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**ORIGINAL RESEARCH**

# Rise of Serum Visfatin in early stages of diabetes is independent of obesity and insulin resistance

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**Abstract**

**Background:** Visfatin, as an adipocytokine, has insulin-mimetic effects including inhibition of hepatic glucose release, augmentation of glucose uptake in adipocytes and myocytes and increase in triglyceride synthesis and its accumulation in pre-adipocytes. However, since the results of this study were not confirmed by subsequent analyses, it was in part retracted. Hence, we aim to evaluate serum visfatin in prediabetes , newly diagnosed type 2 diabetes mellitus subjects and to find correlation of visfatin with BMI, HOMA-IR and HOMA-β) (if any)

**Methods:** 75 prediabetes subjects, 75 newly diagnosed type 2 diabetes mellitus subjects and 75 healthy control subjects (age, gender and body mass index (BMI) matched) were enrolled. BMI, glucose, insulin and visfatin were assessed. Insulin resistance and insulin secretory capacity (measured by homeostasis model assessment: HOMA-IR and HOMA-β) were calculated.

**Results:** Visfatin levels were highly significant in patients with Newly Diagnosed Diabetic compared to controls, whereas significant difference was also found between PDM vs. controls. BMI did not correlate with visfatin in both study groups.Visfatin in prediabetics is not associated with any metabolic parameters i.e. glucose, insulin, HOMA IR and HOMA β. Visfatin concentrations have significant positive association with glucose while significant negative association with HOMA-β in Newly Diagnosed Diabetic subjects.

**Conclusion:** Increased levels of visfatin in prediabetics and Newly Diagnosed Diabetic are not affected by obesity and and insulin resistance.

**Keywords**: Visfatin, prediabetes, obesity, HOMA – IR, HOMA-β, Insulin resistance.



## INTRODUCTION

Diabetes mellitus is one of the main threat to human health in the twenty-first century and therefore should be controlled and managed early to avoid its complications. American Diabetes Association (ADA) has named this early stage of diabetes as Prediabetes. Prediabetes is a condition in which blood glucose or HbA1c levels are higher than normal but not high enough for a diagnosis of diabetes.[1] Once a person has prediabetes, continued loss of beta cell function usually leads to type 2 diabetes. Visfatin, an adipocytokine has important role in regulation of glucose and insulin levels in humans. It displays insulin mimetic effects which was thought to be mediated through the phosphorylation of signal transduction proteins in the insulin signalling pathway and through binding to the insulin receptor at a site distinct from that of insulin.[2]

Recent studies also demonstrated that serum visfatin levels were significantly higher in the diabetic compared with the nondiabetic group and found a significant positive correlation of serum visfatin levels with the obesity indicator BMI and waist circumference, even after adjusting for age, sex, smoking status, blood pressure and lipid profile.[3, 4]Some studies indicate that blood visfatin concentrations significantly correlate with insulin resistance or type 2 diabetes but not with body fat percentage or body mass index (BMI).[5, 6] Other studies demonstrated that the association between diabetes and blood visfatin concentrations was not significant after adjusting for body mass index (BMI) and waist circumference.[7] A

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recent study found that visfatin levels were inversely associated with insulin resistance in nondiabetic obese women with energy restricted diet intervention.[8]

Although there are many evidences linking obesity, serum visfatin and type 2 diabetes. Data about visfatin concentration in prediabetes and Newly Diagnosed Diabetic are limited. Therefore, in present study we investigated serum visfatin levels in prediabetes, Newly Diagnosed Diabetic and compared it with healthy controls. We also found the correlation of visfatin with glucose, insulin, BMI, HOMA- IR and HOMA- β (if any).

## MATERIALS AND METHODS

The subjects included in the study were 75 prediabetic and 75 newly diagnosed type 2 diabetes mellitus patients attending the outpatient clinics or admitted in wards of Department of Medicine, J.L.N. Medical College and its Associated Group of Hospitals, Ajmer. The subjects were considered as prediabetic and diabetic based on the ADA guidelines.[1]75 healthy control subjects of same age group of either gender were selected for the study from volunteers such as doctors, resident doctors, paramedical staff and healthy attendants of patients.

On a prescheduled morning, the subjects were requested to arrive after overnight fast (08 hours) to provide a fasting blood sample. The theme of the study was explained to the subjects and a written consent was taken. One ml blood was collected in EDTA vial for plasma glucose (fasting) estimation. The analysis of plasma glucose was done on the same day as soon as Samples were collected. Three ml blood was collected in plain vial (without any anticoagulant) for estimation of SerumVisfatin and Insulin. Standard OGTT and HbA1c were also performed. After 30 min of collection, the blood samples were centrifuged for 10 min at 3000 rpm to obtain the serum, which was then kept frozen at −20 °C until further biochemical analysis.

BMI was determined following standard procedures. Glucose was measured using the glucoseoxidase method, Insulin and serum visfatin were measured using an enzyme linked immunosorbent assay (ELISA). Insulin secretory capacity (HOMA%B) and insulin resistance (HOMA-IR) were calculated using fasting glucose and fasting insulin by homeostatic model assessment.[9]

The data were analysed using Microsoft Excel 2007 and various websites (statpages, graphpad etc.). The quantitative variables were expressed as the mean ± standard deviation (SD). Variables were presented as Mean ± Standard deviation (S.D.). Differences in the parameters among the groups were analysed by ANOVA test followed by its Tukey HSD post hoc analysis. Correlations between variables were tested using the Pearson correlation test. Partial Correlation analysis was employed to determine the correlation between two variables with the third variable held constant (effect of third variable removed). A p value of <0.05 was considered statistically significant .

**TABLE 1: Principal characteristics of prediabetic, Newly diagnosed Diabetic and healthy subjects**

| | Healthy subjects (n= 75) | Prediabetic subjects (n=75) | Newly diagnosed Diabetic subjects (n=75) | P value Between group 1 and 2 | P value Between group 3 and 1 |
|---|---|---|---|---|---|
| Age (years) | 42±10 | 44±8 | 45±9 | 0.3663 | 0.1067 |
| BMI (Kg/m$^2$) | 26.06±4.94 | 26.24±5.22 | 27.66±4.26 | 0.9716 | 0.1071 |
| Male/Female | 48/27 | 56/ 19 | 52/23 | -- | -- |
| F. Glucose (mg/dl) | 89.58±11.30 | 117.72±6.38 | 160.63±35.90 | <0.0001 | <0.0001 |
| Insulin (µIU/ml) | 8.16±3.90 | 11.98±2.68 | 11.88±1.95 | <0.0001 | <0.0001 |
| HOMA- IR (units) | 1.86±1.06 | 3.50±1.13 | 4.74±1.22 | <0.0001 | <0.0001 |
| HOMA β (units) | 108.82±62.25 | 79.08±37.31 | 46.50±32.84 | 0.0003 | <0.0001 |
| Visfatin (ng/ml) | 3.12±1.56 | 4.70±2.66 | 5.35±3.70 | 0.0017 | <0.0001 |

Data represents Mean ± SD.

P value <.001 is considered extremely significant while p<.05 is significant.

**TABLE 2: Correlation coefficients of visfatin with various variables in prediabetic subjects**

| Visfatin vs | r value | P value | Statistical Significance* |
|---|---|---|---|
| BMI (Kg/m$^2$) | .07 | > 0.05 | NS |
| Fasting Glucose (mg/dl) | .00 | > 0.05 | NS |
| Insulin (µIU/ml) | .04 | > 0.05 | NS |
| HOMA- IR (units) | .04 | > 0.05 | NS |
| HOMA β (units) | .04 | > 0.05 | NS |

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**TABLE 3: Correlation coefficients of visfatin with various variables in Newly diagnosed diabetic subjects**

| Visfatin vs | r value | P value | Statistical Significance* |
|---|---|---|---|
| BMI (Kg/m$^2$) | 0.08 | > 0.05 | NS |
| Fasting Glucose (mg/dl) | 0.22 | < 0.005 | VS |
| Insulin (µIU/ml) | 0.04 | > 0.05 | NS |
| HOMA- IR (units) | 0.02 | > 0.05 | NS |
| HOMA β (units) | -0.24 | < 0.005 | VS |

**TABLE 4: Partial Correlation of S. Visfatin with HOMA IR and HOMA β (with BMI held constant) in Prediabetic subjects**

| Visfatin vs | r value | P value | Statistical Significance* |
|---|---|---|---|
| HOMA- IR (units) | 0.02 | > 0.05 | NS |
| HOMA β (units) | 0.04 | > 0.05 | NS |

**TABLE 5: Partial Correlation of S. Visfatin with HOMA IR and HOMA β (with BMI held constant) in Newly diagnose diabetic subjects**

| Visfatin vs | r value | P value | Statistical Significance* |
|---|---|---|---|
| HOMA- IR (units) | 0.00 | > 0.05 | NS |
| HOMA β (units) | -0.23 | < 0.05 | S |

*P value <.001 is considered extremely significant while p<.05 is significant.

## RESULTS

Principal characteristics of prediabetic, Newly diagnosed diabetic and healthy subjects are presented in Table 1. There was no significant difference between healthy, prediabetic, Newly diagnosed diabeticsubjects regarding mean age (42±10, 44±8 and 45±9 years), BMI ( 26.06±4.94, 26.24±5.22 and 27.66±4.26 kg/m2) and male to female ratio (48/27, 56/ 19 and 52/23).Serum visfatin levels show increasing trend going from healthy subjects to Prediabetic subjects to Newly diagnosed diabetic(3.12±1.56, 4.70±2.66, 5.35±3.70 P < 0.001).Serum glucose, Insulin, Insulin resistance (HOMA-IR) were significantly high in prediabetics (p< .001)and Newly diagnosed diabetic(p<0.001) while Insulin secretory capacity (HOMA β ) was significantly low compared to healthy controls.(p<0.001)

Anthropometric measures (i.e. BMI ), Insulin and Insulin resistance (HOMA-IR) does not correlate significantly with visfatin in both study groups. Serum glucose shows significant positive correlation with visfatin and Insulin secretory capacity (HOMA β) shows significant negative correlation with visfatin.(P <.05) only in Newly diagnosed diabetic subjects as in Table 2 and 3. There was no significant correlation of visfatin and HOMA- IR even after adjusted with BMI while HOMA β shows significant negative correlation in Newly diagnosed diabetic subjects when adjusted with BMI. (Table 4 and 5)

## DISCUSSION

Prediabetic subjects have significantly higher levels of visfatin as compared to healthy control subjects. A number of studies have reported higher circulating levels of visfatin in diabetic and obese subjects [10-16] while few research shows higher visfatin levels among impaired glucose tolerance subjects.[17, 18] Increased level of serum visfatin suggests that hyperglycemia and development of type 2 diabetes is delayed through hypersecretion of adipose tissue derived visfatin as it possesses insulin mimetic effects. Therefore, increased serum visfatin may be a compensatory mechanism or part of pathophysiology of diabetes mellitus.

No significant correlation of visfatin levels with insulin resistance is consistent with other studies [18, 3, 21]. They also reported no correlation of visfatin levels with insulin sensitivity in IFG, IGT as well as IFG-IGT. Although serum visfatin was raised in the hyperglycaemic states, no significant correlation of fasting blood glucose with visfatin was observed in prediabetic subjects, which contradicts the findings of previous studies [24, 18, 21]. The reason for this discrepancy is unclear, but it may result from the study different population because ethnic heterogeneity can affect visfatin levels or the small increase in glucose in prediabetic subjects is not sufficient to show its correlation with visfatin. It is also assumed that increased visfatin in patients with the IFG (metabolic syndrome) may play role in the pathogenesis of inflammatory disorders.

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Our study showed that visfatin has significant positive association with glucose and significant negative association with HOMA-β which is in concordance with Lopez et. al who found that increased visfatin in patients with type 2 as a result of β cell dysfunction .They demonstrated a negative correlation of visfatin with β cell function by studying acute insulin secretion assessed via an intravenous glucose tolerance test.[16] Wajchenberg et. al has seen increased visfatin in newly diagnosed type 2 diabetics as a result of β cell deterioration.[19] This study was also supported by Kowalska et. al who found insulin's inability to suppress visfatin production in insulin resistant conditions.[20] However, Dogru et. al indicated that hyperglycemia causes an increase in plasma visfatin levels in people with type 2 DM but not with IGT and the increase gets prominent as glucose intolerance worsens which is line with our study.

It has been reported that visfatin is not correlated with the amount of body fat and trunk fat in young men.[22] Berndt et. al found no correlation between visfatin and visceral adiposity determined by computed tomography, which is reliable method for measurement of visceral fat mass.[4] Esteghamati et. al also showed that the elevation of visfatin in type 2 diabetic patients is independent of obesity and insulin resistance.[14]The lack of correlation between visfatin and BMI found in our patients was also confirmed by other authors in diabetes[16], in obese non-diabetic patients[23] and in non obese patients with newly diagnosed type 2 diabetes and impaired glucose tolerance.[21]Our study was not able to find correlation with insulin resistance even after adjustment with BMI while the correlation with HOMA β was unaffected. Hence, visfatin is independent of obesity and insulin resistance as suggested by Esteghmati *et al.* 2011.

In conclusion, this study shows that Hyperglycemia causes hypersecretion of adipose tissue derived visfatin in people with prediabetes and the increase gets prominent as glucose intolerance worsens. Increased visfatin levels in newly diagnosed type 2 diabetics are a result of impaired insulin secretion and not insulin resistance i.e. Insulin is unable to suppress visfatin production in insulin resistant conditions. Fasting glucose levels may also play a key role in the elevation of visfatin levels. Due to multifactorial regulation of visfatin, other processes may also be involved in the increase of visfatin i.e. eiher as compensatory mechanism as it has insulin mimetic effects or inflammatory processes. Hence to summarise, rise of visfatin in prediabetics and NDT2D is independent of obesity and insulin resistance.

Limitation of our study is further division of prediabetic subjects into sub-groups with larger sample size.

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