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Research Article

ASSOCIATION BETWEEN HYPOTHYROIDISM AND METABOLIC SYNDROME IN TYPE 2 DIABETIC PATIENTS: A CROSS SECTIONAL STUDY

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ABSTRACT
The present study was conducted in Regional Hospital Hamirpur, Himachal Pradesh, India. A total of 217 adults aged 20-50 (mean age 37.82 ± 8.90 years) of both the sexes were randomly selected. Out of which, 117 were diabetic patients and 100 euthyroid non-diabetic controls group. The concentration of Thyroid stimulating hormone (TSH), triiodothyronin (T3), thyroxin (T4) and insulin were evaluated with direct immune assay. The level of glucose and lipid profile parameters was measured using diagnostic kits. The results showed that the level of TSH was significantly ($P<0.0001$) increased in both subclinical and clinical hypothyroid diabetic patients in comparison to euthyroid control. T3 and T4 levels were significantly ($P<0.0001$) decreased in patients as compared to control group. The level of insulin and glucose were significantly increased in hypothyroid patients. The level of high density lipoprotein (HDL) was significantly decreased and level of low density (LDL), triglycerides and very low density lipoprotein (VLDL) increased in subclinical and clinical hypothyroid diabetic patients. We concluded that insulin sensitivity act as a mediator of thyroid induced lipid changes in diabetic patients.

Key Words: *Diabetes, Hypothyroid, Thyroid Hormones*

INTRODUCTION
Thyroid hormones are key regulators of many metabolic process though their effect on protein, carbohydrate and lipid metabolism (Peppa *et al.*, 2010). Hypothyroidism, like obesity is one of the pathophysiological conditions most frequently associated with disorders of lipid metabolism and finally dyslipidemia which is one of the major risk factors of coronary disease (Limbu *et al.*, 2008). The pathophysiology of thyroid dysfunction in diabetes is still unclear; however thyroid antibodies have been suggested to be causative factors (Yasmine *et al*., 2006). Although there have been several large cross-sectional studies examining the association between thyroid dysfunction and metabolic abnormalities, few have studied type 2 diabetes. Thyroid hormones also influence on various aspects of lipid metabolism including synthesis, mobilization, and degradation (Zhu and Chang, 2010). Overt hypothyroidism is associated with dyslipidemia and increased artheosclerotic vascular disease (Peppa *et al.*, 2011).
The aim of the present study was to investigate the role of insulin sensitivity as a mediator of thyroid-induced lipid changes in hypothyroid diabetic patients.

MATERIALS AND METHODS
A total of 217 adults aged 20-50 (mean age 37.82 ± 8.90 years) of both the sexes were randomly selected from Regional Hospital Hamirpur, Himachal Pradesh, India. Out of which, 117 were diabetic patients and 100 euthyroid non-diabetic controls group. Venous blood samples were collected from the selected patients and controls after at least 8 hour fasting in non heparinized vacutainers and left for 20 minutes to allow clotting. Clear sera were obtained by centrifugation at 2000 rpm for 15 minutes and stored at 20°C for further biochemical analysis.
Thyroid function was evaluated by measuring serum levels of TSH, T3, and T4 with a direct enzyme immune assay (Biocheck, Inc. California and Bio Montecelio, Italy). The serum was also used for analyzing fasting blood glucose and insulin.

Lipid profile panel test: Serum total cholesterol, HDL, triglycerides measured by using Mindray BA-At 80 (Human Diagnostics Reagents, germany) and LDL, VLDL was calculated by Friedwald and Frederickson formula.

The study was approved by institutional Human Ethical committee.

Data Analysis

All the data was expressed as mean ± standard deviations (S.D.). One way analysis of variance (ANOVA) with post-hoc analysis was used to compare the variables in different groups. Association between variables was assessed by Pearson's bivariate cofficient of correlation. Two sided P values of <0.05 were considered statistically significant. The statistical program used was SPSS for windows version 16.0 (Statistical Package for Social Sciences Inc., Chicago, Illinois, USA).

RESULTS

Thyroid Function Hormones

Table 1 illustrates the level of thyroid hormones in hypothyroid diabetic and non diabetic euthyroid subjects. There was significant (F=1014, P<0.0001) elevation in the mean level of thyroid stimulating hormone (TSH) in both subclinical and clinical hypothyroid diabetic patients in comparison to non-diabetic control. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05) elevation in mean level of TSH, in control vs subclinical hypothyroid (q = 35.98, 95% CI -10.62 to -8.806 mean difference of -9.711) and clinical hypothyroid (q = 62.11, 95% CI -17.39 to -15.60, mean difference of -16.50). The TSH levels also showed significant (q = 22.55, 95% CI 5.775 to 7.793, mean difference 6.784) increase in clinical hypothyroids in comparison to subclinical patients.

Triiodothyronine (T3) is a hormone synthesized and stored in thyroid gland. T3 concentration in both subclinical and clinical hypothyroid diabetic groups were significantly (F=2335, P<0.0001) lowered than the control group. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05) decline in the mean level of T3 in control vs clinical hypothyroid (q = 90.34, 95% CI 1.204 to 1.297) with the mean difference of 1.250 and subclinical vs clinical hypothyroid group (q = 78.49, 95% CI -1.283 to -1.178 with -1.231 mean difference).

The concentration of mean serum thyroxine (T4) was significantly (F = 1474, P<0.0001) decreased in both sub-clinical and clinical hypothyroid diabetic patients as compared to non-diabetic control. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05,) decrease in T4 levels in control vs subclinical hypothyroid (q = 6.143, 95% CI 0.2120 to 0.7220 mean difference of 0.4670) and in clinical diabetic hypothyroid (q = 73.41, 95% CI 5.240 to 5.742, mean difference of 5.491). There was also a significant (P<0.05) decrease in subclinical vs clinical hypothyroid diabetics (q = 56.30 95% CI -5.308 to -4.470).

Insulin

Post hoc multiple comparison after one way ANOVA revealed a significant (F = 1675, P<0.0001, Table 1) increase in the mean serum insulin (random) level in both subclinical (q = 42.65, -11.74 to -10.03, mean difference -10.880, P<0.05) and clinical (q = 80.68, 95% CI -21.09 to -19.41, mean difference, -20.250, P<0.05) hypothyroid patients as compared to non-diabetic control. In subclinical vs clinical hypothyroids, serum insulin (random) significantly (q = 32.96, 95% CI 8.417 to 10.32, mean difference 9.371) increased.

Glucose

Mean serum glucose (random) levels were significantly (F = 682.1, P<0.0001, Table 2) higher in hypothyroid diabetic patients as compared to control. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05) increase in serum glucose (random) in all study groups. Maximum increase in serum glucose (random) was observed in clinical hypothyroid diabetic patients (q = 50.98, 95% CI -96.99 to -85.01).

Table.1 Serum thyroid hormones and insulin in non-diabetic and diabetic subjects

Parameter	Study group			F-value
	Non diabetic euthyroid subjects	Hypothyroid diabetic patients		
		Subclinical	Clinical	
TSH (µIU/ml)	2.84 ± 0.71	12.55 ± 2.51*	19.34 ± 3.51*	1014
T3 (mg/dl)	1.51 ± 0.12	1.49 ± 0.10*	0.26 ± 0.13*	2335
T4(µg/dl)	7.77 ± 0.90	7.30 ± 0.36*	2.28 ± 0.17*	1474
Insulin (µlU/ml) (random)	16.76 ± 1.74	27.64 ± 2.72*	37.01 ± 2.25*	1675

*Values are Mean ± SD; F-value ANOVA; *P<0.0001*

Table.2 Comparison of biochemical changes in non-diabetic euthyroid and hypothyroid Diabetic patients

Parameter (mg/dl)	Study group			F-value
	Non diabetic euthyroid subjects	Hypothyroid diabetic patients		
		Subclinical	Clinical	
Glucose Postprandia	133.80 ± 12.70	187.11 ± 12.17*	224.80 ± 21.35*	682
HDL	59.15 ± 7.33	47.28 ± 4.50*	38.53 ± 3.18*	252.9
TC	172.86 ± 15.50	216.74 ± 18.56*	227.70 ± 20.01*	217.6
VLDL	19.97 ± 2.33	31.78 ± 2.75*	34.26 ± 2.70*	707.9
LDL	93.53 ± 16.26	137.67 ± 19.71*	154.91 ± 20.02*	239.2

*Values are Mean ± SD; F-value ANOVA; *P<0.0001*

High Density Lipoprotein (HDL)

The mean serum levels of HDL were significantly (F = 252.9, P<0.0001, Table 2) decreased in the subclinical and clinical hypothyroid diabetic patients in comparison to the non-diabetic controls. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05) decrease in HDL (q = 17.62 to 31.11 95% CI 9.610 to 22.84, mean difference 11.87 to 20.62) in both subclinical vs clinical hypothyroid diabetics. In subclinical hypothyroid vs clinical hypothyroids HDL concentration showed significant (q = 11.65, 95% CI -11.27 to -6.23) decrease with the mean difference of -8.747.

Total Cholesterol (TC)

The mean serum level of TC were significantly (F = 217.6, P<0.0001, Table 2) elevated in the subclinical as well as clinical hypothyroid diabetic patients as compared to the non-diabetic controls. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05) increase in serum total cholesterol of diabetic patients. The total cholesterol level showed significant (q = 21.18 to 26.90, 95% CI -50.83 to -48.00 mean difference -43.88 to -54.84) increase in subclinical and clinical hypothyroids vs control. There was also significant (P<0.05, q = 4.748, 95% CI 3.218 to 18.71 mean difference of 10.96) in subclinical to clinical hypothyroid diabetic patients.

Very Low Density Lipoprotein (VLDL)

The serum concentration of VLDL was significantly (F = 707.9, P<0.0001, Table 2) elevated in the subclinical and clinical hypothyroid patients in comparison to non-diabetic patients. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05) increase in serum VLDL. The VLDL levels showed a significant (q = 39.05 to 48.01, 95% CI -12.82 to -13.29, mean difference -11.810 to -14.280) increase in subclinical and clinical hypothyroids as compared to control. There was a significant (q = 7.341, 95% CI 1.344 to 3.605, mean difference of 2.474) elevation in subclinical vs clinical hypothyroid diabetics.

Low Density Lipoprotein (LDL)

The mean serum concentration of LDL was found significantly (F = 239.2, P<0.0001, Table 2) higher in comparison to non-diabetic control. Post hoc Tukey's multiple comparison test after one way ANOVA described a significant (P<0.05) increase in serum LDL. There was significant (q = 20.57 to 29.07 95% CI = -51.34 to -54.25 mean difference = -44.14 to -61.38) increase in subclinical and clinical hypothyroid diabetics as compared to non-diabetic controls. In subclinical vs clinical hypothyroid diabetics, LDL showed a significant (q = 7.207, 95% CI 9.213 to 25.26, mean difference of 17.24) elevation.

CORRELATION ANALYSIS

Pearson's correlation described significant (P<0.05) negative correlation of serum triglycerides with T3 (Y = 186.06x -56.09*, r = -0.5246, Fig 1) and T4 (Y = 260.08x -38.98*, r = -0.4739, Fig 2). However, correlation between serum TG and TSH (r= 0.35781) was statistically non significant.

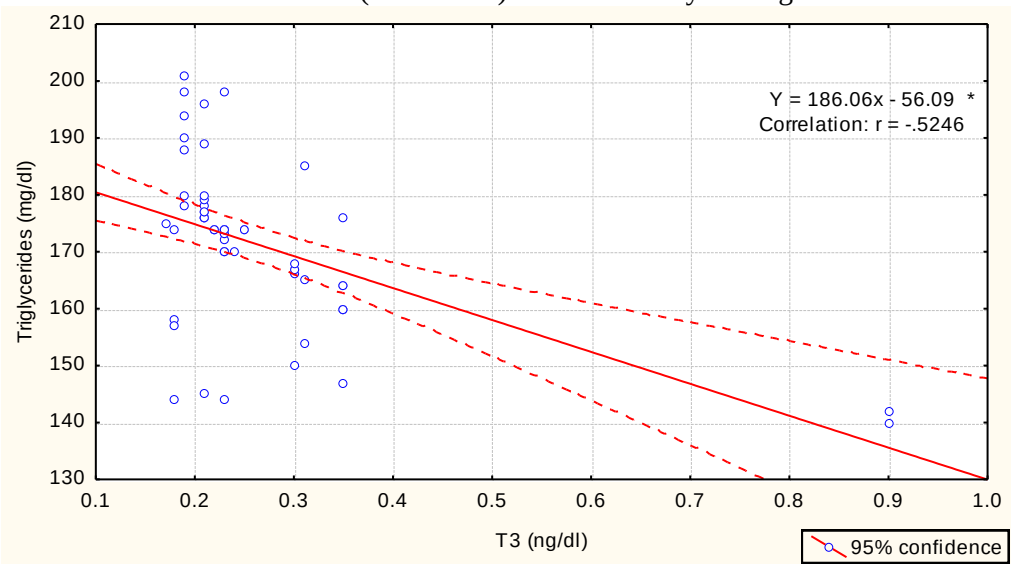

Figure 1: Scatter plot showing correlation between triglycerides and serum T3 in hypothyroid diabetic patients

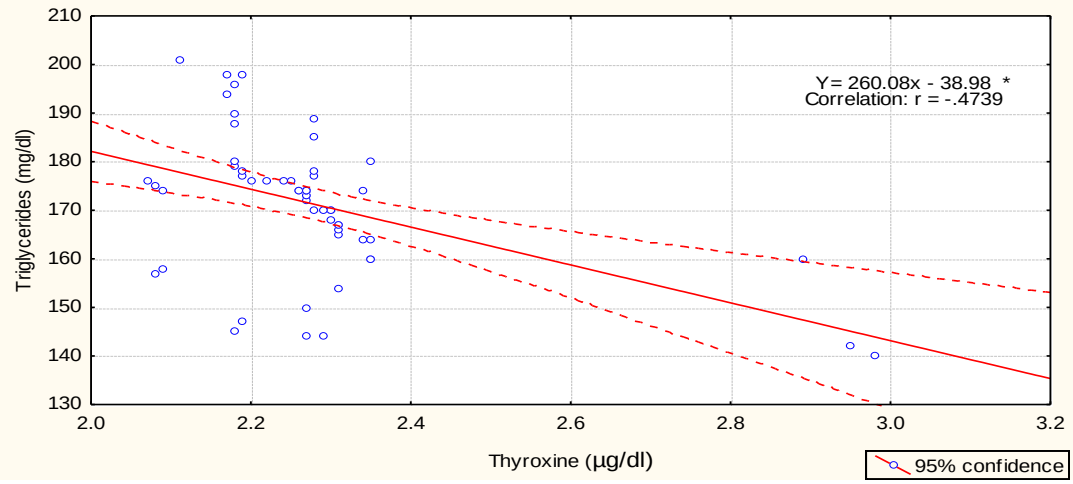

Figure 2: Scatter plot showing correlation between triglycerides and serum T4 in hypothyroid diabetic patients

Pearson's bivariate correlation revealed that the serum levels of TSH were negatively correlated (Y = 47.838x -0.4812, r = -0.5314) with HDL in hypothyroid diabetic patients (Fig 3). The Pearson's correlation revealed positive correlation between serum T3 and HDL (Y = 35.099x +13.033*, r = 0.53496, P<0.05, Fig 4) and T4 vs HDL (Y = 15.408x + 10.150*, r = 0.54164, P<0.05, Fig 5).
The serum TSH levels was positively correlated with total cholesterol (Y = 173.35x + 2.8105*, r = 0.49333, P<0.05) in hypothyroid diabetic patients (Fig 6). The Pearson's coefficient showed negative correlation between T3 and total cholesterol (Y = 251.02x -88.49*, r = -0.5774, P<0.05, Fig 7), T4 and total cholesterol (Y = 384.40x -68.78, r = -0.5834, Fig 8).

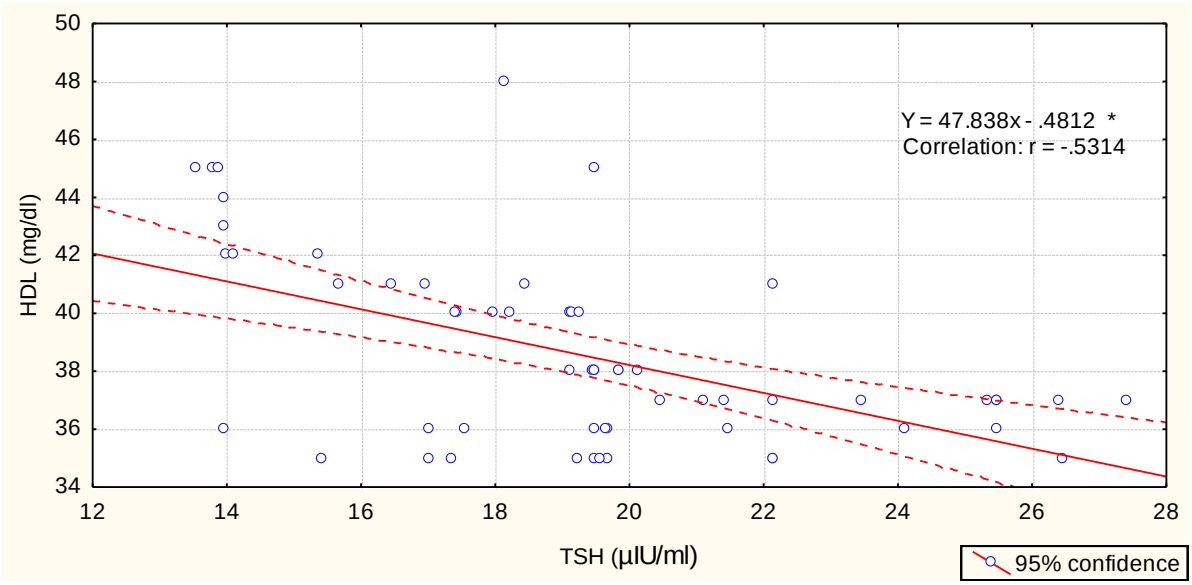

Figure 3: Scatter plot showing correlation between HDL and serum TSH in hypothyroid diabetic patients

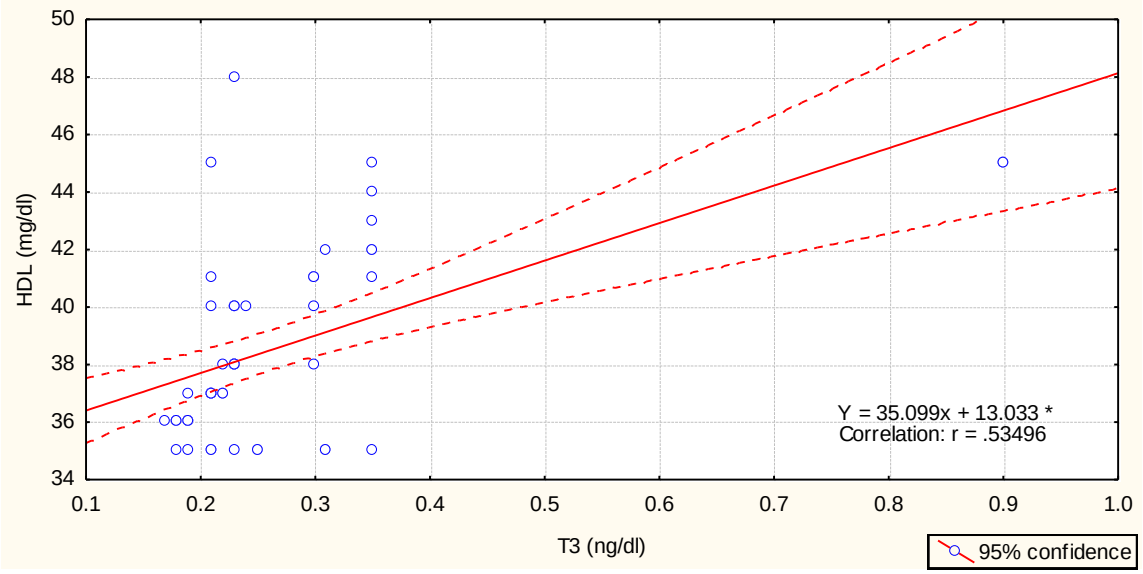

Figure 4: Scatter plot showing correlation between HDL and serum T3 in hypothyroid diabetic patients

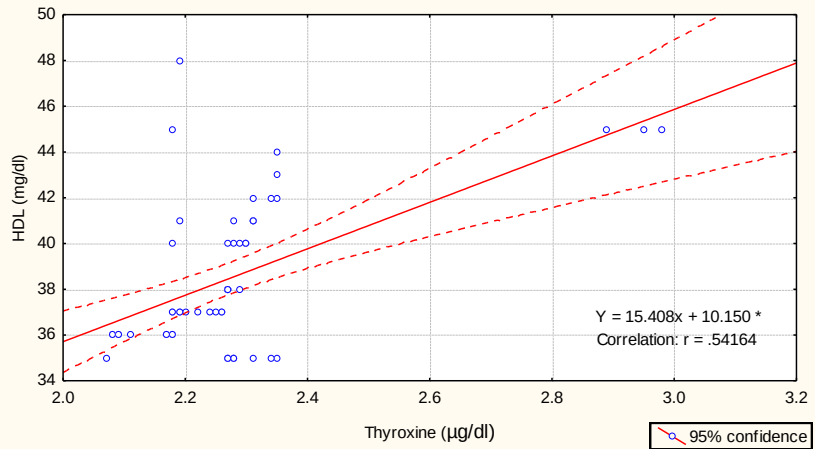

Figure 5: Scatter plot showing correlation between HDL and serum T4 in hypothyroid Diabetic patients

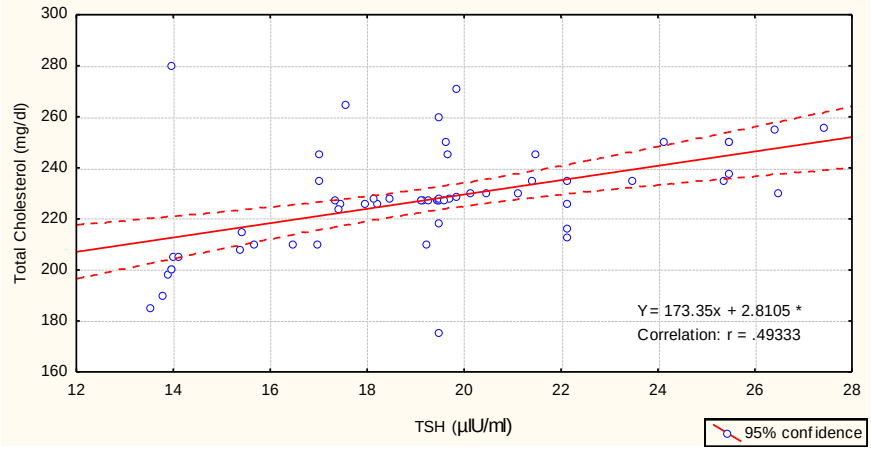

Figure 6: Scatter plot showing correlation between cholesterol and serum TSH in hypothyroid diabetic patients

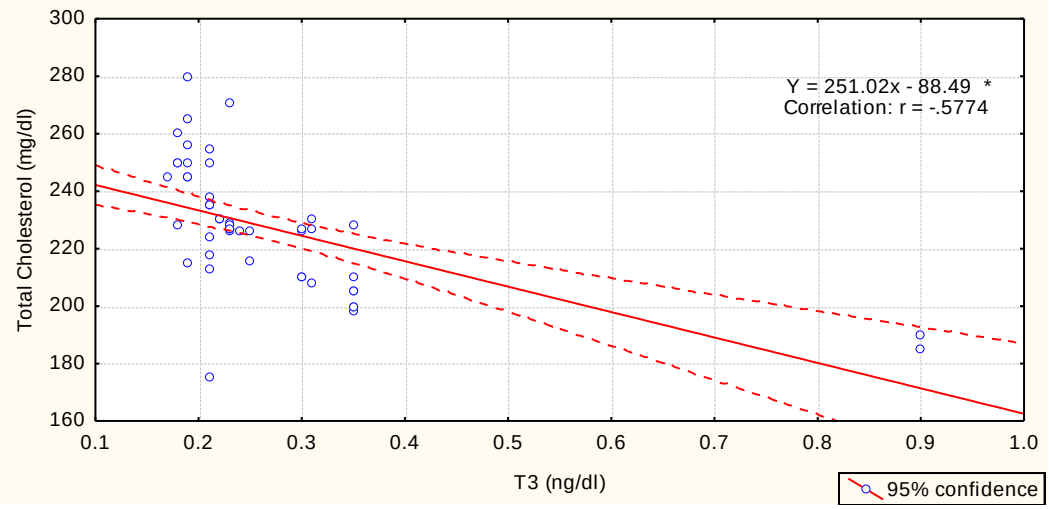

Figure 7: Scatter plot showing correlation between cholesterol and serum T3 in hypothyroid Diabetic patients

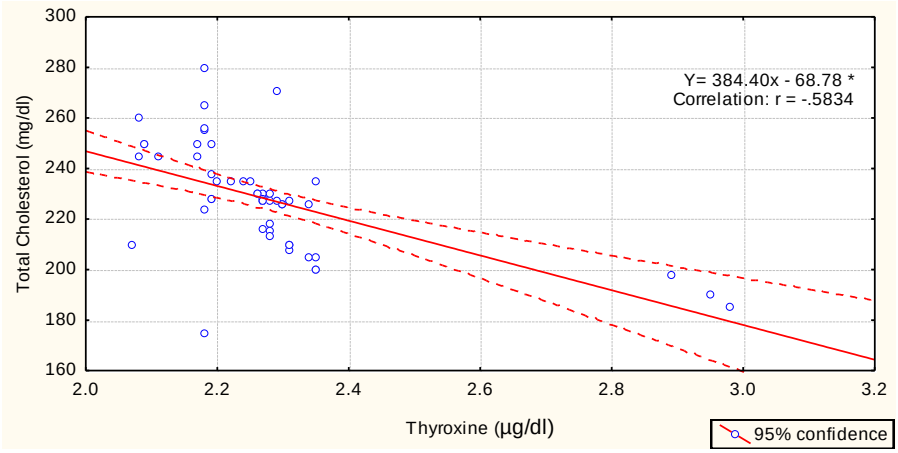

Figure 8: Scatter plot showing correlation between cholesterol and serum T4 in hypothyroid Diabetic patients

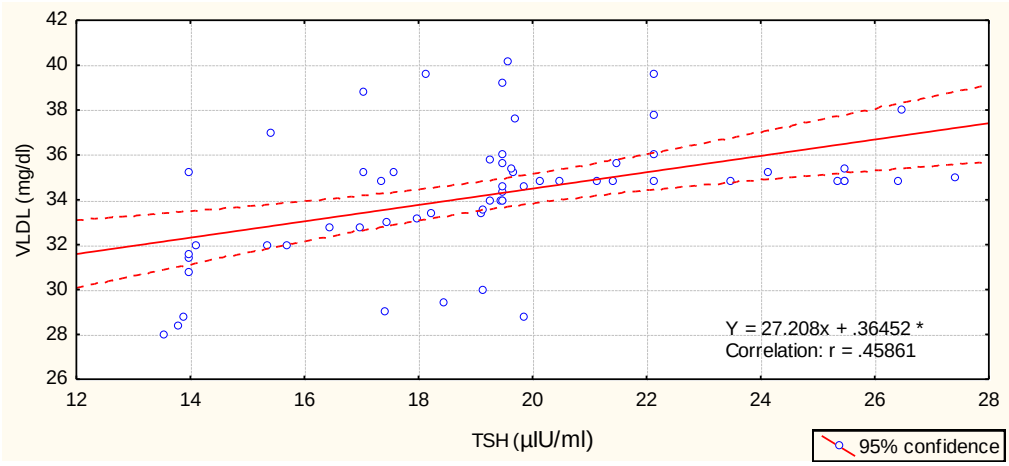

Figure 9: Scatter plot showing correlation between VLDL and serum TSH in hypothyroid Diabetic patients

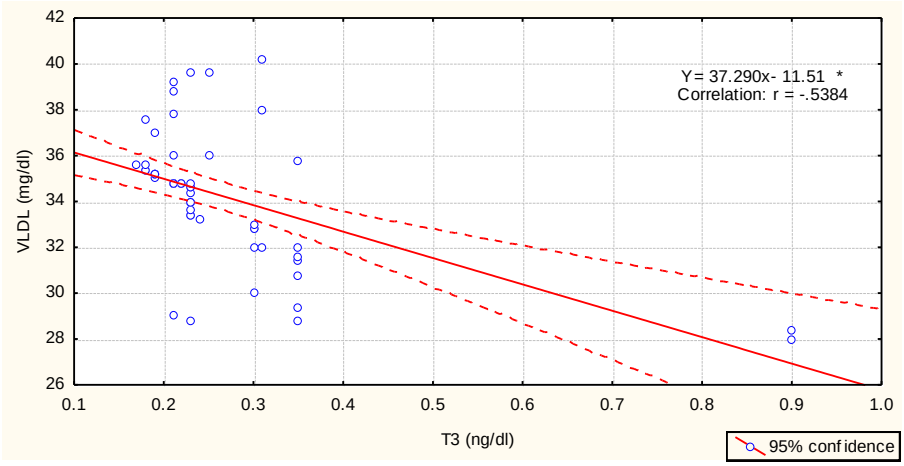

Figure 10: Scatter plot showing correlation between VLDL and serum T3 in hypothyroid Diabetic patients

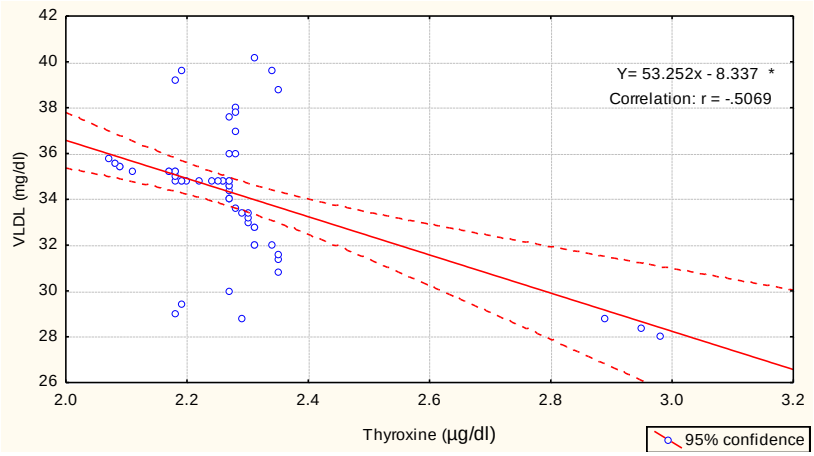

Figure 11: Scatter plot showing correlation between VLDL and serum T4 in hypothyroid Diabetic patients

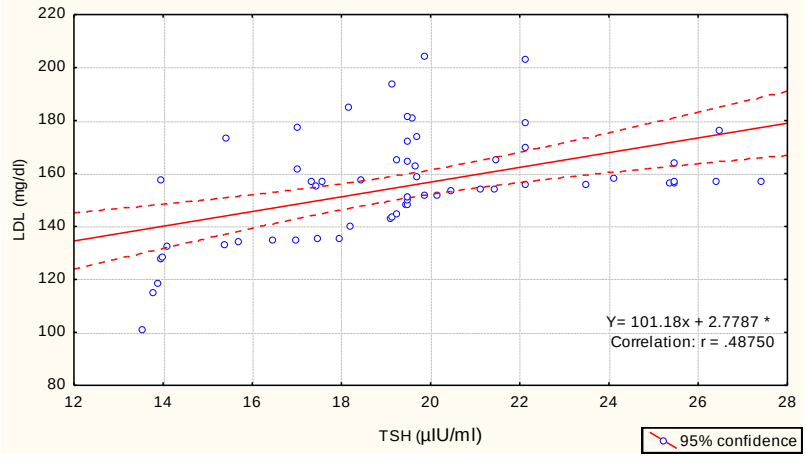

Figure 12: Scatter plot showing correlation between LDL and serum TSH in hypothyroid diabetic patients

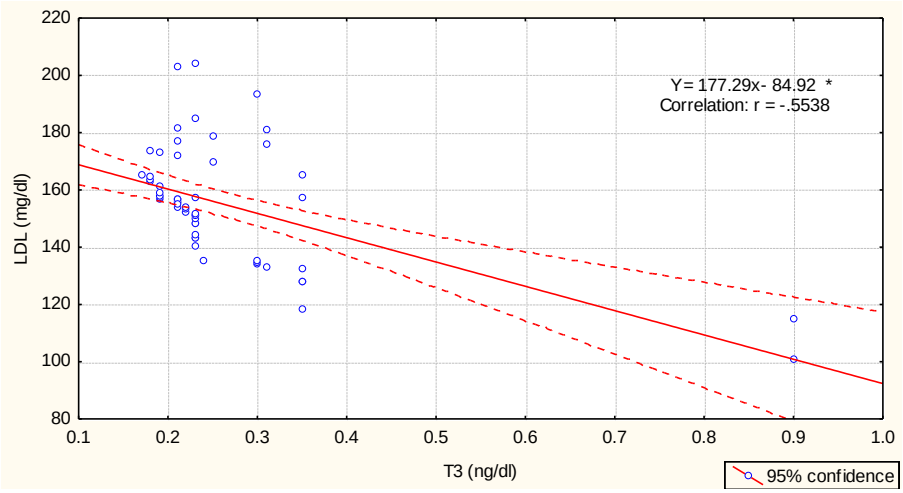

Figure 13: Scatter plot showing correlation between LDL and serum T3 in hypothyroid diabetic Patients

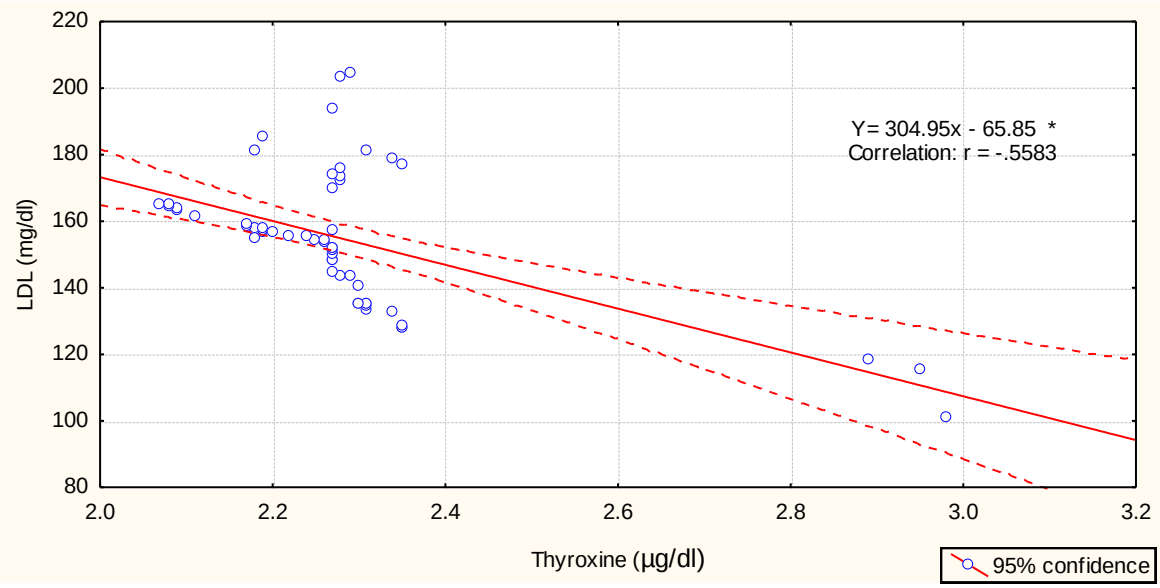

Figure 14: Scatter plot showing correlation between LDL and serum T4 in hypothyroid diabetic Patients

Pearson's bivariate correlation revealed a significant (Y = 27.208x + 0.36452*, r = 0.45861, P<0.05) positive correlation between TSH and VLDL (Fig. 9), negative correlation between T3 and VLDL (Y = 37.290x -11.51*, r = -0.5384, P<0.05, Fig 10) and T4 vs VLDL (Y = 53.252x -8.337*, r = -0.5069, Fig 11). Pearson's bivariate correlation revealed a significant (Y = 101.18x + 2.7787*, r = 0.48750, P<0.05, Fig.12) positive correlation of TSH with LDL, negative correlation between T3 and LDL (Y = 177.29x - 84.92*, r = -0.5538, P<0.05, Fig 13) and T4 vs LDL (Y = 304.95x -65.85*, r = -0.5583, Fig 14).

DISCUSSION

The abnormal high level of TSH in the diabetic patients was noted in the present study, while the T3 level was decreased. These findings were supported by the study in Bangladeshi type 2 diabetics with significantly low T3 level (Rashid *et al.,* 2007). In our study TSH level was elevated and the serum T3 and T4 levels were normal in subclinical hypothyroid diabetics. These findings were in consistence with the subclinical hypothyroidism characterized by normal serum levels of thyroid hormones with mildly elevated serum TSH concentration (Serter *et al.,* 2004). TSH increases iodide uptake and oxidation that leads to organification and coupling, which are necessary steps to produce the thyroid hormones T4 and T3. Of the thyroid hormones secreted, 90% is T4, and 9% is T3. T3 derives from deiodination of T4; therefore, 80% of circulating T3 is from T4 (Porterfield, 1997). The thyroid hormone profile is altered in uncontrolled diabetes with an increase in reverse T3 and decrease in serum T3 and T4 (Saunders, Hall and Sonsken, 1978). Diabetes mellitus appears to influence thyroid function in two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T4 to T3 in the peripheral tissue.

Thyroid hormones have well described effects on glucose and lipid metabolism (Pepp *et al*., 2010). There is a continuous association of thyroid hormone and insulin in glucose metabolism (Dimitriadis and Raptis, 2001, Lacobellis *et al.,* 2005). Thyroid hormone action has long been recognized as an important determinant of glucose homeostasis (Weinstein *et al.,* 1994; Torrance *et al.,* 1997). Many studies revealed that T3 and insulin both stimulate the expression of hexokinase and glycogen synthase which are respectively responsible for uptake and disposal of glucose via formation of glucose-6 phosphate and glucose-1 phosphate (Kim *et al.,* 2002). The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis (Dimitriadis and Raptis, 2001).

In type 1 and type 2 diabetes, the metabolism of foodstuff is altered (Briscoe *et al.*, 2006). Lack of insulin or insulin resistance prevents the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, blood glucose concentration increases, cell utilization of glucose decreases and utilization of fats and proteins increases (Briscoe *et al.,* 2006). In hypothyroidism, the synthesis and release of insulin is decreased (Ahren *et al*., 1985). The rate of hepatic glucose output is decreased probably due to reduced gluconeogenesis (Dimitriadis *et al*., 2001). In type 2 diabetes mellitus subjects lower levels of T3 and higher levels of insulin failed to maintain normoglycemic condition and this further enhanced the hyperinsulinemia. Consistent hyperglycemia in the hyperinsulinemic and insulin resistance subjects might be attributed to this disturbed balance between insulin and T3, which fail to maintain normal glycemia. The results of the present study show that the homeostasis relationship of insulin and T3 is gradually lost with the parallel development of insulin resistance and insufficiency of insulin to the cells. Insulin resistance with the hyperglycemia, hyperinsulinemia, and the altered natures of skeletal muscle fibres with lower ratio of oxidative to glycolytic enzymes, reduced the glucose disposal via reduced oxidative of glucose (Crunkhorn and Petti, 2008).

In the present study, the diabetic patients with thyroid dysfunction tended to have higher levels of blood lipids viz; triglycerides, HDL, cholesterol, LDL and VLDL compared to control. The findings are in concord with the previous studies of Mahato *et al*. (2011), Sivakumar *et al*. (2012). The association of hypothyroidism with lipid profile has been estimated earlier (Tayal *et al*., 2008). Thyroid hormones also influence various aspects of lipid metabolism including synthesis, mobilization and degradation (Zhu and Cheng, 2010). Most hypothyroid, as well as patients with subclinical hypofunction, showed high serum concentrations of LDL cholesterol (Zhu and Cheng, 2010 and Peppa *et al*., 2011).

Thyroid hormones are involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes of serum lipids (Peppa *et al*., 2011, Brenta *et al*., 2007, Tzotzas *et al*., 2000). More importantly, hypothyroidism is accompanied by a variety of abnormalities in plasma lipid metabolism, including elevated triglyceride and LDL cholesterol concentrations (Walsh *et al.,* 2005). Overt hypothyroidism is associated with significant increase in circulating levels of total and LDL-C (O'Brien *et al*., 1993). The abnormally high concentration of serum lipid in diabetes is mainly due to the increase in mobilization of free fatty acids from peripheral fat depots (Bopama *et al*., 1997). Insulin resistance, an important factor in type 2 diabetes mellitus, leads to excessive liberation of free fatty acids from adipose tissue (Chubb *et al.,* 2005 and Pasupathi *et al.,* 2008).

Dyslipidemia is a reported complication of overt hypothyroidism in non-diabetic (Staub *et al.,* 1992, Elder *et al*., 1990, Johnston *et al.,* 1993) and diabetic (Gray *et al.,* 1981) subjects. Insulin effects the liver apolipoprotein production. It regulates the enzymatic activity of lipoprotein lipase and cholesterol ester transport protein. All these factors are likely cause of dyslipidemia in diabetes mellitus (Goldberg, 1996). Overt hypothyroidism leads to an increase in the plasma cholesterol levels (Tunbridge *et al*., 1997; Duntas, 2002; Maratou *et al*., 2009). Most studies in the subclinical hypothyroidism show comparable but less pronounced associations (Biondi and Klein, 2004, Canaris *et al.,* 2000). The relative insulin deficiency that occurs in type 2 diabetes impairs the action of lipoprotein lipase and results in lower HDL-C levels and higher triglycerides levels, which may improve with improved glycemic control (Brunzell and Chait 1997).

REFERENCES

Ahren B, Lundquist I, Hedner P, Valdemarsson S and Schersten B (1985). Glucose tolerance and insulin and C peptide responses after various insulin secretary stimuli in hyper and hypothyroid subjects before and after treatment. *Diabetes Research* **2**(2) 95-103.

Biondi B and Klein I (2004). Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine* **24** 1-13.

Brenta G, Berg G, Arias P, Zago V, Schnitman M, Muzzio ML, Sinay I and Schreier L (2007). Lipoprotein alterations, hepatic lipase activity, and insulin sensitivity in subclinical hypothyroidism: response to L-T4 treatment. *Thyroid* **17** 453-460.

Briscoe J and Davis SN (2006). Hypoglycemia in type 1 and type 2 diabetes: physiology, pathophysiology, and management. *Clinical Diabetes* **24** 115-121.

Brunzell JD and Chait A (1997). Diabetic dyslipidemia: pathology and treatment. In: Porte D Jr, Sherwin J, editors. Ellenberg and Rifkin's Diabetes Mellitus. Appleton and Lange Inc; East Norwalk 1077-1098.

Carnaris GJ, Manowitz NR, Mayor G and Ridgway EC (2000). The Colorado thyroid disease prevalence study. *Archeives International Medicen* **160**(4) 526-534.

Chubb SAP, Davis WA and Davis TME (2005). Interactions among thyroid function, insulin sensitivity, and serum lipid concentrations: The Fremantle diabetes study. *Journal Clinical Endocrinology Metabolism* **90**(9) 5317-5320.

Crunkhorn S and Patti ME. (2008). Links between thyroid hormone action, oxidative metabolism and diabetes risk? *Thyroid* **18**(2) 227-237.

Dimitriadis GD and Raptis SA (2001). Thyroid hormone excess and glucose intolerance. *Experimental Clinical Endocrinology Diabetes* **109**(2) S225-S239.

Duntas LH. (2002). Thyroid disease and lipids. *Thyroid* **12** 287-293.

Elder J, McLelland A, O'Reilly DS., Packard CJ, Series JJ and Shepherd J (1990). The relationship between serum cholesterol and serum thyrotropin, thyroxine and tri-iodothyronine concentrations in suspected hypothyroidism. *Annals Clinical Biochemistry* **27**(Pt2) 110-113.

Goldberg IJ (1996). Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis. *Journal Lipid Research* **37** 693-707.

Gray RS, Smith AF and Clarke BF. (1981). Hypercholesterolemia in diabetics with clinically unrecognised primary thyroid failure. *Hormone and Metabolic Research* **13**(9) 508-510.

Kim SR, Tull ES, Talbott EO, Vogt MT and Kullar LH (2002). A hypothesis of synergism: the interrelation of T3 and insulin to disturbances in metabolic homeostasis. *Medical Hypotheses* **59** 660-666.

Lacobellis G, Ribaudo MC, Zappaterreno A, Lannucci CV and Leonetti F (2005). Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. *Clinical Endocrinology* **62** 487-491

Limbu YR, Rai SK and Ono K (2008). Lipid profile of adult Nepalese population. *Nepal Medical Collage Journal* **1** 4-7.

Mahato RV, Gyawali P, Raut PP, Regmi P, Singh KP, Pandeya DR and Gyawali P (2011). Association between glycaemic control and serum lipid profile in type 2 diabetic patients: Glycated haemoglobin as a dual biomarker. *Biomedical Research* **22**(3) 375-380.

Maratou E, Hadjidakis D, Kollias A, Tsegka K, Peppa M, Alevizaki M, Mitrou P, Lambadiari V, Boutati E, Nikzas D, Tountas N, Economopoulos T, Raptis SA and Dimitriadis G (2009). Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *European Journal Endocrinology* **160**(5) 785-790.

O'Brien T, Dinneen SF, O'Brien PC and Palumbo PJ (1993). Hyperlipidemia in patients with primary and secondary hypothyroidism. *Mayo Clinical Proceedings* **68**(9) 860-866.

Pasupathi P, Bakthavathsalam G, Saravanan G and Sundaramoorthi R (2008). Screening for thyroid dysfunction in the Diabetic/Non-Diabetic population. *Thyroid Science* **3**(8) CLS1-CLS6.

Peppa M, Betsi G and Dimitriadis G (2011). Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease. *Journal Lipids* 575-840.

Porterfield SP, St. Louis M and Mosby (1997). The thyroid gland. International Endocrine Physiology 57-81.

Rashid DA, Rashid MA, Hannan JMA, Faruque NQ and Ali L (2007). Association of thyroid dysfunction with young diabetic subjects in a Bangladeshi population. *Bangladesh Medical Journal* **36** (2) 34-38.

Saunders J, Hall SHE and Sonksen PH (1978). Thyroid hormones in insulin requiring diabetes before and after treatment. *Diabetologica* **15** 29-32.

Serter R, Demirbas B, Culha C and Cakal E (2004). The effect of L-thyroxine replacement therapy on lipid based cardiovascular risk in sub clinical hypothyroidism. *Journal Endocrinology Investigation* **27**(10) 897-903

Shivkumar S, Prasad KC and Sivasubramanian J (2012). Biochemical studies on blood sample of patients with diabetes mellitus. *International Journal Physioligy* **3**(5) 368-372.

Staub JJ, Althaus BU, Engler H, Ryff AS, Trabucco P, Marquardt K, Burckhardt D, Girard J and Weintraub BD (1992). Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. *American Journal Medicen* **92**(6) 631-642.

Tayal D, Goswami B, Gupta VK and Mallika V (2008). Evaluation of lipid profile in hypothyroid patients. Our experience. *Thyroid Research Practice* **5**(2) 43-47.

Torrance CJ, Devente JE, Jones JP and Dohm GL (1997). Effects of thyroid hormone on GLUT4 glucose transporter gene expression and NIDDM in rats. *Endocrinology* **138** 1204-1214.

Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T and Smith PA (1977). Lipid profiles and cardiovascular disease in the whickham area with particular reference to thyroid failure. *Clinical Endocrinology* **7**(6) 495-508.

Tzotzas T, Krassas GE, Konstantinidis T and Bougoulia M (2000). Changes in lipoprotein(a) levels in Clinical and subclinical hypothyroidism before and during treatment. *Thyroid* **10** 803-808.

Walsh JP, Bremner AP, Bulsara MK, O'leary P, Leedman PJ, Feddema P and Michelangeli V (2005). Thyroid dysfunction and serum lipids: a community- based study. *Clinical Endocrinology* **63**(3) 670-675.

Weinstein SP, OBoyle E, Fisher M and Haber RS (1994). Regulation of glutz glucose transporter expression in liver by thyroid hormone: evidence for hormonal regulation of the hepatic glucose transport system. *Endocrinology* **135** 257-273.

Yasmin T, Ghafoor F, Malik TSRN and Khan AU (2006). Pattern of thyroid autoimmunity in type 1 and type 2 diabetics. *Journal College Physicians Surgery Pakistan* **16**(12) 751-754.

Zhu X and Cheng SY (2010). New insights into regulation of lipid metabolism by thyroid hormone. *Current Opinion Endocrinology Diabetes Obesity* **17** 408-413.