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Visfatin: Potential Role as Therapeutic Biomarker in Type 2 Diabetes Mellitus

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KEYWORDS

Visfatin, Insulin resistance, Diabetes mellitus, Adipokine

ABSTRACT:

Background: Type 2 Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to pathophysiologic abnormalities, like insulin resistance, impaired insulin secretion and deregulated hepatic glucose production. Visfatin is an adipokine which acts synergistically with insulin to increase glucose cellular uptake, stimulate glucose transfer to the muscle and adipose tissue and prevents hepatic glucose production. It also upregulates the production of the pro- and anti-inflammatory cytokines such as IL-1β, IL-1Ra, IL-6, IL-10 and TNF-α in human monocytes suggesting a potential role of visfatin in the pathogenesis of vascular inflammation in obesity and type 2 DM.

Materials and Methods: In this study, samples of 90 cases and 90 controls were included. Each sample was tested for fasting plasma glucose, serum lipid profile, serum insulin and serum visfatin. The data were analyzed by unpaired students t-test and linear regression analysis using IBM SPSS version 22 statistics software.

Results: The mean fasting plasma glucose level in control group is 84 ± 14.3 mg/dL and that of cases is 178.8 ± 94.5 mg/dL. The mean serum visfatin level in controls is 104.9 ± 60.2 pg/mL and that of cases is 161.1 ± 79.8 pg/mL. The mean serum fasting insulin in controls is 7.1 ± 4.2 mU/L and that of cases is 11.3 ± 2.6 mU/L. The mean HOMA-IR in controls is 1.8 ± 1.2 and that of cases is 5.1 ± 1.4. We observed a positive correlation ($r = 0.833$) between serum insulin and serum visfatin, which is statistically significant ($p<0.05$).

Conclusion: The raised Serum visfatin in Diabetes Mellitus may be a compensatory mechanism to the insulin resistant state present in these patients. Hyperglycemia seen in Diabetes Mellitus stimulates visfatin secretion from adipocytes, which in turn increases glucose-stimulated insulin secretion from beta cells of pancreas, leading to Hyperinsulinemia. But the exact mechanism of its action is still not elucidated.

BACKGROUND

Type 2 Diabetes mellitus (DM) or non-insulin dependent diabetes or adult-onset diabetes, comprises of approximately 95% of all diabetes mellitus. It is a group of metabolic diseases characterized by hyperglycemia mainly due to three pathophysiologic abnormalities. Those are Insulin resistance, impaired insulin secretion and impaired hepatic glucose production. [1]

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The criteria for diagnosis of Diabetes mellitus (as per American Diabetes Association) are:

1) Fasting plasma glucose of ≥126 mg/dL (7.0 mmol/L).

2) 2 hours plasma glucose of ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT), after a dose of 75gm of glucose.

3) Glycated haemoglobin (HbA1C) of ≥6.5%.

4) Random plasma glucose level of ≥200 mg/dL (11.1 mmol/L) in a patient with symptoms of hyperglycemia or hyperglycemic crisis [2].

Insulin Resistance is defined as attenuated biological response to normal or elevated Insulin level [3]. Classically it is measured by Hyperinsulinemic euglycemic glucose clamp method. As it is a very tedious method, various surrogate markers are used to measure Insulin Resistance. In this study, we measured Insulin Resistance by HOMA-IR method. HOMA –IR is a convenient & widely acceptable marker of Insulin Resistance and calculated by the formula:

HOMA-IR = Glucose (mg/dL) × Insulin (mU/L) / 405 [4]

Visfatin or Pre B-cell colony-enhancing factor (PBEF) or Nicotinamide phospho ribosyltransferase (Nampt) is an adipokine, identified in the year 2004. It is a polypeptide comprising of 491 amino acids with a molecular mass of 52 kDa.[5]. It is mainly secreted by visceral adipose tissue and it acts synergistically with insulin to increase glucose cellular uptake, stimulate glucose transfer to the muscle and adipose tissue and prevents hepatic glucose production [1]. It also upregulates the production of the pro- and anti-inflammatory cytokines such as IL-1β, IL-1Ra, IL-6, IL-10 and TNF-α in human monocytes which has substantial role in infectious and inflammatory diseases.[5]

Visfatin is released predominantly from macrophages rather than from visceral adipocytes. It activates intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) in leukocytes inducing their adhesion to endothelial cells and aortic endothelium. This process is mediated by the pro-inflammatory transcription factor i.e Nuclear Factor-κB (NF-κB) in a reactive oxygen species (ROS) dependent manner as visfatin increases the transcriptional activity of NF-κB in human vascular endothelial cells which causes activation of the matrix-metalloproteinases (MMP). Visfatin also activates monocyte chemotactic protein-1(MCP-1) and endothelial nitric oxide synthase (eNOS) by activating protein kinase and mitogen-activated protein (MAP) kinase leading to improved endothelial cell function, angiogenesis and atherosclerosis. These findings provide supportive evidence for a potential role of visfatin in the pathogenesis of vascular inflammation in obesity and type 2 DM[1]. Therefore, the present study aimed to evaluate the level of Serum Visfatin in Type 2 Diabetes Mellitus patients and to find the association of Visfatin with Insulin Resistance.

AIM OF THE STUDY

The aim of the present study is To evaluate the level of Serum Visfatin in Type 2 Diabetes Mellitus patients; o find the association of Visfatin with Insulin Resistance.

MATERIALS AND METHODS

MATERIAL

This is a Case-Control study comprising of samples of 90 cases and samples of 90 controls. The case group comprised of diagnosed Type 2 DM patients attending the in-patient and out-patient Department of Medicine, S.C.B. MCH, Cuttack, Odisha, India. The control group included age and sex matched normal healthy volunteers. This study was conducted at the Department of Biochemistry, S.C.B. MCH, Cuttack, Odisha, India.

INCLUSION CRITERIA

Clinically diagnosed cases of Type 2 Diabetes Mellitus patients (as per ADA) without any complication.

EXCLUSION CRITERIA

1) Any congenital anomaly; 2) Any obvious organic lesion/chronic inflammatory disease; 3) History of Smoking; 4) History of Alcoholism; 5) Any other endocrine disorders. In the control group, subjects with family history of Diabetes Mellitus, chronic metabolic diseases and chronic inflammatory diseases were excluded. All the case records were collected in a specific proforma. Consent (informed and written) was obtained from all subjects.

METHOD

After obtaining the written consent of both patients and controls, 5 ml of fasting venous blood was collected, of which 3 ml was kept in plain vials for serum biochemical analysis and 2 ml in oxo-fluoride

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vials for plasma glucose. These were processed in Regional Diagnostic Center, S.C.B MCH and were subjected to following tests: 1) Fasting plasma glucose and serum lipid profile were done by auto-analyser using standard commercial kits adapted to auto-analyser. 2) Serum insulin and serum visfatin by ELISA kit adapted to LISA-SCAN and insulin resistance was calculated by HOMA-IR.

DATA ANALYSIS

The data were collected on the predetermined proforma. All the data are represented as MEAN±S.D. The data were analyzed by unpaired students t-test and linear regression analysis using IBM SPSS version 22 statistics software.

OBSERVATION

The comparison of demographic profile among cases and controls has been shown in Table 1. It showed that the mean age, height and weight for control group are 44.4±9.9 years, 166.3±5.6 cm, 72±9.4 kg respectively and that of case group are 53.5±12.2 years, 156.6±9.4 cm, 64.8±12.3 kg respectively. The difference between the mean age, height and weight of controls and cases were statistically significant ($p<0.05$). The mean BMI of control group is 26.2±3.7 kg/m^2 and that of cases is 26.4±3.9 kg/m^2, which is not statistically significant.

The mean fasting plasma glucose (FBS) level in control group is 84 ± 14.3 mg/dL and that of cases is 178.8 ± 94.5 mg/dL, which is statistically significant ($p<0.001$). The mean serum Visfatin level in controls is 104.9 ± 60.2 pg/mL and that of cases is 161.1 ± 79.8 pg/mL, which is statistically significant ($p<0.05$). The mean serum fasting Insulin in controls is 7.1 ± 4.2 mU/L and that of cases is 11.3 ± 2.6 mU/L, which is statistically significant ($p<0.05$). The mean HOMA-IR in controls is 1.8 ± 1.2 and that of cases is 5.1 ± 1.4, which is statistically significant ($p<0.05$), as shown in Table 2.

The mean serum cholesterol and LDL levels in controls are 170 ± 37.9 mg/dL, 94.8 ± 35.7 mg/dL, and that of cases are 216.4 ± 50.7 mg/dL, 134.9 ± 45.1 mg/dL respectively, which are statistically significant ($p<0.001$). The difference between the mean serum TGL, HDL and VLDL levels among cases and controls are not statistically significant, as shown in Table 3.

Table 1: Comparison of demographic profile among the study groups

PARAMETERS	CONTROLS (MEAN ± S.D.) (N=90)	CASES (MEAN ± S.D.) (N=90)	p VALUE
AGE (years)	44.4±9.9	53.5±12.2	0.0011*
HEIGHT (cm)	166.3±5.6	156.6±9.4	<0.0001**
WEIGHT (kg)	72±9.4	64.8±12.3	0.0084*
BMI (kg/m^2)	26.2±3.7	26.4±3.9	0.8247

Table 2: Comparison of FBS and Visfatin among study groups

PARAMETERS	CONTROLS (MEAN ± S.D.) (N=90)	CASES (MEAN ±S.D.) (N=90)	p VALUE
FBS (mg/dL)	84 ± 14.3	178.8 ± 94.5	0.0002**
VISFATIN (pg/mL)	104.9 ± 60.2	161.1 ± 79.8	0.0016*
INSULIN (mU/L)	7.1 ± 4.2	11.3 ± 2.6	0.0290*
HOMA-IR	1.8 ± 1.2	5.1 ± 1.4	0.0018*

Table 3: Comparison of Lipid profile among study groups

PARAMETERS	CONTROLS (MEAN ± S.D.) (N=90)	CASES (MEAN ±S.D.) (N=90)	p VALUE
T. CHOLESTEROL	170 ± 37.9	216.4 ± 50.7	<0.0001**

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(mg/dL)			
TGL (mg/dL)	127.3 ± 46	166.6 ± 109	0.0695
HDL (mg/dL)	49.3 ± 5.3	47.8 ± 6.4	0.2922
LDL (mg/dL)	94.8 ± 35.7	134.9 ± 45.1	0.0001**
VLDL (mg/dL)	25.4 ± 9.1	30.8 ± 15.8	0.0976

*significant at p<0.05; **significant at p<0.001; p>0.05: not significant

The correlation between serum Visfatin and fasting blood glucose levels in Type 2 Diabetes Mellitus patients is depicted in Table 4. We observed no significant correlation between FBS and serum Visfatin levels in Type 2 Diabetes Mellitus patients.

Table 4: Correlation between serum Visfatin and FBS in cases group

	Pearson correlation (r-value)	p value
FBS	0.028	0.851

The correlation between serum Visfatin and HOMA-IR in Type 2 Diabetes Mellitus patients is depicted in Table 5. We observed no significant correlation between serum Visfatin levels and HOMA-IR in Type 2 Diabetes Mellitus patients.

Table 5: Correlation between serum Visfatin and HOMA-IR in cases group

	Pearson correlation (r-value)	p value
HOMA-IR	0.242	0.098

The correlation between serum Visfatin and serum triglyceride levels in Type 2 Diabetes Mellitus patients is depicted in Table 6. We observed no significant correlation between serum Visfatin and serum triglyceride levels in Type 2 Diabetes Mellitus patients.

Table 6: Correlation between serum Visfatin and TGL in cases group

	Pearson correlation (r-value)	p value
TGL	0.012	0.936

In our study, the multivariable linear regression came as:

$$y = 0 - 0.129x_1 + 0.838x_2$$

where, y = serum insulin; x_1 = serum visfatin; x_2 = HOMA-IR

This means that when Visfatin increases by 1 unit, insulin decreases by 0.129 units, provided the HOMA-IR is remaining constant. Similarly, when HOMA-IR increases by 1 unit, insulin increases by 0.838 units, provided Visfatin remains constant, as depicted in Figure 1. We observed a positive correlation (r=0.833) between the variables, which is statistically significant (p<0.05).

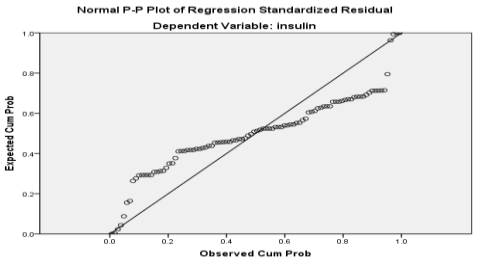

Figure 1: Multivariable linear regression analysis between dependent variable (serum insulin) and independent variables (serum Visfatin and HOMA-IR) in Type 2 Diabetes Mellitus patients.

	Regression coefficient (beta)	p value
Visfatin	-0.129	0.028
HOMA-IR	0.838	0.000

Predictors: Visfatin, HOMA-IR; Dependent variable: Insulin

DISCUSSION

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia due to defective insulin secretion or its action or both. Type 2 Diabetes Mellitus comprises of approximately 95% of all diabetes mellitus.[6] WHO has recognized both obesity and diabetes mellitus as epidemic diseases of the 21st century.[7] Obesity is a frequent concomitant of

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type 2 diabetes mellitus. Approximately 90% of type 2 diabetics are overweight or obese. One of the major risk factors in the development of Type 2 Diabetes Mellitus is obesity. Increase in lipid concentration in cytoplasm of adipocytes, myocytes and hepatocytes, along with obesity causes insulin resistance in peripheral tissues.[8] This is a promising area in scientific research as increased Type 2 Diabetes Mellitus risk in obese subjects can be explained by the changes in adipose tissue functions. Apart from being the energy storage, the adipose tissue is also an important endocrine organ which secretes numerous substances with biological activity, including adipokines. Recent studies show that disturbance of adipokine secretion may contribute to peripheral insulin resistance development and/or impairment of production and action of insulin.[9]

Visfatin or Nampt (Nicotinamide phosphoribosyl transferase) or Pre B-cell colony Enhancing Factor-1 (PBEF-1), is a 52 kDa peptide comprising of 491 amino acids. **Fukuhara et al**. was the first to describe visfatin in 2005. It is expressed mainly by visceral adipose tissue with insulin-like effects.[10] Visfatin/NAMPT synthesizes NAD^+ by catalyzing the rate-limiting step i.e., transfer of a phosphoribosyl residue from 5-phosphoribosyl-1-pyrophosphate (PRPP) to nicotinamide producing nicotinamide mononucleotide (NMN), which is then converted to NAD by nicotinamide mononucleotide adenylyltransferase (Nmnat).[11] Visfatin upregulates the production of the pro- and anti-inflammatory cytokines IL-1β, IL-1Ra, IL-6, IL-10, and TNF-α in human monocytes which play a substantial role in a wide range of infectious and inflammatory diseases.[12] Visfatin acts as an insulinomimetic hormone. It exerts this action by binding with insulin receptor at a site different from that of insulin. It increases the phosphorylation of IRS-1/2, Akt and MAPK, leading to activation of insulin signaling pathways. [13,14]

The present study evaluates the level of serum visfatin in Type 2 Diabetes Mellitus patients and its association with Insulin Resistance, which is calculated by Homeostasis model assessment (HOMA).

Our study shows significant difference in Age (53.5±12.2 vs. 44.4±9.9 years), Weight (64.8±12.3 vs. 72±9.4 kg) and Height (156.6±9.4 vs. 166.3±5.6 cm) among the cases and controls respectively ($p<0.05$), but no significant difference in BMI (26.4±3.9 vs. 26.2±3.7 kg/m^2) is seen among the cases and controls respectively ($p>0.05$), as depicted in Table 1.

We found that there is a significant difference in Fasting Blood Glucose (178.8 ± 94.5 vs. 84 ± 14.3 mg/dL) and Serum Visfatin (161.1 ± 79.8 vs. 104.9 ± 60.2 pg/mL) among the cases and controls respectively ($p<0.05$) as depicted in Table 2. This finding is in accordance with that of **Hossein Hajianfar et al.** [15], **Mehmet Kara et al.** [16] and **Seham Mohamed Saied El Nakeeb et al.** [1]

We observed nonsignificant positive correlation between FBS and serum visfatin levels ($r=0.028$, $p=0.851$) in Type 2 Diabetes Mellitus patients which is depicted in Table 4. This finding is consistent with that of **Samiha A. Abd Rabo et al.** [17] Hyperglycaemia induces an increase in visfatin concentration by stimulating the synthesis of visfatin in adipocytes and its release of stored form from the adipocytes. Depending on duration and magnitude of glucose elevation in the blood, adipocytes regulate the release of visfatin by PI3-kinase/AKT pathway. Therefore, quantification of visfatin may serve as a marker of glucose homeostasis.[18]

Raised serum visfatin levels in type 2 DM patients can be due to impaired visfatin signaling in target tissues or dysregulated biosynthesis in response to hyperglycemia or hyperinsulinemia.[17] Elevated serum visfatin can be a compensatory mechanism of adipose tissue to increase glucose dependant insulin secretion by beta cells in response to increasing insulin resistance.[19] Study shows that the monomeric isoform of eNampt is responsible of diabetes and inflammation by causing impaired glucose tolerance, impaired pancreatic insulin secretion, elevated blood glucose, and the presence of systemic and tissue inflammation, without changing NAD^+ levels.[20]

We found a significant difference in Serum Insulin (11.3 ± 2.6 vs. 7.1 ± 4.2 mU/L) and HOMA-IR (5.1 ± 1.4 vs. 1.8 ± 1.2) levels among the cases and controls respectively ($p<0.05$), as depicted in Table 2. This finding is consistent with that of **Mehmet Kara et al.** [16] and **Anna Kamińska et al.** [21] Type 2 Diabetes mellitus is characterized by Insulin Resistance and Hyperinsulinemia which leads to Glucose Intolerance and hyperglycemia.

In this study, we performed multivariable linear regression analysis between serum insulin, taken as dependent variable, and serum Visfatin and HOMA-IR, taken as independent variables in Type 2 Diabetes

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Mellitus patients (Figure 1). We observed a positive correlation (r=0.833) between the variables, which is statistically significant ($p<0.05$). We observed a negative correlation (Regression coefficient, β=-0.129) between serum insulin and serum visfatin and a positive correlation (β=0.838) between serum insulin and HOMA-IR. This means that when Visfatin increases by 1 unit, insulin decreases by 0.129 units, provided the HOMA-IR is remaining constant. Similarly, when HOMA-IR increases by 1 unit, insulin increases by 0.838 units, provided Visfatin remains constant. Studies have shown that insulin is a negative regulator of Visfatin. Visfatin causes glucose stimulated insulin secretion from beta cells of Islet of Langerhans, and rise in serum insulin level provides negative feedback for Visfatin secretion from adipocytes. [11,22,23,24]

We observed nonsignificant positive correlation between serum Visfatin levels and HOMA-IR (r=0.242, p=0.098) in Type 2 Diabetes Mellitus patients, as depicted in Table 5. This finding is consistent with the findings of **Dogru T et al.** [25] and **Claudio Pagano et al.** [26] Many studies have found significant positive correlation between serum Visfatin and HOMA-IR in diabetes mellitus patients. The reason for this discrepancy is currently lacking.

Dyslipidemia is a common feature of diabetes mellitus contributed by several factors such as hyperglycemia, insulin deficiency or resistance and adipocytokines. Firstly, insulin deficiency or resistance activates intracellular hormone-sensitive lipase leading to increased release of non-esterified fatty acids (NEFA) from triglycerides of adipose tissue, which in turn leads to increase hepatic triglyceride production, causing increased secretion of apolipoprotein B (apoB). Secondly, deficiency of insulin produces larger VLDL (rich in triglyceride) as there is loss of inhibitory effect of insulin on production of hepatic apoB and triglyceride secretion in VLDL.[27]

In diabetic patients more amount of LDL cholesterol is generated and HDL cholesterol levels are depressed as there is increase in production of triglyceride-rich lipoproteins (chylomicrons and VLDL). This is due to the fact that the rate of transfer of Cholesteryl ester from other lipoproteins into the triglyceride-rich lipoproteins by cholesteryl ester transfer protein, is increased in diabetes. This produces cholesteryl ester-depleted HDL and simultaneously, LDL become triglyceride-rich. Further removal of triglyceride by hepatic lipase results in smaller, denser HDL and LDL particles, which causes major atherogenic change.[27]

We observed a significant difference in total cholesterol (216.4 ± 50.7 vs. 170 ± 37.9 mg/dL) and LDL (134.9 ± 45.1 vs. 94.8 ± 35.7 mg/dL) among the cases and controls respectively ($p<0.05$), but no significant difference is seen in serum TGL (166.6 ± 109 vs. 127.3 ± 46 mg/dL), HDL (47.8 ± 6.4 vs. 49.3 ± 5.3 mg/dL) and VLDL (30.8 ± 15.8 vs. 25.4 ± 9.1 mg/dL) levels among cases and controls respectively ($p>0.05$), which is depicted in Table 3. This finding is in accordance with that of **Hossein Hajianfar et al.** [15]

We observed no significant correlation between serum Visfatin and serum triglyceride levels (r=0.012, p=0.936) in Type 2 Diabetes Mellitus patients, which is depicted in Table 6. This finding is consistent with the study of **Samiha A. Abd Rabo et al.** [17] **Kowalska et al.** demonstrated that rise in Free Fatty Acids (FFA) in the presence of hyperinsulinemia, causes an increase in serum visfatin. FFAs rapidly induce hyperinsulinemia and insulin resistance in both the skeletal muscle and the liver by competing for glucose usage, increase in hepatic gluconeogenesis, and glucose output. FFAs may alter insulin secretion and insulin clearance by the liver, thus contributing to Hyperinsulinemia. Therefore, they hypothesized that in the insulin-resistant condition caused by an acute elevation of serum FFAs, the inhibitory effect of insulin on visfatin secretion might be abolished.[24]

CONCLUSION

Serum Visfatin is raised in Diabetes Mellitus may be as a compensatory mechanism to the insulin resistant state present in these patients. Hyperglycemia seen in Diabetes Mellitus stimulates Visfatin secretion from adipocytes, which in turn increases glucose-stimulated insulin secretion from beta cells of pancreas, leading to Hyperinsulinemia. As there is an insulin resistant state, probably caused by increased free fatty acids, the Visfatin binds to the insulin receptor at a site different from that of insulin. This leads to phosphorylation of insulin receptor, IRS1/2, Akt/PKB and MAPK, causing their activation and eventually increasing glucose uptake. Therefore, Visfatin seems to be an intricate part of the compensatory mechanism of insulin sensitivity. But the exact mechanism of its action is still not elucidated.

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Based on the findings of this study, we can conclude that Visfatin has a direct relationship with the pathogenesis of Diabetes Mellitus; but the available research on therapeutic role of Visfatin remains controversial as on date. However, more multicentric research with larger series may elucidate the therapeutic role of Visfatin in Type 2 Diabetes Mellitus.

Conflict of interest - None

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