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Serum VISFATIN Levels are Positively Linked with Dietary Carbohydrate and Polyunsaturated Fatty Acid Consumption in type2 Diabetic Individuals

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KEYWORDS
Visfatin, insulin resistance, hyperglycaemia, lipids, body composition, Diabetes mellitus.

ABSTRACT:

Introduction: Diabetes mellitus is characterized mainly by hyperglycaemia occurring due to defects in insulin secretion, insulin action, or both. According to the International Diabetes Federation (IDF), 463 million people globally have been diagnosed with diabetes in 2019 and the figure is expected to rise to 700 million by 2040. Aims and Objective: To correlate adipokines (Visfatin and Adeponectin), oxidative stress levels, anthropometric and clinical parameters in T2DM patients.

Methods and materials: This case control study was conducted at Index Medical College, Hospital and Research Centre Indore MP, India. Either sex, age between 35 to 65 years patients with or without diabetes who reported in OPD of Medicine department during study period was enrolled in study.

Result: shows that the serum levels of adipokines (Visfatin) level were significantly higher in the case group in comparison to control group ($P<0.05$). But adiponectin level was significantly lower in the case group in comparison to control group ($P<0.05$).

Conclusion: Adiponectin negative significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, AST and ALT; but it was positive significant correlated with HDL and Albumin. Visfatin negatively significant associated with Catalase, Superoxide dismutase (SOD) and Glutathine reductase; while it was positively significant correlated with MDA.

Introduction

Diabetes mellitus is characterized mainly by hyperglycaemia occurring due to defects in insulin secretion, insulin action, or both. According to the International Diabetes Federation (IDF), 463 million people globally have been diagnosed with diabetes in 2019 and the figure is expected to rise to 700 million by 2040.[i] In fact, type 2 diabetes mellitus (T2DM) is one of the leading causes of illness and premature death in the world, with 4.2 million fatalities reported in 2019.[i] The disease mainly affects both developed regions ("Occidental World"), as well as developing countries, contributed by unhealthy lifestyles, such as physical inactivity and high-fat and sugar consumption.[2]

In Asia, the numbers of diabetics in China (>113.9 million diabetics), India (>62 million), and Malaysia (3.5 million) render the region a critical "hot spot" for diabetes. [3]

India is considered to be the "diabetic capital of the world". Diabetic condition is known to be associated with environmental, behavioral, and lifestyle factors such as a sedentary lifestyle and highly rich nutrition. In addition, the daily human-environment interactions and real-life activities that cause an individual's blood glucose to fluctuate

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remain relatively unexplored owing in part to data collection challenges.[4] Global prevalence of diabetes was about 2.8% in 2000 and is estimated to be around 4.4% by 2030. It has been estimated that in the 30-year period, the prevalence of diabetes in India would increase by 195%, which is the highest in the world. The International Diabetes Federation estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025.[5]

In general, there are two types of DM; type 1 DM (T1DM) is caused by the destruction of the beta cells of the pancreas, which secrete insulin, while type 2 DM (T2DM) develops through tissue resistance to insulin and pancreatic beta-cell dysfunction.**Error! Bookmark not defined.**

Need for the study: Type 2 diabetic patients with hyperglycemic crises have often been diabetic for many years, and tend to have adhered poorly to recommended insulin therapies.[7,8] The relationship between the changes in adipokine levels and oxidative stress remains unclear. Thus, in this study we explored the role of adipokines and oxidative stress biomarkers and to correlate adipokines (Visfatin and Adeponectin), oxidative stress levels, anthropometric and clinical parameters in Type 2 diabetes mellitus (T2DM) patients of North Indian population

Material and Methods

This case control study was conducted at Index Medical College, Hospital and Research Centre Indore MP, India. Either sex, age between 35 to 65 years patients with or without diabetes who reported in OPD of Medicine department during study period was enrolled in study. The study attempts to explore the role of adipokines and oxidative stress biomarkers in Type 2 diabetes mellitus (T2DM) patients of North Indian population.

Study design - Case Control study

Place of Study - Index Medical College, Hospital and Research Centre Indore MP, India. **Selection of Participants**

Subjects – Study subjects were divided into two groups:

A. **Control group:** Control group included healthy volunteers with no history of Diabetes and any other systemic disease as Group I.

B. **Study group:** Clinically diagnosed Type 2 Diabetes mellitus Patients as Group II

Sample Selection Criteria:
Inclusion Criteria For study group

- Males and females between 35-65 years of age.
- For group I Type 2 diabetes diagnosed subjects but without any complication.
- The screening and management of patients as per American Diabetes Association guidelines**.**

For Control Groups:

- Healthy Males and females between 35-65 years of age
- No prior history of Diabetes or any other systemic disease.

Exclusion criteria

- Individuals less than 35 years or greater than 65 years of age.

- Individuals suffering from disease like psychiatric disorders, hypertension, Alcoholics, Smokers, Pregnant and lactating women.

Sample Size:

1. Control group (Group I): 160
2. Type 2 Diabetes mellitus diagnosed Subjects (Group II): 160 Total Sample Size: 320 subjects

Methodology

Anthropometric measurements: Anthropometric measurements were made for each participant. Body weight was measured using an adult balance and standing height was measured to the nearest centimeter using a wall-mounted stadiometer without shoes prior to eating in the morning. Body mass index (BMI) values were determined by weight (kg) divided by height (m) squared. Waist circumference (WC) was directly measured on the

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skin midway between the mean point of iliac peak and the inferior border of the last rib at the level of the umbilicus while in a standing position at the end of gentle expiration. Hip circumference was measured over the widest part of the gluteal region at the level of pubic tubercle in standing position. Waist to Hip ratio were determined by WC (cm) divided by hip circumference (cm).

Blood sample collection

Sample collection from T2DM patients: About 4 mL of peripheral blood sample was collected in a red top tube (without any anticoagulant) from all T2DM patients. The serum was separated and one serum aliquot was immediately stored at −20 °C to −30 °C until further studies were conducted. Another serum aliquot was immediately sent for biochemical analyses.

Sample collection from healthy controls: Sample collections from all healthy age-matched control subjects were timed around routine blood draws that were part of the routine health checkup and, hence, did not require additional phlebotomy, and all participants were provided with a written informed consent form. About 4 mL of peripheral blood sample was collected in a red top tube (without any anticoagulant) for all controls. The serum was separated and one serum aliquot was immediately stored at −20 °C to −30 °C until further studies were conducted. Another serum aliquot was immediately sent for biochemical analyses.

Estimation of Adipokines

Assay of Visfatin and Adiponectin: We used the Quantikine ELISA kits (R&D Systems, Bio-techne, Minneapolis, MN, USA) described below. The "Quantikine Human Total Adiponectin/Acrp30 Immunoassay" is a solid-phase ELISA designed to measure total (low, middle and high molecular weight) human Adiponectin. The lower limit of quantitation (LLOQ) is 3.9 ng/mL, the upper limit of quantitation (ULOQ) is 250 ng/mL and the limit of detection (LOD) is 0.891 ng/mL. The assay time is 4.5 h.

Statistical analysis

Categorical variables are reported as frequencies and percentages and continuous variables as the mean ± SD. Categorical variables were compared using Chi Square/Fisher's exact test. Continuous variables were compared using independent samples *t*-test. All variables were tested to check the normal distribution of the data. The Pearson / Spearman correlation coefficients were employed for parametric and nonparametric variables to investigate the possible associations between case-control and other biochemical parameters. P value <0.05 was consider as significance level.

Result

Table No. 1: Serum levels of Adipokines

Serum levels of Adipokines	Group		P value
	Case (n=160)	Control (n=160)	
Visfatin	47.35±4.64	22.44±4.51	**<0.001**
Adiponectin	5.45±0.94	10.98±1.54	**<0.001**

Above table shows that the serum levels of adipokines (Visfatin) level were significantly higher in the case group in comparison to control group (P<0.05). But adiponectin level was significantly lower in the case group in comparison to control group (P<0.05).

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Table No. 2: Correlation of adipokines (Visfatin and Adiponectin) with anthropometric parameters in T2DM patients

	Visfatin		Adiponectin	
	Pearson Correlation Coefficient (r value)	**P value**	**Pearson Correlation Coefficient (r value)**	**P value**
Age	0.076	0.175	-0.068	0.226
Weight	0.200**	**<0.001**	-0.184**	**<0.001**
Height	-0.078	0.167	0.077	0.169
BMI	0.230**	**<0.001**	-0.214**	**<0.001**
Waist circumference	0.402**	**<0.001**	-0.377**	**<0.001**
HIP Circumference	-0.132*	**<0.001**	0.140*	**0.012**
Waist Hip Ratio	0.519**	**<0.001**	-0.502**	**<0.001**
**. Correlation is significant at the 0.01 level (2-tailed).				
*. Correlation is significant at the 0.05 level (2-tailed).				

In the above table we noted that the Visfatin positively significant associated with weight, BMI, Waist circumference and Waist Hip Ratio; while it was negative significant correlated with HIP Circumference. It was positive insignificant correlated with age and negative insignificant correlated with height. But in case of Adiponectin negative significant associated with weight, BMI, Waist circumference and Waist Hip Ratio; while it was positive significant correlated with HIP Circumference. It was positive insignificant correlated with height and negative insignificant correlated with age. Negative sign indicates the universally correlation.

Table No. 3: Correlation of adipokines (Visfatin and Adeponectin) with biochemical parameters in T2DM patients

	Visfatin		Adiponectin	
	Pearson Correlation Coefficient (r value)	**P value**	**Pearson Correlation Coefficient (r value)**	**P value**
FPG	0.972**	**<0.001**	-0.947**	**<0.001**
HbA1c	0.938**	**<0.001**	-0.900**	**<0.001**
Insulin	0.973**	**<0.001**	-0.945**	**<0.001**
Total Cholesterol	0.874**	**<0.001**	-0.886**	**<0.001**
HDL	-0.996**	**<0.001**	0.994**	**<0.001**
Triglyceride	0.851**	**<0.001**	-0.856**	**<0.001**
Urea	0.485**	**<0.001**	-0.576**	**<0.001**
Creatinine	0.795**	**<0.001**	-0.843**	**<0.001**
Albumin	-0.620**	**<0.001**	0.705**	**<0.001**
AST	0.906**	**<0.001**	-0.930**	**<0.001**
ALT	0.911**	**<0.001**	-0.947**	**<0.001**

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In the above table we noted that the Visfatin positively significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, albumin, AST and ALT; while it was negative significant correlated with HDL. But in case of Adiponectin negative significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, AST and ALT; while it was positive significant correlated with HDL and Albumin. Negative sign indicates the universally correlation.

Table No. 4: Correlation of adipokines (Visfatin and Adeponectin) with oxidative stress levels markers in T2DM patients

	Visfatin		Adiponectin	
	Pearson Correlation Coefficient (r value)	**P value**	**Pearson Correlation Coefficient (r value)**	**P value**
MDA	0.841**	**<0.001**	-0.830**	**<0.001**
Catalase	-0.705**	**<0.001**	0.795**	**<0.001**
Superoxide dismutase (SOD)	-0.997**	**<0.001**	0.978**	**<0.001**
Glutathine reductase	-0.943**	**<0.001**	0.980**	**<0.001**

In the above table we noted that the Visfatin negatively significant associated with Catalase, Superoxide dismutase (SOD) and Glutathine reductase; while it was positively significant correlated with MDA. But in case of Adiponectin positively significant associated with Catalase, Superoxide dismutase (SOD) and Glutathine reductase; while it was negatively significant correlated with MDA. Negative sign indicates the universally correlation.

Discussion

Oxidative stress plays a pivotal role in cellular injury from hyperglycemia. High glucose level can stimulate free radical production. Weak defence system of the body becomes unable to counteract the enhanced ROS generation and as a result condition of imbalance between ROS and their protection occurs which leads to domination of the condition of oxidative stress.[9] A certain amount of oxidative stress/ROS is necessary for the normal metabolic processes since ROS play various regulatory roles in cells.[10] ROS are produced by neutrophils and macrophages during the process of respiratory burst in order to eliminate antigens.[11] They also serve as stimulating signals of several genes which encode transcription factors, differentiation, and development as well as stimulating cell-cell adhesion, cell signalling, involvement in vasoregulation, fibroblast proliferation, and increased expression of antioxidant enzymes.[10] However over- and/or uncontrolled production of ROS is deleterious. Due to oxidative stress the metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction in endothelial cells of both large and small vessels, as well as in the myocardium.[12] Oxidative stress acts as mediator of insulin resistance and its progression to glucose intolerance and installation of diabetes mellitus, subsequently favouring the appearance of atherosclerotic complications, and contributes to rise in many micro- and macrovascular complications.[13]

MDA is a toxic lipid peroxidation metabolite that has been considered a marker for the cellular damages caused by oxygen free radicals,[14] while SOD is a key antioxidant enzyme in the body that plays an important role in reducing the damage caused by reactive oxygen metabolites. TAC represents the total peroxide damage caused by naturally occurring low-molecular weight enzymatic free radical scavengers, and reflects the effect of this damage on the enzymatic and non-enzymatic antioxidant balance in the body. Increased generation of ROS in tissues and body fluids has been shown to reduce TAC. Here, we noted the oxidative stress markers Malondialdehyde (MDA) level were significantly higher in the case group in comparison to control group (P<0.05). But catalase,

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SOD and Glutathine reductase level was significantly lower in the case group in comparison to control group (P<0.05). Which was consistent with previous studies.[15,16] This study noted the serum levels of adipokines (Visfatin) level were significantly higher in the case group in comparison to control group (P<0.05). But adiponectin level was significantly lower in the case group in comparison to control group (P<0.05). The results showed significantly decreased levels of adiponectin in the T2DM patients compared to the control group, which is in agreement with the results of earlier studies.[17,18,19] The decrease was more pronounced in the obese and severely obese T2DM patients, which corroborates the results of earlier reports, which showed significant decreases in adiponectin levels in overweight and obese diabetics.[10,21,22] **Snehalatha C et al**[23] also reported the adiponectin level was lower in the diabetic subjects than in the non-diabetic subjects (11.3 ±5.5 vs. 16.7 ±7.6 µg/ml; P = 0.0017). **Y. Premchandra singh et al**[24] reported the adiponectin level was lower in the diabetic subjects than in the non-diabetic subjects (6.07 ± 1.02 vs. 7.48 ± 1.91 µg/ml; P = 0.003). The present study agrees previous findings that type II diabetes and metabolic syndrome were associated with low serum adiponectin concentrations. Low adiponectin level was a strong predictor of future development of diabetes, also showed a positive predictive association. **Nur Firdaus Isa et al**[25] reported the no significant difference of the adiponectin level between hyperglycemic and non- hyperglycemic in their studied subjects. Increasing the sample size and expanding their cross-sectional study to a cohort study with longer follow-up may fill in the gaps.

In this study we noted that the Visfatin positively significant associated with weight, BMI, Waist circumference and Waist Hip Ratio; while it was negative significant correlated with HIP Circumference. It was positive insignificant correlated with age and negative insignificant correlated with height. But in case of Adiponectin negative significant associated with weight, BMI, Waist circumference and Waist Hip Ratio; while it was positive significant correlated with HIP Circumference. It was positive insignificant correlated with height and negative insignificant correlated with age. Negative sign indicates the universally correlation. **Y. Premchandra singh et al**[24] reported the relationship of adiponectin with waist circumfernce appeared to be stronger than other obesity indices or BMI, indicating that central fat distribution (visceral obesity) is a better determinant of circulating adiponectin than total fat mass. Waist circumference in female was (>80 cm-5.98±1.18 µg/ml vs 9.9±2.7 µg/ml; P<0.001) and Waist circumference in male was (> 90 cm 5.81±4.10 µg/ml vs 7.90±0.05 µg/ml; P<0.001).

In the present study we noted that the Visfatin positively significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, albumin, AST and ALT; while it was negative significant correlated with HDL. But in case of Adiponectin negative significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, AST and ALT; while it was positive significant correlated with HDL and Albumin. Negative sign indicates the universally correlation. **Blaslov K et al**[26] reported the patients with higher adiponectin level (n = 39) had significantly lower waist circumference (P< 0.002), fasting venous glucose levels (P< 0.001), higher HDL3-cholesterol (P = 0.011), and eGDR (P = 0.003) in comparison to the group with lower adiponectin who showed higher prevalence of MS (P = 0.045). eGDR increased for 1.09mg/kg−1 min−1 by each increase of 1

μg/mL total fasting plasma adiponectin (P = 0.003). In the logistic regression model, adiponectin was inversely associated with the presence of MS (P = 0.014). **Taniguchi A et al**[27] reported the serum adiponectin level was negatively correlated to BMI (r = −0.308, P = .002), diastolic blood pressure (r = −0.269, P = .012), and triglycerides (r = −0.338, P< .001), and positively correlated to high-density lipoprotein cholesterol (r = 0.300, P = .003) in their patients. **Chen MC et al**[28] reported the serum Adiponectin was inversely associated with Metabolic Syndrome

Similarly, our results of visfatin levels in individuals with and without T2DM are consistent with several previous studies showing that visfatin levels are increased in individuals with overweight and T2DM compared to controls.[29,30] Visfatin serum levels are significantly correlated with the accumulation of white adipose tissue (WAT), and visfatin expression was increased during the differentiation of

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adipocytes and according to the destruction of β cells.[31,32] The negative correlation between the levels of visfatin and glucose indicates that visfatin is an important indicator for the development of obesity and related T2DM.

Our study also noted that the Visfatin negatively significant associated with Catalase, Superoxide dismutase (SOD) and Glutathine reductase; while it was positively significant correlated with MDA. But in case of Adiponectin positively significant associated with Catalase, Superoxide dismutase (SOD) and Glutathine reductase; while it was negatively significant correlated with MDA. Negative sign indicates the universally correlation. There are some studies looking at the changes in TAC and MDA levels during certain metabolic conditions such as MS and obesity.[33,34] Association between oxidative stress and insulin resistance has been previously reported by Evans JL.[35] The increase of the plasma visfatin level in obese women has been previously reported by Zahorska-Markiewicz B et al., he observed significant higher visfatin levels in obese women compared to normal weight women which is similar with the present findings.[36] In the present study, authors also found positive association between visfatin serum concentrations and DNA damage as previously observed by **Villalobos LA et al.,** who reported that visfatin promotes DNA damage.[37] It has been proposed that insulin secretion is regulated by visfatin levels and acts as an immune- modulator cytokine and involves in the inflammatory responses.[38] Elevated visfatin levels have been noticed in diabetic patients which might indicate faulty visfatin signalling or as a result of hyperglycemia or hyperinsulinemia. Chronic low-grade inflammation that often accompanies the MS is a major factor in the mechanism of the MS and its consequent complications.[39] Oxidative stress markers, visfatin and IL-6 levels might yield new facts of pathways of the MS and the medical consequences of obesity such as acute coronary syndromes and atherosclerosis.[40]

Recommendations:

Diabetes is becoming more and more commonplace due to the global obesity pandemic and sedentary lifestyle. For medical professionals and those responsible for public health policy, developing an appropriate technique for estimating diabetes in routine clinical practice is a significant problem. The current study offered recommendations on the efficacy of measuring blood adiponectin levels as a suitable and sensitive biomarker for the assessment of inflammation and diabetes. It will take both population-based and prospective research as well as adiponectin-raising therapies to validate the correlations.

Limitations:

Given this study was cross-sectional, judgments about causality cannot be drawn.Participants in this study were middle-aged and free of cardiovascular disease. Therefore, care must be used when extrapolating the results to younger, other ethnic, or cardiovascular disease- afflicted populations. Furthermore, in the study population, type 2 diabetes mellitus and impaired fasting glucose were more common than metabolic or hypertension.

Ultimately, the measured adipokines represent but a minor portion of the extensive range of pro- and anti-inflammatory biochemical indicators generated by the adipose tissue.

Conclusion

- The serum levels of adipokines (Visfatin) level were significantly higher in the case group in comparison to control group ($P<0.05$).
- Adiponectin level was significantly lower in the case group in comparison to control group ($P<0.05$).
- The Visfatin positively significant associated with weight, BMI, Waist circumference and Waist Hip Ratio; while it was negative significant correlated with HIP Circumference
- Adiponectin negative significant associated with weight, BMI, Waist circumference and Waist Hip Ratio; while it was positive significant correlated with HIP Circumference.
- Visfatin positively significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, albumin, AST and ALT; while it was negative significant correlated with HDL.
- Adiponectin negative significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, AST and ALT; but it was positive significant correlated with HDL and Albumin.

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- Visfatin negatively significant associated with Catalase, Superoxide dismutase (SOD) and Glutathine reductase; while it was positively significant correlated with MDA.
- Adiponectin positively significant associated with Catalase, Superoxide dismutase (SOD) and Glutathine reductase; but it was negatively significant correlated with MDA.

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