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Leptin have positive correlation with Fasting blood sugar, Glycated hemoglobin, Total cholesterol, Low density lipoprotein and Urea. A case control study done in Zoram medical college, Falkawn, Mizoram.

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Abstract
Background and aims*: Type 2 diabetes mellitus is one of the most common chronic diseases in almost all the countries, and continues to increase in numbers and significance, as changing lifestyles lead to reduced physical activity. Adipocyte is also an important endocrine gland, a metabolic factor that produce a wide variety of adipocytokines such as adiponectin, resistin, tumor necrosis factor, leptin, and interleukin. Leptin, the satiety hormone,made by adipose cells helps to regulate energy balance by inhibiting hunger. Leptin is opposed by the actions of the hormone ghrelin, the hunger hormone. Both hormones act on receptors in the arcuate nucleus of the hypothalamus to regulate appetite to achieve energy homeostasis. The objective of the study is to find out whether leptin level is associated with type 2 diabetes mellitus.* ***Methods****: A case-control study with subgroup analysis, 60 cases and 50 controls. Cases comprises of patients fulfilling criteria of diagnosis of type 2 diabetes based on WHO definition and controls as those individuals who are otherwise free from any systemic diseases. Leptin, blood glucose and lipid parameters were measured in fasting serum samples. Leptin was estimated using Enzyme linked immunoassay(Elisa).* ***Results****: Although, there is no significant variation between the groups in mean leptin level despite case group having higher mean (9.91 ± 15.62) compared to normal group (5.11± 2.66), diabetic patients are found to have higher leptin level as compared to the normal study group. Also, there is positive association between fasting blood sugar, total cholesterol, glycated hemoglobin, low density lipoprotein and ureawith leptin (P<0.01) which is highly significant.* ***Conclusions****: In the study, high leptin level is found to be a strong independent predictor of diabetes. Leptin shows positive correlation with fasting blood glucose, HbA1c, Total cholesterol, Low density lipoprotein and Urea. Further studies on leptin and its role in islet cell biology should be conducted which may lead to new treatment for diabetes.*

Keywords: Leptin, Type 2 diabetes mellitus, Fasting blood sugar, Glycated hemoglobin (HbA1c), Lipid profile, Urea.

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I. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.The National Diabetes Data Group (1979) have classified diabetes into two major groups based on therapy i.e., Type 1 or Insulin Dependent Diabetes Mellitus (IDDM) and Type 2 Diabetes Mellitus or Non-Insulin Dependent Diabetes Mellitus. Diagnosis of diabetes is by blood tests such as fasting plasma glucose, oral glucose tolerance test. Diabetes is one of the first disease described with an Egyptian manuscript from before common era mentioning "too great emptying of the urine." The first described cases are to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as madhumeha or honey urine noting that the urine would attract ants.The term "diabetes" or "to pass through" was first used in 230 before common era by the Greek Appollonius of Memphis.The disease was rare during the time of Roman empire with Galen commenting that he had only seen two. Criteria for diagnosing Diabetes mellitus have been issued by consensus panel of expert from the National Diabetes Data Group and World Health Organisation WHO in 1997. According to this criteria normoglycaemia refers to fasting plasma glucose (FPG) ≥ 100 mg/dl, 2 hrs post prandial plasma glucose (PG) ≥ 140 mg/dl; Diabetes relates to FPG > 126 mg/dl and 2 hrs PG > 200 mg/dl. Fasting is defined as no calorie intake for the last 8hrs. New revised American diabetes association (ADA) criteria for the diagnosis of diabetes (2011) has been published. To solve this problem, recently the International Diabetes Federation (IDF) has offered a new definition for metabolic

syndrome in 2005 as having the following parameter : Central obesity with ethnic-specific cut–off values in Asians, waist circumference (WC) > 90cm in men and > 80cm in women , if BMI is > 30 kg/m2 then central obesity can be assumed plus any two of the following : i) Raised triglyceride level: ≥ 150 mg/dl (≥1.7mmol/L) or specific treatment for this abnormality ii) Reduced high density lipoprotein (HDL) – cholesterol: < 40 mg/dl (<1.03mmol/L) in men and < 50 mg/dl (<1.29 mmol/L) in women or specific treatment for this abnormality iii) Raised blood pressure: Systolic > 130 mmHg or Diastolic > 85 mmHg or treatment of previously diagnosed hypertension iv) Raised fasting plasma glucose: > 100 mg/dL (>5.6 mmol/L) or previously diagnosed type 2 diabetes mellitus. If above 5.6 mmol/L oral glucose tolerance test is strongly recommended, but is not necessary to define presence of syndrome The mechanisms by which insulin resistance may exert an atherogenic effect include the build up of triglyceride and free fatty acids. High concentration of plasma free fatty acids (FFA) are common in type 2 diabetes with early detection signifying a shift for the individual from impaired glucose tolerance to type 2 diabetes. Significantly, low high density lipoprotein (HDL) - cholesterol and high triglyceride are frequently found with insulin resistance, with or without type 2 diabetes. Leptin (from Greek λεπτός leptos, "thin"), the "satiety hormone" is a hormone made by adipose cells that helps to regulate energy balance by inhibiting hunger. Leptin is opposed by the actions of the hormone ghrelin, the "hunger hormone". Both hormones act on receptors in the arcuate nucleus of the hypothalamus to regulate appetite to achieve energy homeostasisin obesity, a decreased sensitivity to leptin occurs, resulting in an inability to detect satiety despite high energy stores. When leptin binds with the leptin receptor, it activates a number of pathways. Leptin resistance may be caused by defects in one or more part of this process, particularly the Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway. Mice with a mutation in the leptin receptor gene that prevents the activation of Signal Transducer and Activation of Transcription 3 (STAT3) are obese and exhibit hyperphagia. The Phosphoinositide 3-Kinase (PI3K) pathway may also be involvedin leptin resistance, as has been demonstrated in mice by artificial blocking of PI3K signaling. The PI3K pathway also is activated by the insulin receptor and is therefore an important area where leptin levels and reduced expression of leptin receptor mRNA in rats. Leptin functions by binding to the leptin receptor. The ob (lep) gene (ob for obese, lep for leptin) is located on chromosome 7 in humans.Leptin is a hormone made by fat tissue that acts on brain to regulate food intake and body weight. Leptin is an important adipose tissue derived hormone that has been shown to be involved in pathways influencing the risk of cardiovascular disease and diabetes mellitus. An analog of human leptin metreleptin (trade name Myalept) was first approved in Japan in 2013, and in the United States (U.S.) in February 2014. In the U.S. it is indicated as a treatment for complications of leptin deficiency, and for the diabetes and hypertriglyceridemia associated with congenital or acquired generalized lipodystrophy.

II. Materials and Methods

This case-control study was carried out on patients of department of General Medicine Department at Zoram medical college, Falkawn, mizoramfrom March 2018- February 2019. A total of 110 adult subjects (both male and female) of aged ≥18 years were for in this study.

Study design: Case-control study which comprises of 60 diabetic patients and control comprises of 50 healthy individuals with no history of diabetes mellitus.

Sample size: 110 patients.

Sample size calculation:

Inclusion criteria: Patients suffering from type 2 diabetes mellitus attending the General Medicine OPD, Diabetic OPD and who are admitted in the General ward irrespective of sex, age and economic status were taken as the study group. A group of normal healthy individuals of comparable age, sex who are free of any systemic disease were also included in the control group.

Exclusion criteria: Patients who are not diabetic or not willing to give consent were excluded from participating in the study.

Procedure methodology

After written informed consent was obtained, a well-designed questionnaire was used to collect the data of recruited patients. All patients attending Diabetes clinic were interviewed and was explained to them about the study for improving understanding of diabetes. They were asked about their history and medications, during this time measurements like weight, height, waist circumference etc. were also taken. Patients also provided complete investigations they had from previous check-ups like lipid profile, glycated hemoglobin (HbA_{1c}) etc.

Collection of sample: 2ml of venous blood was collected by venipuncture from patient's antecubital vein after an overnight fast. The blood was collected in EDTA vial for estimation of leptin leptin. Plasma for Leptin estimation was prepared by immediate centrifugation of EDTA whole blood and the plasma was immediately frozen and stored in aliquots at -20ºc.

Leptin: Leptin is estimated by DRG Leptin (Sandwich) ELISA kit manufactured by DRG Instruments GmbH, Germany Frauenberstrabe 18, D-35039 Maburg. This assay has a limit of detection of 0.05 µg/L. Day to day CVs were typically 13% at 0.32 µg/L and 5.8% at 2.14 µg/L.

Leptin ELISA Sandwich kit was obtained from DRG.com. It provides a method for the quantitative determination of human leptin in serum or plasma.

Total cholesterol estimation: CHOD PAP Method: Enzymatic colorimetric test for cholesterol with lipid clearing factors (LCS).Total cholesterol was determined after enzymatic hydrolysis and oxidation. The indicator quinoneimine was formed from hydrogen peroxide and 4-aminophenazone in the presence of phenol and peroxidase.

Calculation of the LDL and VLDL cholesterol concentration:LDL cholesterol and VLDL cholesterol values in mg/dl were indirectly calculated by using the following formulae of Friedewald WT et al.

Estimation of fasting blood glucose:

Fasting blood glucose was measured by Glucose liquid color kit manufactured by HUMAN, Germany using Glucose oxidase (GOD/PAP) method.

HbA1c was done using Fast Ion Exchange Resin Separation Method, Human

Statistical analysis

Database was constructed in Microsoft excel 2007 and statistical analysis was done using IBM statistical package for the social sciences (SPSS 17.0). Data were expressed in percentages, mean with standard deviation. Pearson correlation coefficient test were done to analyse the data. $p< 0.05$ was considered statistically significant.

III. Results

In this study, there were in total 110 participants which was sub-grouped into 60 cases DM and another 50 healthy individuals with no history of DM.

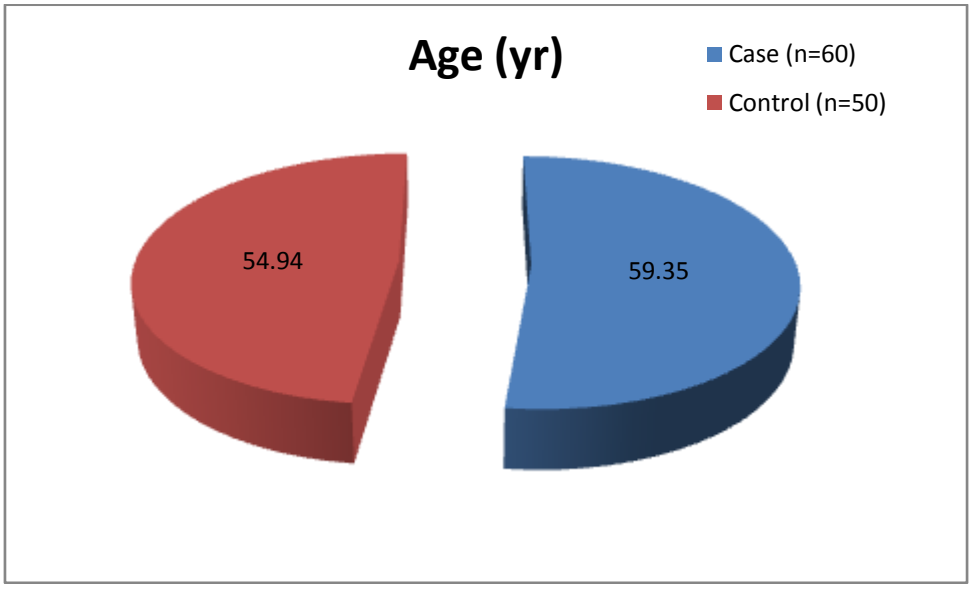

Fig-1: Showing comparison of group-wise mean age (yr.) of patients

Parameters	Leptin	
FBS	r	.376**
	P-value	.003
RBS	r	.436**
	P-value	.000
GHb	r	.328*
	P-value	.015
TC	r	.394**
	P-value	.002
HDL	r	-.293*
	P-value	.023
LDL	r	.315*
	P-value	.014
TG	r	.175
	P-value	.180
Urea	r	.115
	P-value	.380
Creatinine	r	-.100

	P-value	.448

r: Karl Pearson correlation coefficient;

P: probability of difference due to chance factors; **: P<.01; *:P<.05

Table-1

Correlation between leptin and each parameter of diabetes

Karl Pearson correlation coefficient "r" is applied to establish correlation between each parameter; mentioned in table-1; for diabetes with leptin and their findings are lay down in the table-1. Among the parameters considered only two viz., HDL and Creatinine have negative correlation with leptin whereas the remaining parameters have positive correlation with leptin.

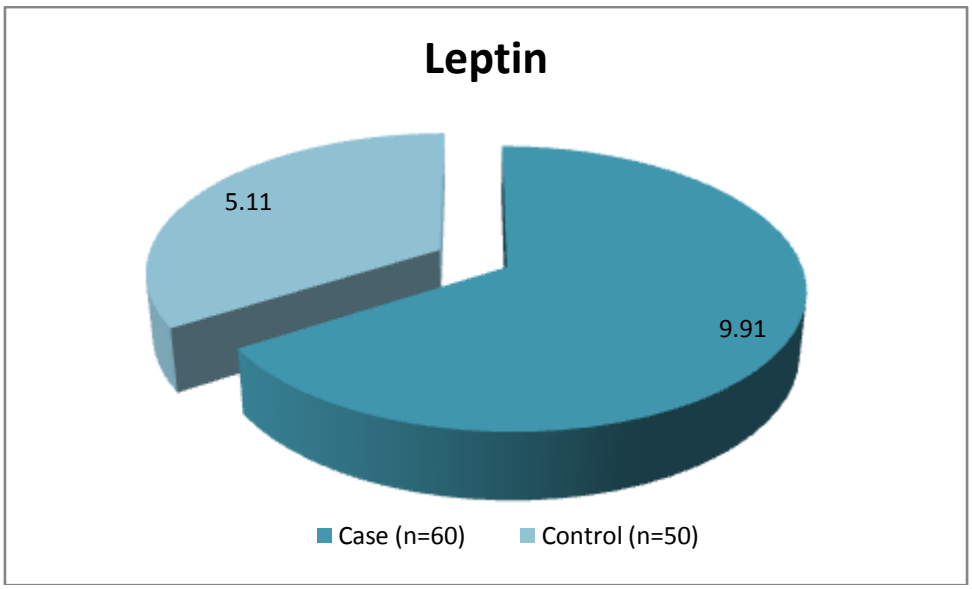

Fig-2: Showing comparison of group-wise mean leptin of patients

High leptin	No. of cases	Percentage
High	20	33.3
Normal	40	66.7
Total	60	100.0

Here in table-2, leptin is classified into high and normal; and the corresponding number of case along with percentage is displaced within the table itself. It may be perceived that highest percentage (66.7) of patients has normal leptin while remaining percentage (33.3) has high leptin.

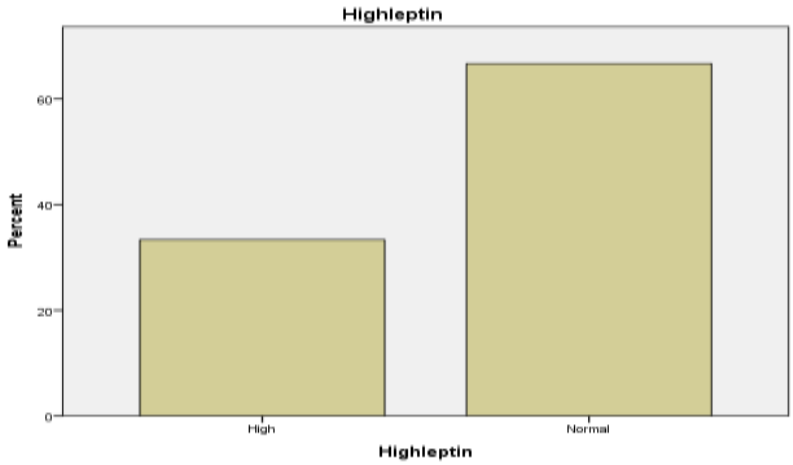

Fig-3: Showing comparison of high leptin of diabetes

IV. Discussion

In the present study, diabetes mellitus is defined by using criteria for diagnosing diabetes mellitus which have been issued by consensus panel of expert from the National Diabetes Data Group and WHO where FPG > 126mg/dl and 2 hrs PG > 200mg/dl. Diabetes mellitus is now a common disease globally. As such, many studies have also been done in India related with diabetes and many other developed countries where type 2 diabetes make up about 90% of diabetes cases which is equivalent to about 6% of the world's population in adult. The reason of increasing rate of type 2 diabetes mellitus could be due to change in lifestyles like decrease in exercise, and increasing rates of obesity in developed countries ranking India as number one as of 2000 when it was recognized as a global epidemic by the World Health Organization.Although , there is no significant variation between the groups in mean leptin level despite case group having higher mean (9.91 ± 15.62) compared to normal group (5.11± 2.66) diabetic patients are found to have higher leptin level as compared to the normal study group. This is because the study group comprises of people suffering from type 2 diabetes mellitus and decrease pre-proinsulin mRNA expression in beta cells thus decrease the synthesis and reduces the release of insulin from human pancreatic beta cells which lead to the development of type 2 diabetes mellitus. There is also positive association between fasting blood glucose with leptin ($P<0.01$) which is highly significant. This suggest that insulin concentration may contribute to the pathogenesis of leptin and its effects on glucose metabolism and hyperglycemia. Also, leptin have a positive association with total cholesterol, triglyceride, low density lipoprotein which is found to be significant ($P<0.05$). This explained the relationship that raised leptin level in type 2 diabetes patients could also be a risk factor for developing cardiovascular disease. In the management of type 2 diabetes, appropriate markers are needed and inflammatory markers, including IL-6 should also be considered along with leptin.

V. Conclusion

Leptin is an adipose tissue derived protein. High levels are seen in type 2 diabetes with insulin resistance, obesity. The study was done to assess the leptin value in type 2 diabetes and to see the interrelationships based on leptin, lipid parameters. In the study, leptin level is found to be significantly related with cholesterol, blood glucose, Glycated haemoglobin and Low density lipoprotein ($p<0.05$). It may be percieved that highest percentage (66.7%) of patients has normal leptin while remaining percentage (33.3%) has high leptin level.

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