ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 09 | September - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DIABETES OR OBESITY; MAJOR EFFECTOR OF ALTERED LEVELS OF GHRELIN AND LEPTIN

Biochemistry

Lakshmi G.L — Anthropological Survey of India, Southern Regional Center; Mysuru, Karnataka, India; JSS Research Foundation, Mysuru, India.

Shruti Dasgupta — Centre for DNA Fingerprinting and Diagnostics, Hyderabad, Telangana, India.

Mohammed Salman — Anthropological Survey of India, Southern Regional Center; Mysore, Karnataka, India.

Sanjay K. R — Department of Biotechnology, JSS Science and Technology University, Mysore, India.

ABSTRACT

Background: Ghrelin and leptin are the key hormones involved in the energy homeostasis and plays a relevant role in regulating hunger and satiety stimuli afferent to the brain. Abnormalities in the levels of ghrelin and leptin are often associated with the obesity and type 2 diabetes complications. However, there are no studies clarifying whether ghrelin and leptin levels have stronger association with obesity or Type 2 diabetes (T2DM).
Aims: To evaluate and compare the independent effect of major defining factors of obesity and diabetes on ghrelin and leptin concentrations.
Materials And Methods: Anthropometric measures such as height, weight, waist (WC) and hip circumference (HC), Body mass index (BMI), Basal metabolic rate (BMR), fat percentage, lean body mass, were taken. Assessed daily physical activity and energy intake. Biochemical parameters such as fasting glucose, postprandial glucose, HBA1c, ghrelin, leptin and insulin levels were measured.
Statistical Analysis: One-way analysis of variance (ANOVA), Chi-square ($\chi 2$) test Pearson's correlation coefficients, Multiple stepwise linear regression model analysis were performed.
Result: The diabetic subjects irrespective of obesity showed significantly higher waist to hip ratio, HOMAIR levels of fasting blood glucose, postprandial glucose and significantly lower levels of Ghrelin than non-diabetics. Similarly, obese subjects irrespective of diabetes have significantly higher BMR and higher levels of Leptin than non-diabetics. A significantly higher BMI, fat mass percentage and lower lean body mass percentage were observed in obese subjects irrespective of diabetes than non-obese subjects. Among non-obese, diabetics have higher BMI, Fat mass percentage and lower lean body mass percentage. The levels of insulin were significantly higher in diabetic obese subjects. HOMAIR ($P \leq 0.0001$) and Postprandial glucose ($P \leq 0.05$) showed negative independent effect and QUICKI ($P \leq 0.0001$) showed positive independent effect on the levels of ghrelin. BMI ($P \leq 0.05$) showed a positive effect and lean body mass percentage ($P \leq 0.0001$) showed an inverse effect on levels of leptin.
Conclusion: It is evident from the study that low levels of ghrelin are predominantly associated with diabetes parameters when compared to parameters of obesity and on the contrary increased leptin levels have much stronger association with measures of obesity than diabetes. Evidence of altered leptin and ghrelin levels in these disorders infers vice versa, their respective roles in obesity and lean diabetes.

KEYWORDS

Ghrelin, Leptin, Type 2 Diabetes mellitus, Obesity

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity has become a major public health concern in recent years. T2DM is a chronic metabolic disorder characterized by hyperglycaemia resulting from the flaws in the insulin secretion, insulin action or the combination of both [1]. Growing incidence of T2DM is attributed to the transition in the food habits and the sedentary life style leading disturbed energy balance [2] that further leads to weight problems, which is one of the major risk factors of chronic conditions such as obesity and T2DM. Therefore, hormones involved in regulating energy balance are considered as potential risk factors for obesity and type 2 diabetes. Ghrelin and leptin are the two hormones which are known to play a pivotal role in regulation of food intake and maintenance of body weight and energy homeostasis [3].

Ghrelin, a peptide of 28 amino acids mainly secreted by X-A cells in the stomach, is an endogenous ligand for the growth hormone (GH) secretagogue receptor 1α [4]. Basic function of the ghrelin is promoting GH release [5], apart from that ghrelin is also involved in regulating food intake [6], energy metabolism [7] and body weight [8]. Ghrelin is an orexigenic hormone responsible for the meal initiation that acts on hypothalamus via ghrelin receptor [9]. Study on rodents have reported in positive energy balance, obesity and a reduction of stomach production and secretion of ghrelin as a result of prolonged exposure to high fat diets [10]. Evidences suggests that ghrelin enhances adipogenesis, increases fat storage enzyme activity and reduced fat utilization [11]. Studies have also demonstrated the involvement of ghrelin in glucose metabolism and take part in regulation of insulin sensitivity and insulin release [12,13].

Leptin, a hormone produced by adipocytes plays a key role in regulation of body fat stores [14]. In rodents and humans, it has been demonstrated that leptin signals to key regulatory centers in the hypothalamus leading to decreased food intake and increased energy expenditure that regulate body weight and energy homeostasis [3]. The relationship between serum leptin levels and measures of adiposity such as body mass index, waist circumference has been well established [15]. Studies also suggest that in humans, leptin is also found to be associated with insulin resistance and diabetes [16]. Leptin receptors are present on human hepatocytes, and Leptin was shown to modulate several insulin induced activities in these cells. Leptin antagonizes insulin signaling by decreasing insulin-induced tyrosine phosphorylation of Insulin Receptor Substrate (IRS), it increases phosphoenolpyruvate-carboxykinase and decreases glucokinase expression leading to increased gluconeogenesis and decreased glycolysis [17]. Though it is evident from the research that ghrelin and leptin are involved in the development of diabetes and obesity both, however it is controversial whether obesity or diabetic parameters are more strongly correlated with the levels of ghrelin or leptin. But some obese people never develop T2DM, and some type 2 diabetics are extremely lean. Hence the present study aimed to assess the comparative effect of obesity and diabetes on the levels of ghrelin and leptin so as to clarify what acts as a major predictor of their concentrations.

MATERIALS AND METHODS

A total of 426 unrelated participants aged between 25-65 years enrolled under the Mysore Family Diabetic Study were selected for the present study after obtaining informed consent from each individual, consisting of 123 Diabetics and 303 non diabetics. Participants under medication (e.g. glucocorticoids, anti-depressants), pregnant or lactating women were excluded from the study. The study was approved by the institutional ethical committee, Anthropological Survey of India.

A standardized questionnaire was administered to all the participants to elicit the detailed information on demographic data, personal and family history of chronic disorders, medication intake, smoking habits, alcohol consumption, regular physical activity, nutrition intake. Physical activity during the day was categorized into light, moderate

and vigorous, based on the Physical Activity level (PAL) values calculated as the ratio of the 24-hour energy expenditure to the BMR [18]. Dietary intake was assessed using quantitative food frequency questionnaire and energy intake was calculated for individuals [19]. Anthropometric measurements such as height, weight, waist circumference (WC) and hip circumference (HC) were taken. Body mass index (BMI), Basal metabolic rate (BMR), Lean body mass and Fat mass were measured using Bio-impedance Analyzer (Biodynamics Corporation, USA).

Blood samples were collected after 12 hours overnight fasting to estimate Fasting blood glucose (FGLU) and glycated hemoglobin (HbA1c; %). Blood sample was collected after 2 hours of administering 75g of glucose to the subjects [20] to estimate Postprandial plasma blood glucose. using automated biochemical analyzer EM360 (Transasia, Germany) and ERBA kits. Ghrelin, leptin and insulin concentration in plasma was quantified using multiplex assay kits (HMH-34K-07 7plex kit, Millipore Corporation®, Billerica, MA, USA), that included pre-mixed and fully customized panels that utilize the Luminex xMAP technology platform (Luminex Corp, TX, USA). Homeostasis model assessment (HOMA-IR) according to the formula: HOMA-IR = [glucose (nmol/L) * insulin (μU/mL)/22.5], using fasting values [23]. Insulin sensitivity was assessed using fasting plasma insulin concentrations and a quantitative insulin sensitivity check index {QUICKI 1/[log (fasting insulin) log (fasting glucose)]} [24].

BMI was categorized as normal (BMI≤25 kg/m^2) and obese or overweight (BMI>25kg/m^2) [21]. Self-reported cases and individuals with FPG > 126 mg/dl and PGLU > 200 mg/dl were defined as diabetes [20]. Diabetics under treatment and long-term management of blood glucose were defined as controlled diabetes with HbA1c values 6% - 8%. On the contrary above 8% were considered uncontrolled diabetes [22]. All self-reported cases were further validated by medical record review and supplementary questionnaires. Accordingly, samples were segregated into 4 catagories -Diabetic obese, Non-diabetic Obese, Diabetic Non-obese and Normal Controls.

Statistical Analysis:

All statistical analysis was done using SPSS 17.0. The analysis has been carried out after segregating the cases and controls further into four groups - Diabetic obese, Non-diabetic Obese, Diabetic Non-obese and Normal Controls. The results have been reported as mean ± standard deviation for continuous variables. One-way analysis of variance (ANOVA) was used to analyze the statistical differences in the mean of various parameters between these four groups. Chi-square ($\chi 2$) test was used to compare the proportion of the subjects between different dichotomized variables. Pearson's correlation coefficients were measured to assess the interrelationship between all the variables defining obesity & diabetes with ghrelin and leptin levels. Multiple stepwise linear regression model analysis was applied to determine the independent effect of segregated parameters defining diabetes and obesity along with other common covariates (age, gender, physical activity and energy intake) on levels of ghrelin and leptin in two different sets of analysis. The collinearity between segregated parameters defining diabetes and obesity were evaluated by tolerance values. If high co linearity existed between two variables defining same characteristic, only one among them was selected for stepwise regression.

RESULT

Table 1. Data distribution among the groups based on presence or absence of Diabetes and Obesity

	Diabetic obese (N=47)	Diabetic Non-Obese (N=76)	Non diabetic Obese (N=98)	Normal Controls (N=205)
Age (years)	53.212 ±12.799*^	53.447 ±10.864*^	44.989 ± 11.412*$^{\#}$	40 ± 15.774^$^{\#}$
WHR	0.899 ± 0.099*^	0.913 ± 0.079*^	0.864 ± 0.082$^{\#}$	0.860 ± 0.08$^{\#}$
BMI	31.01 ± 2.889*$^{\#}$	24.563 ± 2.275*^	30.561 ±3.028*$^{\#}$	23.230 ±2.768^$^{\#}$
BMR	1488.043± 278.973*$^{\#}$	1343.919 ± 300.64^	1547.587 ± 269.506*$^{\#}$	1339.280 ± 289.53^
Lean Body Mass%	61.682 ± 6.150*$^{\#}$	66.653 ± 6.950*^	63.202 ± 5.427*$^{\#}$	69.807 ± 7.455^$^{\#}$
Fat Mass%	38.317 ± 6.149*$^{\#}$	33.213 ± 6.767*^	36.826 ± 5.632*$^{\#}$	30.128 ± 7.387^$^{\#}$
Energy Intake (Kcal)	2474.901 ± 530.218	2535.580 ± 510.928	2512.336 ± 586.571$^{\#}$	2415.096 ± 550.735$^{\#}$
FGLU (mg/dl)	157.446 ± 65.494*^	146.657 ± 68.570*^	88.262 ± 10.192$^{\#}$	86.563± 9.860$^{\#}$
PGLU (mg/dl)	253.635 ± 109.270*^	232.2 ± 89.630*^	117.280 ± 29.455$^{\#}$	110.980 ± 22.675$^{\#}$
HbA1c (%)	8.092 ± 2.382*^	8.383 ± 2.542*^	6.015 ± 1.293*$^{\#}$	5.420 ± 1.165^$^{\#}$
Insulin (μIU/mL)	57.385 ± 33.235*^$^{\#}$	48.145 ± 35.587*^	32.380± 21.313*$^{\#}$	20.807 ± 16.530^$^{\#}$
QUICKI	0.265 ± 0.030	0.266 ± 0.043	0.286 ± 0.066	0.280 ± 0.108
HOMA IR	1157.867 ± 130.593*^	1042.968 ± 122.023*^	328.313 ± 58.890$^{\#}$	202.830 ± 71.098$^{\#}$
Ghrelin (pg/ml)	137.878 ±130.681*^	172.567 ± 142.340*^	333.786 ± 129.54$^{\#}$	358.198 ± 129.29$^{\#}$
Leptin (ng/ml)	29.204 ± 23.662*#	14.009 ± 13.102^	28.033 ± 15.817*#	13.428 ± 12.078

Note: (*) depicts P ≤ 0.05 as compared to Normal Controls (^) depicts P ≤ 0.05 as compared to Non Diabetic Obese ($^{\#}$) depicts P ≤ 0.05 as compared to Diabetic Non Obese.

The above table 1 demonstrates the comparative distribution of the variables in the samples classified into 4 groups based on clinical history of diabetes and/or obesity (BMI≥23). The diabetics whether or not they are obese are significantly older than the non-diabetics. The diabetic subjects irrespective of obesity have significantly higher waist to hip ratio, HOMAIR levels of fasting blood glucose, postprandial glucose and significantly lower levels of Ghrelin than non-diabetics. The obese subjects irrespective of diabetes have significantly higher BMR and higher levels of Leptin than non-diabetics. In general, obese subjects whether or not are diabetics have higher BMI, fat mass percentage and lower lean body mass percentage than non-obese. However, among non-obese, diabetics have higher BMI, Fat mass percentage and lower lean body mass percentage. The levels of insulin were significantly different in all the groups, highest in diabetic obese, followed by diabetic non-obese, non-diabetic obese and lowest in normal controls.

Table 2. Distribution Of Categorical Data Across The Groups With Presence Or Absence Of Diabetes And Obesity

	Diabetic Obese (N=47)	Diabetic Non-Obese (N=76)	Non diabetic Obese (N=98)	Normal Controls (N=205)
Gender				
Male	27.7% (13)	48.7% (37)	26.5% (26)	45.4% (93)
Female	72.3% (34)	51.3% (39)	73.5% (72)	54.6% (112)
Physical Activity				
Light	55.3% (26)	47.4% (36)	66.3% (65)	57.6% (118)
Moderate	42.6% (20)	50.0% (38)	30.6% (30)	37.1% (76)
Vigorous	2.1% (1)	2.6% (2)	3.1% (3)	5.4% (11)

Table 2 depicts the frequency distribution and percentages of two categorical parameters such as gender and physical activity among the four groups. Both the percentage of females in Diabetic obese (72.3% (34)) and non-diabetic obese (73.5% (72)) group are observed to be very high when compare to the frequency percentages of males in the same groups Diabetic obese (27.7% (13)) and non-diabetic obese (26.5% (26)). However, very minor differences were observed in the frequency percentages of male and female in groups diabetic non obese (Male = 48.7% (37), Female = 51.3% (39)) and Normal controls (Male = 45.4% (93), Female = 54.6% (112))

In all the four groups people in high percentages are found to carry out light to moderate physical activity. Very less number of people performs vigorous and regular physical activity and the highest is 5.4% (11) are those who are normal controls. Highest is the 50.0% (38) of people who perform moderate physical activity are diabetic but not obese and 66.3% (65) are those who perform light physical activity or carry out a sedentary life style are obese but are not Diabetic.

Correlations between all the variables defining obesity & diabetes with ghrelin and leptin levels have been depicted in Table 3. Ghrelin levels were found to have negative correlations with age, Waist Hip Ratio

(WHR), Body Mass index (BMI), Basal Metabolic rate (BMR), Fat Mass Percentage, Fasting Glucose, Post prandial glucose, HbA1C and positive correlations with Lean body mass percentage. However, Leptin levels were found to be negatively correlated with Lean Body Mass percentage and positively correlated with age, Waist Hip Ratio (WHR), Body Mass index (BMI), Basal Metabolic rate (BMR), Fat Mass Percentage and insulin levels.

Table 3: Pearson Correlation Coefficients Between Variables Defining Obesity & Diabetes With Ghrelin And Leptin Levels

	Ghrelin (pg/ml)	Leptin (pg/ml)
Age	- 0.192**	0.138**
Energy (Kcal)	0.025	-0.028
Waist Hip Ratio (WHR)	-0.247**	0.215**
Body Mass index (BMI)	-0.512**	0.481**
Basal Metabolic rate (BMR)	-0.305**	0.123*
Lean Body Mass percentage (%)	0.185**	-0.566**
Fat Mass percentage (%)	- 0.188**	0.564**
PGLU (mg/dl)	- 0.227**	-0.031
HbA1c (%)	- 0.249**	0.038
HOMA IR	- 0.044	0.059
QUICKI	0.031	0.078
FGLU (mg/dl)	-0.196**	-0.077
Insulin (µIU/mL)	0.038	0.184**

**Correlation is significant at the 0.01 level (2-tailed).
*Correlation is significant at the 0.05 level (2-tailed).

Table 4. Effect Of Parameters Defining Diabetes And Other General Covariates On Levels Of Ghrelin And Leptin

	R^2	Age	Gender	Energy Intake	HOMA IR (Insulin Resistance)	QUICKI (Insulin Sensitivity)	Postprandial glucose (mg/dl)
Ghrelin (pg/ml)	0.465				- 0.405**	0.357**	- 0.140^
Leptin (ng/ml)	0.289	0.206**	0.532**	0.093^	-	-	0.097^

Table 4 depicts the multiple stepwise regression standardized coefficient and R^2 values for the accepted model for each dependent variable; (^P≤0.05, *P≤0.001, **P≤0.0001).

Note: Variables tested for the models were postprandial glucose, HbA1C, HOMAIR, QUICKI, age, gender, physical activity and energy intake.

Multiple stepwise linear regression model analysis was applied to determine the independent effect of parameters defining diabetes such as postprandial glucose, HbA1C, HOMAIR (insulin resistance), QUICKI (insulin sensitivity) and adjusted for the covariates such as age, gender, physical activity and energy intake on ghrelin and leptin levels. To avoid high co linearity between the variables fasting glucose and fasting insulin levels were not included for step wise regression as the variables were defining HOMAIR and QUICKI.

HOMAIR and Postprandial glucose showed negative independent effect and QUICKI showed positive independent effect on the levels of ghrelin and the best accepted model comprising these variables explains 46 % of variability in the levels of ghrelin. About 29% of variability in the levels of leptin is explained by the covariates age, gender, energy intake and post prandial glucose levels, however on removing the covariates age, gender, energy intake none of the variables defining diabetes was found to be correlated with the leptin levels.

Table 5. Effect Of Parameters Defining Obesity And Other General Covariates On Levels Of Ghrelin And Leptin

	R^2	Gender	BMI	WHR	Lean Body Mass %
Ghrelin (pg/ml)	0.077		- 0.099^	- 0.196**	0.152*
Leptin (ng/ml)	0.42	0.255**	0.316**	-	- 0.250**

Note: Table 5 depicts the multiple stepwise regression standardized coefficient and R^2 values for the accepted model for each dependent variable; (^P≤0.05, *P≤0.001, **P≤0.0001).

Variables tested for the models were BMI, WHR, Lean Body mass percentage BMR, Fat mass percentage, age, gender, physical activity and energy intake.

Multiple stepwise linear regression model analysis was applied to determine the independent effect of parameters defining obesity such as BMI, WHR, Lean Body mass percentage, BMR, Fat mass percentage and adjusted for the covariates such as age, gender, physical activity and energy intake on ghrelin and leptin levels. Almost 42 % (R^2 value) of variability in the leptin levels was explained by positive effect of gender, BMI and inverse effect of lean body mass percentage. Even on removing the covariate "gender" from the model R^2 value persists to 39% with surviving independent variables BMI, BMR and lean body mass percentage. Only 7 % variability was predicted by the model consisting of lean body mass percentage with positive effect and inverse effect of BMI and WHR on ghrelin levels was obtained.

DISCUSSION

Leptin is a hormone that works as a mediator in the stomach–hypothalamus pathway and provides information about the body's energy storage in adipocytes. Also, its level is associated with obesity [25]. Ghrelin is mainly involved in the maintenance of body weight by promoting food intake [3], energy metabolism [7] and fat deposition. Ghrelin has metabolic actions like decrease in insulin secretion from the pancreas, reducing in energy consumption by the body and effects on growth and peripheral metabolism especially of fats and carbohydrates [26,27]. Leptin acts in contrast to ghrelin, leptin functions as a feedback mechanism that signals to key regulatory centers in the brain to inhibit food intake and to regulate body weight and energy homeostasis [3] and also it reduces the amount of ghrelin secreted from the stomach. A disruption of the energy homeostasis may lead to metabolic abnormalities such as diabetes and obesity. Hence understanding the role of such biomarkers in energy homeostasis regulated diabetes is essential in understanding the disease. Though it has been well established that abnormalities in the circulating systems of leptin and ghrelin contribute to the development of obesity [3,28]and diabetes [29,30], the idea that whether ghrelin and leptin levels are more influenced in case of obesity or diabetes is still unclear. Hence the present study aimed to assess the effect of obesity and diabetes on the levels of ghrelin and leptin so as to clarify the controversial idea that whether the diabetes or obesity plays the leading and prominent role alterations of ghrelin and leptin concentrations.

In the present study samples were segregated into four groups based on diabetic and obesity status, so that the independent effect of occurrence of obesity and diabetes on ghrelin and leptin levels can be assessed in the study population. Our study revealed a significant difference in the most of the measured variables among the groups. The diabetic subjects irrespective of whether they have obesity or not showed significantly lower levels of ghrelin than non-diabetics, suggesting that lower levels of ghrelin may be associated with occurrence of diabetes among the individuals even with normal BMI. Extensive studies have mentioned that ghrelin has a role in the development of metabolic syndrome and type 2 diabetes [31]. Studies on obese diabetic patients have shown that blood ghrelin levels play important role in regulating insulin and glucose metabolism [30] and also a previous study advocated that ghrelin reduces insulin secretion from beta cells in obesity-induced type 2 diabetic [32], which clearly suggests that ghrelin may have a pivotal role in obesity induced diabetes and hence ghrelin concentration in expected to vary between obese and non-obese diabetics. However, in our study ghrelin concentration was found to be lower in subjects with type 2 diabetes than subjects without type 2 diabetes irrespective of their BMIs and no significant difference was observed within diabetic obese and diabetic non-obese. Similarly, previous studies on diabetic patients have suggested that the ghrelin concentration is similar in both obese and thin type 2 diabetic patients [33]. Even though adiposity is known to be an important determinant of ghrelin concentrations in diabetics subjects but studies had shown significant difference in ghrelin levels even after adjusting BMI, [34] that invokes the need of further investigation in this regard.

The present study showed that the plasma levels of ghrelin are more

strongly associated with insulin resistance, insulin sensitivity and post prandial glucose than with BMI, WHR and lean body mass. The ghrelin deficiency may lead to insulin resistance associated with decreased somatotrophic effects [48]. Although correlation does not prove causation, but it has been previously suggested that the relationship of active ghrelin with insulin resistance may depend on the suppressive effect of insulin, whose serum concentration increases during insulin resistance, on the secretion of active ghrelin into the systemic circulation. [47]. Tong et al. [35] demonstrated that, in healthy subjects circulating ghrelin suppresses glucose stimulated insulin secretion and deteriorates glucose tolerance. Hence our results are also in accordance with the previous findings. It could also be speculated that low blood ghrelin levels might affect the growth hormone / insulin like growth factor -1 -axis which might increase insulin resistance and eventually lead to the development of Type 2 diabetes mellitus which in fact is not necessarily adiposity dependent. Poykko et al. [34], reported association between ghrelin and fasting insulin concentrations as well as the association between ghrelin and insulin sensitivity, suggesting that low ghrelin is independently associated with fasting insulin concentrations, insulin resistance and type 2 diabetes. Similar results have been observed between the ghrelin concentrations and insulin resistance in other studies [36,37]. Mohamed et al.,[14] in their study reported a significant association between low levels of plasma ghrelin and FBS, PPBS and HbA1c. This is in accordance with our results where ghrelin showed a negative correlation with postprandial glucose. Though there are studies demonstrating the involvement of Ghrelin in glucose metabolism and its role in regulation of insulin release and insulin sensitivity [12,13], however clinical studies investigating the pathophysiological role of ghrelin in development of T2DM independent of obesity are needed to explain such associations.

Leptin concentrations were significantly higher in obese subjects irrespective of their diabetic status This is in agreement with a previous study on Pakistani population where they found serum leptin level significantly higher in healthy obese as compared to non-obese subjects [38]. Leptin levels are normally high in obese people, which is theoretically more than sufficient to suppress appetite and accelerate metabolism [39] and known to be associated with leptin resistance [40]. This leads to disrupted leptin signaling in the hypothalamus and does not properly inhibit food intake and fails to increase energy expenditure [41]. A great number of studies have reported association between leptin levels and obesity. A positive association between leptin levels and BMI revealed in the present study is in agreement with the previous studies. Studies have evidenced a positive association between leptin concentrations and BMI in obese subjects [42,14], indicating that elevated levels of leptin in obese subjects is a sign energy imbalance. Previous studies have reported conflicting results on relationship between leptin concentration and BMR, the positive association found in the present study is in accordance with the earlier studies [43,44]. In the present study the inverse relationship between was observed between body mass and leptin levels, the possible explanation for this inverse association is that reduction of the body fat the decreases the circulating levels of leptin though BMI remains same [45]. In addition, studies have also found the exponential increase in the circulating levels of leptin with increasing body fat [46]. Though studies have reported the association between leptin levels and diabetic parameters [14], in the present study measures of obesity showed a stronger correlation with leptin levels in comparison with diabetic parameters.

CONCLUSION:

Leptin and Ghrelin have been extensively associated with obesity and obesity induced diabetes in plenty of studies. To our knowledge this is the first study to compare the associations of leptin and ghrelin concentrations with obesity and diabetes defining factors. It is evident from the study that low levels of ghrelin are predominantly associated with diabetes defining parameters such as insulin resistance, sensitivity and postprandial glucose. On the contrary increased leptin levels were found to have stronger association with measures of obesity such as BMI and lean body mass than parameters defining diabetes. Hence it can be reversibly concluded that lower levels of ghrelin may have role in etiology of lean diabetes or diabetes independent of obesity and higher levels of leptin can be a key predictor of obesity. Unfortunately, since a very little is known about the pathophysiology of non adipogenic diabetes, this study may append a new insight to our knowledge. In order to strengthen this meaningful association, studies on animal models, that assess the effect of both ghrelin and leptin administration which can ameliorate IR and reduce body weight respectively can be proposed.

Acknowledgement:

Authors acknowledge JSS Science and Technology University, University of Mysuru, Mysuru and Anthropological Survey of India, Southern Regional Center; Mysuru for providing support to conduct the research work

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