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Comparison of leptin levels in thin and obese type 2 diabetes mellitus patients with non diabetics in relation to basal metabolic rate

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***Abstract*---**Background: Leptin is considered to have a role in regulation of body weight and energy metabolism. Increased level of serum Leptin is considered as a component of metabolic syndrome. Also resistance to Leptin in β-cells results in hyperinsulinemia due to the absence of inhibitory effect of Leptin on insulin secretion. This may lead to the exhaustion of β-cells in the pancreas leading to the progression of Type 2 DM. Our study was put forward to identify the Leptin levels among diabetic and non-diabetic individuals and its correlation with body mass index. Materials & Methods: In each group 40 subjects were recruited. Their samples were collected and Leptin was assayed using ELISA kit. Other parameters like Fasting and Post Prandial Glucose, HbA1c, Cholesterol, Triglycerides, High Density Lipoprotein and Low Density Lipoprotein were also analyzed as a supportive measure. Result & Conclusion: There was no significant difference in Leptin levels in both obese diabetic and obese control

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groups. Leptin level was confined to the lower side in thin groups. There is a significant positive correlation between Leptin and body mass index. Female subjects have got increased Leptin value than male subjects. This confers that Leptin is a marker of obesity rather than Diabetes Mellitus.

***Keywords*---**diabetes mellitus, patients, leptin, body mass index.

Introduction

Diabetes mellitus (DM) is characterized by chronic hyperglycemia associated with alterations in the metabolism of carbohydrate, fat and protein. The major prevalent type of diabetes is type [2]. It affects more than 90% of the population suffering from diabetes globally[1]. There is a rapid increase in the number of diabetic patients and this fiery growth is noted in both rural and urban areas. Type 2 diabetes is characterized by insulin resistance, as a result of which the cells do not use insulin appropriately[2].

Insulin resistance was found to result from a blend of genetic as well as environmental factors. It is defined as the deprivation of insulin to exert its biological functions at effective circulating levels in normal subjects[3]. It is found in non-diabetic individuals who are obese and in patients with Type-2 DM. It is a distinctive sign of defective action of insulin. The impairment of beta cell function is allied with the insulin resistance mediated increased beta-cell demand which is required for developing increased glucose values in fasting status. The foremost flaw is loss of secretion of insulin that is induced by glucose labeled as selective glucose insensitivity[4]. Excess increase in blood glucose levels renders the beta cells insensitive to glucose. Genetic factors also pave way to the progression of diabetes. Genes that affect beta cell apoptosis, beta cell regeneration, sensing glucose levels, ion channels, energy transduction, microtubules or microfilaments, metabolism of glucose and other islet proteins mandatory for the synthesis, binding, progress and discharge of secretory granules[5]. Environmental factors ranging from dietary habits to level of physical activity are chief determinants in the development of Type-2 DM[6].

Obesity is associated with insulin insensitivity and is the most significant predictive risk factor for development of Type-2 DM. The deposition of fat in varying anatomic locations also has its own effect on morbidity. Among the distribution, intra-abdominal and abdominal subcutaneous fat is given a distinct importance. If an abnormal waist to hip ratio exists, then a person is more prone to develop many complications[7]. The most important complications are as insulin resistance, diabetes, hypertension, hyperlipidemia, and hyperandrogenism in women[8]. Intra-abdominal and/or upper body fat is more strongly correlated to these complications than to overall adiposity. The function of adipocytes as endocrine cell is to release various molecules. This includes Leptin which helps in maintaining equilibrium of energy, cytokines such as tumor necrosis factor (TNF)

and interleukin (IL)-6, complement factors such as factor D also known as adipsin, plasminogen activator inhibitor I which is a prothrombotic activator, and a constituent ofthe blood pressure regulating system, angiotensinogen[9].

Leptin is a 16 kilo Dalton protein hormone made up of 167 amino acids. It is derivedfrom the Greek word 'leptos' which means lean. It is encoded by ob gene located on chromosome 7 in humans. It plays a vital part in regulation of food ingestion, balancing energy and functions as a metabolic and neuroendocrine hormone. The foremost function of leptin is in regulating body weight[10]. Leptin receptors were located in the choroid plexus and hypothalamus, a region regulating food intake, appetite and body weight. Leptin by binding to its receptor acts mainly to inhibit hunger by various mechanisms[11, 12] which make a person to consume less food and to metabolize more amounts of fuels. Leptin also exerts its effects on organs other than hypothalamus. These effects on peripheral targets are due to the distribution of Leptin receptors on various cell types[13].

Materials & Methods

Study population

Ethical clearance was obtained from the Institutional Human Ethics Committee. An informed consent was taken from the patients before sample collection. The study design is a case control study in which obese type 2 diabetic (n =40) and thin type 2 diabetics (n =40) are selected as cases. The diagnosis of Type 2 diabetes is based on case record description which is based on insulin level and other factors at the time of diagnosis. Cases were selected from diabetic patients attending Endocrinology and Medicine OPD. Patients satisfying the diagnosis, inclusion criteria and BMI (measured by the investigator), and not coming under exclusion criteria, were given explanation about this study. If they were willing to participate, the consent forms were filled and the samples were collected. The samples were processed and stored for analysis. Control individuals were mainly selected from the master health check up. Person fulfilling the control group criteria was requested to participate in the study. If they were willing, the consent forms were filled and then the blood samples were collected. Their samples werealso processed and stored for analysis. Patient data were retrieved from their case sheet.

Collection of blood samples

As cases are diabetics and controls are patient attending master health check up, fasting sample – fluoride vacutainer for fasting plasma glucose, EDTA vacutainer for HbA1C and clot activator vacutainer for lipid profile were collected routinely. The 2nd hour post prandial plasma glucose sample was also collected routinely. The left over serum in the clot activator vacutainer tube used for lipid profile was transferred to secondary labeled plain tube. This sample wasstored at -20 degree Celsius for Leptin assay[3, 13].

Statistical analysis

The data obtained after the estimation of Leptin, Body Mass Index, Fasting Glucose, Post Prandial Glucose, Cholesterol, Triglycerides, HDL, LDL and HbA1c were statistically analyzed using IBM SPSS software version 19.The data distribution was displayed by histogram, dot plot and scatter plot. The data summary was represented by bar diagram. The dependence of categorical variable was tested with Chi Square test. For comparing two groups t test was used. For comparing multiple group means one way ANOVA (Analysis Of Variance) was done. For post hoc testing, Tukey and Games Howel were used according to the group n and equivalence of variance. Significance was assessed at 5% level. The correlation between quantitative parameters were done using Pearson and further checked with scatter plot. For correction of right side skewed data, natural logarithm transformation was used.

Results

Figure 1: Leptin levels among study groups

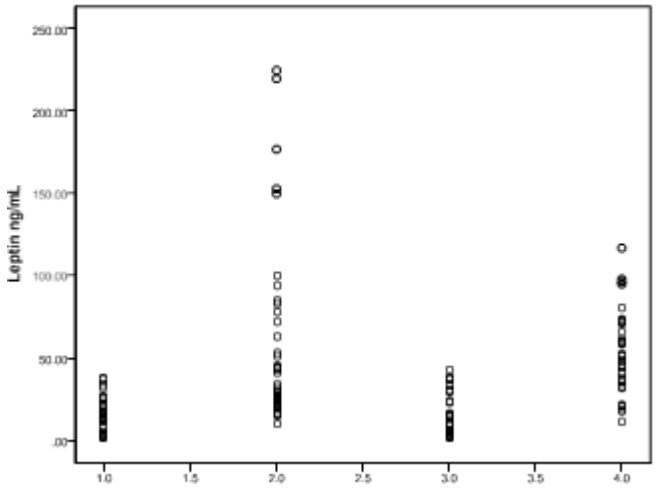


Table 1: Leptin levels among study groups

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	68598.467	3	22866.156	23.591	.000
Within Groups	151205.469	156	969.266		
Total	219803.936	159			

Table 2: Comparison (multiple) of leptin levels among study groups (Post hoc test by Tukey)

	Mean Difference(I-J)	Std. Error		95% Confidence Interval	
				Lower	Upper

(I) Study groups	(J) Study groups			Sig.	Bound	Bound
Thin Diabetic	Obese Diabetic	-43.97500*	6.96156	.000	-62.0537	-25.8963
Thin Nondiabetic	Obese Nondiabetic	.28750	6.96156	1.000	-17.7912	18.3662
		-38.15000*	6.96156	.000	-56.2287	-20.0713
Obese Diabetic	Thin Diabetic	43.97500*	6.96156	.000	25.8963	62.0537
	Thin Nondiabetic	44.26250*	6.96156	.000	26.1838	62.3412
	Obese Nondiabetic	5.82500	6.96156	.837	-12.2537	23.9037
Thin Nondiabetic	Thin Diabetic	-.28750	6.96156	1.000	-18.3662	17.7912
Obese Diabetic		-44.26250*	6.96156	.000	-62.3412	-26.1838
Obese Nondiabetic		-38.43750*	6.96156	.000	-56.5162	-20.3588
Obese	Thin Diabetic	38.15000*	6.96156	.000	20.0713	56.2287
Nondiabetic	Obese Diabetic	-5.82500	6.96156	.837	-23.9037	12.2537
Thin Nondiabetic		38.43750*	6.96156	.000	20.3588	56.5162

*. The mean difference is significant at the 0.05 level.

Figure 2: Comparison (multiple) of leptin levels among study groups

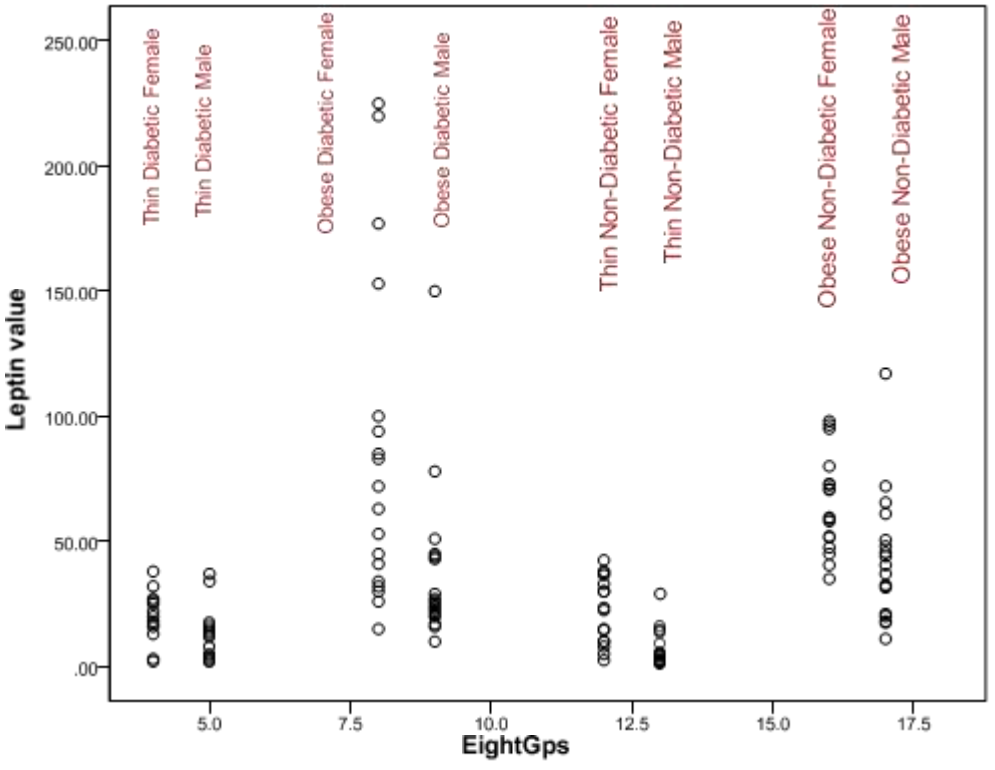


Table 3: Leptin levels among study groups

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	98556.354	7	14079.479	17.651	.000
Within Groups	121247.582	152	797.681		
Total	219803.936	159			

Table 4: Comparison (multiple) of leptin levels among study groups (Post hoc test by Games-Howell)

(I) EightGps	(J) EightGps	Mean Difference(I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Thin Female	Diabetic ThinDiabeticMale	9.19780	3.17764	.117	-1.3043	19.6999
	ObeseDiabeticFemale	-63.12406*	15.15967	.010	-114.4808	-11.7674
	ObeseDiabeticMale	-15.26190	7.14256	.419	-38.7673	8.2435
	ThinNonDiabeticFemale	-1.43985	4.13210	1.000	-14.8541	11.9744
	ThinNonDiabeticMale	13.23810*	3.06527	.006	2.9945	23.4817
	ObeseNonDiabeticFemale	-41.90476*	4.96636	.000	-58.0128	-25.7967
	ObeseNonDiabeticMale	-21.41353*	6.34706	.043	-42.3715	-.4556
Thin Diabetic Male	ThinDiabeticFemale	-9.19780	3.17764	.117	-19.6999	1.3043
ObeseDiabeticFemale	ObeseDiabeticMale	-72.32186*	15.03079	.003	-123.4321	-21.2116
ThinNonDiabeticFemale	ThinNonDiabeticMale	-24.45971*	6.86478	.030	-47.2990	-1.6204
ObeseNonDiabeticFemale		-10.63765	3.63090	.103	-22.4858	1.2105
ObeseNonDiabeticMale		4.04029	2.34628	.673	-3.4155	11.4961
		-51.10256*	4.55784	.000	-66.0508	-36.1544
		-30.61134*	6.03277	.001	-50.8098	-10.4128
Obese Female	Diabetic ThinDiabeticFemale	63.12406*	15.15967	.010	11.7674	114.4808
	ThinDiabeticMale ObeseDiabeticMale	72.32186*	15.03079	.003	21.2116	123.4321
	ThinNonDiabeticFemale	47.86216	16.33534	.109	-6.0588	101.7831
	ThinNonDiabeticMale	61.68421*	15.26112	.012	10.1314	113.2370
	ObeseNonDiabeticFemale	76.36216*	15.00744	.001	25.2948	127.4295
	ObeseNonDiabeticMale	21.21930	15.50781	.861	-30.8341	73.2727
		41.71053	16.00352	.203	-11.4412	94.8623
Obese Male	Diabetic ThinDiabeticFemale	15.26190	7.14256	.419	-8.2435	38.7673
	ThinDiabeticMale	24.45971*	6.86478	.030	1.6204	47.2990
	ObeseDiabeticFemale	-47.86216	16.33534	.109	-101.7831	6.0588
	ThinNonDiabeticFemale	13.82206	7.35542	.575	-10.1969	37.8410
	ThinNonDiabeticMale	28.50000*	6.81350	.008	5.7691	51.2309
	ObeseNonDiabeticFemale	-26.64286*	7.85447	.034	-51.9945	-1.2912
	ObeseNonDiabeticMale	-6.15163	8.79278	.997	-34.3483	22.0451

Thin Female	NonDiabetic	ThinDiabeticFemale	1.43985	4.13210	1.000	-11.9744	14.8541
		ThinDiabeticMale	10.63765	3.63090	.103	-1.2105	22.4858
		ObeseDiabeticFemale	-61.68421*	15.26112	.012	-113.2370	-10.1314
		ObeseDiabeticMale	-13.82206	7.35542	.575	-37.8410	10.1969
		ThinNonDiabeticMale	14.67794*	3.53298	.006	3.0659	26.2900
		ObeseNonDiabeticFemale	-40.46491*	5.26790	.000	-57.3973	-23.5325
		ObeseNonDiabeticMale	-19.97368	6.58568	.084	-41.5112	1.5638
Thin Male	NonDiabetic	ThinDiabeticFemale	-13.23810*	3.06527	.006	-23.4817	-2.9945
		ThinDiabeticMale	-4.04029	2.34628	.673	-11.4961	3.4155
		ObeseDiabeticFemale	-76.36216*	15.00744	.001	-127.4295	-25.2948
		ObeseDiabeticMale	-28.50000*	6.81350	.008	-51.2309	-5.7691
		ThinNonDiabeticFemale	-14.67794*	3.53298	.006	-26.2900	-3.0659
		ObeseNonDiabeticFemale	-55.14286*	4.48022	.000	-69.9116	-40.3741
		ObeseNonDiabeticMale	-34.65163*	5.97434	.000	-54.7305	-14.5728
Obese Female	NonDiabetic	ThinDiabeticFemale	41.90476*	4.96636	.000	25.7967	58.0128
		ThinDiabeticMale	51.10256*	4.55784	.000	36.1544	66.0508
		ObeseDiabeticFemale	-21.21930	15.50781	.861	-73.2727	30.8341
		ObeseDiabeticMale	26.64286*	7.85447	.034	1.2912	51.9945
		ThinNonDiabeticFemale	40.46491*	5.26790	.000	23.5325	57.3973
		ThinNonDiabeticMale	55.14286*	4.48022	.000	40.3741	69.9116
		ObeseNonDiabeticMale	20.49123	7.13874	.111	-2.5581	43.5406
Obese Male	NonDiabetic	ThinDiabeticFemale	21.41353*	6.34706	.043	.4556	42.3715
		ThinDiabeticMale	30.61134*	6.03277	.001	10.4128	50.8098
		ObeseDiabeticFemale	-41.71053	16.00352	.203	-94.8623	11.4412
		ObeseDiabeticMale	6.15163	8.79278	.997	-22.0451	34.3483
		ThinNonDiabeticFemale	19.97368	6.58568	.084	-1.5638	41.5112
		ThinNonDiabeticMale	34.65163*	5.97434	.000	14.5728	54.7305
		ObeseNonDiabeticFemale	-20.49123	7.13874	.111	-43.5406	2.5581

	Age	BMI	Glufas	Glupp	Chol	Tgl	Hdl	Ldl	A1c	Leptin	LeptinLn
Age	1.00	0.01	0.06	0.08	-0.03	-0.03	-0.02	-0.03	0.22	0.06	0.00
BMI	0.01	1.00	-0.08	-0.03	0.13	0.09	-0.08	0.15	0.02	0.60	0.70
Glufas	0.06	-0.08	1.00	0.84	0.14	0.39	-0.08	0.09	0.72	-0.08	-0.11

Glupp	0.08	-0.03	0.84	1.00	0.06	0.30	-0.06	0.02	0.72	-0.08	-0.04
Chol	-0.03	0.13	0.14	0.06	1.00	0.51	0.07	0.92	0.01	0.13	0.16
Tgl	-0.03	0.09	0.39	0.30	0.51	1.00	-0.26	0.44	0.26	0.05	0.03
Hdl	-0.02	-0.08	-0.08	-0.06	0.07	-0.26	1.00	-0.21	-0.10	0.00	0.06
Ldl	-0.03	0.15	0.09	0.02	0.92	0.44	-0.21	1.00	-0.03	0.12	0.12
A1c	0.22	0.02	0.72	0.72	0.01	0.26	-0.10	-0.03	1.00	0.00	-0.01
Leptin	0.06	0.60	-0.08	-0.08	0.13	0.05	0.00	0.12	0.00	1.00	0.79
LeptinLn	0.00	0.70	-0.11	-0.04	0.16	0.03	0.06	0.12	-0.01	0.79	1.00

Figure3: Comparison (multiple) of leptin levels among males and females

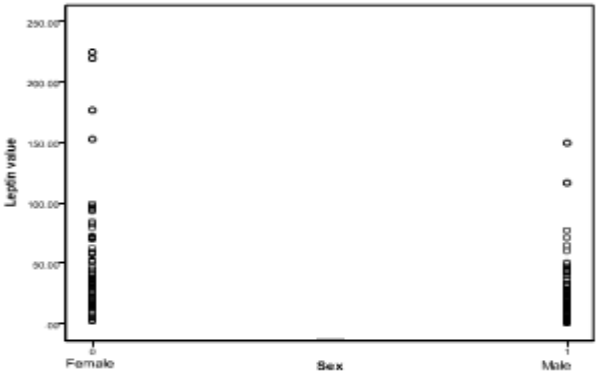
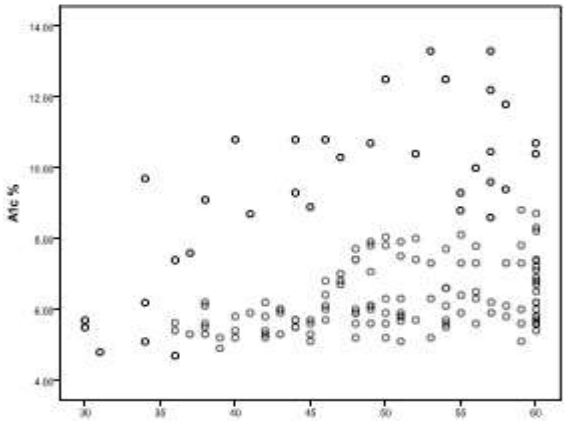
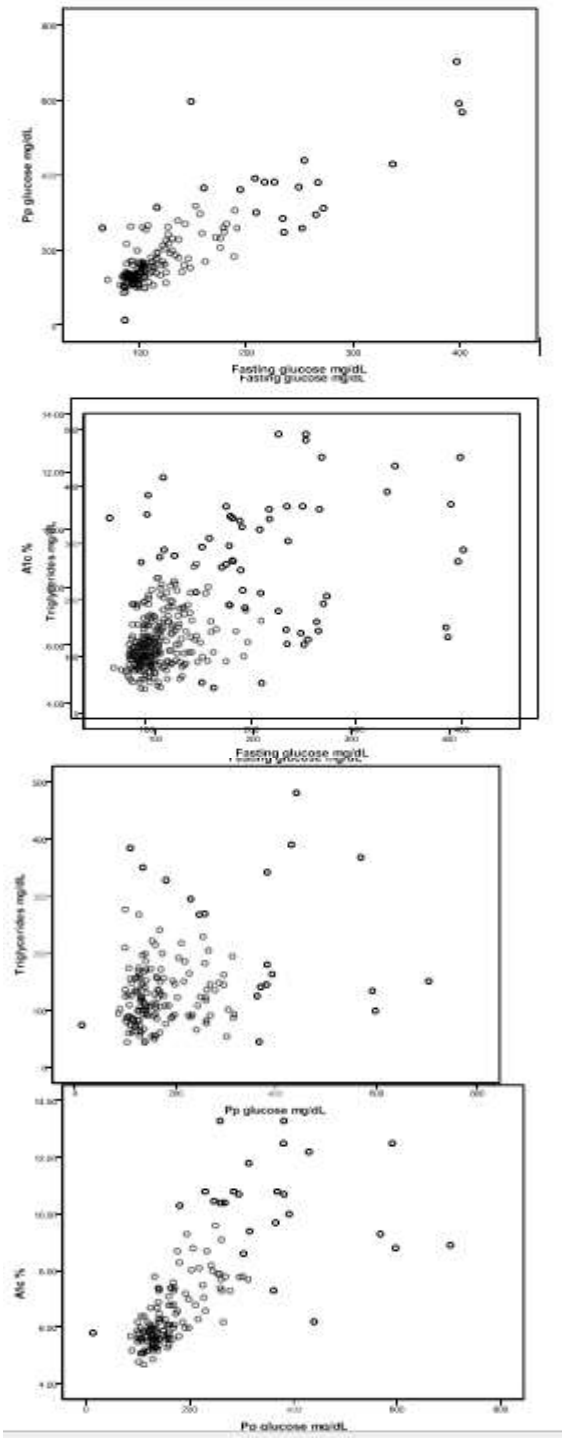
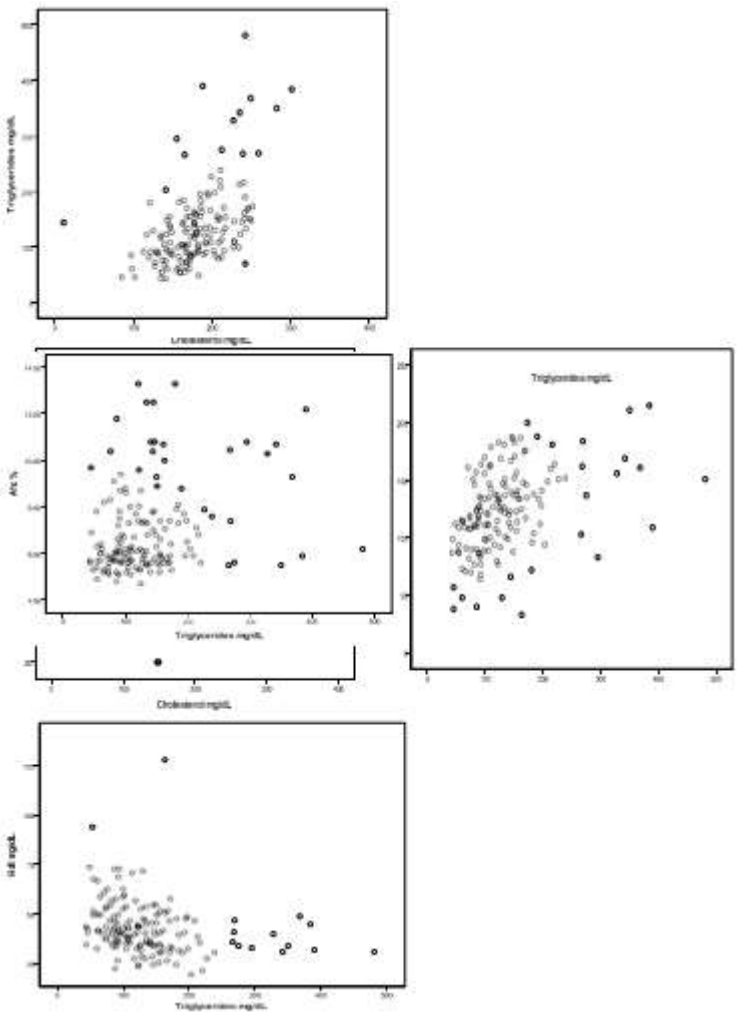


Figure 4: scatter plots of significant correlations




Pp glucose mg/dL
Fasting glucose mg/dL
A1c %
Triglycerides mg/dL
Fasting glucose mg/dL
Triglycerides mg/dL
Pp glucose mg/dL
A1c %
Pp glucose mg/dL



Discussion

Leptin distribution is confined to lower side both in thin diabetic and thin non diabetic groups while there is some dispersion to higher side in obese groups. The Leptin distribution in obese diabetic group shows a right skewing. So the natural logarithm and log10 transformations are applied to the distribution. After the transformation the distribution is showing slight right skewing in all groups except the obese diabetic group. Anyhow the natural logarithm of leptin is used for examining the correlation between quantitative variables. The Leptin distribution was also clearly divided between obese and thin, irrespective of diabetic status and this result was consistent with the studies conducted by Piyali Das et al in 2013[14]. We examined the influence of sex. The female group mean was significantly different from male group mean. This mandates sex wise sub grouping and comparison. The sub group wise Leptin level distribution was given in the table 4. The comparison of the sub group was done by ANOVA and

Games Howel post hoc test as the numbers of data in each group were not equal and the equivalence of the variance cannot be assumed.

The eight sub groups were compared with each other and 56 combinations were possible. Significant difference in Leptin level was observed between obese and thin in 26 combinations (coloured yellow). Obesity was associated with higher level of Leptin. In 19 combinations (green) there was no difference and here the uniting factor among the comparisons was obese versus obese or thin versus thin. Hence, in 45 out of 56 combinations the deciding factor was obese/thin. Among the remaining groups, 6 combinations (orange) have no significant difference between the groups. Here the obesity/thin and male/female effects were acting in opposite direction, resulting in no significant difference. There was a significant difference in 5 combinations (blue) and here the deciding factor was sex. Females have higher Leptin level. Our result was consistent with the finding of Couillard et al and many other studies which showed that Leptin level increases in females[15]. This was due to the fact that women have higher percentage of fat in the body. Females have increased ratio of subcutaneous to visceral fat. This was consistent with the finding that Leptin strongly correlates with the body fat mass. Few studies illustrate that there was an unconstrained production of Leptin by adipocytes in women than men[16]. Casabiel et al have demonstrated a higher ratio of subcutaneous to omental Leptin mRNA expression in females[17]. Estrogens stimulate Leptin secretion in women and androgens have an inhibitory effect[16].

The correlation between the quantitative parameters was assessed by correlation coefficient and scatter plots. BMI–Leptin correlation had an r value of 0.6 and the scatter plot also showed a linear positive correlation. Log transformed Leptin levels showed even better correlation with r value 0.7. Ahsan et al have showed similar findings in their study[18]. Positive correlation was also observed between following parameters: Fasting glucose and post prandial glucose, Fasting glucose and HbA1c, Post prandial glucose and HbA1c &Total cholesterol and LDL cholesterol. These correlations were well established relations. There were negative correlations in Triglyceride-HDL cholesterol and HDL cholesterol-LDL cholesterol pairs, which were not supported in their respective scatter plot. These negativecorrelations were also expected ones only.

The age distribution of the 4 study groups were between 30 and 60 years. But in the diabetic groups and thin non-diabetic group the distribution was more towards 60 years. In the obese non diabetic group the distribution was uniform throughout the age range. Though this difference was slightly reflected in ANOVA with a significance of 0.019, the post hoc Tukey test didn't show difference between these groups. The sex distribution was even and there was no significant difference in Chi Square test. The distribution of BMI was according to the inclusion criteria used to separate the groups. The fasting and corresponding post prandial plasma glucose levels were also measured in our study. As expected the non diabetic groups were having lower values while the diabetic groups were having higher values. Interestingly, the thin diabetic group was having higher plasma glucose level than the obese diabetic. The distribution of fasting plasma

glucose values, shown as dotplot of different groups, also illustrates the same. In ANOVA between groups, the thin diabetic group have a significant higher mean than the obese diabetic. But this was not observed in post prandial plasma glucose levels. Otherwise, the expected significant differences between diabetic and non diabetic groups were observed in dot plots and ANOVA.

HbA1c data was clearly divided between diabetic and non diabetic groups. There was no difference between obese and thin. This was in accordance with a study performed by Ghorban Mohammad zadeh et al[19]. Among the lipid profile parameters, total cholesterol and HDL cholesterol showed no significant differences between the four groups. LDL cholesterol of obese non diabetic was significantly higher than the thin diabetic. Triglyceride levels were significantly lower in thin non diabetic group than other groups.

Conclusion

- Leptin is not elevated in thin diabetic when compared with thin non-diabetic. The development of type 2 diabetes mellitus in thin individuals may not be related to Leptin level.
- Obesity and female sex are associated with increased Leptin level and not with type 2 diabetes mellitus.
- Hence BMI and Leptin have a linear positive correlation. This confers that Leptin is amarker of obesity rather than Diabetes Mellitus.

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