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Original Research Article

Serum Thyroid Hormones Pictures in Non Thyroidal Illness Syndrome and Circulating Leptin Concentration in Patients with Uncontrolled Type 2 Diabetes Mellitus in a Group of Bangladeshi Population

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Abstract

Background: Thyroid diseases and diabetes mellitus are common endocrine disorders and Euthyroid Sick Syndrome is very common in uncontrolled type2 Diabetes Mellitus. As of thyroid hormones; the catabolic hormone Leptin is thought be closely linked with Diabetes Mellitus and Euthyroid Sick Syndrome. ***Objective:*** To evaluate the thyroid hormone pictures in absence of clinical thyroid diseases among type2 diabetic subjects in a Bangladeshi population. To see the baseline serum leptin concentration in a group of Bangladeshi adult population and to document how the leptin is related to glycemic status and Sick Euthyroid syndrome in the setting of uncontrolled type 2 Diabetes Mellitus. ***Method:*** This case and control study was carried out in the Endocrinology Department in collaboration with the Bio-Medical Research Group (BMRG), Research Division, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrinology and Metabolism (BIRDEM)), Dhaka, Bangladesh during the period of January 2000 to December 2002. A total of 100 type 2 diabetic subjects, 30-50 years of age, irrespective of glycemic status, duration of diabetes, Body Mass Index (BMI) and sex were recruited from the outpatient department (OPD) of BIRDEM hospital. Control subjects (n=30) were selected from friends and family of the patients within 5 years of age band without diabetes or impaired glucose regulation {Impaired Fasting Glycemia (IFG), Impaired Glucose Tolerance (IGT)} determined according to American Diabetic Association (ADA) criteria [37] and having no clinical thyroid diseases or other evident systemic diseases documented on clinical evaluation. ***Results:*** It was observed that mean± SD of the thyroid hormone pictures in diabetic and control subjects were; TT_3 (ngm/dl) {in controls (88.91±15.88) and in diabetic subjects (84.27±22.29)} was not statistically significant to each other (p=0.209). Mean±SD of TT_4 (µgm/ dl) in control subjects was 8.32±1.64 and in the diabetic subjects was 9.26±1.44, which is almost similar in both the groups (p= 0.589). FT4: (pgm/ml) in control subjects was 2.60±0.54 and in diabetics was 2.53±1.72 (p= 0.830). FT_4. (µgm/ dl) in control subjects was 1.43±0.22 and in diabetics subjects 1.36±0.25. (p 0.179). TSH (µlu/ml) in control subjects was 1.34±1.00 and in diabetic subjects 1.54±1.21 (p: 0.411). FT_3; FT_4 and TSH showed no significant difference between control and diabetic subjects. Thyroid hormones (TT_3, TT_4, FT_3, FT_4) and TSH were reanalyzed according to HbA1c and BMI category and showed no significant differences. But when the FPG and HbA1c goes beyond 12 mmol/l and 10% respectively there was more worsening thyroid hormone pictures in comparison to groups whose FPG and HbA1c were below 12mmol/l and 10%. It was also noticed that there was a tendency to develop lower thyroid hormone pictures and more deteriorating glycemic status in patient with low and normal BMI groups in comparison to higher BMI groups of patients. Insulin and leptin were found to have strong positive correlation with BMI and other indices of obesity. Serum leptin was also found to be positively correlated with FPG and HbA1c upto a certain limit, but HbA1c went beyond 10%; serum leptin concentration tended to be declined. Serum leptin and Insulin showed strong positive correlation to each other's. Thyroid hormones and TSH were re-analyzed and its relationship to FPG, HbA1c, fasting serum Insulin and Leptin were explored. Fasting serum

Insulin and Leptin showed no significant differences among the different thyroid hormones groups. ***Conclusion:*** Uncontrolled type2 diabetes mellitus is associated with alteration of thyroid hormone pictures particularly affecting TT_3, FT_3 and TSH. This biochemical feature is more evident if the BMI of the Diabetic subjects is low or within the normal range and also the more worsening the glycemic status, there were more deteriorating serum thyroid hormone pictures. Serum leptin was not found to have any relation with these changes.

Keywords: Leptin, Euthyroid Sick Syndrome (ESS), Diabetes mellitus, Body mass index (BMI).

INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action or both associated with hyperglycemia and disturbances in carbohydrate, lipid and protein metabolism. The chronic hyperglycemia of Diabetes is associated with long term damages, dysfunction and failures of various organs specially the heart, blood vessels, kidneys, eyes and nerves [1, 2].

Thyroid diseases and diabetes mellitus are the two most common endocrine disorders [3]. Diabetic patients have increased prevalence of thyroid disorder, with hypothyroidism being the most common [4]. In diabetic patients, thyroid dysfunction varies from 2.2% -17%. Diabetic women are more commonly affected by thyroid dysfunctions than men [5]. Hypothyroidism occurs from a deficiency of thyroid hormones is a very common thyroid problem in diabetic patients [6]. Thyroid hormones and insulin are the antagonistic, and involved in the metabolism of carbohydrates, proteins, and lipids. Thyroid hormone as well as insulin is altered if there is functional impairment of the thyroid gland and endocrine pancreatic beta cells [7]. 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 T_4 to T_3 in the peripheral tissue. Increased hyperglycemia causes reversible reduction of the activity and hepatic concentration of T_4-5'-deiodinase, low serum T_3, increase in reverse T_3 and also variation in the level of T_4 [8].

Leptin the product of ob gene secreted by mature adipocytes from white adipose tissues and is supposed to transmit a satiety signal into the central nervous system. It is a hormone involved with body weight homeostasis by reduction in food intake and increase in energy expenditure. It was observed that plasma leptin levels is strongly correlated with BMI and other indices of adiposity like Waist Hip (W/H) ratio, percent body fat and total fat mass and also the fasting Insulin levels in both Rodents and human [9-13]. Obese state is associated with dyslipidemia, hyperinsulinemia, insulin resistance and glucose intolerance with considerable morbidities and mortalities [14-16]. The risk of development of type2 Diabetes becomes greater with increasing obesity and insulin resistance. So that increasing adipose tissue mass could lead to insulin resistance, hyperinsulinemia, hyperleptinemia and Diabetes Mellitus [9].

Euthyroid Sick syndrome (ESS) or Non-thyroidal illness Syndrome (NTIS) identifies abnormalities of thyroid function tests observed in patients with systemic non-thyroidal illnesses and in those patients undergoing surgery or fasting [22-24]**.** Abnormalities of thyroid function tests observed in ESS or NTIS includes 1) Low T_3 Syndrome 2) Low T_3 and T_4 syndrome 3) High TT_4 syndrome 4) other abnormalities like low TT_3 and TSH, high TSH and low TT_3 and TT_4 [25].

Thyroid hormones are also among the major regulatory hormones in maintenance of energy expenditure; adipose tissue masses and appetite raise the question of an interaction between leptin and thyroid hormones. Leptin was studied among ESS or NTIS patients in the setting of acute severe sepsis, Diabetic ketoacidosis, and critically ill hospitalized patients and in patients with intensive care setting with controversial results [17-21]. Leptin and thyroid hormones have the property of common metabolic effects in maintaining body weight homeostasis by regulating eating behavior and energy expenditure. Pathogenesis of type2 diabetes involves predominantly insulin resistance with compensatory hyperinsulinemia which is truer in case of obese individuals [37] and these types of patients were found hyperleptinemic in many studies done until recently in abroad. So that it's an opportunity to document the interaction of leptin and thyroid hormones in modulating the synthesis and secretion of each other in patients with uncontrolled type2 diabetes mellitus.

Experiments on both animal and human models Diabetes Mellitus was found to be associated with alteration of thyroid hormone picture in absence of clinical thyroid diseases irrespective of the type of diabetes. In both type1and type2 diabetes significant reduction of bothTT_3 and FT_3, increased rT_3 and high rT_3/T_3 ratio was demonstrated [26-29]. Serum FT_4 and FT_4I were normal, TT_4 was normal or suppressed and TSH was found normal or slightly elevated [30, 31]**.** All the parameters of thyroid function specially TT_3, FT_3 and rT_3 become normal when Euglycemia was achieved [27, 32, 33]. More over it was found that reduction of FT_3 and TT_3, rise of rT_3 are significantly correlated with the severity of hyperglycemia and the thyroid secretory response to large dose of TSH is also declined in uncontrolled diabetes mellitus which frequently improves with improved glycemic control [34]**.**

A previous study among young Bangladeshi diabetic population demonstrated significant alteration of thyroid hormone pictures in absence of clinical thyroid diseases which is consistent with the other study done in abroad earlier [35]**.** But ESS or NTIS in the setting of type2 diabetes was not investigated extensively earlier and there is no available data regarding the changes in thyroid hormone pictures in patients with uncontrolled type2 Diabetes Mellitus among Bangladeshi population. Although there are few studies in abroad; which revealed that that there are significant alteration of thyroid hormones in uncontrolled type2 diabetic subjects [32, 33, 36, 37]. As most of these studies did not exclude other causes of ESS or NTIS which are responsible for activating inner ring de-iodination or inhibition of outer ring de-iodination of T_4 to produce T_3 from T_4 instead of rT_3 [38]**;** the result was found to be poorly representative.

In the above context our present study was designed to document the changes of thyroid hormones pictures in absence of clinical thyroid diseases among Bangladeshi population in the setting of uncontrolled type2 diabetes mellitus. As Leptin was previously not measured in Bangladeshi Population and its interaction with glycemic status, insulin and thyroid hormones in our population was completely unknown. So our present study was also aimed to document the basal serum leptin and its relation to glycemic status and thyroid hormones in the study population.

OBJECTIVES AND METHODS

1. To evaluate the circulating thyroid hormone pictures in absence of clinical thyroid diseases among type2 diabetic subjects in a group of Bangladeshi population.
2. To measure the baseline serum Leptin concentration and to document whether it is related to glycemic status, serum insulin and thyroid hormones in the setting of uncontrolled type2 diabetes mellitus
3. To documents the relationship of serum Leptin with BMI and other anthropometric indices of obesity irrespective of glycemic status in a group of population in Bangladesh.

METHODOLOGY

Types of study

This was a case and control study.

Place and duration of study

The study was conducted in the Endocrinology department in collaboration with the Bio-Medical Research Group (BMRG), Research Division, BIRDEM, and Dhaka, Bangladesh during the period of January 2000 to December 2002.

Study population

A total of 100 type 2 diabetic subjects, 30-50 years of age, irrespective of glycemic status, duration of diabetes, BMI and sex were recruited from the outpatient department (OPD) of BIRDEM hospital. Prior to recruitment, diabetes mellitus was confirmed according to current American Diabetic Association (ADA) criteria for the diagnosis and classification of diabetes mellitus [37]**.** Control subjects (n=30) were selected from friends and family of the patients within 5 years of age band without diabetes or impaired glucose regulation (IFG, IGT) determined according to ADA criteria [37] and having no clinical thyroid diseases or other evident systemic diseases documented on clinical evaluation. Informed written consent was taken from all recruited diabetic and control subjects for the purpose of the study.

Exclusion criteria

1. Type 2 diabetes with acute metabolic de-compensation.
2. Type 2 diabetes with clinically detectable thyroid diseases.
3. Type 2 Diabetes with clinically diagnosed other acute or chronic systemic diseases.
4. Diabetic subjects with overt nephropathy in which serum creatinine > 2mg/dl
5. Pregnancy and postmenopausal woman.

METHOD

Selection criteria as per availability and was given an appointment to come in a particular date. Preparation of the subjects and collection of blood of the Controls and diabetic subjects that were assigned for the purpose of study done according to [24]. They were requested to fast overnight for at least eight hours and in the subsequent morning 16 ml of venous blood was drawn from the ante-cubital vein by using 25 cc disposable plastic syringe with 18G needle for the estimation of fasting serum leptin, insulin, C-peptide, glucose, HbAlc, TT_3, TT_4, FT_3, FT_4 and TSH. One ml of collected venous blood was taken in an anticoagulant containing vial for estimation of HbAlc. Remaining 15ml of blood was kept in 3 separate plain test tubes in equal amounts (5ml in each) to centrifuge immediately. Blood sample contained in the test tube was centrifuged for 15 minutes at a rate of 4000 rpm. A total of 200 µl of serum was collected in appropriately labeled eppendorf in duplicate with the help of micropipette for each of the biochemical parameters. Then the serum sample was preserved immediately at -30° C for analysis.

FPG was measured by glucose oxidase method and HbA1c was measured by HPLC based analyzer, Leptin was measured by ELISA method, Insulin, c-peptide, TT3, TT4, FT3, FT4 and TSH was measured by Chemiluminescence technique in Immulite Auto-analyzer.

History and clinical examination

Detailed socio-demographic and clinical data were recorded in a pre-designed case record form. These include age, sex, residing area, occupation, socioeconomic status, dietary habit, exercise, alcohol and smoking habit, duration of diabetes, associated diseases like hypertension, obesity, dyslipidemia, coronary artery disease, cerebrovascular diseases, peripheral vascular diseases and crystal deposition diseases. Family history of these diseases were also been noted. Classical and non-classical features of diabetes mellitus and any adverse outcome of diabetes on life style were noted by taking history from the diabetic subjects.

Height, weight, BMI, waist circumference, hip circumference, waist hip ratio (WHR), waist height ratio (WHtR) of all the controls and diabetic subjects were recorded. Percent body fat and total fat mass was measured by "Body logic Body fat monitor; Omron Corporation, Japan." Biceps, Triceps, Subscapular and Suprailliac skin fold thickness (SFT) was measured by using appropriate tools. Systolic and diastolic blood pressure of all patients and control subjects was recorded. Blood pressure was measured by using mercury sphygmomanometer after at least 5 minutes of recumbence in a calm and quiet environment. Systolic blood pressure 130 mm Hg and the diastolic blood pressure 85 mm Hg was taken as the cut-off value for categorizing the normal and the abnormal values among diabetic population **[**38**].** Diabetic neuropathy was tested by appropriate clinical test. Autonomic function test were done by documenting the heart rate variability and blood pressure response on standing. Motor neuropathy was tested by eliciting jerks and reflexes by the percussion hammer. Retinopathy of all diabetic subjects was screened by routine dilated fundoscopy in the BIRDEM opthalmology outpatient department.

STATISTICAL ANALYSIS

All the data were expressed as mean± standard deviation, median (range) and/or number and percentage (%) as appropriate. Statistical analysis was done by using SPSS 7.5 packages for windows. Appropriate statistical test of significance like unpaired t test, one way analysis of variance (ANOVA) and Mann-Whitney test was used as necessary. $P < 0.05$ was taken as minimum level of significance.

Data presentation

Tabulation and / or drawing either in the form of graph or in the form of diagram were utilized as necessary for data presentation.

RESULTS

Table-1: Demographic status of the study group

Groups	Age mean ± SD	Annual Income Median (Range)	Family Member	SBP mean ± SD	DBP mean ± SD	Duration of DM, years
Controls (n =30)100	39.53± 5.24	120000 (30000-220000)	6 ±1	120 ±23	80±7	--
DM (n=100)	39.24± 5.79	100000 (20000-200000)	6± 2	124 ±17	80±10	0.02 (0.01- 6)
t/p value		u/p value	t/p value			
Cont vs DM	-.248/0.804	1114/0.32*	1.1770/.241	1.177/0.241	1.101/0.273	--

In table-1 shows demographic status of the study group where mean±SD age of the control and diabetic subjects were 39.5±5.2 and 39.2±5.8 respectively. Duration of diabetes is one month to six years. Systolic and diastolic blood pressure of the control and diabetic subjects were almost similar and it was within normal range. The table given below showed it in detail:

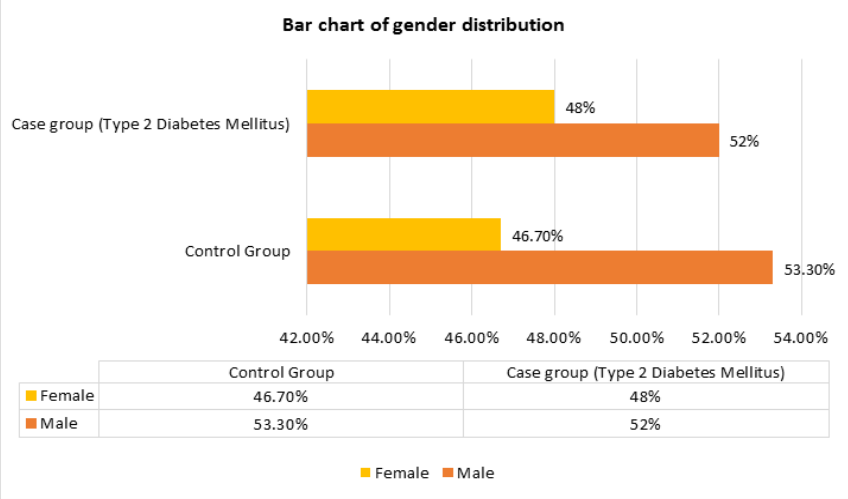

Fig-1: Gender distribution of the study group

In figure-1 shows gender distribution of the study group where both the groups have shown in the figures in details. Male persons are 53/3% and females are 46.7% in controls and in type Diabetic group male patients are 52% and females are 48%.

Table-2: Clinical status of the study group

Clinical history		Controls		Type-2 Diabetes mellitus	
		Number	Percentage	Number	Percentage
Sex	Male	16	53	52	52
	female	14	47	48	48
Type of work	Sedentary	27	90	84	84
	Physical work	3	10	16	16
Exercise	Regular	11	37	23	23
	Irregular	19	63	57	57
	No Exercise	0	0	20	20
Smoking	Smoker	2	7	20	20
	Non Smoker	27	90	70	70
	Past Smoker	1	3	10	10
FH diabetes	Present	16	53	65	65
	Absent	14	47	23	23
FH HTN	Present	15	50	48	48
	Absent	15	50	36	36
FH obesity	Present	14	44	46	46
	Absent	16	56	54	54
FH CAD	Present	8	27	24	24
	Absent	22	73	52	52
FH CVD	Present	7	24	27	27
	Absent	23	76	50	50
H/O CAD	Present	1	4	38	38
H/O CVD	Present	0	0	06	6
Retinopathy	Present	0	0	35	35
Neuropathy	Present	0	0	35	35
Nephropathy	Present	0	0	25	25
Anti DM drugs	Present	0	0	24	24
Typical Symptoms	Present	0	0	37	37
Atypical Symptoms	Present	0	0	63	63

In table-2 shows clinical status of the study group where 53 out of 100 controls and 65 out of 100 diabetics have family history of diabetes. Family history of hypertension was found in 50 out of 100 and 48 out of 100 controls and diabetic subjects respectively. Family history of obesity was found in 44% controls and 46% diabetic subjects. Around 27% of controls and 24% of diabetic subjects have family history of coronary artery diseases (CAD) and 24% of control and 27% of diabetic patients have family history of cerebrovascular diseases (CVD). Early retinopathy and neuropathy were observed in 45.5% and 36.5% diabetic subjects. Nephropathy was documented in 25 diabetic subjects.

Table-3: Anthropometric Characteristic of the Diabetic and control subjects

Parameters	Control group			Diabetic group			P value			*t/p value
	**MC	**FC	**TC	**MD	**FD	**TD	MC vs MD	FC vs FD	MD vs FD	TC vs TD
BMI	24.42± 3.16	26.11± 2.85	25.2± 3.09	24.41± 2.85	26.33± 3.77	25.3± 3.43	1.00	1.00	0.023	0.172/ 0.864
Waist Circumference	88.13± 6.35	87.29± 8.83	87.73± 9.19	90.06± 7.72	94.81± 10.49	92.34± 9.42	1.00	0.035	0.049	2.455/ 0.015
Hip Cercumference	90.94± 5.79	90.86± 7.27	93.7± 7.08	91.77± 7.20	95.40± 9.13	93.51± 8.35	1.00	1.00	0.135	-0.113/ 0.91
W/H Ratio	0.97± 0.04	0.90± 0.09	0.94± 0.08	0.98± 0.07	0.99± 0.06	0.99± 0.07	1.00	0.001	1.00	3.14/ 0.002
W/Ht Ratio	0.53±	0.56±	0.54±	0.55±	0.61±	0.58±	100	0.009	0.000	2.57/

	0.03	0.06	0.05	0.04	0.06	0.07				0.011
% Body fat	25.55± 5.05	33.77± 5.96	29.39± 6.82	24.65± 5.09	32.26± 6.51	28.38± 6.95	100	100	0.000	0.72/ 0.74
Total Fat Mass	16.79± 5.71	22.03± 6.19	19.24± 6.40	16.49± 5.0	21.45± 6.10	18.87± 6.06	1.000	1.00	0.000	-0.29/ 0.77
Biceps SFT	8.73± 3.45	13.14± 2.98	10.78± 3.90	8.54± 2.61	11.81± 3.12	10.12± 3.09	1.00	0.866	0.000	-0.93/ 0.35
Triceps SFT	12.13± 2.59	16.41± 4.95	14.18± 6.04	11.93± 3.03	17.85± 5.16	14.7± 5.12	1.00	1.00	0.000	-0.79/ 0.44
Suprailliac SFT	21.51± 6.35	27.07± 5.32	24.10± 6.4	21.96± 6.19	28.76± 6.77	25.23± 7.29	1.00	1.000	0.0000	0.76/ 0.45
Subscapular SFT	24.07± 7.05	26.69± 6.81	24.10± 6.44	22.57± 6.02	28.18± 5.82	25.62± 4.16	1.00	1.000	0.013	0.58/ 0.56

**(MC=Male control, FC= Female Control, TC= Total Control, MD=Male Diabetic, FD= Female Diabetic, TD=Total Diabetic)
Results are expressed as mean±SD, p value was calculated using Anova Bonferrony. *t/p value was calculated using unpaired 't' test

Table-3: shows that FC and FD have significantly higher BMI than the MC and MD (p=.05). FD also showed higher BMI than the MD at p=0.023 level. FD has significantly higher waist circumference than FC (p=0.035) and MD (p=0.049). TD have higher waist circumference than TC (t/p=2.455/0.015). FD have higher hip circumference than MD (p=0.135). MC have higher W/H ratio than FC, FD have higher W/H ratio than FC, TD also have higher W/H ratio than TC which are significant at p=0.05 levels. FC, FD and TD have significantly higher W/Ht ratio than MC, MD and TC respectively at p=0.05 levels. FC and FD have significantly higher % body fat and total fat mass than the MC and MD at p= 0.05 levels. Similar observation was also found in case of Biceps, Triceps, Suprailliac and Subscapular SFT.

Table-4: Thyroid hormone status in diabetic and control subjects

Parameters	Control			DM			P value			*t/p value
	MC**	FC**	TC**	MD**	FD**	TD**	MCvs MD	FC vs FD	MD vs FD	TC vs TD
TT_3	93.67± 17.14	83.46 ±12.78	88.91 ±15.88	85.02 ±22.7	83.46 ±22.0	84.27 ±22.3	0.912	1.00	1.00	-1.268 /0.209
TT_4	8.54± 1.9	8.07± 1.31	8.32 ±1.64	8.22 ±1.90	8.63 ±1.69	9.26 ±9.44	1.00	1.00	1.00	0.54/ 0.589
FT_3	2.69 ±0.36	2.56 ±0.55	2.60 ±0.54	2.40 ±0.68	2.37 ±0.74	2.53 ±1.72	0.816	1.00	1.00	0.215/ 0.83
FT_4	1.49 ±0.21	1.37 ±0.23	1.43± 0.22	1.43 ±0.18	1.31 ±0.27	1.36 ±0.25	1.00	1.00	0.065	-1.35/ 0.179
TSH	1.33 ± 0.88	1.35 ±1.16	1.34 ±1.00	1.26 ±0.89	1.84 ±1.42	1.54 ±1.21	1.00	0.961	0.08	0.824/ 0.411

**(MC=Male control, FC= Female Control, TC= Total Control, MD=Male Diabetic, FD= Female Diabetic, TD=Total Diabetic)

In table-4 shows thyroid hormone status in diabetic and control subjects. Mean±SD of TT3; (ngm/dl) in controls (88.91±15.88) and in diabetic subjects (84.27±22.29) was not statistically significant to each other (p=0.209). Mean±SD of TT4 (µgm/dl) in control subjects was 8.32±1.64 and in the diabetic subjects was 9.26±1.44, which is almost similar in both groups (p= 0.589). FT3 (pgm/ml) in control subjects was 2.60±0.54 and in diabetics was 2.534±1.72 (p= 0.830). FT4 (ngm dl) in control subjects was 1.43±0.22 and in diabetics subjects 1.36±0.25. (p 0.179). TSH (µlu/ml) in control subjects was 1.34±1.00 and in diabetic subjects 1.54±1.21. (p: 0.411). FT3; FT4 and TSH showed no significant difference between control and diabetic subjects.

Table-5: Mean serum level of TT3, FT3 and TSH in patients with low levels of hormones and also in patients with normal values of hormones

Groups	TT3	FT3	TSH
Groups with Low level of Thyroid hormone	58.46±12.32	1.31±0.44	0.50±0.49
Groups with Normal level of Thyroid hormone	93.81±16.91	2.53±0.59	1.50±0.86
T/p value	-11.45/0.0001	-6.83/0.0001	-6.018/0.0001

(Results are expressed as mean±SD, p value was calculated using ANOVA Bonferrony, t/p value was calculated using unpaired't' test)

Table-5 showed that the mean serum TT3 in patients with low T3 syndrome groups of patients and in patients with normal values of TT3 were 58.46±12.32 and 93.81±16.91 respectively which was statistically significant (p=0.0001) between the two groups. Mean Serum TSH level in low TSH group was 0.47±0.395 and in normal TSH group was 1.50±0.86 which was statistically different significantly (p=0.0001) from each other. Serum FT3 levels in low FT3 groups and normal FT3 groups of patients were 1.31±0.44 and 2.53±0.59 respectively which was statistically different between the two groups.

Table-6: FPG, HbA1c, baseline Serum Leptin, Insulin and C-peptide level among diabetic and control subjects

Parameters	Controls			DM			U/p value			
	**MC	**FC	**TC	**MD	**FD	**TD	MC vs MD	FC vs FD	TC vs TD	MD vs FD
**Leptin	1.29 (0.05-2.49)	4.03 (0.05-8.66)	1.65 (0.05-8.66)	0.71 (.11-2.420)	2.74 (.25-13.28)	1.21 (0.11-13.3)	278/ 0.046	241/ 0.110	1206/ 0.10	296.5 /0.000
**Insulin	7.25 (4.0-17.8)	8.15 (4.0-15.4)	8.05 (4.0-17.8	6.35 (1.90-31.11)	8.4 (2.3-48.9)	7.8 (1.9-48.9)	356.5/ 0.39	327.5/ 0.886	1397.5/ 0.56	1001.5/ 0.089
**C-peptide	0.60 (.05-1.97)	0.45 (0.28-1.03)	0.48 (0.05-1.97)	0.79 (0.62-2.7)	0.80 (0.11-5.11)	0.75 (0.06-5.11)	394/ 0.756	127/ 0.000	1102/ 0.028	996/ 0.082
FPG	5.54± 0.75	5.72± 0.74	5.63± 0.74	10.97± 5.17	10.71± 4.05	10.85± 4.67	0.000	0.001	10.78/ 0.000	1.00
HbA1c	6.07± 0.67	6.13± 0.64	6.10± 0.64	10.22± 2.63	9.13± 2.21	9.7± 2.49	0.000	0.000	13.07/ 0/000	0.08

**(MC=Male control, FC= Female Control, TC= Total Control, MD=Male Diabetic, FD= Female Diabetic, TD=Total Diabetic)

**Serum Leptin, insulin and C-peptide level were expressed as Median (Range).
FPG and HbA1c are expressed as mean±SD

In table-6 shows leptin, insulin, C-peptide, FPG and HbA1c level among diabetics and control subjects. Serum leptin levels in control subjects {1.65 (0.05-8.66)} was found lower their diabetic counterpart {1.21 (0.11-13.3)}, but it was not significant: (P=0.1000). But the leptin levels in male controls {1.29 (0.05-2.49)} was found significantly (P 0.000) lower than the female controls {4.03 (0.05-8.66)}. Similar observation was also noted in comparison between male diabetic {0.71 (0.11-2.42)}: and female diabetic subjects {2.74 (0.25-13.28)}; (p= 0.0001). FD have significantly higher serum Insulin and C-peptide levels than the MD (U/p=1001.5/0.089 and 996/0.082 respectively). FD have higher C-peptide levels than FC and MC, TD have higher C-peptide than the TC.

Table-7: Thyroid hormone pictures, glycemic status, serum insulin and leptin in diabetic subjects when categorized according to HbA1c

Groups	TT_3	TT_4	FT_3	FT_4	TSH	FPG	HbA1c	S Insulin	S C-Peptide	Serum Leptin
GroupA n=13	78.42± 24.50	8.77± 1.15	2.40 ±0.59	1.37± 0.25	1.37± 0.25	5.97± 1.8	6± 0.56	5.9 (3.5-12.5)	0.88 (0.11-5.1)	2.26 (0.44-6.8)
GroupB n=15	89.71± 24.33	8.00 ± 1.53	2.35± 0.61	1.22± 0.27	1.90± 1.40	7.7± 1.9	7.37± 0.32	8.0 (3.2-16.3)	0.71 (0.12-2.1)	3.08 (0.70-7.9
GroupC n=72	84.19 ±21.51	8.45 ±1.95	2.35± 0.73	1.39± 0.24	1.41± 1.11	12.39 ±4.5	10.84± 1.89	7.9 (19-48.9)	0.74 (0.06-3.6)	0.98 (0.11-13)
P value								U/p value		
A vs B	0.554	0.773	0.255	0.774	0.135	0.749	0.09	75/ 0.30	88.5/ 0.67	79/0.39
A vs C	1.000	1.000	1.000	1.000	1.000	0.000	0.000	343/ 0.13	392/ 0.35	291.5/ 0.03
B vs C	1.000	1.000	1.000	0.97	0.862	0.000	0.000	513/ 0.76	469/ 0.42	253.5/ 0.001

(Group A=HbA1c < 7%, Group B=HbA1c 7%-8%, Group C=HbA1c > 8%)
(P value was calculated using one way analysis of variance, U/p value was calculated using Non-parametric Mann Whitney U test.)

In table-7 shows thyroid hormone pictures in diabetic subjects according to HbA1c. Thyroid hormones (TT_3, TT_4, FT_3, FT_4) and TSH were analyzed according to HbA1c category and showed no significant difference. Significant differences in serum leptin level was observed in different HbA1c groups. It was observed that the higher the HbA1c there was a tendency to be higher serum leptin concentration.

Table-8: Thyroid hormone pictures, Glycemic status, serum leptin and insulin among Diabetic subjects when categorized according to BMI

Groups	Serum Leptin	Serum Insulin	Serum C peptide	FPG mg/dl	HbA1c %	TT_3	TT_4	FT_3	FT_4	TSH
BMI A N=55	0.80(0.11 -0.83	6.0(1.9-38.0)	0.74(0.06-3.62)	11.77± 5.18	10.35± 2.63	81.45 ±20.70	8.51± 1.77	2.31± 0.68	1.41± 0.26	1.28 ±0.89
BMI B N=35	1.80(0.25 -13.3)	8.6(2.3-48.9)	0.76(0.12-5.11)	9.66± 3.79	8.83± 2.01	89.54± 24.58	8.46± 1.78	3.02± 2.72	1.32± 0.26	1.78 ±1.51
BMI C N=10	4.5(1.26-7.3)	14.9(4.9 -21.5)	0.94(0.20-2.13)	9.96± 3.30	9.10± 2.01	81.33± 20.62	7.74± 2.15	2.00± 0.56	1.29± 0.18	2.09 ±1.30
u/p value				P Value						
A Vs B	524/ 0.000	710/ 0.036	811/ 0.21	0.108	.013	0.285	1.000	0.164	0.721	0.160
A vs C	49/ 0.000	140/ 0.014	219/ 0.30	0.761	.399	1.000	1.000	1.000	0.651	1.000
B vs C	93/ 0.024	120 /0.13	172/ 0.93	1.000	1000	0.913	1.000	0.288	1.000	1.000

(BMI A=BMI upto 25). (BMI B=BMI 25.1-30). (BMI C=BMI>30)
(P value was calculated by ANOVA Bonferrony, U/p value was calculated using Mann-Whitney U test):

Table-8 showed that when TT_3, TT_4, FT_3, FT_4 and TSH were grouped according to BMI category and compared separately among control and Diabetic subjects in three BMI groups; no significant difference was observed. Significant differences of serum leptin and insulin was observed in different BMI groups. It was observed the higher the BMI, there were significantly higher serum leptin and insulin among the diabetic subjects.

Table-9: Glycemic Status, Fasting Serum Leptin and Insulin, indices of obesity in patients with low T_3 syndrome and in patients with having normal T_3 among the Diabetic subjects categorized according to BMI groups

Groups		FPG	HbA1c	BMI	% body Fat	Total Fat Mass	Fasting Serum Insulin		Fasting S. Leptin	
BMI A	Low T_3	14.24±7.13	10.74± 3.15	23.16± 1.39	23.46±5.45	7.6 (1.92-18.3)	7.6 (1.92-18.3)		0.76 (0.23-5.57)	
	Normal T_3	1018± 3.61	10.18± 2.39	22.74± 1.89	25.48±5.84	5.55 (1.9-38.0)	5.55 (1.9-38.0)		0.82 (0.11-6.83)	
	t/p value	1.96/ 0.064	0.721/ 0.474	0.813/ 0.420	-1.210 /0.23	0.585/ 0.560	u/p value	*281/ 0.44	u/p value	0.813/0.420
BMI B	Low T_3	9.55± 4.40	9.08/± 2.41	27.19± 1.25	33.31±4.83	8.0 (2.3-47)	8.0 (2.3-47)		3.9 (0.25-10.29)	
	Normal T3	9.70± 3.68	8.76± 1.93	27.33± 1.45	3.72±5.82	8.8 (3.5-48.9)	8.8 (3.5-48.9)		1.66 (0.32-13.28)	
	t/p value	-.094/ 0.925	0.380/ 0.706	-0.233/ 0.817	1.146/ 0.26	0.644/ 0.524	u/p value	*99/ 0.72	u/p value	78/ 0.24
BMI C	Low T_3	10.45±0.64	9.55± 1.34	33.41± 3.61	36.85±6.29	13.4 (5.3-21.5)	13.4 (5.3-21.5)		4.27 (1.26-7.28)	
	Normal T_3	9.84± 3.73	8.99± 2.54	31.63± 1.60	37.30±4.10	14.9 (4.9-20.8)	14.9 (4.9-20.8)		4.5 (2.08-6.33)	
	t/p value	0.222/ 0.83	0.294/ 0.776	1.144/ 0.286	-.182/ 0.901	0.335/ 0.726	u/p value	*7.0/0.79	u/p value	8.0/ 1.00

(BMI A=BMI upto 25). (BMI B=BMI 25.1-30). (BMI C=BMI>30). t/p value was calculated by using "student t test".
*U/p value was calculated by using Non Parametric Mann Whitney test

Table-9 showed that when diabetic patients with low T_3 and Normal T_3 were reanalyzed according to BMI category then it was found that low T_3 subjects having normal BMI showed significantly higher serum fasting glucose (14.24±7.13) levels compared to the patients with normal T_3 (10.66±3.61).but here no differences was observed in serum leptin and insulin and other indices of obesity in patients with normal T3 groups of subjects and in patients with low T3 syndrome

Table-10: Glycemic status, Fasting serum Leptin and Insulin, % body fat and total fat mass in different status of thyroid hormones

Groups		FPG	HbA1c	Fasting S. Insulin	Fasting S. Leptin	BMI	%Body Fat	Total Fat Mass
TT_3	Low TT_3 (n=27)	12.57± 6.44	10.16± 2.89	7.7 (1.9-47.0)	1.05 (0.23-10.29)	25.11± 3.35	27.37± 3.74	18.12± 5.93
	Normal TT_3 (n=73)	10.21± 3.63	9.52± 2.32	8 (1.9-48.9)	1.22 (0.11-13.28)	25.41± 3.45	28.72± 6.83	19.14± 6.13
	t/p value	2.30/ 0.024	1.572/ 0.119	972/ 0.92*	950/0.78*	-0.384/ 0.702	-0.856/ 0.394	-0.753/ 0.453
FT_3	Low FT_3 (n=12)	11.45± 5.09	9.98± 2.43	7.4 (4.4-38.0)	1.18 (0.39-7.87)	26.59± 3.52	30.42± 7.24	21.42± 5.94
	Normal FT_3 (n=88)	10.77± 4,61	9.66± 2.51	7.8 (1.9-48.9)	1.21 (0.11-13.28)	25.16± 3.33	28.07± 6.91	18.52± 6.03
	t/p value	0.475/ 0.636	0.426/ 0.671	480.5/ 0.61*	480.5 /0.62*	1.357/ 0.178	1.096/ 0.276	1.562/ 0.122
TSH	Low TSH (n=12)	12.24± 4.16	10.86±2 .48	8.3 (1.9-48.9)	1.57 (0.39-2.68)	25.27± 1.82	30.19± 7.65	19.98± 5.0
	Normal TSH (n=88)	10.81± 4.78	9.65± 2.48	7.7 (1.96-47.0)	1.2 (0.11-13.28)	25.21± 3.65	27.63± 6.66	18.40± 6.20
	t/p value	0.986/ 0.327	1.573/ 0.137	461.5/ 0.48*	488.5/ 0.48*	0.449/ 0.218	1.524/ 0.782	0.982/ 0.624

t/p value was calculated by using "student t test".
*U/p value was calculated by using Non Parametric Mann Whitney test

Table-10 showed the analysis of TT_3, FT_3 and TSH and its relationship to FPG, HbA1c, Fasting serum insulin, BMI and also with %body fat and total fat mass. 27 diabetic subjects have shown T_3 levels below the lower limit of normal range at FPG levels12.57±6.44 and HbA1c 10.16±2.89. FPG value was significantly (p=0.024) higher in low T_3 group compared to normal TT3 group. 12 diabetic subjects were found to have FT_3 below the lower limit of normal range at FPG level 11.45±5.09 and HbA1c level 9.98±2.43.Again 12 diabetic subject were found to have TSH below the lower limit of normal range at FPG level 12.24±4.16 and HbA1c level 10.86±2. Fasting serum leptin and insulin levels showed no significant differences among the different groups of TT_3, FT_3 and TSH. Similar observation was also noted in case of %body fat, total fat mass and in BMI.

Figure 2: Relationship of FPG and serum TT3 when FPG is below 12 momol/l

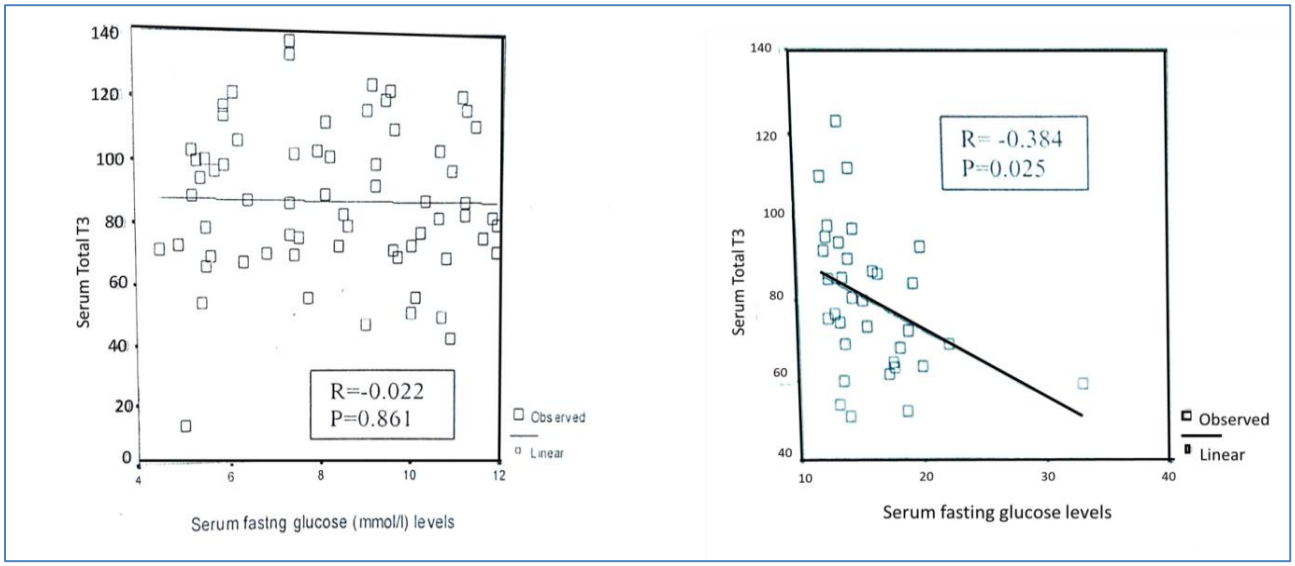

Figure 2: Relationship of FPG with Serum TT3 of the Diabetic Subjects when FPG <12mmol/l (Showed almost no correlation to each other)

Figure 3: Relationship of FPG with Serum TT3 when FPG is above 12 mmol/l

Figure 3: Relationship of FPG with Serum TT3 of the Diabetic subjects when FPG>12mmol/l (Showed strong negative correlation to each other)

Figure 4: Relationship of Serum TT3 with Serum Leptin of the Diabetic Subjects with Low T3

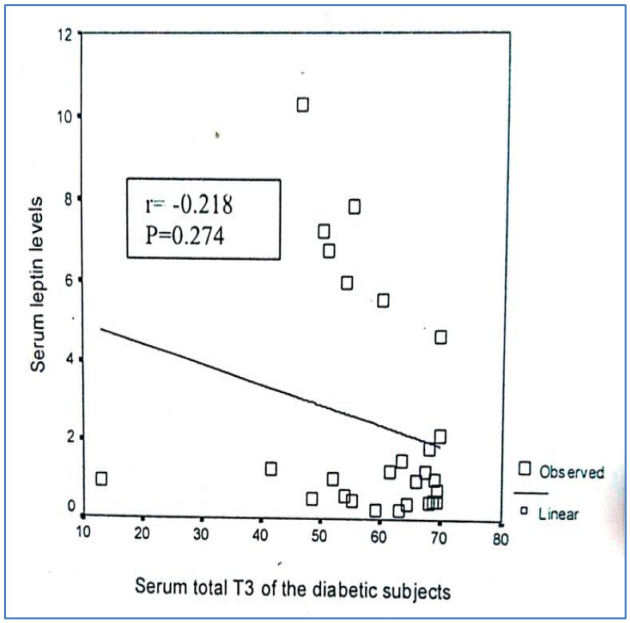

Figure 4: Shows that Serum Leptin has a tendency to have positive association with with TT3. But this is not statistically significant. Showed that Leptin has almost no correlation with low T3

Figure 5: Relationship of BMI with Serum Leptin of the Diabetic Subjects

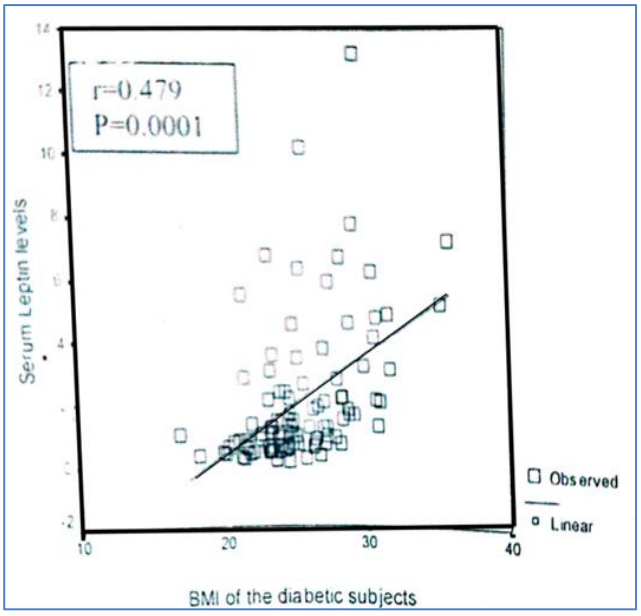

Figure 5: Showed that Serum Leptin has showed strong positive correlation with BMI among the Diabetic subjects

Figure 6: Relationship of BMI (upto 25) with Serum leptin of the Diabetic subjects

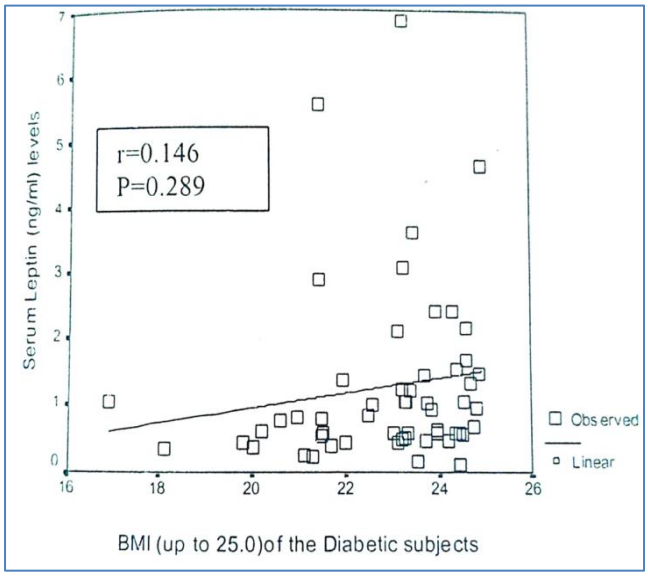

Figure 6: Shows that diabetic patients with BMI <25 have a very little or no correlation with Serum Leptin.

Figure 7: Relationship of BMI (upto 25.1-30) with Serum Leptin of the Diabetic Subjects

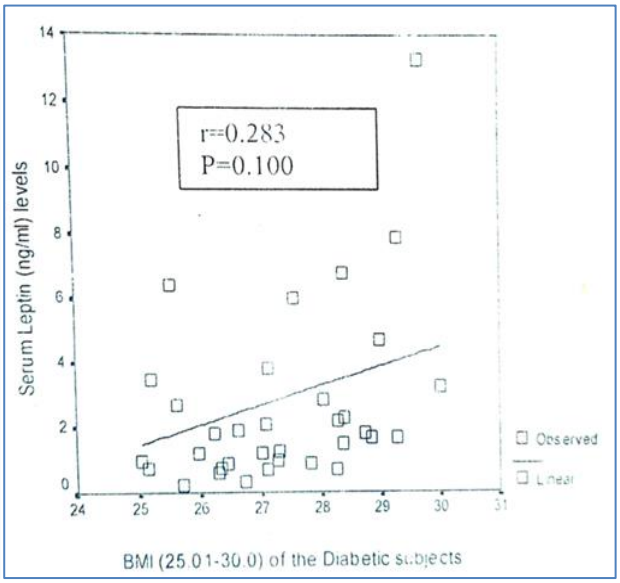

Figure 7: Shows that Serum Leptin has a tendency to be higher with increasing BMI among the Diabetic Subjects.

Figure 8: Relationship of BMI (upto >30) with Serum leptin of the Diabetic subjects

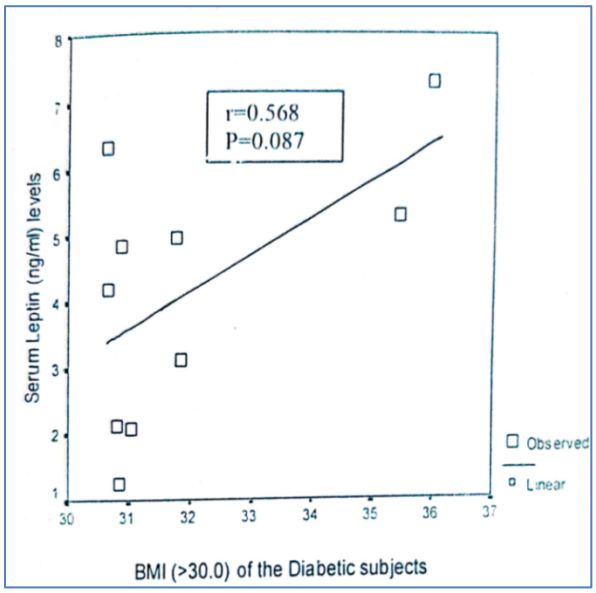

Figure 8: Shows strong positive correlation with Serum Leptin among the Diabetic Subjects having BMI >30

Figure 9: Relationship of BMI with Serum Leptin of the control subjects

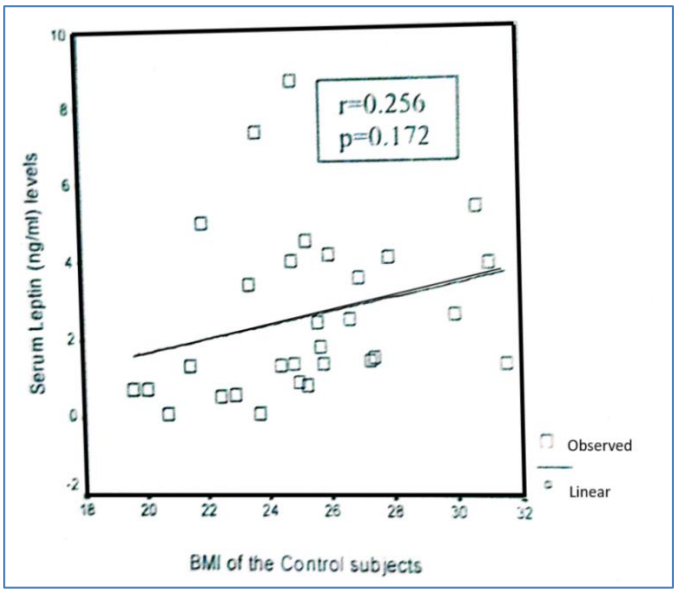

Figure 9: Shows that Serum Leptin has a tendency to be have positive association with BMI. But it is not significant at p=.05 level.

Figure 10: Relationship of BMI and Serum Insulin of the Diabetic Subjects

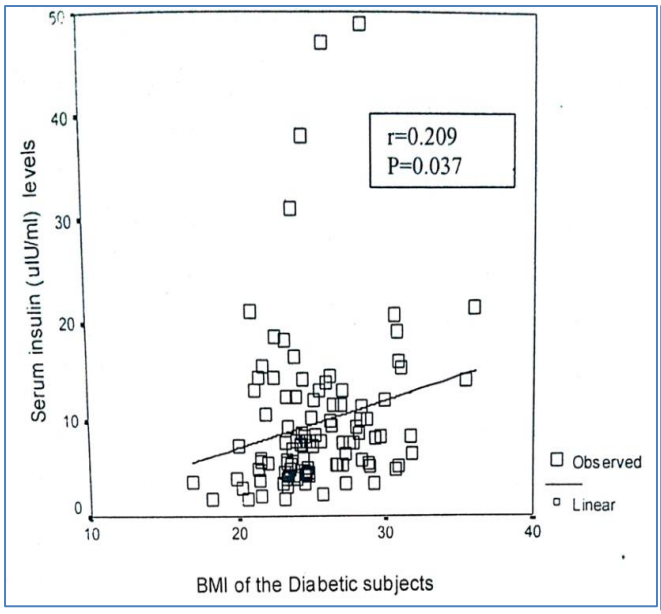

Figure 10: Shows that Serum Insulin has strong positive correlation withBMI among the Diabetic Subjects

Figure 11: Relationship of % Body Fat and Serum Insulin of the Diabetic Subjects.

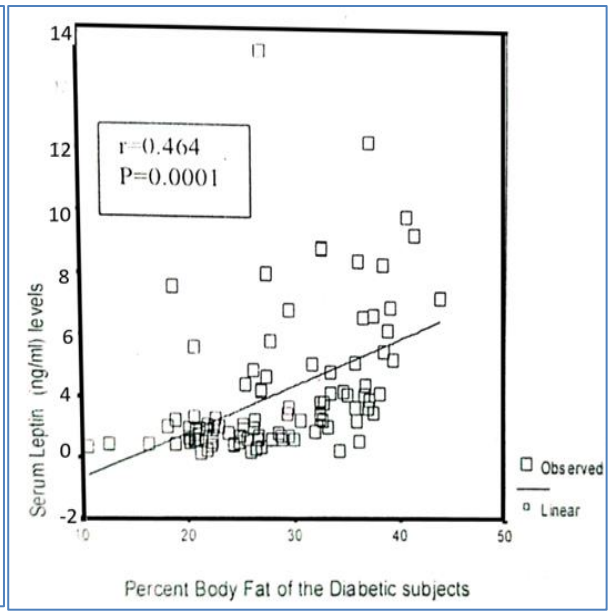

Figure 11: Shows that Serum Leptin has strong positive association with %body fat among Diabetic Subjects

Figure 12: Relationship of Serum Leptin and Total Fat Mass of the Diabetic Subjects

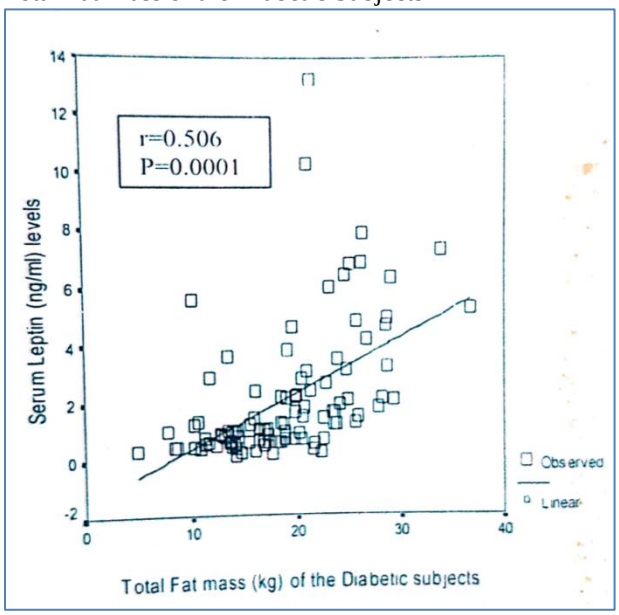

Figure 12: Shows that Serum Leptin has strong positive association with Total Fat Mass among the Diabetic Subjects

Figure 13: Relationship Serum Leptin and % Body Fat among the Control Subjects

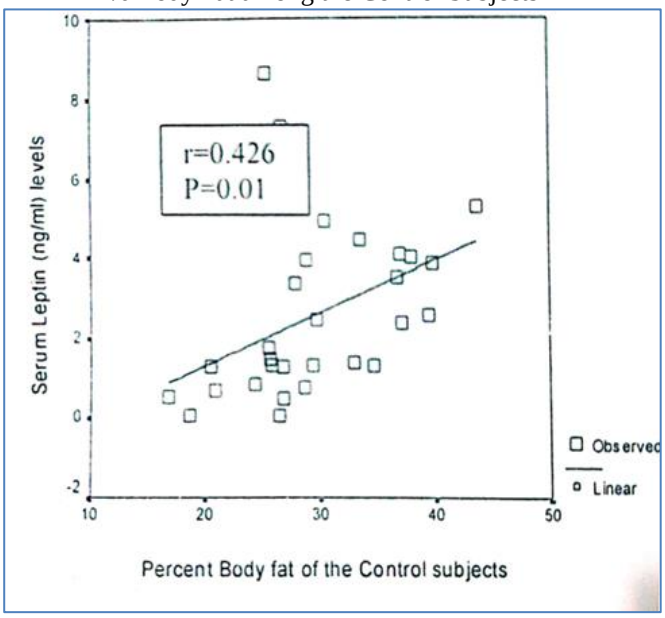

Figure 13: Shows that Serum Leptin is positively associated with % Body Fat among the Control Subjects

Figure 14: Relationship serum Leptin and C-peptide of the Diabetic Subjects

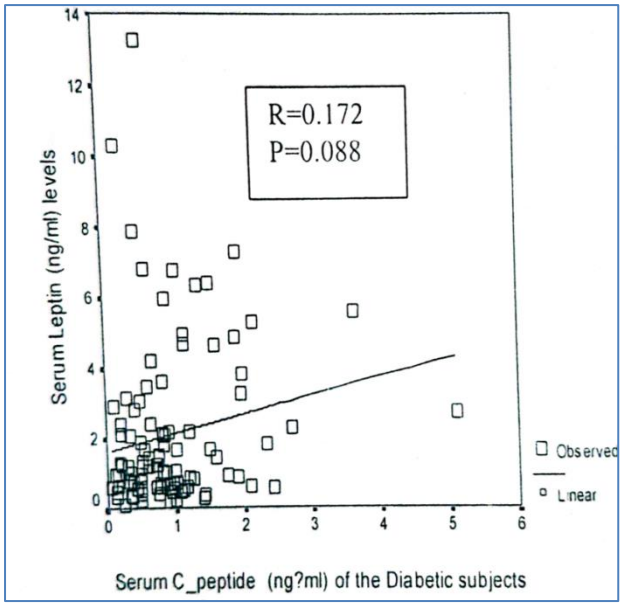

Figure 14: Shows that Serum Leptin and C-Peptide is positively associated with each other among the Diabetic Subjects

Figure 15: Relationship of serum Leptin and HbA1c of the Diabetic subjects

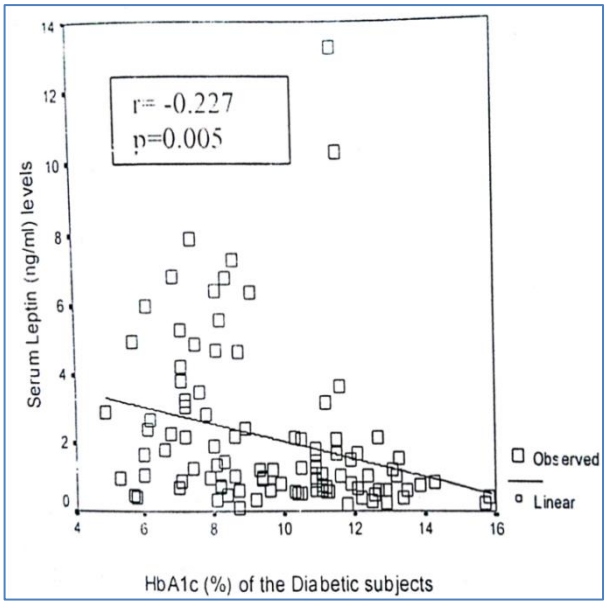

Figure 15: Shows that Serum Leptin is negatively correlated with HbA1c among the Diabetic Subjects

Figure 16: Relationship of Serum Leptin and Serum Insulin of the Diabetic subjects

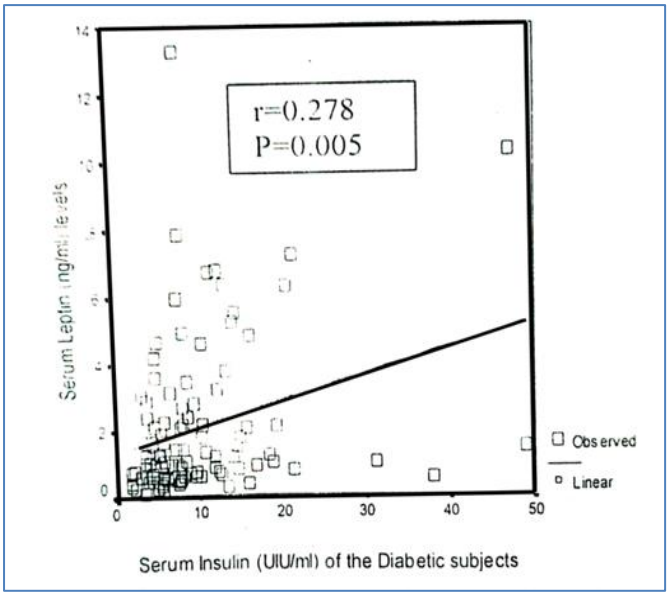

Figure 16: Shows that Insulin and Leptin is positively associated with each other among the Diabetic Subjects

Figure 17: Relationship of Total Fat Mass with Serum Leptin of the Control Subjects

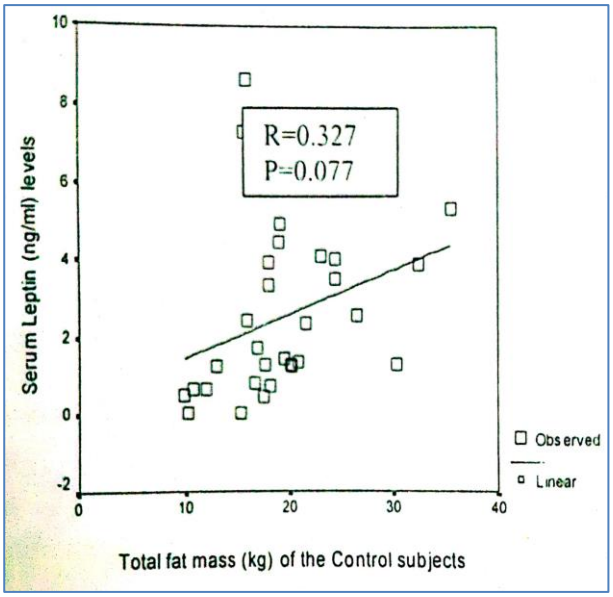

Figure 17: Shows that Serum Leptin and Total Fat Mass is positively associated with each other among the control subjects

DISCUSSION

Some studies done earlier in abroad; the mean age (mean±SD) in years of type 2 diabetic patients who were participated in study was (47.5±7.4) coincides with the fact that type 2 diabetes mellitus usually develops after the age 40 years [9,26,27]. Whereas in our study the mean age (mean±SD) of the control and diabetic subjects were 39.5±5.2 and 39.2±5.8 respectively.

Serum leptin was measured in this study for the first time among the Bangladeshi population. So that the present study attempted to document the baseline serum leptin concentration among healthy population, variation of serum leptin in different glycemic status and BMI groups among type2 diabetic subjects. This study was also aimed to find out the sexual variation of serum leptin irrespective of glycemic status and its relation to thyroid hormones among uncontrolled type2 diabetic subjects.

The baseline serum leptin concentration among our healthy adult population (table-6,7,8) doesn't seem to differ from values documented for many diverse group of populations [55] where they have found that median (range) of serum leptin levels in healthy male subjects having BMI 21-25 was 1.1 (0.5-3.3) and in female subjects in the same BMI groups was 3.2 (1.1-8.5). Serum leptin levels in male subjects having BMI 26-30 was 1.8 (0.8-4.9) and in their female counterpart was 5.6 (1.8-11.1) and BMI with 31-35 have serum leptin levels 3.2 (1.2-8.2) and 8.8 (2.2-18.6) in male and female respectively.

Serum leptin levels was found to be positively correlated with BMI in both controls and diabetic subjects and in diabetic subjects it have shown strong positive correlation at p=0.0001 levels *(fig:-5,9).* Female subjects have shown significantly higher values (3-4 times) than their male counterparts irrespective of BMI and glycemic status (table-6). Similar degrees of hyperleptinemia was also found in in male and female subjects when they were categorized according to BMI (table-8). This findings is similar to the findings of the other studies done in abroad 21.Whwn serum leptin levels was reevaluated on the basis of BMI; leptin levels were found to be increased significantly with increasing BMI (p=value BMI A vs B=0.0001, A vs C=0.0001, B vs C=0.024) *(fig:-6,7,8).* Similar type of response was also found in control subjects though it was not statistically significant at p=0.05 levels *(fig:-9).* Percent body fat, total fat mass and other indices of obesity were also found to have strong positive correlation to serum leptin similarly to BMI at p=0.05 levels in both Diabetic and control subjects *(fig:-11,12,13,17)* which was found to be more obvious in diabetic subjects. This finding is consistent with the findings of the other study [50].

When glycemic status was taken into consideration; serum leptin was found to have higher values among diabetic subjects than the matched control subjects. But it was found significant at p=0.05 levels only in comparison to MC vs MD and in MD vs FD it was found significant at p=0.0001 levels *(table-6).*

Serum leptin concentration was again evaluated in relation to glycemic status categorized according to HbA1c. Leptin levels was found to be positively correlated with glycemic status up to a certain limit, that is the more the FPG and HbA1c , there was more circulating leptin among the diabetic subjects. But when HbA1c goes beyond 10% serum leptin was found tended to be declined in comparison to other HbA1c groups *(fig:-15 and table-7).* It suggests that most of the newly diagnosed type2 diabetic subjects were hyperleptinemic at least in the early stages of the diseases. As because due to the natural courses of the type2 diabetes mellitus these group of patients might be initially presented with biochemical features of insulin resistance particularly in those individuals with high BMI which is supported by others studies [47, 48]. No significant differences of insulin was found in control and diabetic subjects; but when categorized according to BMI significant increment of serum insulin was observed with increasing BMI among the diabetic subjects *(fig:-10)* which indicate that high BMI group of patients are associated with hyperinsulinemia and insulin resistance.

Serum leptin was assessed in relation to insulin and C-peptide. It was found that serum insulin and leptin were positively associated with each other's in both control and diabetic subjects *(fig:-16).* When the study subjects were divided into three BMI and HbA1c groups this relationship was maintained all through. This finding is consistent with the hyperleptinemic/ hyperinsulinemic or insulin resistant/ leptin resistant hypothesis in obese type2 diabetic subjects [51, 52]. This type of relation was also marked in case of leptin and C-peptide *(fig:-14).*

Thyroid hormones among control and Diabetic subjects was evaluated and it was found that the differences observed in serum thyroid hormones and TSH levels between controls and diabetic subjects were not statistically significant. When the thyroid hormones and TSH were reevaluated on the basis of BMI and HbAlc groups among the diabetic subjects, similar observation was noted *(table 6 and 7).* But when serum TT_3, TT_4, FT_3, FT_4, and TSH values of all the diabetic subjects were divided into two groups by applying the cut off values to each hormone into normal values of thyroid hormones group and TSH with low values of thyroid hormones groups and TSH among the diabetic subjects, 27 diabetic patients were found to have low TT_3 below the lower limit of normal range than that of their normal counterpart which was significant at p=0.0001 level *(table-5 and 9),* 12 patients were found to have serum FT_3 levels which was significantly (p=0.0001) lower than their normal counterpart groups. Again 12 diabetic subjects were found to have low TSH level than their normal groups. 4 diabetic subjects were found to have significantly lower serumTT_4 when compare to normal TT_4 groups. When the TT_3. FT_3, TT_4, and TSH groups were reanalyzed in relation to fasting serum glucose and HbA1c, low thyroid hormones and low TSH group have significantly (p=0.0001) higher fasting serum glucose and HbA1c than the groups with hormones within the normal range (table-9,10). The diabetic patients with Low TT_3 showed strong negative correlation to FPG and HbA1c and no correlation in patients with normal TT_3 (*Fig:2 and 3).* This finding is consistent with the findings of the other studies done in abroad in both type 1 and type 2 diabetic subjects [24-29, 41-44]**.** Our findings showed that around the level of 12mmoll of fasting serum glucose was associated with marked alteration of thyroid hormone picture in the blood in absence of clinical thyroid diseases. When low TT_3 group was categorized according to BMI, diabetic subjects having BMI within normal range was found to have more deteriorating fasting serum glucose, HbA1c and serum TT_3 levels; compare to other BMI groups (Table-9). This finding suggests that changes in thyroid hormone possibly much more obvious in young diabetic groups who are mostly have low or normal BMI than the type2 diabetic subjects that are mostly associated with obesity and higher degrees of BMI. These findings also supports the findings of the others study done in abroad [34] and also in the cell and molecular biology department of BIRDEM, Dhaka, Bangladesh [35]**.** Our findings also conclude that BMI and other indices of obesity possibly have very little or no impact on serum thyroid hormones and TSH levels until and unless they are associated with very high serum fasting glucose levels beyond 12mmol/l *(fig:2, 3).*

Serum leptin levels were assessed separately among the diabetic subjects associated with significantly low serum TT3 levels. Serum leptin levels was found to be negatively correlated with lowTT3 state among the diabetic subjects, though it was not significant at p=0.05 levels *(fig:-4).* As mentioned earlier a previous study documented the declining of serum leptin concentration among the clinically hypothyroid patients [53]. Our findings differ the findings of the SR Bornstein et al which documented the increment of serum leptin concentration in low TT3 Syndrome in the setting of acute severe infection [17]. Raised serum leptin concentration in this study was possibly due to the effect of stress induced release of corticosteroid. As because it was found that hypercortisolimic state is associated with marked hyperleptinemic response [54]. But our findings in ESS are consistent with the findings of Corsonello A *et al.* [18] which documented the declining of serum leptin concentration in elderly Sick Euthyroid Syndrome patients.

CONCLUSION

1. Serum leptin concentration is almost similar to that of other population as reported earlier in European subjects. Also there was a substantial sexual diamorphism in serum leptin levels with about 3 to

4 times higher values in female irrespective of obesity and diabetes.
2. Serum leptin was found to have strong positive correlation with BMI and other indices of obesity irrespective of glycemic status. It was also found that serum leptin and insulin is positively associated with each other.
3. Uncontrolled type 2 diabetes mellitus is associated with alteration of thyroid hormone pictures particularly altering the TT_3, FT_3 and TSH in absence of clinically evident thyroid diseases.
4. This biochemical feature of "Sick Euthyroid Syndrome" is more evident if the BMI of the subjects is low or normal range and it was also found that the more worsening the glycemic status as determined by FPG and HbA1c, there was more deteriorating circulating serum thyroid hormone pictures and TSH.
5. Uncontrolled type2 diabetes mellitus was found to have associated with ESS or NTIS and serum leptin was found to have negative or no correlation with ESS or NTIS.

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Conflict of Interest

There was no conflict of interest with any person, organization, groups, companies, diagnostic laboratories or any other financial institutions in conducting the research works.

Ethical Declaration

This research work was duly approved by the Institutional Ethical Committee of the BIRDEM Academy, Dhaka, Bangladesh.

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