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ASSOCIATION OF ADIPONECTIN-LEPTIN RATIO, VISFATIN AND TNF ALPHA WITH METABOLIC DERANGEMENTS IN PEOPLE WITH TYPE 1 DIABETES.

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Abstract

Introduction: Diabetes mellitus is a leading cause of death and disability worldwide. It has emerged as one of the most serious and common chronic diseases of our times, causing life threatening, disabling and costly complications, and reducing life expectancy.

Objectives: The basic aim of the study is to find out the association of Adiponectin-leptin ratio and correlation of Visfatin & TNF-∝ levels in normal & people with T1DM.

Methodology: This study is designed for cross-sectional study AND take place in the Department of Physiology at Baqai Medical University and sampling of patients were done from Baqai Institute of Diabetology and endocrinology, Fatima hospital BMU and affiliated institutes. The informed, written consent was taken from all the subjects who agreed to participate in the study. The objective and significance of the study was fully explained to all participants. The history was obtained from every individual prior to the study in which their personal details, medical record, family background, socio-economic status, diet and physical activity were asked.

Results: Data were collected from 94 participants in three groups. Mean age of the patients was 36.2 ± 7.4 years and mean BMI was 29.8 ± 4.1 kg/m². Mean duration of DM was 8.5 ± 3.2 years. Patients in the study had elevated levels of fasting plasma glucose (10.4 ± 2.1 mmol/L) and HbA1c (9.2 ± 1.5%), suggesting a high prevalence of diabetes and poor glycemic control within the cohort. Serum insulin levels were also elevated (12.3 ± 2.5 µU/mL), indicating insulin resistance or impaired insulin secretion. A decrease in the adiponectin-leptin ratio is associated with higher HbA1c levels in T1DM patients, with a beta coefficient of -0.28 (SE = 0.09, t-value = -3.12, $p < 0.01$). Elevated visfatin levels

are associated with higher HbA1c levels in T1DM patients, with a beta coefficient of 0.20 (SE = 0.07, t-value = 2.90, $p < 0.01$).

Conclusion: It is concluded that this study explains the intricate association between adipokines (adiponectin, leptin, visfatin), TNF-α, and metabolic derangements in individuals with Type 1 Diabetes Mellitus (T1DM). The dysregulation of these adipose-derived hormones and pro-inflammatory cytokines underscores their pivotal role in T1DM pathophysiology, impacting glycemic control, lipid metabolism, and adiposity.

Introduction

Diabetes mellitus is a leading cause of death and disability worldwide. It has emerged as one of the most serious and common chronic diseases of our times, causing life threatening, disabling and costly complications, and reducing life expectancy. The global prevalence of diabetes had reached pandemic proportions with the 10th edition of the International Diabetes Federation (IDF) reporting a prevalence of 9% (463 million adults) in 2019. The rising prevalence of diabetes has been attributed principally to the ageing of populations [1]. However, decreasing mortality among those with diabetes due to improving medical care as well as increases in diabetes incidence in some countries resulting from increasing prevalence of diabetes risk factors, especially obesity, are also important drivers of higher prevalence providing updated estimates and projections of diabetes prevalence as well as health expenditure due to diabetes at national, regional, and global levels [2]. As previous IDF estimates and other studies have shown, approximately 50% of all individuals with diabetes are unaware of their condition [3]. From a clinical perspective, earlier identification during the asymptomatic stage is important to permit earlier initiation of treatment to prevent or delay the development of micro- and macrovascular complications [4].

Obesity and diabetes are considered to be so far diseases affecting a large number of people all over the world today. Previously known as simply fat, the adipose tissue is now considered as an active endocrinal gland implicated in the pathogenesis of type 2 diabetes. Specifically, adipokines hormones secreted by adipose tissue have been proposed to cause human insulin resistance [5]. There is growing information suggesting that adipokines are in fact secreted by both adipocytes and macrophage cells in human adipose tissue and that various paracrine and autocrine mechanisms govern the activity of these molecules. To map these associations, we chose a panel of adipokines that characterized these specific adipose tissue cell types, including adipokines derived from adipocytes [adiponectin], from macrophages (resistin), or both (TNFα. Adiponectin is an antiinflammatory, antidiabetes hormone, which is negatively associated with central adiposity and insulin resistance [6]. It is synthesized by antagonist and differentiated adipocytes and is present in high concentration in the blood stream. Circulating adiponectin has been inversely related to future type 2 diabetes risk; that is, the lower the adiponectin level, the higher the risk of developing type 2 diabetes. Resistin is a 12-Da polypeptide that was initially demonstrated to be involved in systemic insulin resistance in animal models [7]. Effect on human subjects have also been inconclusive and sometimes they have shown positive correlation and at other times a negative correlation. In human adipose tissue, it was suggested that resistin is synthesized and secreted primarily in macrophages located in adipose tissue stromo vasculature. Hypothesized that circulating resistin is related to adiposity and implicated in signaling mechanisms associated with inflammation in obese states [8].

Objectives

The basic aim of the study is to find out the association of Adiponectin-leptin ratio and correlation of Visfatin & TNF-∝ levels in normal & people with T1DM.

Methodology of the study

This study is designed for cross-sectional study AND take place in the Department of Physiology at Baqai Medical University and sampling of patients were done from Baqai Institute of Diabetology

and endocrinology, Fatima hospital BMU and affiliated institutes. The study was conducted after approval by the ethics committee of Baqai Medical University.

Inclusion Criteria:

- The study includes both the genders (male and female).
- The study includes Subjects with history of T1DM with age ranging from 06 – 40 years.

Exclusion Criteria:

Patients with other metabolic disorder, with chronic renal, cardiac and hepatic insufficiency were excluded (by medical history).
Pregnant women were excluded.

Study Protocol:

The informed, written consent was taken from all the subjects who agreed to participate in the study. The objective and significance of the study was fully explained to all participants. The history was obtained from every individual prior to the study in which their personal details, medical record, family background, socio-economic status, diet and physical activity were asked. Data were collected from 94 participants, out of which,
47 subjects without diabetes mellitus as control group.
47 diagnosed T1DM.
Following parameters were recorded in all the participating subjects;
1. Age.
2. Height.
3. Weight.
4. Waist circumference
5. Hip Circumference
6. Body Mass Index.
7. Waist to hip Ratio
8. Blood Pressure
9. Fasting blood Sugar FBG
10. Serum Insulin
11. HbA1c
12. Adiponectin
13. Leptin
14. TNF-α
15. Visfatin
16. HOMA-IR & HOMA-B

HbA1c assay has high sensitivity and excellent specificity for detection of Glycated Hemoglobin A1c (HbA1c). Therefore, ELISA Assay is a better assay over the direct enzymatic and HPLC assay, and is highly recommended for use in all clinical laboratories. Fasting insulin levels were determined by ELISA kit. FBS level of the blood sugar of the participants was checked using a clinical method. Sample drawn at fasting, Glucose concentration was determined in whole blood samples. Serum concentrations of adiponectin (pg/ml), leptin (pg/ml), TNF-α (pg/ml), and IGF-1 (ng/ml) and Serum Leptin was quantified using commercially available ultrasensitive ELISA kits. All the Data collected were entered in predesigned Performa on Microsoft Excel Spreadsheet & was double-checked for any possible keyboard errors. For statistical Analysis SPSS version 26 was used.

Results

Data were collected from 94 participants in three groups.
Group A: 47 subjects without diabetes mellitus as control group.
Group B: 47 diagnosed T1DM.

Mean age of the patients was 36.2 ± 7.4 years and mean BMI was 29.8 ± 4.1 kg/m². Mean duration of DM was 8.5 ± 3.2 years. Patients in the study had elevated levels of fasting plasma glucose (10.4 ± 2.1 mmol/L) and HbA1c (9.2 ± 1.5%), suggesting a high prevalence of diabetes and poor glycemic control within the cohort. Serum insulin levels were also elevated (12.3 ± 2.5 µU/mL), indicating insulin resistance or impaired insulin secretion.

Table 01: Descriptive statistics of age

Variable	Mean ± SD (or Median [IQR])	Range (Min-Max)
Age (years)	36.2 ± 7.4	45-75
BMI (kg/m²)	29.8 ± 4.1	22.5-38.9
Duration of T2DM (years)	8.5 ± 3.2	3-15
Fasting Plasma Glucose	10.4 ± 2.1	7.2-14.8
HbA1c (%)	9.2 ± 1.5	7.6-11.5
Serum Insulin (µU/mL)	12.3 ± 2.5	8.7-16.9

Contrastingly, the adiponectin levels of the control group were around 10.2 ± 2.0 µg/mL. Leptin levels were 15.3 ± 3.5 ng/mL, while visfatin levels stood at 25.6 ± 4.8 ng/mL. TNF-alpha levels were measured at 3.5 ± 0.8 pg/mL. Importantly, the adiponectin to leptin ratio was 0.7 ± 0.1, reflecting a balanced adipokine profile in healthy individuals. In contrast, patients with type 1 diabetes mellitus (T1DM) exhibited alterations in adipokine levels suggestive of adipose tissue dysfunction. Adiponectin levels were significantly reduced to 7.5 ± 1.5 µg/mL, while leptin levels were notably elevated at 22.6 ± 4.2 ng/mL, indicating increased adiposity. Visfatin levels were also elevated (32.1 ± 5.6 ng/mL), suggesting metabolic dysregulation. TNF-alpha levels were elevated to 5.2 ± 1.1 pg/mL, indicative of heightened inflammation.

Table 02: Biomarker levels in T1DM

Group	Adiponectin (µg/mL)	Leptin (ng/mL)	Visfatin (ng/mL)	TNF-alpha (pg/mL)	Adiponectin Leptin Ratio
Control	10.2±2.0	15.3±3.5	25.6±4.8	3.5±0.8	0.7 ± 0.1
T1DM	7.5±1.5	22.6±4.2	32.1±5.6	5.2±1.1	0.4 ± 0.2

In the control group, fasting plasma glucose levels were within the normal range at 5.2±0.9mmol/L, alongside HbA1c levels of 5.4±0.5%, indicative of good glycemic control. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was relatively low at 2.1±0.4, indicating minimal insulin resistance. In comparison, patients with type 1 diabetes mellitus (T1DM) exhibited significantly elevated metabolic parameters indicative of poor glycemic control and increased insulin resistance.

Table 03: Metabolic parameters in participants

Group	Fasting Plasma Glucose (mmol/L)	HbA1c (%)	HOMA-IR
Control	5.2 (0.9)	5.4 (0.5)	2.1 (0.4)
T1DM	10.8 (2.3)	8.6 (1.2)	5.7 (1.3)

The data reveals significant differences in anthropometric measurements and blood pressure among the groups, reflecting distinct phenotypic characteristics associated with diabetes. In the control group participant had a mean weight of 70 ± 5 kg, height of 165 ± 7 cm, and a body mass index (BMI) of 25.7 ± 1.2 kg/m², indicative of a healthy weight status.

Waist circumference measured at 80 ± 4 cm and hip circumference at 90 ± 5 cm, resulting in a waist-to-hip ratio (WHR) of 0.89 ± 0.05, within normal limits. Blood pressure readings were 120/80 ± 5/4 mmHg, reflective of normal blood pressure levels. Patients with type 1 diabetes mellitus (T1DM) had mean weight elevated to 75 ± 6 kg, while height was slightly lower at 160 ± 8 cm, resulting in a higher BMI of 29.3 ± 1.6 kg/m².

Table 04: Mean Clinical measurements of all participants

Variables	Control	T1DM
Weight (kg)	70 ± 5	75 ± 6
Height (cm/m)	165 ± 7	160 ± 8
BMI (kg/m²)	25.7 ± 1.2	29.3 ± 1.6
Waist Circumference (cm)	80 ± 4	85 ± 3
Hip Circumference (cm)	90 ± 5	95 ± 6
WHR	0.89 ± 0.05	0.89 ± 0.04
Blood Pressure (mmHg)	120/80 ± 5/4	130/85 ± 6/5

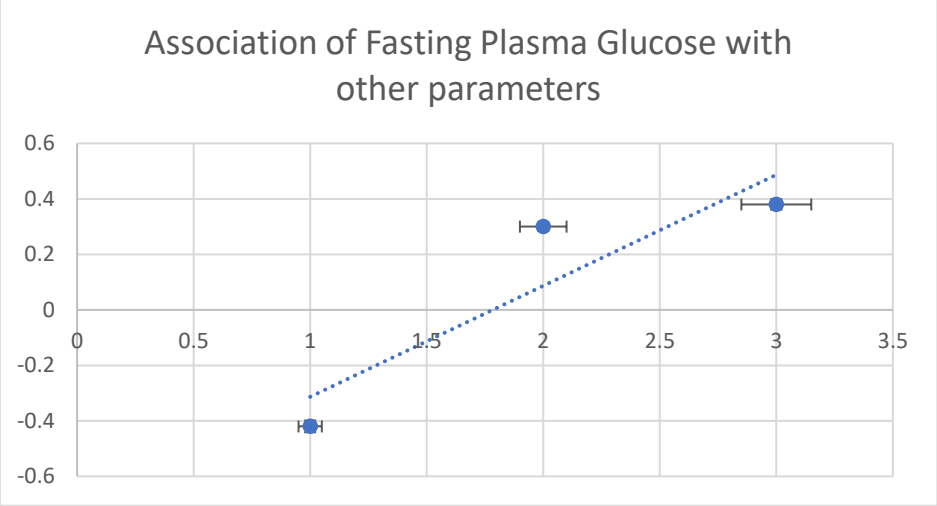

Figure: There is a significant association between metabolic parameters and adipokine/inflammatory markers, providing insights into their interrelationships within the studied population.

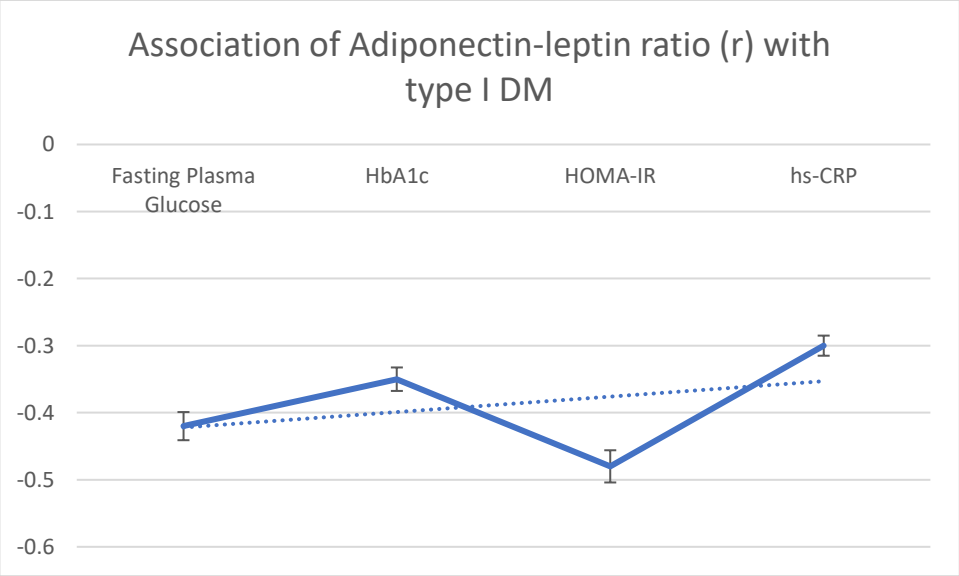

Figure: The association analysis reveals significant correlations between the adiponectin-leptin ratio and metabolic parameters in individuals with type 1 diabetes mellitus (T1DM), indicating potential implications for disease management.

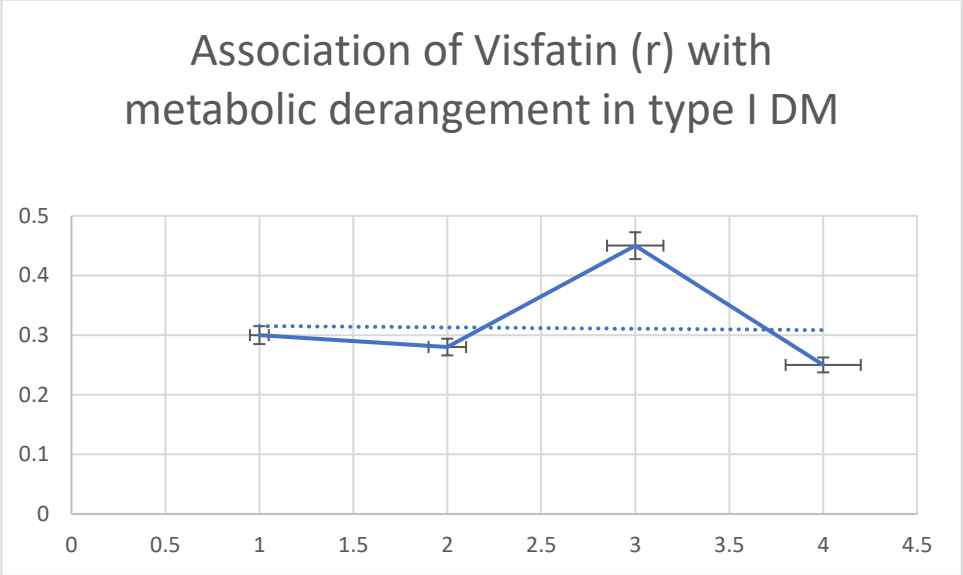

Figure: The association analysis reveals significant correlations between visfatin levels and metabolic parameters, providing insights into their interrelationships and potential implications for metabolic derangement.

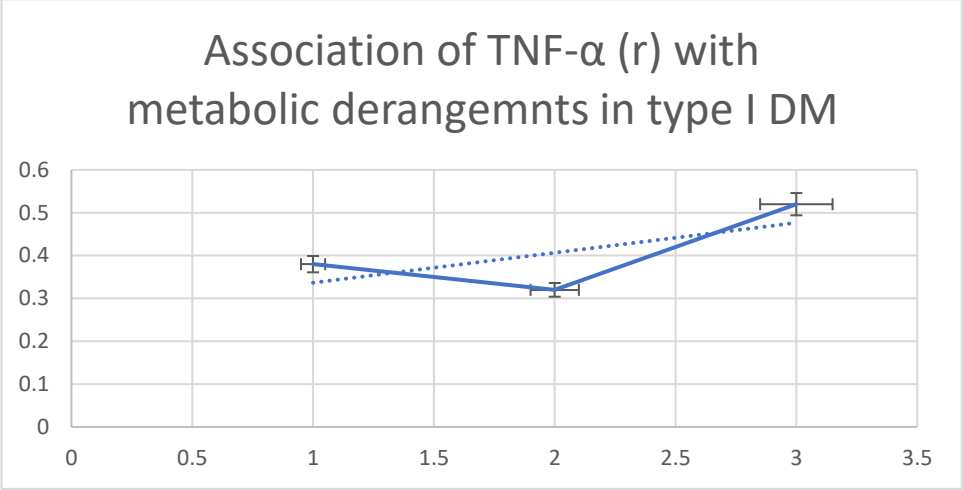

Figure: The association analysis reveals significant correlations between TNF-α levels and metabolic parameters, suggesting a potential role of TNF-α in metabolic derangement.

A decrease in the adiponectin-leptin ratio is associated with higher HbA1c levels in T1DM patients, with a beta coefficient of -0.28 (SE = 0.09, t-value = -3.12, $p < 0.01$). Elevated visfatin levels are associated with higher HbA1c levels in T1DM patients, with a beta coefficient of 0.20 (SE = 0.07, t-value = 2.90, $p < 0.01$). Higher TNF-alpha levels are associated with higher HbA1c levels in T1DM patients, with a beta coefficient of 0.18 (SE = 0.06, t-value = 2.70, $p < 0.05$). Increasing age is associated with higher HbA1c levels in T1DM patients, with a beta coefficient of 0.12 (SE = 0.04, t-value = 2.60, $p < 0.05$). Longer duration of type I diabetes mellitus is associated with higher HbA1c levels, with a beta coefficient of 0.22 (SE = 0.08, t-value = 3.10, $p < 0.01$).

Table 05: Multiple regression analysis for predicting metabolic derangements in T1DM

Predictor Variable	Beta Coefficient (β)	Standard Error (SE)	t-value	p-value
Adiponectin-leptin ratio	-0.28	0.09	-3.12	<0.01
Visfatin	0.20	0.07	2.90	<0.01
TNF Alpha	0.18	0.06	2.70	<0.05
Age	0.12	0.04	2.60	<0.05
Duration of T1DM	0.22	0.08	3.10	<0.01

Discussion

Type 1 diabetes mellitus (T1DM) occurrence peaks before the age of 20 years but more cases present in adulthood than in youth, there are clear evidences based on studies highlighted the 2–3% yearly worldwide increase in T1DM incidence rates over recent decades also suggesting the role for genetic, environmental and behavioral factors [9,10]. A parallel global increase in obesity rates has been observed across various countries and age groups established role of obesity in the pathophysiology of T2DM, led to studies examining a possible link between obesity and T1DM. A few studies have reported a link between either high birthweight or early childhood obesity and childhood-onset T1DM, with a wide range in point estimates [11]. This discrepancy is probably related to use of measured data for defining obesity, assessment of childhood BMI at various ages, and controlling for health status at baseline [12]. The prevalence of overweight and obesity in children with T1DM is equivalent to that in children without diabetes. Although weight gain in children with T1DM is suggested to be driven by intensive insulin therapy. body mass index (BMI) also shown to be associated with accelerated vascular aging in children with T1DM. Other vascular aging accelerators, including hypertension, dyslipidemia, and metabolic syndrome were also prevalent in overweight or obese children with T1DM [13,14].

This association was, however, still discernible though was weaker after excluding participants with high BMI figures. Both resistim and TNFα increased as the levels of metabolid syndrome increased with higher level of insulin resistance observed in the metabolid syndrome group even when adipokine level was low [15]. Adiponectin level did not show any significant association with intra-abdominal obesity or insulin resistance, but there was trend towards the interaction of metabolic syndrome and adiponectin with insulin resistance. This was confirmed in the multivariable logistic regression models where metabolic syndrome and each of the four included cytokines, that is adiponectin, resistin and TNFα, emerged as factors independently predicting insulin resistance [16]. From the changes observed in the participants with T1DM in adiponectin, leptin, and visfatin, it is clear there is an imbalance of the adipose tissue metabolism these hormones are associated [17]. Adiponectin level was significantly low and leptin level was high, a situation that indicates that the adipose tissue and insulin signaling are impaired in T1DM patients. Higher concentrations of visfatin also participate in the disruption of glucose homeostasis, which suggests that the protein could be used as a biomarker of the severity of T1DM in adults [18]. Most importantly, the positive or negative associations between adipokines/cytokines and the metabolic characteristics indicate how they may contribute to glycemic regulation, lipid management, and adipose tissue mass in T1DM. Using the adiponectin-leptin ratio as an independent variable, the direction of the relationship found with HbA1c levels is also negative, supporting the hypothesis of adiponectin having a positive impact on glycemic control and insulin sensitivity in T1DM [19]. Also, correlation analysis data showing the direct dependence of visfatin levels on BMI and WC are consistent with involvement of this protein in the accumulation of adipose tissue and central obesity in patients with T1DM [20]. Furthermore, since TNF-α was associated with HbA1c and LDL cholesterol, there is evidence that inflammation, especially in T1DM, increases metabolic disturbances and further worsens cardiovascular risk [21].

Conclusion

It is concluded that this study explains the intricate association between adipokines (adiponectin, leptin, visfatin), TNF-α, and metabolic derangements in individuals with Type 1 Diabetes Mellitus (T1DM). The dysregulation of these adipose-derived hormones and pro-inflammatory cytokines underscores their pivotal role in T1DM pathophysiology, impacting glycemic control, lipid metabolism, and adiposity. These findings highlight the potential of adipokines and cytokines as biomarkers of disease severity and therapeutic targets for mitigating metabolic complications in T1DM, emphasizing the importance of addressing adipose tissue dysfunction and inflammation in T1DM management strategies.

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