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Original Article

Biochemistry Section

Association of Adiponectin-Leptin Ratio and HOMA-IR in Obese Patients with and without Type 2 Diabetes Mellitus: A Cross-sectional Study

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ABSTRACT

Introduction: Obesity is one of the leading causes of morbidity and mortality due to associated risk factors, including Type 2 Diabetes Mellitus (T2DM). Obese and diabetic patients have lower amounts of adiponectin. Leptin, a hormone released by adipocytes that controls hunger, is crucial in the emergence of obesity. Furthermore, it has been claimed that the Adiponectin/Leptin Ratio (ALR) correlates with Insulin Resistance (IR) better than adiponectin or leptin alone.

Aim: To evaluate adiponectin, leptin, and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) in obese subjects with and without T2DM and compare the variations, if any, from the normal subjects.

Materials and Methods: This hospital-based, cross-sectional study was carried out at Sri Guru Ram Das (SGRD) University of Health Sciences, Amritsar, and Punjab Institute of Medical Sciences (PIMS), Jalandhar from January 2020 to December 2022. A total of 125 subjects of either gender aged above 18 years, visiting the medicine Outpatient Department (OPD) of PIMS, Jalandhar, were included in the study. Among them, 25 healthy volunteers served as controls. Serum levels of Adiponectin, Leptin, and Insulin were estimated using the Enzyme-Linked Immunosorbent Assay (ELISA) method. The data obtained were statistically analysed using one-way Analysis of Variance (ANOVA) test (with Bonferroni post-hoc).

Results: A total of 125 participants were analysed in the present study, with 50 being obese with T2DM (mean age: 50.22±8.6 years), 50 being obese without T2DM (mean age: 46.9±9.8 years), and 25 being non obese non diabetic individuals (controls) (mean age: 42.8±9.09 years). A higher number of females 78 (62.4%) reported to the OPD compared to males 47 (37.6%). Although no statistical significance was found, there was a considerable decrease in adiponectin levels in obese and obese with T2DM subjects. Moreover, the leptin levels and HOMA-IR were increased in obese and obese with T2DM subjects compared to the control subjects.

Conclusion: ALR may be used as a clinical marker for assessing the morbidity due to obesity and in T2DM subjects. Moreover, lifestyle modifications can be targeted to prevent IR.

Keywords: Adipose tissue, Glycated haemoglobin, Homeostatic model assessment of insulin resistance, Insulin levels

INTRODUCTION

Obesity, a multifactorial disease, is defined as an increase in body weight beyond the requirements of the skeletal physical structure [1]. It is a significant risk factor for a number of non communicable diseases such as cardiovascular disease, cancer, hypertension, and Type 2 Diabetes Mellitus (T2DM) in particular [2]. Urbanisation and declining physical activity, leading to obesity, are major factors in the emergence of T2DM [3]. However, T2DM has a strong correlation with obesity, and the number of people with diabetes attributable to obesity is anticipated to double to 300 million by 2025 [4]. Abnormalities in the metabolism of carbohydrates, fats, and proteins, resulting from deficiencies in insulin secretion, insulin action, or both, are hallmarks of T2DM [5].

Studies have shown that differences in adipose tissue cellularity also play a significant role in the development of obesity [6,7]. The energy status and deposition of the adipose deposit appear to affect the pattern of adipocytokine secretion [1]. Furthermore, changes in adipokine secretion due to shifts in energy reserves also influence metabolism and contribute to metabolic diseases, including T2DM. Hence, it is crucial for clinicians to treat obesity in patients with DM because even a small weight loss of 3-5% improves glucose tolerance and glycated haemoglobin (HbA1c), reduces the need for glucose-lowering medications, and prevents prediabetes from progressing to T2DM [8].

Out of the two adipokines, leptin and adiponectin, the latter is widely prevalent in the body. This proteinaceous hormone with 244 amino acids plays a crucial role in the metabolism of carbohydrates, speeds up the oxidation of fatty acids, and improves insulin sensitivity, thereby lowering levels of blood sugar, free fatty acids, and triglycerides [9]. It is also observed that low levels of adiponectin are linked to an increased risk of developing obesity-related co-morbidities such as diabetes mellitus, atherosclerosis, and coronary heart disease [10]. Additionally, because adiponectin also functions as an insulin-sensitising hormone in the liver and muscles, low levels of adiponectin exacerbate obesity-related peripheral insulin resistance [11].

In 1994, scientists identified leptin, a protein predominantly produced by white adipose tissue [12]. The increase in circulating leptin levels causes hypothalamic leptin resistance, which suppresses anorexigenic and energy expenditure signals and exacerbates obesity [11]. Leptin levels are high in obese individuals who are leptin resistant and are directly correlated with fat mass [13]. Recently, a new biomarker of adipose tissue dysfunction called the ALR has shown a negative correlation with Body Mass Index (BMI). Furthermore, it has been reported that in individuals with hyperglycaemia, the ALR correlates more strongly with Insulin Resistance (IR) than adiponectin, leptin, or even HOMA-IR [13]. ALR can act as an independent measure of IR in people with T2DM [14].

IR, the inability of a known amount of insulin to improve glucose uptake and utilisation, is a common pathophysiological problem [15]. Understanding the pathogenesis of IR is becoming increasingly important as a guide to future therapy, as well as health and

economic policies [16]. HOMA-IR, a reliable measure of IR, is an independent predictor of T2DM, and obesity is often the primary factor contributing to elevated HOMA-IR scores [17]. Although many studies have been done on leptin and adiponectin [18,19], there is a paucity of data on their association with insulin levels and HOMA-IR. Moreover, this type of study has not been done in Punjab, India. Besides lifestyle management, it is also crucial for clinicians to fully comprehend adipokines. This will aid in developing newer preventive and therapeutic interventions for obesity and its related co-morbidities.

Thus, present study was done to estimate serum levels of adiponectin, leptin, insulin, and to calculate ALR and HOMA-IR in obese subjects with and without T2DM, as well as non obese, non diabetic individuals (controls) and also to study the association between these biomarkers in obese subjects with and without T2DM, as well as non obese, non diabetic individuals (controls).

MATERIALS AND METHODS

This hospital-based, cross-sectional study was conducted at SGRD University of Health Sciences, Amritsar, in collaboration with the Outpatient Department (OPD) patients of PIMS, Jalandhar, Punjab, India from January 2020 to December 2022. The study was approved by the Research and Ethical committees of the institution (Ref No: Patho 691/19, dated 21-10-2019). Informed consent was also obtained from all the participants.

Inclusion criteria: Obese patients with and without T2DM, of either gender, above 18 years of age, and visiting the Medicine OPD of Punjab Institute of Medical Sciences, Jalandhar, were included as cases. Participants with a BMI ≥25 kg/m^2 were considered obese, and those with a BMI <25 kg/m^2 were considered non obese according to the World Health Organisation (WHO) Asia Pacific guidelines [20]. The American Diabetes Association (ADA) 2019 criteria were used for the diagnosis of diabetes mellitus [21]. Non obese and non diabetic individuals of either gender, above 18 years of age, were taken as control subjects.

Exclusion criteria: Pregnant and lactating women, patients with liver and renal diseases, hypothyroidism, malignancy, chronic congestive heart failure, and various haematological abnormalities (including significant anaemia) were excluded from the study. Patients with T1DM, on insulin, and on anti-inflammatory drugs, statins, and steroids were also excluded from the study.

Sample size: Diwan AG et al., compared serum levels of leptin in diabetics and non diabetics and found that serum leptin levels were significantly higher (17.35±11.60 U/mL) in diabetic subjects compared to non-diabetic ones (11.19±5.71 U/mL) (p-value ≤0.045) [22]. This data was used in the following formula to calculate sample size:

$n= (Z\alpha/2+Z\beta)^{2*}(SD*2)/d^2$

n= Sample size

Zα/2= Z value at 5% error (1.96)

Zβ= Z value at 10% (1.28)

SD= Average standard deviation of leptin among diabetics and non-diabetics=(SD1+SD2)/2

d=effect size

The above values were entered into G*Power version 3.1 software. The effect size was calculated to be 0.6737. The software calculated the sample size in obese individuals with diabetes and obese individuals without diabetes to be 48 each. Additionally, 25 healthy individuals were included as a control group. The unequal sample size for the control group was due to stringent inclusion/exclusion criteria applied to them. Nevertheless, it was ensured that for statistical comparisons, the unequal sample size was taken into account.

Data collection: A fasting blood sample (5 mL) was collected under aseptic conditions by venipuncture, and investigations were performed using Roche 311, Roche 411, and ELISA reader (Erba LisaScan II). Serum Adiponectin, Leptin, and Insulin were assayed by ELISA using kits from Diagnostic Biochem Canada and Qualisa.

Normal values: Reference values for Adiponectin were as follows:

- BMI <25 kg/m^2=3.4-19.5 µg/mL
- BMI 25-30 kg/m^2=2.6-13.7 µg/mL
- BMI >30 kg/m^2=1.8-9.4 µg/mL [23]

Expected normal values for Leptin were as follows:

- Lean women=3.7-11.1 ng/mL
- Lean men=2.0-5.6 ng/mL [24]

Normal expected values of leptin for lean people were mentioned in the kit insert. No specific range was established and mentioned in the kit insert regarding obese people, but leptin levels are higher than normal expected values in obese individuals [24].

Expected normal values for insulin were as follow:

Adult (normal)=0.7-9.0 µIU/mL

Diabetic (Type 2)=0.7-25 µIU/mL [25]

STATISTICAL ANALYSIS

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) software version 21.0 (SPSS Inc., USA). The data obtained were statistically analysed using mean±SD. Mean values of parameters were compared among the three study groups using a one-way ANOVA test (with Bonferroni post-hoc). The Chi-square test was used for categorical variables.

RESULTS

Out of a total of 125 subjects included in the study, 50 (40%) were obese, 50 (40%) were obese with T2DM, and 25 (20%) were non obese non diabetic (controls). A higher number of females reported in the OPD compared to males. The maximum number of subjects in the obese with T2DM group (n=30, 60%) and obese without T2DM group (n=20, 40%) were in the age group of 51-60 years, whereas in the control (non obese non diabetic) group, the age range was 31-50 years [Table/Fig-1].

Parameters	Group n (%)			Total	p-value
	Obese with T2DM	Obese	Control		
Age (years)					
20-30	1 (2.00)	5 (10.00)	2 (8.00)	8 (6.40)	<0.05*
31-40	7 (14.00)	12 (24.00)	9 (36.00)	28 (22.40	
41-50	12 (24.00)	13 (26.00)	9 (36.00	34 (27.20)	
51-60	30 (60.00)	20 (40.00)	5 (20.00)	55 (44.00)	
Total	50 (100)	50 (100)	25 (100)	125 (100)	
Mean age (M±SD)	50.22±8.6	46.9±9.8	42.8±9.09		<0.01**
Gender					
Female	31 (62.00)	33 (66.00)	14 (56.00)	78 (62.40)	0.38*
Male	19 (38.00)	17 (34.00)	11 (44.00)	47 (37.60)	
Total	50 (100)	50 (100)	25 (100)	125 (100)	

[Table/Fig-1]: Socio-demographic profile of subjects under study.
*analysed using chi-square test; **analysed using one-way ANOVA with Bonferroni post-hoc
No subjects were available between 18-20 years of age

It was observed that levels of serum adiponectin and ALR were lower, whereas serum leptin levels were higher in the obese with T2DM group and obese without T2DM group compared to controls [Table/Fig-2].

It was observed that levels of serum insulin, Fasting Blood Sugar (FBS), HbA1c, and HOMA-IR were higher in the obese with T2DM group compared to the obese without T2DM and control group. Moreover, on comparing the obese without T2DM group with the control group, it was seen that the levels of insulin and HOMA-IR

were higher in the former group, whereas FBS and HbA1c values did not show any change [Table/Fig-3].

Variables	Obese with T2DM (n=50) Mean±SD	Obese (n=50) Mean±SD	Control (n=25) Mean±SD	p-value
Adiponectin (µg/mL)	5.6±3.5	6.1±1.5	8.1±1.5	0.13
Leptin (ng/mL)	7.90±1.20	6.50±1.70	4.40±1.20	0.16
ALR	1.40±0.70	1.90±0.60	2.30±1.50	0.17

[Table/Fig-2]: Serum adiponectin, leptin and Adiponectin-Leptin Ratio (ALR) levels in obese with Type-2 Diabetes Mellitus (T2DM), obese without type 2 diabetes mellitus and non obese, non diabetic individuals (controls).
*analysed using one-way ANOVA with Bonferroni post-hoc

Variables	Obese with T2DM (n=50) Mean±SD	Obese (n=50) Mean±SD	Control (n=25) Mean±SD	p-value
Insulin (µIU/mL)	11.1±57	9.9±1.7	5.2±3.1	<0.01
Fasting blood sugar (mg/dL)	160.30±66.02	94.80±12.37	94.80±12.80	
HbA1c (%)	8.4±1.99	5.30±0.47	5.20±0.43	
HOMA-IR	4.5±2.9	2.6±0.80	1.3±0.82	

[Table/Fig-3]: Serum insulin, FBS, HbA1c and HOMA-IR levels in obese with Type-2 Diabetes Mellitus (T2DM), obese without type 2 diabetes mellitus patients and controls.
*analysed using one-way ANOVA with Bonferroni post-hoc

DISCUSSION

The epidemiological transformation in India, from an underweight to an overweight/obese population, is occurring quickly. Obesity has become a significant global concern due to lifestyle modifications brought about by urbanisation. Changes in the lifestyle of a genetically predisposed population, particularly regarding eating habits and physical exercise, have been associated with a high prevalence of obesity and T2DM in Xavante Indians [26]. Obesity is often associated with a proinflammatory endocrine profile, which contributes to the development of metabolic complications such as IR and T2DM [27]. It has also been demonstrated that obesity leads to decreased sensitivity or resistance to various hormones, including adiponectin and leptin [27]. Numerous studies have shown that a majority of individuals with prediabetes eventually progress to diabetes, and overweight or obese individuals with sedentary lifestyles are at a higher risk of experiencing this progression [28,29]. Research indicates that obese individuals have lower serum levels of adiponectin compared to non obese individuals, which was consistent with the results of present study [29]. In present study, both obese and obese T2DM participants had significantly lower mean serum levels of adiponectin compared to the control group.

Adiponectin levels are down-regulated not only in obese individuals but also in people with T2DM, as it plays a significant role in glucose metabolism and insulin resistance. However, adipocytokines like leptin are positively correlated with obesity [30]. Several research studies have noted a significant relationship between inflammatory mediators such as C-Reactive Protein (CRP), adiponectin, and obesity indices, particularly BMI. Previous researchers have found an inverse relationship between adiponectin and BMI [28]. Furthermore, weight loss and a decrease in BMI in the obese group were accompanied by a significant increase in serum adiponectin levels [28].

Similarly, there is a negative correlation between adiponectin levels and the risk of developing T2DM. A cohort study conducted on a middle-aged female population showed an inverse relationship between adiponectin levels and the risk of developing T2DM [31]. Additionally, a meta-analysis study indicated that high levels of adiponectin were associated with a lower risk of T2DM [32]. These results suggest a biological relationship between obesity and T2DM, indicating that increasing adiponectin levels may help improve insulin sensitivity [29]. However, the relationship between insulin and adiponectin levels and their control over each other is still a subject of debate [30].

Leptin, which is produced by adipocytes in response to changes in body fat mass and nutritional status, plays a role in the obesity-related production of low-grade inflammation [33]. Both leptin and adiponectin regulate blood glucose through different mechanisms. In present study, an increased risk of developing T2DM and obesity when leptin levels increased and adiponectin levels decreased was observed. A previous study revealed that circulating levels of leptin are proportional to the degree of obesity, which was consistent with present findings [30]. It has been observed that leptin levels decrease rapidly with calorie restriction. However, the role of leptin as an antiobesity hormone has been questioned because in "common" obesity, high levels of leptin (indicating high energy stores) are often present, and leptin resistance is observed. This suggests that despite elevated levels of leptin, obese individuals may not reduce their caloric intake due to leptin resistance [29]. The ALR has been shown to be a more accurate indicator of IR than either adiponectin or leptin alone, and it is also more accurate than the HOMA-IR [31]. Therefore, present study determined this ratio in subjects who were obese with and without T2DM. When compared to the control group, the ALR was found to be lower in both obese and obese diabetic subjects. Consistent with the results of the present investigation, a population-based cohort study demonstrated that individuals with obesity and T2DM had lower ALR than non obese individuals. Abnormal adipocytokine profiles are associated with obesity and T2DM [14].

The use of HOMA-IR to understand β-cell function and IR in various disorders related to obesity and diabetes mellitus has been extensively researched [34]. HOMA-IR calculation has been the most commonly used method in several studies evaluating insulin sensitivity [35,36]. de Luis DA et al., found a significant positive association between HOMA-IR and BMI, with obese individuals having higher HOMA-IR values than those with normal BMI [37]. In a cross-sectional investigation of Taiwanese participants, the Leptin-Adiponectin Ratio (LAR) and leptin were positively correlated with the HOMA-IR index, while adiponectin had a negative correlation [38]. Lower IR, as measured by HOMA-IR, was associated with a lower risk of developing T2DM in obese individuals in the predominantly Caucasian Framingham Offspring Study, whereas higher insulin resistance predicted an increased risk of T2DM in non obese subjects [39]. Present study showed that HOMA-IR levels increased in obese individuals, and this increase became more pronounced as obesity progressed to T2DM. Therefore, dysregulated glucose homeostasis, specifically HOMA-IR, is crucial for early detection and prediction of T2DM in obese children and adolescents, and may enable early disease management [40].

Further studies are needed to evaluate the mechanisms by which levels of adiponectin and leptin are altered in the population. Additionally, the potential use of these markers in the management and prevention of obesity-related metabolic disorders such as T2DM should be investigated. Since the subjects included in the study were randomly selected, there was a significant difference in the age distribution of the subjects. Future studies should aim to determine the effect of age on these biochemical parameters, ensuring that the age of subjects is equally distributed among different age groups.

Limitation(s)

The study's limitation was that the obese participants were from a local set-up. Selecting subjects from diverse regions of Punjab could have provided more insights into the study outcome, as lifestyle and food patterns vary. More in-depth research should be conducted in a larger population to validate the results.

CONCLUSION(S)

According to this study, it was observed that there were changes in the levels of adiponectin, leptin, and HOMA-IR in subjects with obesity and obesity with T2DM as compared to non-obese non-diabetic individuals. Low serum adiponectin and ALR, high serum

leptin and HOMA-IR levels are associated with an increased risk of obesity with T2DM. Adiponectin and leptin can be important clinical markers for assessing the morbidity and complications of obesity and T2DM. Further research is needed to study factors such as lifestyle modifications, dietary changes, and weight loss. Additionally, it is important to investigate factors that increase adiponectin levels and enhance ALR to aid clinicians in the timely management of obesity and prevent T2DM and its complications. These studies can further inform physicians in formulating therapeutic strategies.

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