-controlled trial. Cooper DS, Halpern R, Wood LC, Levin AA, Ridgway EC L-thyroxine therapy in subclinical hypothyroidism: a double-blind, placebo-controlled trial. 1984; **(101)**: 18-24.
8. Danese MD LP, Meinert CL, Powe NR. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab* 2000; **85**: 2993-3001.
9. StaubbJJ AB, Egler H,Ryff AS,Trabucco P, Marquardt K et al Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve and metabolic impact on peripheral target tissues. *American journal of Medicine*. 1992; **(92)**: 631-42.
10. Caraccio N FE, Monzani F. lipoprotein profile in subclinical hypothyroidism: effect of levothyroxine replacement therapy. A randomized,placebo-controlled study. *J Clin Endocrinol Metabo* 2002; **87**: 1533-8.
11. Meier C SJ, Roth CB, Guglielmetti M,Kunz M, Miserz AR, Drewe J, Huber P, Herzog R, Muller B. TSH controlled L-thyroxine therapy reduces cholestrol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basal thyroid study). *J Clin Endocrinol Metabo*. 2001; **86**: 4860-6.
12. Friedewald WT, Levy, R.T. and Fredrickson D.S. Estimation of the concentration of low-density

lipoprotein cholesterol in Assay Techniques. Clin Chem. 1972; **18(499)**:

13. Staubbj.j. ABU, EnglerH.,Ryff A.S.,Trabucco P.,Marquadt K., Burckardt D., Girard j. and Weintraub B.D. Specrum of subclinical and overt hypothyroidism:effect on thyrotropin prolactin and thyroid reserve and metabolic impact on peripheral target tissues. Specrum of subclinical and overt hypothyroidism:effect on thyrotropin prolactin and thyroid reserve and metabolic impact on peripheral target tissues. 1992; **92**: 631-42.
14. Milionis H.J. KA, Bairaktari E.T.,Elisaf M.S. and Tsatsoulis A. Lipid profile in subclinical hypothyroidism:is L-thyroxine substitution beneficial. Eur J Endocrinol. 2001; **145**: 705-10.