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Original Research Article

CORRELATION OF VISFATIN AND ADEPONECTIN LEVEL WITH OXIDATIVE STRESS LEVEL, LIPID PROFILE AND LIVER FUNCTION TEST PARAMETERS IN T2DM PATIENTS

Onkar Nath Tiwari[1], Shreya Nigoskar[2]

[1]Ph.D Scholar, Department of Biochemistry, Index Medical College Hospital & Research Center (IMCHRC), Malwanchal University, Nemawar Road, NH-59A, District Indore, Madhya Pradesh, India
[2]Professor & Head, Department of Biochemistry, Index Medical College Hospital & Research Center (IMCHRC), Malwanchal University, Nemawar Road, NH-59A, District Indore, Madhya Pradesh, India.

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Corresponding Author:
Dr. Shreya Nigoskar,
Email: Shreyanigoskar@gmail.com

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Abstract

Background: Diabetes mellitus (DM) is chronic disease and major global healthcare problem, affecting both public health and socio-economic wellbeing. Rapid urbanization and changing lifestyle combined with genetic susceptibility results in metabolic syndrome like dyslipidemia and obesity. The aim is to correlate adipokines (Visfatin and Adeponectin) level with oxidative-stress level, Lipid profile and liver function test parameters in T2DM patients. **Materials and Methods:** This case-control study included 160 diabetes cases between 35-65years and 160 healthy similar age and sex in control group. Screening and management were as per American Diabetes Association guidelines. Serum level of Visfatin and adiponectin was estimated by Enzyme linked immune-sorbent assay (ELISA) as per manufacturer's protocol. **Result:** Serum levels of adipokines (Visfatin) level were significantly higher in cases (45.35±4.64) than controls (21.44±4.51). But adiponectin level was significantly lower in cases (5.86±0.94) than controls (10.68±1.54) (P<0.05). Visfatin positively significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, albumin, AST and ALT and significantly negatively correlated with HDL. Adiponectin was negative significant associated with fasting plasma glucose, insulin level, HbA1c, Total Cholesterol, Triglycerides, urea, creatinine, AST and ALT and 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. The Adiponectin positively significant associated with Catalase, SOD and Glutathine reductase but negatively significantly correlated with MDA. **Conclusion:** Association of adiponectin with AST, ALT, albumin, HDL cholesterol, triglycerides, Fasting Blood Sugar and oxidative biomarkers may partly explain lower levels of adiponectin and higher level of visfatin found diabetes cases.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease and is a major global healthcare problem, affecting both public health and socio-economic wellbeing. Diabetes is one of the top 10 causes of death globally and individuals with diabetes have a 2–3-fold increased risk of all-cause mortality.[1] DM is associated with acute consequences, such as diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome, as well as chronic complications, such as renal failure, blindness, cardiovascular disease and diabetic neuropathy.[2] 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,[3] while type 2 DM (T2DM) develops through tissue resistance to insulin and pancreatic beta-cell dysfunction.[3] Lifestyle changes, including urbanization, the increasing pace of life, the consumption of high-calorie diets and lack of physical activity have resulted in a high burden of obesity and concomitant diabetes.[4]

There is significant evidence that suggests a connection between the increased lipid concentration in the cytoplasm of adipocytes, myocytes and hepatocytes and the development of insulin

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resistance in peripheral tissues.[5] Additionally, the common therapies used to treat T2DM (e.g., sulphonyl urea derivatives, thiazolidinediones and insulin) may, in addition, lead to weight gain and subsequent insulin resistance.[6] The pathophysiology of insulin resistance and T2DM has been a focus of many studies.[7] A plausible assumption is that T2DM is partly increased by the altered functions of adipose tissue.[8] Adipose tissue is increasingly understood as a highly active endocrine gland that secretes many biologically active substances, including adipocytokines.[7] There is enough evidence to suggest that changes in adipocytokine secretion do contribute to defective insulin production/action and, concomitantly, result in peripheral insulin resistance.[9] Adipokines such as adiponectin, leptin resistin, visfatin, ghrelin and chemerin seem to play an important role in the onset, progression and complications of T2DM.[9]

Adiponectin is one of the most interesting and abundant adipocytokines, and it has been reported to improve insulin resistance and inflammatory status.[10] This function of adiponectin is potentially performed through its role in increased fatty acid oxidation in the liver and skeletal muscles, as well as through its inhibition of gluconeogenesis in liver.[11] Decreased levels of adiponectin have been associated with obesity-related diseases, including insulin resistance, type 2 diabetes mellitus, and cardiovascular disease.[12] Many studies have associated adiponectin with a low risk of T2DM and, in fact, its levels are shown to be reduced before diabetes onset.[13] Another study revealed that adiponectin levels are lower in prediabetes than in a euglycemic state.[14]

Visfatin is a multifaceted novel adipokine. It is also known as nicotinamide phosphoribosyl transferase (NAMPT) or pre-B cell colony-enhancing factor (PBEF). It has been found to have a vast array of endocrine and autocrine paracrine functions that include cell proliferation, the biosynthesis of nicotinamide mono and dinucleotide and hypoglycemic effects.[15] The increased expression and plasma levels of visfatin are associated with T2DM and abdominal obesity.[16] The hypoglycemic actions of visfatin include the inhibition of the release of glucose from hepatic cells and the activation of glucose uptake in peripheral tissues by binding insulin receptors at a site different from that of insulin.[16] There are contradictory reports about the role of visfatin in insulin resistance and diabetes: some reports suggest a link with visfatin,9,16 while others suggest that visfatin is not independently related to diabetes.[17]

Thus, present case-control study was aimed to find the correlation of Visfatin and Adeponectin level with oxidative stress (Catalase (CAT), Super oxide Dismutase (SOD), Glutathione Peroxidase (Gpx) and Glutathione (GSH) activity) level, Lipid profile and liver function test parameters in diabetes patients.

MATERIALS AND METHODS

The present case-control study was conducted at Index Medical College Hospital & Research Center (IMCHRC), on 160 diabetes, males and females between 35-65 years of age group patients and 160 healthy males and females between 35-65 years of age group enrolled in this study. Individuals who have less than 35 years or greater than 65 years of age, suffering from disease like psychiatric disorders, hypertension, Alcoholics, Smokers, Pregnant and lactating women were excluded from the study. The screening and management of patients was as per American Diabetes Association guidelines.

As per WHO criteria; T2DM is characterized by elevated fasting blood sugar (FBS) (≥126mg/dl) or post-prandial blood sugar (PPBS) (≥200mg/dl) concentrations.[18] The American Diabetes Association (ADA) Standards of Medical Care in Diabetes added that glycated haemoglobin (HbA1c) as an important standard for the diagnosis of pre-diabetes and diabetes (5.7-6.4% and ≥6.5%, respectively).[19]

Estimation of Biochemical parameters: Estimations of Insulin level, plasma glucose, serum lipid profile (Total cholesterol, High density lipoprotein-cholesterol and triglycerides), Liver function test (Total protein, albumin, total bilirubin, direct bilirubin, AST, ALT and ALP), Kidney function test (urea, creatinine, uric acid, calcium, phosphorus, sodium, potassium and chloride) was done using commercially available kits. HbA1c was estimated using HPLC based method. Oxidateive stress markers (Catalase (CAT), Super oxide Dismutase (SOD), Glutathione Peroxidase (Gpx) and Glutathione (GSH) activity) was determined spectrophotometrically. Assay of Visfatin and Adiponectin: Serum level of Visfatin and adiponectin was estimated by Enzyme linked immuno sorbent assay (ELISA) as per manufacturer's protocol.

Categorical/Ordinal data was expressed as percentage, median and range. Independent Sample t test or Mann-Whitney U test was used to test difference between quantitative data among groups. Bivariate analysis (Pearson correlation) was used to find the association of Visfatin and Adiponectin level with anthropometric and sugar profile. A p-value less than 0.05 ($P<0.05$) was considered as statistically significant.

RESULTS

Proportion of male patients was comparably higher in number in both groups and it was insignificantly distributed in both groups ($P>0.05$) [Figure 1]. There was statistically insignificant higher older age population in case group (51.46±8.69) in compare to control group (49.94±7.90) ($P>0.05$) [Figure 2]. Blood Sugar level (Fasting Plasma Glucose, Insulin level and HbA1c) were significantly higher in the case group in comparison to control group ($P<0.001$).

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Lipid profile level (Total cholesterol, and Triacylglycerol) were significantly higher in the case group (P<0.05). while HDL cholesterol was significantly higher in the control group (P<0.05). Kidney function profile (Creatinine and Urea) level were significantly higher in the case group in comparison to control group (P<0.05). Liver function test profile (AST and ALT) level were significantly higher in the case group (P<0.05). But Albumin level was significantly higher in the control group in compare to case group (P<0.05). The oxidative stress markers Malondialdehyde (MDA) level were significantly higher in the case group (P<0.05). But catalase, SOD and Glutathine reductase level was significantly higher in the control group in comparison to case group (P<0.05) [Table 1].

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) [Table 2].

In [Table 3] 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.

In [Table 4] 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.

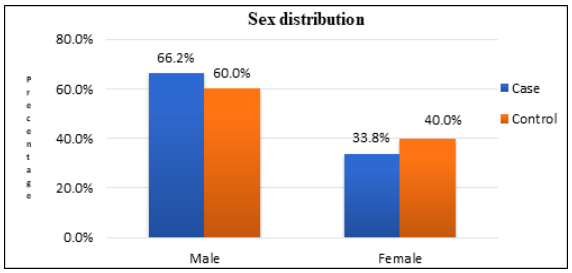

Figure 1: Sex group distribution

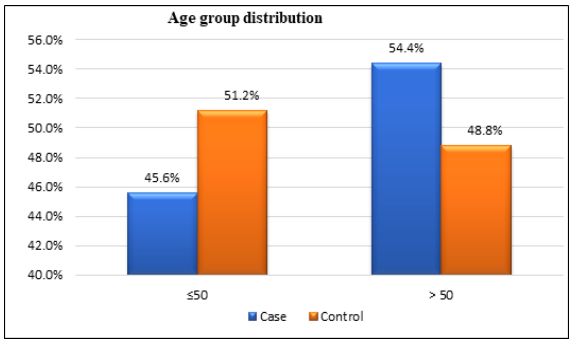

Figure 2: Age group distribution

Table 1: Distribution biochemical parameters in both groups

		Group		P value
		Case (n=160)	Control (n=160)	
Sugar profile	Fasting Plasma Glucose	203.54±43.77	86.44±15.66	<0.001
	Insulin level	40.11±10.74	10.24±3.39	<0.001
	Glycated Haemoglobin (HbA1c)	10.68±2.23	5.77±0.28	<0.001
Lipid profile	Total cholesterol (mg/dl)	204.65±49.63	134.41±25.95	<0.001
	Triacylglycerol (mg/dl)	192.05±66.09	107.78±28.61	<0.001
	HDL cholesterol (mg/dl)	34.88±4.09	54.63±4.74	<0.001
Kidney function profile	Creatinine (mg/dl)	1.15±0.21	0.90±0.18	<0.001
	Urea (mg/dl)	30.88±7.67	28.59±7.91	0.009
Liver function test profile	Albumin (mg/dl)	4.05±0.52	4.41±0.61	<0.001
	AST (mg/dl)	37.51±4.72	29.12±3.79	<0.001
	ALT (mg/dl)	40.19±4.97	29.90±5.33	<0.001
Oxidative stress markers	Malondialdehyde (MDA)	3.23±1.62	1.21±0.45	<0.001
	Catalase	31.42±13.75	49.00±22.84	<0.001
	Superoxide dismutase (SOD)	2.73±0.26	4.36±0.25	<0.001
	Glutathine reductase	38.10±7.86	64.23±12.74	<0.001

Table 2: Serum levels of Adipokines

Serum Adipokines levels	Group		P value
	Case (n=160)	Control (n=160)	
Visfatin	45.35±4.64	21.44±4.51	<0.001
Adiponectin	5.86±0.94	10.68±1.54	<0.001

Table 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

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

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

DISCUSSION

Development of a method for suitable estimate of blood sugar level in regular clinical practice offerings a main challenge for physicians and public health policy makers. The present study provided suggestion of the effectiveness for assessment of serum adiponectin level as an appropriate and sensitive oxidative stress biomarker for the estimation of blood sugar level particularly in our study area.

Our study noted that in case groups, 66.2% male and rest were female and in control groups 60.0% were male and 40.0% were female patients. We found that the statistically insignificant higher older age population in case group distribution in compare to control group (P>0.05). Blood Sugar level (Fasting Plasma Glucose, Insulin level and HbA1c) were significantly higher in the case group in comparison to control group (P<0.001). Lipid profile level (Total cholesterol, Triacylglycerol and HDL) were significantly higher in the case group in comparison to control group (P<0.05). Kidney function profile (Creatinine and Urea) level were significantly higher in the case group in comparison to control group (P<0.05). Liver function test profile (AST and ALT) level were significantly higher in the case group in comparison to control group (P<0.05). but Albumin level was significantly lower in the case group in comparison to control group (P<0.05).

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.[20] A certain amount of oxidative stress/ROS is necessary for the normal metabolic processes since ROS play various regulatory roles in cells.[21] ROS are produced by neutrophils and macrophages during the process of respiratory burst in order to eliminate antigens.[22] 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.[21] 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.[23] 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.[24] MDA is a toxic lipid peroxidation metabolite that has been considered a marker for the cellular damages caused by oxygen free radicals,[25] 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.[26] Increased generation of ROS in tissues and body fluids has been shown to reduce TAC.[27] 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, 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.[11,28,29] 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

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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.[12,29] 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] Snehalatha C et al,[30] 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,[31] 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,[32] 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 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,[33] 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,[34] reported the serum adiponectin level was negatively correlated to BMI (r=−0.308, P=0.002), diastolic blood pressure (r=−0.269, P=0.012), and triglycerides (r=−0.338, P<0.001), and positively correlated to high-density lipoprotein cholesterol (r=0.300, P=0.003) in their patients. Chen MC et al,[35] 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.[36] Visfatin serum levels are significantly correlated with the accumulation of white adipose tissue (WAT), and visfatin expression was increased during the differentiation of adipocytes and according to the destruction of β cells.[37] 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. Association between oxidative stress and insulin resistance has been previously reported by Evans JL.[38] The increase of the plasma visfatin level in obese women has been previously reported by Zahorska-Markiewicz B et al,[39] who observed significant higher visfatin levels in obese women compared to normal weight women which is similar with the present findings. In the present study, authors also found positive association between visfatin serum concentrations and DNA damage as previously observed by Villalobos LA et al,[40] who reported that visfatin promotes DNA damage. 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.[41]

Limitations

This was a cross-sectional study which does not allow for conclusions regarding causality. This study included middle-aged individuals, without prevalent cardiovascular disease. Caution is thus needed in the extrapolation of the findings to other populations, i.e. younger, of other ethnicity or with cardiovascular disease. Moreover, metabolic or hypertension were less prevalent than type 2 diabetes mellitus and impaired fasting glucose in the study population. Finally, the adipokines measured are only a small fraction of the wide array of pro- and anti-inflammatory biochemical indices that are produced by the adipose tissue.

CONCLUSION

In conclusion, the present results suggest that circulating levels of Visfatin are increased and adiponectin are reduced in the presence of the diabetes and also decrease as the number of diabetes parameters increases. The association of adiponectin with AST, ALT, albumin, HDL cholesterol,

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triglycerides, Fasting Blood Sugar and oxidative biomarkers may partly explain the lower levels of adiponectin and higher level of Visfatin found in individuals with diabetes. Further prospective studies are needed to confirm the mechanisms underlying this association.

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